

**DRAFT  
TOXICOLOGICAL PROFILE FOR  
CHROMIUM**

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

September 2008

## 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 Chromium was released in 2000. 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-32  
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 the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

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

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

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

Comments should be sent to:

Agency for Toxic Substances and Disease Registry  
Division of Toxicology and Environmental Medicine  
1600 Clifton Road NE  
Mail Stop F-32  
Atlanta, Georgia 30333

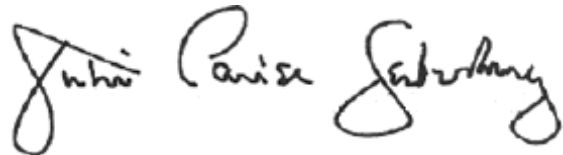
### Background Information

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99 499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the Federal Register on December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see Federal Register notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999 (64 FR 56792); October 25, 2001 (66 FR 54014) and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was 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



Julie Louise Gerberding, 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:

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

### **Other Sections of Interest:**

<b>Section 3.8</b>	<b>Biomarkers of Exposure and Effect</b>
<b>Section 3.11</b>	<b>Methods for Reducing Toxic Effects</b>

---

### **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](mailto: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](mailto: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):

Sharon Wilbur, M.A.  
Henry Abadin, M.S.P.H.  
Mike Fay, Ph.D.  
Diany Yu, M.D.  
Brian Tencza M.S.  
ATSDR, Division of Toxicology and Environmental Medicine, Atlanta, GA

Julie Klotzbach, Ph.D.  
Shelly James, Ph.D.  
Syracuse Research Corporation, 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 chromium. The panel consisted of the following members:

1. Dr. Detmar Beyersmann, Professor Emeritus of Biochemistry, University of Bremen, Germany,
2. John Pierce Wise, Sr., Ph.D., Director, Maine Center for Toxicology and Environmental Health, Professor of Toxicology and Molecular Epidemiology, Department of Applied Medical Sciences, University of Southern Maine, 96 Falmouth St., Portland, ME 04104-9300, and
3. Richard Sedman, Ph.D., Toxicologist, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, CA.

These experts collectively have knowledge of chromium'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 CHROMIUM? .....	2
1.2 WHAT HAPPENS TO CHROMIUM WHEN IT ENTERS THE ENVIRONMENT? .....	2
1.3 HOW MIGHT I BE EXPOSED TO CHROMIUM? .....	3
1.4 HOW CAN CHROMIUM ENTER AND LEAVE MY BODY? .....	3
1.5 HOW CAN CHROMIUM AFFECT MY HEALTH? .....	4
1.6 HOW CAN CHROMIUM AFFECT CHILDREN? .....	5
1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO CHROMIUM? .....	5
1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CHROMIUM? .....	6
1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH? .....	6
1.10 WHERE CAN I GET MORE INFORMATION? .....	7
2. RELEVANCE TO PUBLIC HEALTH .....	9
2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CHROMIUM IN THE UNITED STATES .....	9
2.2 SUMMARY OF HEALTH EFFECTS .....	9
2.3 MINIMAL RISK LEVELS (MRLs) .....	26
3. HEALTH EFFECTS .....	47
3.1 INTRODUCTION .....	47
3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE .....	48
3.2.1 Inhalation Exposure .....	49
3.2.1.1 Death .....	50
3.2.1.2 Systemic Effects .....	50
3.2.1.3 Immunological and Lymphoreticular Effects .....	92
3.2.1.4 Neurological Effects .....	96
3.2.1.5 Reproductive Effects .....	97
3.2.1.6 Developmental Effects .....	99
3.2.1.7 Cancer .....	99
3.2.2 Oral Exposure .....	107
3.2.2.1 Death .....	107
3.2.2.2 Systemic Effects .....	154
3.2.2.3 Immunological and Lymphoreticular Effects .....	170
3.2.2.4 Neurological Effects .....	171
3.2.2.5 Reproductive Effects .....	172

3.2.2.6	Developmental Effects.....	178
3.2.2.7	Cancer .....	181
3.2.3	Dermal Exposure.....	185
3.2.3.1	Death.....	185
3.2.3.2	Systemic Effects.....	193
3.2.3.3	Immunological and Lymphoreticular Effects .....	199
3.2.3.4	Neurological Effects .....	202
3.2.3.5	Reproductive Effects.....	202
3.2.3.6	Developmental Effects.....	202
3.2.3.7	Cancer .....	202
3.3	GENOTOXICITY .....	202
3.4	TOXICOKINETICS .....	224
3.4.1	Absorption.....	226
3.4.1.1	Inhalation Exposure .....	226
3.4.1.2	Oral Exposure .....	228
3.4.1.3	Dermal Exposure.....	233
3.4.2	Distribution .....	234
3.4.2.1	Inhalation Exposure .....	234
3.4.2.2	Oral Exposure .....	236
3.4.2.3	Dermal Exposure.....	240
3.4.2.4	Other Routes of Exposure .....	240
3.4.3	Metabolism .....	244
3.4.4	Elimination and Excretion .....	249
3.4.4.1	Inhalation Exposure .....	249
3.4.4.2	Oral Exposure .....	250
3.4.4.3	Dermal Exposure.....	254
3.4.4.4	Other Routes of Exposure .....	254
3.4.5	Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models .....	256
3.4.5.1	O’Flaherty Model (1993a, 1996, 2001) .....	257
3.5	MECHANISMS OF ACTION .....	264
3.5.1	Pharmacokinetic Mechanisms.....	264
3.5.2	Mechanisms of Toxicity.....	267
3.5.3	Animal-to-Human Extrapolations.....	269
3.6	TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS .....	270
3.7	CHILDREN’S SUSCEPTIBILITY .....	271
3.8	BIOMARKERS OF EXPOSURE AND EFFECT .....	274
3.8.1	Biomarkers Used to Identify or Quantify Exposure to Chromium .....	275
3.8.2	Biomarkers Used to Characterize Effects Caused by Chromium .....	281
3.9	INTERACTIONS WITH OTHER CHEMICALS .....	283
3.10	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE .....	286
3.11	METHODS FOR REDUCING TOXIC EFFECTS.....	287
3.11.1	Reducing Peak Absorption Following Exposure .....	288
3.11.2	Reducing Body Burden.....	290
3.11.3	Interfering with the Mechanism of Action for Toxic Effects.....	292
3.12	ADEQUACY OF THE DATABASE.....	295
3.12.1	Existing Information on Health Effects of Chromium.....	296
3.12.2	Identification of Data Needs .....	300
3.12.3	Ongoing Studies.....	316



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

## LIST OF FIGURES

3-1. Levels of Significant Exposure to Chromium(VI)—Inhalation .....	61
3-2. Levels of Significant Exposure to Chromium(III)—Inhalation.....	69
3-3. Levels of Significant Exposure to Chromium(VI)—Oral .....	134
3-4. Levels of Significant Exposure to Chromium(III)—Oral.....	151
3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance.....	258
3-6. A Physiologically Based Model of Chromium Kinetics in the Rat.....	259
3-7. Relationship Between Water Soluble Chromium(VI) CrA and Daily Increase in Urinary Chromium Levels (CrU) (Pre-exposure Values were Subtracted from End-of-Shift Values).....	280
3-8. Existing Information on Health Effects of Chromium(VI).....	297
3-9. Existing Information on Health Effects of Chromium(III).....	298
6-1. Frequency of NPL Sites with Chromium Contamination.....	348

This page is intentionally blank.

## LIST OF TABLES

3-1. Levels of Significant Exposure to Chromium(VI)—Inhalation .....	51
3-2. Levels of Significant Exposure to Chromium(III)—Inhalation.....	65
3-3. Levels of Significant Exposure to Chromium(VI) —Oral .....	109
3-4. Levels of Significant Exposure to Chromium(III)—Oral.....	140
3-5. Levels of Significant Exposure to Chromium(VI)—Dermal .....	186
3-6. Levels of Significant Exposure to Chromium(III)—Dermal.....	191
3-7. Genotoxicity of Chromium <i>In Vivo</i> .....	203
3-8. Genotoxicity of Chromium(VI) <i>In Vitro</i> .....	208
3-9. Genotoxicity of Chromium(III) <i>In Vitro</i> .....	213
3-10. Chemical-specific Parameters in the Rat and Human Chromium Models .....	260
3-11. Ongoing Studies on Chromium .....	317
4-1. Chemical Identity of Chromium and Compounds.....	320
4-2. Physical and Chemical Properties of Chromium and Compounds.....	328
5-1. Facilities that Produce, Process, or Use Chromium.....	336
5-2. Facilities that Produce, Process, or Use Chromium Compounds .....	338
5-3. Major Manufacturers of Chromium Compounds in 2007 .....	340
5-4. U.S. Chromium Imports and Exports .....	343
5-5. Historical Use of Chromium in the United States and Western World.....	344
6-1. Releases to the Environment from Facilities that Produce, Process, or Use Chromium .....	352
6-2. Releases to the Environment from Facilities that Produce, Process, or Use Chromium Compounds.....	354
6-3. Estimates of U.S. Atmospheric Chromium Emissions from Anthropogenic Sources.....	364
6-4. Chromium Content in Various U.S. Foods.....	368
6-5. Chromium Content in Tissues and Body Fluids of the General Population.....	370

6-6. Industries that May be Sources of Chromium Exposure ..... 372

6-7. Ongoing Studies on Chromium ..... 382

7-1. Analytical Methods for Determining Chromium in Biological Materials..... 384

7-2. Analytical Methods for Determining Chromium in Environmental Samples ..... 388

8-1. Regulations and Guidelines Applicable to Chromium ..... 397



## 1. PUBLIC HEALTH STATEMENT

This public health statement tells you about chromium 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. Chromium has been found in at least 1,127 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 chromium 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 harm you.

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 chromium, 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. PUBLIC HEALTH STATEMENT

**1.1 WHAT IS CHROMIUM?**

Description	<p>Chromium is a naturally-occurring element found in rocks, animals, plants, and soil.</p> <p>The three main forms of chromium are chromium(0), chromium(III), and chromium(VI). Small amounts of chromium(III) are considered to be a necessity for human health.</p>
<p>Uses</p> <ul style="list-style-type: none"> <li>• manufacturing</li> <li>• consumer products</li> </ul>	<p>Chromium is widely used in manufacturing processes.</p> <p>Chromium can be found in many consumer products such as:</p> <ul style="list-style-type: none"> <li>• wood treated with copper dichromate.</li> <li>• leather tanned with chromic sulfate.</li> <li>• stainless steel cookware.</li> </ul>

**1.2 WHAT HAPPENS TO CHROMIUM WHEN IT ENTERS THE ENVIRONMENT?**

Sources	Chromium can be found in air, soil, and water after release from the manufacture, use, and disposal of chromium-based products, and during the manufacturing process.
<p>Break down</p> <ul style="list-style-type: none"> <li>• air</li> <li>• water and soil</li> </ul>	<p>Chromium does not usually remain in the atmosphere, but is deposited into the soil and water.</p> <p>Chromium can change from one form to another in water and soil, depending on the conditions present.</p>



## 1. PUBLIC HEALTH STATEMENT

**1.5 HOW CAN CHROMIUM AFFECT MY HEALTH?**

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

Respiratory tract	<p>Chromium(VI) compounds are more toxic than chromium(III) compounds. The most common health problem in workers exposed to chromium involves the respiratory tract. These health effects include irritation of the lining of the nose, runny nose, and breathing problems (asthma, cough, shortness of breath, wheezing). Workers have also developed allergies to chromium compounds, which can cause breathing difficulties and skin rashes.</p> <p>The concentrations of chromium in air that can cause these effects may be different for different types of chromium compounds, with effects occurring at much lower concentrations for chromium(VI) compared to chromium(III) . However, the concentrations causing respiratory problems in workers are at least 60 times higher than levels normally found in the environment.</p> <p>Respiratory tract problems similar to those observed in workers have been seen in animals exposed to chromium in air.</p>
Stomach and Small Intestine	<p>The main health problems seen in animals following ingestion of chromium(VI) compounds are to the stomach and small intestine (irritation and ulcer) and the blood (anemia). Chromium(III) compounds are much less toxic and do not appear to cause these problems.</p>
Male Reproductive System	<p>Sperm damage and damage to the male reproductive system have also been seen in laboratory animals exposed to chromium(VI).</p>
Cancer	<p>The International Agency for Research on Cancer (IARC) has determined that chromium(VI) compounds are carcinogenic to humans. The National Toxicology Program 11<sup>th</sup> Report on Carcinogens classifies chromium(VI) compounds as known to be human carcinogens.</p> <p>In workers, inhalation of chromium(VI) has been shown to cause lung cancer. An increased in stomach tumors was observed in humans exposed to chromium(VI) in drinking water.</p> <p>In laboratory animals, chromium(VI) compounds have been shown to cause tumors to the stomach,intestinal tract and lung.</p>



## 1. PUBLIC HEALTH STATEMENT

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

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

Detecting exposure	Since chromium is a required nutrient in the body and is normally present in food, chromium is normally present in blood, urine, and body tissues.
Measuring exposure	Higher than normal levels of chromium in blood or urine may indicate that a person has been exposed to chromium. However, increases in blood and urine chromium levels cannot be used to predict the kind of health effects that might develop from that exposure.

**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.

## 1. PUBLIC HEALTH STATEMENT

Some regulations and recommendations for chromium include the following:

Levels in drinking water set by EPA	The EPA has determined that exposure to chromium in drinking water at concentrations of 1 mg/L for 1 day or 10 days is not expected to cause any adverse effects in a child.
Levels in bottled water set by FDA	The FDA has determined that the chromium concentration in bottled drinking water should not exceed 0.1 mg/L.
Levels in workplace air set by OSHA	OSHA set a legal limit for chromium(VI) of 0.0005 mg/m <sup>3</sup> chromium in air averaged over an 8-hour work day, for chromium(III) of 0.5 mg/m <sup>3</sup> chromium in air averaged over an 8-hour work day, and for chromium(0) of 1.0 mg/m <sup>3</sup> chromium in air averaged over an 8-hour work day.

**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](http://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](mailto: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-32  
 Atlanta, GA 30333  
 Fax: 1-770-488-4178

## 1. PUBLIC HEALTH STATEMENT

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/>



## 2. RELEVANCE TO PUBLIC HEALTH

### 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CHROMIUM IN THE UNITED STATES

Chromium is a naturally occurring element present in the earth's crust. Chromium is released to the environment from natural and anthropogenic sources, with the largest release occurring from industrial releases. The industries with the largest contribution to chromium release include metal processing, tannery facilities, chromate production, stainless steel welding, and ferrochrome and chrome pigment production. The estimated atmospheric concentrations of chromium in U.S. urban and nonurban areas typically contains mean total chromium concentrations ranging from 5 to 525 ng/m<sup>3</sup>. The levels of chromium in U.S. fresh waters typically range from <1 to 30 µg/L, with a median value of 10 µg/L. Typical U.S. drinking water supplies contain total chromium levels within a range of 0.2–35 µg/L however, most supplies in the United States contain <5 µg/L of chromium. Recent monitoring data of drinking water supplies in California indicated that 86% of the sources tested had levels of chromium (reported for chromium(VI)) below 10 µg/L. U.S. soil levels of total chromium range from 1 to 2,000 mg/kg, with a mean level of 37 mg/kg. In ocean water, the mean chromium concentration is 0.3 µg/L.

The general population is exposed to chromium by inhaling ambient air, ingesting food, and drinking water containing chromium. Dermal exposure of the general public to chromium can occur from skin contact with certain consumer products or soils that contain chromium. The primary route of nonoccupational workers, however, is food ingestion. Chromium content in foods varies greatly and depends on the processing and preparation. In general, most fresh foods typically contain chromium levels ranging from <10 to 1,300 µg/kg. Present-day workers in chromium-related industries can be exposed to chromium concentrations 2 orders of magnitude higher than the general population.

### 2.2 SUMMARY OF HEALTH EFFECTS

***Chromium as an Essential Nutrient.*** Chromium(III) is an essential nutrient required for normal energy metabolism. The Institute of Medicine (IOM) of the National Research Council (NRC) determined an adequate intake (e.g., a level typically consumed by healthy individuals) of 20–45 µg chromium(III)/day for adolescents and adults. IOM reported average plasma chromium concentrations of 2–3 nmol/L (equivalent to 0.10–16 µg/L) and an average urinary chromium excretion of 0.22 µg/L or 0.2 µg/day.

## 2. RELEVANCE TO PUBLIC HEALTH

Currently, the biological target for the essential effects of chromium(III) is unknown. Chromodulin, also referred to as glucose tolerance factor (GTF), has been proposed as one possible candidate. The function of chromodulin, an oligopeptide complex containing with four chromic ions, has not been established; however, a possible mechanism is that chromodulin facilitates the interaction of insulin with its cellular receptor sites, although this has not been proven.

Whether chromium(III) should be considered an essential element remains controversial. Reports of chromium(III) deficiency are rare and there is no recognized disease that is attributed to chromium deficiency as there is with most other essential minerals (e.g., Wilson's disease for people with copper deficiency). Evidence of overt signs of apparent chromium deficiency in humans is limited to a few case reports. In one such case report, a woman receiving total parenteral nutrition for 3 years exhibited peripheral neuropathy, weight loss, and impaired glucose metabolism. Administration of insulin did not improve glucose tolerance. Administration of 250 µg/day chromium without exogenous insulin resulted in normal glucose tolerance of an oral load of glucose and the absence of peripheral neuropathy. Thus, direct evidence of chromium(III) deficiency in humans is lacking. In animals, severe chromium deficiency is also difficult to induce, but when it was induced hyperglycemia, decreased weight gain, elevated serum cholesterol levels, aortic plaques, corneal opacities, impaired fertility, and lethality were observed. Administration of inorganic trivalent chromium compounds or extracts of brewers' yeast resulted in decreased blood glucose levels and cholesterol levels and regression of atherosclerotic plaques. Improved insulin sensitivity also resulted in an increased incorporation of amino acids into proteins and cell transport of amino acid in rats receiving supplemental chromium. Thus, whether chromium is a true essential element or a pharmacological agent is still under debate.

Studies have shown that chromium supplementation (Brewer's yeast, extracts of brewer's yeast, synthetic chromium compounds with biological activity, chromium(III) picolinate, and inorganic trivalent chromium) in deficient and marginally deficient subjects can result in improved glucose, protein, and lipid metabolism. In general, these studies have demonstrated improved glucose tolerance to an oral glucose load in Type II diabetics (adult onset) and nondiabetic elderly subjects receiving a 4–200 µg/day chromium supplement and improved plasma lipid profiles (e.g., decreased total cholesterol, LDL-cholesterol, and serum lipids and increased in HDL-cholesterol); improvements in serum lipids and cholesterol levels may be secondary to the decreased serum glucose levels.

Chromium picolinate has been used as a dietary supplement to aid in weight loss and increase lean body mass; however, the role of chromium in the regulation of lean body mass, percentage body fat, and weight

## 2. RELEVANCE TO PUBLIC HEALTH

reduction is highly controversial with negative and positive results being reported in the literature. Numerous studies have evaluated the relationship between weight loss or increases in lean body mass in active and sedentary adults and chromium picolinate supplementation, with mixed results reported. Information on adverse health effects of chromium(III) compounds, including dietary supplements, in humans and animals is reviewed below. However, based on a limited number case studies reporting adverse effects in humans ingesting high-dose chromium(III) supplements, individuals using chromium supplements are cautioned to avoid taking more than recommended doses.

***Chromium Toxicokinetics.*** The toxicokinetics of a given chromium compound depend on the valence state of the chromium atom and the nature of its ligands. For inhaled chromium compounds of any valence state, the amount and location of deposition of inhaled chromium will be determined by factors that influence convection, diffusion, sedimentation, and interception of particles in the airways. In general, less water-soluble chromium compounds that deposit in the pulmonary region can be expected to have a longer retention time in the lung than more soluble forms. Most quantitative studies of the gastrointestinal absorption of chromium in humans have estimated the absorption fraction to be <10% of the ingested dose. In general, these studies suggest that the absorption fraction of soluble chromium compounds is higher than insoluble forms (e.g.,  $\text{CrCO}_3$ ), and is higher for soluble chromium(VI) compounds (e.g.,  $\text{K}_2\text{Cr}_2\text{O}_7$ ) than soluble chromium(III) (e.g.,  $\text{CrCl}_3$ ). Chromium(VI) is reduced in the stomach to chromium(III), which lowers the absorbed dose from ingested chromium(VI). Absorption is also affected by nutritional status; the absorption fraction is higher when dietary intakes are lower. Chromium(III) and chromium(VI) can penetrate human skin to some extent, especially if the skin is damaged.

Absorbed chromium distributes to nearly all tissues, with the highest concentrations found in kidney and liver. Bone is also a major depot and may contribute to long-term retention kinetics of chromium. Chromium(VI) is reduced to chromium(III) via the intermediate forms of chromium(V), chromium(IV). Reduction of chromium(VI) to chromium(III) can give rise to reactive intermediates, chromium adducts with proteins and deoxyribonucleic acid (DNA), and secondary free radicals. Chromium(VI) in blood is taken up into red blood cells, where it undergoes reduction and forms stable complexes with hemoglobin and other intracellular proteins, which are retained for a substantial fraction of the red blood cell lifetime. Absorbed chromium can be transferred to fetuses through the placenta and to infants via breast milk. Absorbed chromium is excreted predominantly in urine. Chromium has been shown to be secreted in bile of animals following parenteral (e.g., intravenous) injection of chromium(VI) or chromium (III) compounds. Chromium can also be eliminated by transfer to hair and nails.

## 2. RELEVANCE TO PUBLIC HEALTH

***Health Effects of Chromium.*** The health effects associated with exposures to chromium(VI), chromium(III) and chromium (IV) are reviewed in detail in Chapter 3. In general, chromium(VI) compounds are more toxic than chromium(III) compounds. The higher toxic potency of chromium(VI) compared to chromium(III) is complex. Chromium(VI) enters cells by facilitated uptake, whereas chromium(III) crosses cell membranes by simple diffusion; thus, cellular uptake of chromium(VI) is more effective than of chromium(III). Furthermore, in biological systems, reduction of chromium(VI) to chromium(III) results in the generation of free radicals, which can form complexes with intracellular targets. Health effects of chromium compounds can vary with route of exposure, with certain effects specific for the portal of entry. For example, respiratory effects are associated with inhalation of chromium compounds, but not with oral and dermal exposures, and gastrointestinal effects are primarily associated with oral exposure. However, as described below, effects of chromium are not limited to the portal of entry, with hematological, immunological, and reproductive systems also identified as targets for chromium. In addition to noncancer health effects, results of occupational exposure studies and chronic-duration animal studies indicate that inhalation and oral exposures to chromium(VI) compounds are associated with respiratory and gastrointestinal system cancers, respectively (see discussion under chromium(VI) below for additional information).

***Chromium(VI)***

The primary effects associated with exposure to chromium(VI) compounds are respiratory, gastrointestinal, immunological, hematological, reproductive, and developmental. In addition, dermal and ocular irritation may occur from direct contact. Based on available dose-response data in humans and animals, the most sensitive noncancer effects of chromium(VI) compounds are respiratory (nasal and lung irritation, altered pulmonary function), gastrointestinal (irritation, ulceration and nonneoplastic lesions of the stomach and small intestine), hematological (microcytic, hypochromic anemia), and reproductive (effects on male reproductive organs, including decreased sperm count and histopathological change to the epididymis). As reviewed below, respiratory and gastrointestinal effects appear to be portal-of-entry effects for inhalation and oral exposure, respectively. Similarly, chromium sensitization, the major immunological effect of chromium(VI), typically presents as allergic contact dermatitis resulting from dermal exposures in sensitized individuals, although respiratory effects of sensitization (asthma) may also occur. Accidental or intentional ingestion of extremely high doses of chromium(VI) compounds by humans has resulted in severe respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal,

## 2. RELEVANCE TO PUBLIC HEALTH

and neurological effects as part of the sequelae leading to death or in patients who survived because of medical treatment.

**Respiratory Effects.** The respiratory tract is the major target of inhalation exposure to chromium(VI) compounds in humans and animals. Respiratory effects have been observed in workers in the following chromium-related industries: chrome plating, chromate and dichromate production, stainless steel welding, and possibly ferrochromium production and chromite mining. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. Intermediate- and chronic-duration exposure of workers to chromium(VI) compounds has resulted in epistaxis, chronic rhinorrhea, nasal itching and soreness, nasal mucosal atrophy, perforations and ulceration of the nasal septum, bronchitis, pneumoconiosis, decreased pulmonary function, and pneumonia. In some chromium-sensitive patients, inhalation of airborne chromium(VI) compounds in the workplace has resulted in asthma. Nasal irritation and mucosal atrophy and decreases in pulmonary function have occurred at occupational exposure levels  $\geq 0.002$  mg chromium(VI)/m<sup>3</sup> as chromium trioxide mist. Autopsies of humans who died from cardiopulmonary arrest after ingesting chromium(VI) compounds have revealed pleural effusion, pulmonary edema, bronchitis, and acute bronchopneumonia. Respiratory effects due to ingestion of nonlethal doses are not likely to occur. It is not certain whether skin contact with chromium compounds could result in respiratory effects.

Adverse effects on the respiratory system following inhalation exposure to chromium(VI) have also been observed in animals. Acute- and intermediate-duration exposure to moderate levels of chromium(VI) compounds generally caused mild irritation, accumulation of macrophages, hyperplasia, inflammation, and impaired lung function. A lowest-observed-adverse-effect level (LOAEL) of 0.025 mg chromium(VI)/m<sup>3</sup> as potassium dichromate particles for increased percentage of lymphocytes in bronchoalveolar lavage (BAL) fluid in rats exposed for 28 or 90 days was identified. Obstructive respiratory dyspnea at  $\geq 0.2$  mg chromium(VI)/m<sup>3</sup>, fibrosis at  $\geq 0.1$  mg chromium(VI)/m<sup>3</sup>, and hyperplasia at  $\geq 0.05$  mg chromium(VI)/m<sup>3</sup> were found in the lungs of rats exposed to sodium dichromate for 30 or 90 days. The fibrosis and hyperplasia were reversible. Increases in the levels of total protein, albumin, and activity of lactate dehydrogenase and  $\beta$ -glucuronidase were observed in the bronchoalveolar lavage fluid. Nasal septum perforation, hyperplasia and metaplasia of the larynx, trachea, and bronchus, and emphysema developed in mice exposed to chromium trioxide mists for 1 year. Mice exposed chronically to 4.3 mg chromium(VI)/m<sup>3</sup> as calcium chromate also had epithelial necrosis and hyperplasia of the bronchiolar walls.

## 2. RELEVANCE TO PUBLIC HEALTH

**Gastrointestinal Effects.** Acute oral exposure of humans to lethal or near-lethal doses of chromium(VI) has produced adverse gastrointestinal effects, including abdominal pain, vomiting, gastrointestinal ulceration, hemorrhage and necrosis, and bloody diarrhea. Gastrointestinal effects have also been reported in association with chronic oral exposure of humans to chromium(VI). In a cross-sectional study conducted in 1965 of 155 people whose well water contained 20 mg chromium(VI)/L as a result of pollution from an alloy plant in the People's Republic of China, associations were found between drinking the contaminated water and oral ulcer, diarrhea, abdominal pain, indigestion, and vomiting. Epigastric pain, irritation, and ulceration have been reported in occupational studies of chrome plating and chromate production workers. Exposures in these studies included inhalation and ingestion of chromium (e.g., mucocilliary clearance of inhaled chromium particles to the gastrointestinal tract and/or ingestion secondary to hand-to-mouth activity) and outcomes may have been influenced by other factors, such as stress and diet. Gastrointestinal effects from dermal exposures or absorption of inhaled chromium(VI) are not anticipated.

Studies in animals show that the gastrointestinal system is a primary target of intermediate- and chronic-duration oral exposure to chromium(VI). Adverse effects were observed in the gastrointestinal tract of F344/N rats and B6C3F1 mice exposed to sodium dichromate dihydrate in drinking water for 14 weeks, with LOAEL values of 3.5 mg chromium(VI)/kg/day for duodenal histiocytic infiltration of the duodenum in male and female rats and of 3.1 mg chromium(VI)/kg/day for epithelial hyperplasia in mice. At a higher dose (20.9 mg chromium(VI)/kg/day), more severe effects (ulcer and epithelial hyperplasia and metaplasia of the glandular stomach) were observed in rats. Histopathological changes of the duodenum (epithelial hyperplasia and histiocytic cellular infiltrate) were also reported in a 3-month comparative study in male B6C3F1, BALB/c, and C57BL/6 mice exposed to sodium dichromate dihydrate in drinking water for 14 weeks, a LOAEL values of 2.8 mg chromium(VI)/kg/day. After exposure for 2 years, histopathological changes were observed in the gastrointestinal tract of rats and mice. In male and female rats exposed to 0.77 and 2.4 chromium(VI)/kg/day, respectively, histiocytic infiltration of the duodenum was observed. In mice, duodenal epithelial hyperplasia was observed in males and females at 0.38 mg chromium(VI)/kg/day and histiocytic cellular infiltration of the duodenum was observed in males at 2.4 mg chromium(VI)/kg/day and in females at 3.1 mg chromium(VI)/kg/day.

Results of intermediate-duration inhalation studies in animals yield mixed results regarding the potential for gastrointestinal effects. Although rats exposed by inhalation to  $\leq 0.2$  mg chromium(VI)/m<sup>3</sup> as sodium dichromate for  $\leq 90$  days did not have histopathological changes in the gastrointestinal tract, mice exposed chronically to 4.3 mg chromium(VI)/m<sup>3</sup> were reported to have occasional small ulcerations in the

## 2. RELEVANCE TO PUBLIC HEALTH

stomach and intestinal mucosa; however, the potential of oral exposure via grooming behavior cannot be excluded.

**Immunological Effects.** Exposure to chromium(VI) compounds may lead to allergic sensitization in some individuals. Sensitization to chromium is produced through two types of hypersensitivity reactions: type I, an immediate onset, IgE-mediated immune mechanism, and type IV, a delayed, cell-mediated immune mechanism. Following an induction phase during which the individual becomes sensitized, subsequent exposures result in an allergic response, with symptoms typically presenting as dermatitis or asthma. Sensitization may occur from inhalation, oral, and/or dermal exposure. Estimates of the prevalence of chromium sensitivity in the general U.S. population range from 0.08 to 7%, depending upon the population evaluated. For dermal responses, the allergic response following direct skin contact with chromium compounds is characterized by eczema or dermatitis; typically, chromium-induced allergic contact dermatitis is isolated to areas at the site of contact, rarely occurring in areas remote from the point of contact. However, oral exposure to chromium(VI) has been shown to exacerbate dermatitis of sensitive individuals. The acute response phase lasts for a few days to a few weeks and is characterized by erythema, edema, and small and large blisters; the chronic phase exhibits similar clinical features, but may also include thickened, scaly, and fissured skin. Exposure to chromium compounds in chromium-related occupations appears to be the major cause of chromium contact dermatitis. Patch testing has identified chromium-sensitized workers in the printing and lithography industry, in automobile factories where assemblers handled nuts, bolts, and screws, in wet sandpapering of primer paint where workers were exposed to zinc chromate, in the cement industry, in railroad systems and diesel locomotive repair shops where antirust diesel-engine coolants and radiator fluids contained sodium chromate, in tanneries, and in the welding, plating, wood, and paper industries. Other sources of chromium that have resulted in chromium sensitivity include dichromate-containing detergents and bleach, glues, machine oils, foundry sand, match heads, boiler linings, and magnetic tapes. Exposure to low levels of chromium as found in consumer products could result in sensitization or a reaction in sensitized individuals; therefore, in hypersensitive individuals may develop rashes and erythema from contact with consumer products containing chromium. Oral doses of potassium dichromate exacerbated the dermatitis of sensitive individuals.

Several studies have estimated the exposure level required to elicit a dermal response in chromium-sensitized individuals; exposure levels of 4–25 ppm produced sensitization and elicitation of chromium-induced allergic dermatitis. However, confounding factors, such as variability in testing methods (including different chromium compounds used in challenge testing) and individual sensitivity,

## 2. RELEVANCE TO PUBLIC HEALTH

complicate interpretation of results. Furthermore, the response of an individual to dermal challenge may vary over time due to changes in exposure to the sensitizing agents; if an individual is removed from exposure, circulating IgE levels may decrease, resulting in decreased sensitivity to dermal challenge. Therefore, it is anticipated that the exposure level required to elicit a dermal response in sensitized individuals will be highly variable.

Asthmatic attacks have occurred in chromium-sensitive individuals exposed by inhalation in occupational settings to chromium trioxide vapors and chromium fumes from stainless steel welding. When challenged with sodium chromate or potassium dichromate via nebulizer, chromium-sensitive patients displayed anaphylactoid reactions, characterized by dermatitis, facial angioedema and erythema, nasopharyngeal pruritus, cough, wheezing, bronchospasms, increased plasma histamine levels, urticaria, and decreased forced expiratory volume. While chromium-induced asthma might occur in some sensitized individuals exposed to elevated concentrations of chromium in air, the number of sensitized individuals is low, and the number of potentially confounding variables in the chromium industry is high.

Studies in animals also indicate that the immune system is a target for inhaled and ingested chromium(VI) compounds. Effects reported include stimulation of the humoral immune system and increased phagocytic activity of macrophages, increased proliferative responses of splenocytes to T- and B-cell mitogens and to the antigen mitomycin C and histopathological alteration (histiocytic cellular infiltration) of pancreatic lymph nodes; contact dermatitis has been elicited in guinea pigs and mice.

**Hematological Effects.** As discussed above (*Chromium Toxicokinetics*), chromium(VI) is distributed to and accumulated by the erythrocyte; once inside the cell, it is rapidly reduced to chromium(III) via the reactive intermediates chromium(V) and chromium(IV), and binds to hemoglobin and other ligands. The chromium-hemoglobin complex is relatively stable and remains sequestered within the cell over the life-span of the erythrocyte, with approximately 1% of chromium eluting from the erythrocyte daily. Occupational studies and other studies in humans have not consistently reported hematological effects, although microcytic, hypochromic anemia has been reported in several recent animals studies on chromium(VI) compounds (detailed discussion follows). However, it is possible that small, exposure-related changes in hematological parameters may not have been detected in occupational exposure studies, if values were within normal clinical ranges. Hematological findings in humans exposed to lethal doses of chromium(VI) compounds are difficult to interpret in the context of multiple systemic effects observed leading up to death, including hemorrhage.



## 2. RELEVANCE TO PUBLIC HEALTH

Results of acute-, intermediate-, and chronic-duration studies in animals identify the hematological system as one of the most sensitive effects of oral exposure to chromium(VI). Microcytic, hypochromic anemia, characterized by decreased mean cell volume (MCV), mean corpuscular hemoglobin (MCH), hematocrit (Hct), and hemoglobin (Hgb), was observed in rats and mice orally exposed to chromium(VI) compounds for exposure durations ranging from 4 days to 1 year. The severity of anemia exhibited dose- and duration-dependence, with maximum effects observed after approximately 3 weeks of exposure; with increasing exposures durations (e.g., 14 weeks–1 year), anemia is less severe, presumably due to compensatory hematopoietic responses. In general, effects observed in rats were more severe than those in mice.

Acute exposure of male rats to sodium dichromate dihydrate in drinking water for 4 days, produced a slight, but statistically significant decrease (2.1%) in MCH in rats exposed to 2.7 mg chromium(VI)/kg/day, but not at 0.7 mg chromium(VI)/kg/day. With increasing doses ( $\geq 7.4$  mg chromium(VI)/kg/day), additional decreases in MCH and decreased MCV were observed. Similar effects were observed in male and female rats exposed for 5 days, with effects observed at 4.0 and 4.1 chromium(VI)/kg/day, respectively; a no-observed-adverse-effect level (NOAEL) was not established. Although the magnitude of changes to hematological parameters after acute exposure was minimal, since severe effects on hematological parameters were observed following intermediate exposure durations, with severity peaking at exposure durations of 22 days to 3 months, the minimal hematological alterations observed following acute exposure are considered to be indicative of adverse hematological effects.

More severe microcytic, hypochromic anemia occurred in rats and mice following exposure to sodium dichromate dihydrate in drinking water for 22 or 23 days. Decreased Hct, Hgb, MCV, and MCH occurred at  $\geq 0.77$  mg chromium(VI)/kg/day, with decreases exhibiting dose-dependence; effects were not observed at 0.21 mg chromium(VI)/kg/day. After exposure for 3 months to 1 year, microcytic, hypochromic anemia in rats and mice was less severe than that observed after 22 or 23 days. Hematological effects, including decreased hematocrit, hemoglobin, and erythrocyte count, have also been reported in rats exposed to chromium trivalent oxide mist for 90 days, with a LOAEL value of 0.23 mg chromium(VI)/m<sup>3</sup>.

**Reproductive Effects.** Results of studies in humans and animals suggest that chromium(VI) causes adverse reproductive effects, although evidence from studies in animals is much stronger than from studies in humans. Although information regarding reproductive effects in humans is limited, the following effects have been reported: a significant increase in the number of morphologically abnormal



## 2. RELEVANCE TO PUBLIC HEALTH

observed in rats and mice exposed to  $\geq 37$  mg chromium(VI)/kg/day or 52 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 20 or 90 days prior to mating. Pre- and postimplantation loss and decreased litter size was also observed in mice exposed to  $\geq 46$  mg chromium(VI)/kg/day as potassium dichromate in drinking water throughout gestation. Significant decreases in the number of implantations and viable fetuses were observed when male mice exposed to 6 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 12 weeks were mated with unexposed female mice; however, sperm count was not measured and the classification of non-viable fetuses was not presented in this report. However, a similarly designed study did not find any alterations in the number of implantations or viable fetuses in unexposed female rats mated with males exposed to 42 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 12 weeks. It is not known if the species difference contributed to these conflicting results. Decreases in the number of implantations and viable fetuses and an increase in the number of animals with resorptions were also seen in females exposed for 12 weeks to 6 mg chromium(VI)/kg/day as potassium dichromate mated with unexposed males.

**Developmental Effects.** No studies were located regarding developmental effects in humans after exposure to chromium compounds. A number of oral exposure animal studies have shown that chromium(VI) is a developmental toxicant following pre-mating and/or *in utero* exposure. In developmental studies in rats and mice, gestational exposure produced increased postimplantation loss, decreased number of live fetuses/litter, decreased fetal weight, internal and skeletal malformations, and delayed sexual maturation in offspring; however, these effects were observed at relatively high doses (e.g.,  $\geq 35$  mg chromium(VI)/kg/day). In mated female rats administered 35.7 mg chromium(VI)/mg/day as potassium dichromate by gavage on gestational days 1–3, a decreased number of pregnancies were observed; exposure on gestational days 4–6 resulted in decreased number of viable fetuses and increased number of resorptions, but did not alter the number of pregnancies. Exposure of female rats to  $\geq 37$  mg chromium(VI)/kg/day and mice to  $\geq 52$  mg chromium(VI)/kg/day to potassium dichromate(VI) in drinking water for 20 or 90 days followed by mating to unexposed males resulted in fetal mortality (postimplantation losses, resorptions, and decreased number of live fetuses), decreased growth (decreased fetal body weights and crown-rump length), reduced ossification, subdermal hemorrhagic patches, and kinky tails. Similar effects (increased resorptions, increased postimplantation losses, subdermal hemorrhages, decreased cranial ossification, tail kinking, and decreased fetal body weight and decreased crown-rump length) were observed in the offspring of mice exposed to 46 mg chromium(VI)/kg/day as potassium dichromate in drinking water during gestation. In mice exposed to 53 mg chromium(VI)/kg/day as potassium dichromate in drinking water during gestational days 6–14, fetal mortality,

## 2. RELEVANCE TO PUBLIC HEALTH

subdermal hemorrhagic patches, and reduced ossification were observed in the offspring. Impaired development of the reproductive system (delayed vaginal opening) was observed in the offspring of mice exposed to 66 mg chromium(VI)/kg/day as potassium dichromate in the drinking water on gestation day 12 through lactation day 20.

**Dermal Effects.** Chromium(VI) compounds can produce effects on the skin and mucous membranes. These include irritation, burns, ulcers, and an allergic type of dermatitis. Irritation of respiratory mucosal tissues, nasal septum ulcers, and perforation are reviewed above under Respiratory Effects and allergic dermatitis is reviewed above under Respiratory Effects and Immunological Effects. Most dermal effects reported were either due to occupational intermediate-chronic exposure or acute exposure to high levels of chromium compounds. Environmental exposure to chromium compounds is not likely to result in dermal effects. Acute dermal exposure to chromium(VI) compounds can cause skin burns. Application of a salve containing potassium chromate to the skin of some individuals to treat scabies resulted in necrosis and sloughing of the skin, and some individuals even died as a result of infections of these areas. A worker whose skin came into direct contact with the chromic acid as a result of an industrial accident developed extensive skin burns.

Although skin contact with chromate salts may cause rashes, untreated ulcers or sores (also called chrome holes) on the skin can be a major problem because they can deeply penetrate the skin with prolonged exposure. For example, in an early case of a tannery worker, the penetration extended into the joint, necessitating amputation of the finger. However, chrome sores heal if exposure is discontinued, leaving a scar. Chrome sores are more often associated with occupational exposure to chromium(VI) compounds. Although chrome sores are more likely associated with direct dermal contact with solutions of chromates, exposure of the skin to airborne fumes and mists of chromium(VI) compounds may contribute to the development. Industries that have been associated with the development of chrome sores in workers include chromate and dichromate production, chrome plating, leather tanning, planographic printing, and chromite ore processing. Among the chromium(VI) compounds that workers in these industries are exposed to are chromium trioxide, potassium dichromate, sodium dichromate, potassium chromate, sodium chromate, and ammonium dichromate.

In addition, tonsillitis, pharyngitis, atrophy of the larynx, and irritation and ulceration of mouth structures and buccal mucosa can occur from exposure to high levels of chromium(VI) compounds. These effects were seen in workers in chrome plating plants, where excessively high concentrations of chromium trioxide fumes were present. High incidences of inflammation of oral structures, keratosis of the lips,

## 2. RELEVANCE TO PUBLIC HEALTH

gingiva, and palate, gingivitis, and periodontitis were also observed in chromate production workers. Oral doses of potassium dichromate exacerbated the dermatitis of chromium sensitized individuals.

Dermal effects observed in animals after direct application of potassium dichromate to their skin include inflammation, necrosis, corrosion, eschar formation, and edema in rabbits and skin ulcers in guinea pigs.

**Ocular Effects.** Ocular effects can occur as a result of direct contact of eyes with chromium(VI) compounds. Effects reported include corneal vesication in a man with ocular exposure to a drop or crystal of potassium dichromate and congestion of the conjunctiva, discharge, corneal scar, and burns in chromate production workers as a result of accidental splashes.

**Genotoxicity.** Numerous studies have evaluated the genotoxicity of chromium(VI) compounds. Results of occupational exposure studies in humans, although somewhat compromised by concomitant exposures to other potential genotoxic compounds, provide evidence of chromium(VI)-induced DNA strand breaks, chromosome aberrations, increased sister chromatid exchange, unscheduled DNA synthesis, and DNA-protein crosslinks. Although most of the older occupational exposure studies gave negative or equivocal results, more recent studies have identified chromosomal effects in exposed workers. Findings from occupational exposure studies are supported by results of *in vivo* studies in animals, *in vitro* studies in human cell lines, mammalian cells, yeast and bacteria, and studies in cell-free systems.

**Cancer.** Occupational exposure to chromium(VI) compounds in various industries has been associated with increased risk of respiratory system cancers, primarily bronchogenic and nasal. Among the industries investigated in retrospective mortality studies are chromate production, chromate pigment production and use, chrome plating, stainless steel welding, and ferrochromium alloy production. Numerous studies of cancer mortality among chromate production workers have been reported. Collectively, these studies provide evidence for associations between lung cancer mortality and employment in chromate production, with risks declining with improved industrial hygiene. Less consistently, nasal cancers have been observed. In chromate pigment and chrome plating workers, elevated lung cancer rates in comparison to reference populations (e.g., standard mortality ratios [SMRs]) and increased lung cancer rates in association with increased potential for chromium exposure (e.g., job type, employment duration) have been reported. Workers in the stainless steel welding and ferrochromium alloy industries are exposed to chromium(VI) compounds, as well as other chemical hazards that could contribute to cancer (e.g., nickel); however, results of studies of cancer mortality in

## 2. RELEVANCE TO PUBLIC HEALTH

these populations have been mixed. Environmental exposure of humans to chromium(VI) in drinking water resulted in statistically significant increases in stomach cancer.

Chronic inhalation studies provide evidence that chromium(VI) is carcinogenic in animals. Mice exposed to 4.3 mg chromium(VI)/m<sup>3</sup> as calcium chromate had a 2.8-fold greater incidence of lung tumors, compared to controls. In addition, numerous animal studies using the intratracheal, intrapleural, and intrabronchial routes of exposure show that chromium(VI) produces respiratory tract tumors. However, no carcinogenic effects were observed in rats, rabbits, or guinea pigs exposed to 1.6 mg chromium(VI)/m<sup>3</sup> as potassium dichromate or chromium dust 4 hours/day, 5 days/week.

Exposure rats and mice to sodium dichromate dihydrate in drinking water for 2 years resulted in cancers of the gastrointestinal tract. In male and female rats, the incidences of neoplasms of the squamous epithelium of the oral mucosa and tongue were significantly increased in males (7.0 mg chromium(VI)/kg/day) and females (5.9 mg chromium(VI)/kg/day); in mice, the incidence of neoplastic lesions of the small intestine (duodenum, jejunum, and ileum) was increased in males at 2.4 mg chromium(VI)/kg/day and females at 3.1 mg chromium(VI)/kg/day. The National Toxicology Program (NTP) concluded that results demonstrate clear evidence of carcinogenic activity in male and female F344/N rats (increased incidences of squamous cell neoplasms of the oral cavity) and in male and female B6C3F1 mice (increased incidences of neoplasms of the duodenum, jejunum, or ileum). Mice exposed to chromium(VI) as potassium chromate (9 mg chromium(VI)/kg/day) in drinking water for three generations (880 days) showed statistically significant increases in the incidence of forestomach adenoma or carcinomas of the forestomach and in the incidence of forestomach adenomas alone, compared to control; however, study authors concluded that evidence of carcinogenicity was equivocal.

NTP lists certain chromium compounds as substances that are *known to be human carcinogens*. This classification is based on sufficient evidence for a number of chromium(VI) compounds (calcium chromate, chromium trioxide, lead chromate, strontium chromate, and zinc chromate). The International Agency for Research on Cancer (IARC) classified chromium(VI) as *carcinogenic to humans (Group 1)* and metallic chromium and chromium(III) compounds as *not classifiable as to their carcinogenicity to humans (Group 3)*. EPA has classified chromium(VI) as *a known human carcinogen* by the inhalation route of exposure.

## 2. RELEVANCE TO PUBLIC HEALTH

***Chromium(III)***

Although much less information is available on the health effects of chromium(III) compounds compared to that for chromium(VI) compounds, chromium(III) compounds appear to be less toxic than chromium(VI) compounds. Health effects associated with exposure to chromium(III) compounds have been reported in studies of occupationally exposed populations and individuals; however, interpretation of study results is complicated by concomitant exposures to chromium(VI) or other compounds that can induce adverse health effects. Similarly, interpretation of findings in case reports of exposures to dietary supplements containing high-dose chromium(III) are also complicated, since most supplements contain numerous chemicals; thus, the most reliable information on adverse health effects of chromium(III) is obtained from studies in animals. Chromium(III) picolinate, a dietary supplement, has been shown to be mutagenic in bacterial and mammalian cells *in vitro*.

The primary effects of chromium(III) compounds are on the respiratory and immunological systems. As described below, respiratory effects appear to be portal-of-entry effects for inhalation exposure. Similarly, chromium allergic dermatitis, the major immunological effect of chromium(III), is typically elicited by dermal contact in sensitized individuals; however, initial sensitization may result from inhalation, oral, or dermal exposure or from a combination of these exposure routes. Conflicting results of studies in animals have been reported in developmental and reproductive studies of chromium(III) compounds; however, results provide evidence of adverse effects on the developing and adult reproductive system. Evidence of developmental or reproductive effects of chromium(III) in humans has not been identified. Based on results of chronic-duration oral studies in animals, chromium(III) compounds (chromium acetate, chromium chloride, chromium nicotinate, chromium oxide, chromium picolinate) do not appear to produce gastrointestinal, hematological, hepatic, renal, cardiovascular, endocrine, or musculoskeletal effects. This is in contrast to chromium(VI) compounds which produce effects in the gastrointestinal, hematological, hepatic and renal systems.

**Respiratory Effects.** Occupational exposure studies and case reports indicate that respiratory effects occur from exposure of humans to chromium(III) compounds; however, results of these studies are difficult to interpret since most study populations were also exposed to chromium(VI) compounds or other compounds associated with respiratory effects, and/or the studies were not adequately controlled for other confounding factors (e.g., respiratory diseases). Acute- and chronic-duration studies in animals indicate that the respiratory tract is the primary target of inhaled chromium(III). Analysis of BAL fluid from rats exposed for 5 days to 3–30 mg chromium(III)/m<sup>3</sup> as basic chromium sulfate (soluble) showed

## 2. RELEVANCE TO PUBLIC HEALTH

alterations, including increased amounts of cell debris and lysed cells and significant decreases in nucleated cells and in the percentage of segmented neutrophils and mononuclear cells; cytoplasmic accumulation of a yellow crystalline material in mononuclear cells was observed in BAL fluid of rats exposed to 3–30 mg chromium(III)/m<sup>3</sup> as chromic oxide (insoluble). With longer exposure (13 weeks), histopathological changes to respiratory tissues and increased lung weights were observed in rats exposed to  $\geq 3$  mg chromium(III)/m<sup>3</sup> chromic oxide or basic chromium sulfate. However, differences were observed in severity and location of respiratory effects produced by insoluble chromic oxide and soluble basic chromium sulfate; effects of chromic oxide were less severe and isolated to the lung and respiratory lymph tissues, whereas the effects of basic chromium sulfate were more severe and observed throughout the respiratory tract (e.g., nose, larynx, lung, and respiratory lymph tissues). Differences in the respiratory toxicity of these compounds may be due to differences in chemical-physical properties (e.g., solubility, acidity). Studies examining respiratory effects from chronic-duration inhalation exposure were not identified. Respiratory effects from oral or dermal exposure to chromium(III) compounds have not been reported.

**Immunological Effects.** As discussed above for chromium(VI) compounds, exposure to chromium compounds may induce allergic sensitization in some individuals. In patients with known chromium-induced allergic dermatitis, positive results have been reported using patch tests with chromium(III) compounds as the challenge agent, suggesting that allergic sensitization to chromium(III) can occur. In sensitized patients, dermal responses were elicited using a concentration of 1 mg chromium(III)/L as chromium trichloride. However, since positive responses were also observed on challenge with chromium(VI) compounds, it is unclear if individuals were sensitized to both chromium(VI) and chromium(III) or if cross-sensitivity occurs between chromium(VI) and chromium(III). Studies in animals show that chromium(III) can induce sensitization and that cross-reactivity occurs between chromium(VI) and chromium(III). Sensitization to chromium(III) was observed in guinea pigs treated with a series of intradermal injections of 0.004 mg chromium(III)/kg as chromium trichloride. In guinea pigs sensitized with chromium(III), cross-sensitivity with chromium(VI) was observed on patch test challenge.

**Reproductive Effects.** Adverse reproductive effects have been observed in rats and mice exposed orally to chromium(III) compounds, although conflicting results have been reported. Adverse reproductive effects have been reported following acute- and intermediate-duration exposure of animals to chromium(III) by gavage or in drinking water; effects include decreased number of pregnancies in female rats administered 33.6 mg chromium(III)/kg/day, alterations in sexual behavior, aggressive





## 2. RELEVANCE TO PUBLIC HEALTH

no effects on pregnancy rates, implantations, viable fetuses, or resorptions were observed. Thus, the available evidence does not indicate that exposure to chromium(III) consistently produces adverse developmental effects.

**Cancer.** No studies evaluating the carcinogenic activity of chromium(III) compounds in humans were identified. In male rats exposed to dietary chromium picolinate for 2 years, the incidence of preputial gland adenoma was significantly increased in males at 61 mg chromium(III)/kg/day, with the incidence also exceeding the historical control ranges; however, the incidence was not increased at a higher dose (313 mg chromium(III)/kg/day) and similar lesions were not observed in corresponding tissues in female rats or in male and female mice. Therefore, NTP considered the evidence of carcinogenic activity to be equivocal. The relationship of preputial gland adenoma to male reproductive function in this study was not defined.

### 2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for chromium. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), 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.

## 2. RELEVANCE TO PUBLIC HEALTH

***Inhalation MRLs—Chromium(VI)***

***Acute.*** The inhalation database for acute-duration exposure of humans to inhaled chromium(VI) compounds is limited to a few studies reporting signs of respiratory irritation (dyspnea, cough, wheezing, sneezing, rhinorrhea, choking sensation), dizziness, and headaches in individuals or small numbers of workers ( $n \leq 5$ ) exposed to high concentrations of chromium(VI) (Lieberman 1941; Meyers 1950; Novey et al. 1983). In addition, acute inhalation exposure of individuals previously sensitized to chromium compounds has produced symptoms of asthma and signs of respiratory distress consistent with a type I allergic response (decreased forced expiratory volume, facial erythema, nasopharyngeal pruritus, blocked nasal passages, cough, and wheeze) (Leroyer et al. 1998; Olaguibel and Basomba 1989); however, the available data are not adequate to characterize the exposure-response relationship for effects of acute inhalation challenge in sensitized individuals. No other effects of acute inhalation exposure of humans to chromium(VI) have been reported.

The acute toxicity of inhaled chromium(VI) in animals has not been well investigated, and most studies are 4-hour lethality studies (American Chrome and Chemicals 1989; Gad et al. 1986). Nasal hemorrhage was observed in two of five rats after inhalation for 10 days to 1.15 mg chromium(VI)/m<sup>3</sup> during a 13-week exposure study (Kim et al. 2004), with no nasal effects observed at 0.49 mg chromium(VI)/m<sup>3</sup>. However, only a small number of animals were evaluated and histopathological evaluations of the respiratory tract (or other tissues) were not conducted following the acute-duration period; thus, data are not suitable for defining NOAEL or LOAEL values for respiratory effects. Although longer duration inhalation studies show that the respiratory tract is a sensitive target of inhaled chromium(VI), the data are insufficient to determine acute-duration exposure levels that would produce respiratory tract, or other effects. In the absence of studies that could be used to identify the targets of low level exposure, an acute-duration inhalation MRL for hexavalent chromium was not derived.

***Intermediate***

- An inhalation MRL of  $5 \times 10^{-6}$  mg chromium(VI)/m<sup>3</sup> has been derived for intermediate (15–364 days) exposure for dissolved hexavalent chromium aerosols and mists.

The available data on inhalation exposure of humans and animals to chromium(VI) compounds indicate that dissolved chromium(VI) compounds (aerosols and mists) and particulate chromium(VI) compounds have different toxic potencies for producing adverse respiratory effects. Although the respiratory system is the most sensitive target for inhalation exposure to both types of chromium(VI) compounds, the

## 2. RELEVANCE TO PUBLIC HEALTH

primary respiratory effects of inhaled chromic acid mists are observed in the nose (see the following discussion), while the effects of inhaled particulate chromium(VI) compounds occur throughout the respiratory tract. Since toxic potencies of these compounds appear to be different and the likelihood for environmental exposure to chromium trioxide (e.g., chromic acid mist) and other soluble chromium(VI) compound mists is less than the likelihood for environmental exposure to particulate chromium(VI) compounds, distinct intermediate-duration inhalation MRLs have been derived for dissolved chromium(VI) compounds (aerosols and mists) and particulate chromium(VI) compounds.

The intermediate-duration inhalation database for humans exposed to dissolved chromium(VI) aerosols and mists consists of occupational exposure studies on chromium trioxide mists (Gibb et al. 2000a, 2000b; Gomes 1972; Kleinfeld and Rosso 1965; Lindberg and Hedenstierna 1983); these studies identify the upper respiratory tract as the primary target of exposure. Upper respiratory effects include nasal irritation, ulceration, and mucosal atrophy and rhinorrhea, with LOAEL values ranging from 0.002 to 0.1 mg chromium(VI)/m<sup>3</sup>. Other effects (e.g., non-respiratory) specific for dissolved chromium(VI) aerosols and mists in humans have not been reported. Exposure to chromium(VI) compounds (not compound-specific) can produce allergic sensitization, which may manifest as symptoms of asthma upon subsequent inhalation exposures (Keskinen et al. 1980; Leroyer et al. 1998; Moller et al. 1986; Olaguibel and Basomba 1989). The exposure route for the initial sensitization in an occupational setting is most likely a combination of inhalation, oral, and dermal exposures; however, the available data do not define the exposure-response relationship for chromium sensitization by inhalation.

Available animal studies on the effects of intermediate-duration exposure to dissolved chromium(VI) aerosols and mists identify the respiratory tract as the primary target, with LOAEL values ranging from 0.49 to 3.63 mg chromium(VI)/m<sup>3</sup> (Adachi 1987; Adachi et al. 1986; Kim et al. 2004). Respiratory effects reported in animals exposed to chromium(VI) trioxide include alveolar inflammation in rats (Kim et al. 2004) and nasal septal perforation and symptoms of emphysema in mice (Adachi 1987; Adachi et al. 1986). The only other effect (e.g., non-respiratory) observed in animal studies on dissolved chromium(VI) aerosols and mists were hematological effects and decreased body weight in rats exposed to chromium trioxide mist for 13 weeks. Hematological effects include decreased in hematocrit at  $\geq 0.23$  and 1.15 mg chromium(VI)/m<sup>3</sup> (but not 0.49 mg chromium(VI)/m<sup>3</sup>) decreased hemoglobin at  $\geq 0.49$  mg chromium(VI)/m<sup>3</sup> and decreased erythrocyte count at 1.15 mg chromium(VI)/m<sup>3</sup> (Kim et al. 2004). In this study, body weight gain was also decreased by ~9%, with NOAEL and LOAEL values of 0.49 and 1.15 mg chromium(VI)/m<sup>3</sup>, respectively.

## 2. RELEVANCE TO PUBLIC HEALTH

Based on a comparison of LOAEL values for respiratory effects, hematological effects, and decreased body weight gain, the respiratory tract was identified as the most sensitive effect of intermediate-duration inhalation exposure to dissolved chromium(VI) aerosols and mists. The lowest LOAEL value of 0.002 mg chromium(VI)/m<sup>3</sup> was reported for nasal irritation, mucosal atrophy, and ulceration and decreases in spirometric parameters observed in workers exposed to chromic acid mist (Lindberg and Hedenstierna (1983)); therefore, this value was selected as the basis for derivation of the intermediate-duration inhalation MRL for dissolved chromium(VI) aerosols and mists. The population evaluated by Lindberg and Hedenstierna (1983) included 85 male and 19 female chrome plating workers exposed to chromic acid and a reference group of 119 auto mechanics not exposed to chromium. Workers were assessed for nose, throat, and chest symptoms, were inspected for effects in nasal passages, and were given pulmonary function tests. The length of worker exposures to chromic acid ranged from 0.1 to 36 years, with a mean of 2.5 years, spanning both intermediate and chronic durations. Since the study population included workers exposed for an intermediate duration, data are considered appropriate for derivation of the intermediate-duration inhalation MRL. Nasal irritation (p<0.05), mucosal atrophy (p<0.05), and ulceration (p<0.01), and decreases in spirometric parameters (forced vital capacity, forced expired volume in 1 second, and forced mid-expiratory flow) were observed in workers occupationally exposed to  $\geq 0.002$  mg chromium(VI)/m<sup>3</sup> as chromic acid. Approximately 60% of the exposed subjects were smokers, but no consistent association between exposure and cigarette smoking was observed. Additional details on study methods and results are provided in Appendix A.

The LOAEL of 0.002 mg chromium(VI)/m<sup>3</sup> was multiplied by 8 hour/24 hour and by 5 days/7 days to yield a duration-adjusted LOAEL (LOAEL<sub>ADJ</sub>) of 0.0005 mg chromium(VI)/m<sup>3</sup>. The intermediate-duration MRL of  $5 \times 10^{-6}$  was obtained by dividing the LOAEL<sub>ADJ</sub> (0.0005 mg chromium(VI)/m<sup>3</sup>) by an uncertainty factor of 100 (10 for human variability and 10 for extrapolating from a LOAEL).

- An inhalation MRL of 0.0003 mg chromium(VI)/m<sup>3</sup> was derived for intermediate exposures to particulate chromium(VI) compounds.

As discussed above, available data on inhalation exposure of humans and animals to chromium(VI) compounds indicate that dissolved chromium(VI) compounds (aerosols and mists) and particulate chromium(VI) compounds have different toxic potencies for producing adverse respiratory effects (the primary target organ). Furthermore, since the likelihood for environmental exposure to chromium trioxide and other soluble chromium(VI) compound mists is less than the likelihood for environmental exposure to particulate chromium(VI) compounds, distinct intermediate-duration inhalation MRLs have

## 2. RELEVANCE TO PUBLIC HEALTH

been derived for dissolved chromium(VI) compounds (aerosols and mists) and particulate chromium(VI) compounds.

Although few animal studies have reported adverse effects of intermediate-duration inhalation exposure to particulate chromium(VI) compounds (Cohen et al. 1998; Glaser et al. 1985, 1990), results of available studies conducted in rats indicate that the respiratory tract is the primary target organ. In rats exposed to inhaled sodium dichromate for 30–90 days, adverse respiratory effects included obstructive respiratory dyspnea, increased lung weights, hyperplasia of the lung, focal inflammation of the upper airway, and alterations to BAL fluid concentrations of lactate dehydrogenase, protein, and albumin, with a LOAEL value of 0.2 mg chromium(VI)/m<sup>3</sup> (Glaser et al. 1990). Other effects reported in the Glaser et al. (1985, 1990) studies were an increased percentage of lymphocytes in BAL fluid (LOAEL of 0.025 mg chromium(VI)/m<sup>3</sup>), increased serum phospholipids and triglycerides (NOAEL and LOAEL values of 0.1 and 0.2 mg chromium(VI)/m<sup>3</sup>, respectively), increased white blood cell count (LOAEL value of 0.05 mg chromium(VI)/m<sup>3</sup>), decreased body weight gain (NOAEL and LOAEL values of 0.1 and 0.2 mg chromium(VI)/m<sup>3</sup>), and an enhanced immune response to sheep erythrocytes (LOAEL 0.025 mg chromium(VI)/m<sup>3</sup>); however, the toxicological significance of these findings is uncertain. Effects that may be indicative of altered immune function (altered white blood cell counts and cytokine levels in BAL fluid) were observed in rats exposed to 0.36 mg chromium(VI)/m<sup>3</sup> as potassium chromate or barium chromate for 2–4 weeks (Cohen et al. 1998); however, results of this study are difficult to interpret, since effects were not clearly adverse, only one exposure level was evaluated, and histopathological assessment of respiratory tissues (or other tissues) was not conducted.

Based on the available data, respiratory effects were identified as the most sensitive target of intermediate-duration exposure to particulate chromium(VI) compounds, with the study by Glaser et al. (1990) selected as the critical study. In this study, 8-week-old male Wistar rats (30 animals/group) were exposed 22 hours/day, 7 days/week to 0, 0.05, 0.1, 0.2, or 0.4 mg chromium(VI)/m<sup>3</sup> as sodium dichromate aerosol particulates. Detailed discussion of study methods is presented in Appendix A. No deaths or abnormal clinical signs occurred at any of the exposures. Obstructive respiratory dyspnea occurred at  $\geq 0.2$  mg chromium(VI)/m<sup>3</sup> after 30 and 90 days. Mean lung weight was increased in all exposure groups and was statistically increased at 0.05 mg chromium(VI)/m<sup>3</sup> for 30 days, and at 0.1 mg chromium(VI)/m<sup>3</sup> for 90 days and in the 90-day plus recovery period group. Histological examination revealed slight hyperplasia in high incidence at 0.05 mg chromium(VI)/m<sup>3</sup> at 30 days. Lung fibrosis occurred at 0.1 mg chromium(VI)/m<sup>3</sup> for 30 days, but was not seen in rats exposed for 90 days. Accumulation of macrophages was observed in all exposed rats, regardless of exposure concentration or

## 2. RELEVANCE TO PUBLIC HEALTH

duration. Histology of upper airways revealed focal inflammation. Results of bronchoalveolar lavage (BAL) analysis provided further information of the irritation effect. Total protein in BAL fluid was significantly increased in all exposed groups, but declined in the recovery period. Albumin in BAL fluid increased in a dose-related manner at all concentrations in the 30-day group, but recovery started during 90-day exposure and continued during the 30-day observation period. The activities of lactate dehydrogenase and  $\beta$ -glucuronidase, measures of cytotoxicity, were elevated at 0.2 and 0.4 mg chromium(VI)/m<sup>3</sup> for 30 and 90 days, but returned to control values during the recovery period. The number of macrophages in the BAL fluid had significantly increased after 30 and 90 days, but normalized during the recovery period. The macrophages were undergoing cell division or were multinucleate and larger. This activation of macrophages was not observed in the recovered rats. Additional details on study results are presented in Appendix A.

Results of the benchmark concentration (BMC) analysis of the Glaser et al. (1990) data conducted by Malsch et al. (1994) were identified as the basis for derivation of an intermediate-duration inhalation MRL for hexavalent chromium particulate compounds. Using the 90-day exposure data (as described above), Malsch et al. (1994) developed BMCLs (defined as the 95% lower limit on the concentration corresponding to a 10% relative change in the end point compared to the control) for lung weight and BAL fluid levels of lactate dehydrogenase, protein, and albumin. Prior to conducting the benchmark analysis, Malsch et al. (1994) adjusted the dose-response data for intermittent exposure (22 hours/day). Duration-adjusted data were then fitted to a polynomial mean response regression model by the maximum likelihood method to derive BMCLs. The lowest BMCL, 0.016 mg chromium(VI)/m<sup>3</sup> for alterations in lactate dehydrogenase levels in BAL fluid, was selected to derive the intermediate-duration inhalation MRL. The BMCL of 0.016 mg chromium(VI)/m<sup>3</sup> was converted to a human equivalent concentration (BMCL<sub>HEC</sub>) of 0.010 mg chromium(VI)/m<sup>3</sup> using the regional deposited dose ratio (RDDR) program (EPA 1994c) (see Appendix A for details).

The intermediate-duration inhalation MRL of 0.0003 mg chromium (VI)/m<sup>3</sup> for hexavalent chromium particulate compounds was derived by dividing the BMCL<sub>HEC</sub> of 0.010 mg chromium(VI)/m<sup>3</sup> by a composite uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

## 2. RELEVANCE TO PUBLIC HEALTH

*Chronic*

- An inhalation MRL of  $5 \times 10^{-6}$  mg chromium(VI)/m<sup>3</sup> has been derived for chronic ( $\geq 365$  days) exposure for dissolved hexavalent chromium aerosols and mists.

The chronic-duration inhalation database for humans exposed to dissolved chromium(VI) aerosols and mists consists of occupational exposure studies on chromium trioxide mists, reporting effects to the respiratory, renal, and gastrointestinal systems (Franchini and Mutti 1988; Gibb et al. 2000a, 2000b; Hanslian et al. 1967; Lindberg and Hedenstierna 1983; Lucas and Kramkowski 1975). Respiratory effects included bleeding nasal septum, nasal mucosal atrophy, nasal septal ulceration and perforation, epistaxis, rhinorrhea, and decreased lung function, with LOAEL values ranging from 0.002 to 0.414 mg chromium(VI)/m<sup>3</sup>. Effects indicative of renal toxicity include increased retinol binding protein and tubular antigen and increased urinary  $\beta$ -2-microglobulin (Franchini and Mutti 1988; Lindberg and Hedenstierna 1983); LOAEL values for these effects range from 0.004 to 0.05 mg chromium(VI)/m<sup>3</sup>. Gastrointestinal effects reported in workers include stomach pains, cramps, and ulcers, with a LOAEL value of 0.004 mg chromium(VI)/m<sup>3</sup> (Lucas and Kramkowski 1975). Other effects specific for dissolved chromium(VI) aerosols and mists in humans exposed for chronic exposure durations have not been reported. Exposure to chromium(VI) compounds (not compound-specific) can produce allergic sensitization, which may manifest as symptoms of asthma upon subsequent inhalation exposures (Keskinen et al. 1980; Leroyer et al. 1998; Moller et al. 1986; Olaguibel and Basomba 1989). The exposure route for the initial sensitization in an occupational setting is most likely a combination of inhalation, oral, and dermal exposures; however, the available data do not define the exposure-response relationship for chromium sensitization by inhalation. Studies in animals evaluating the effects of chronic-duration exposure to dissolved chromium(VI) aerosols and mists were not identified.

Based on a comparison of LOAEL values for respiratory, renal and gastrointestinal effects in workers, the respiratory tract was identified as the most sensitive effect of chronic-duration inhalation exposure to dissolved chromium(VI) aerosols and mists. The lowest LOAEL value of 0.002 mg chromium(VI)/m<sup>3</sup> was reported for nasal irritation, mucosal atrophy, and ulceration and decreases in spirometric parameters in workers occupationally exposed to chromic acid mist (Lindberg and Hedenstierna (1983); therefore, this value was selected as the basis for derivation of the chronic-duration inhalation MRL for dissolved chromium(VI) aerosols and mists. The population evaluating in this study had a mean exposure duration of 2.5 years, with a range of 0.1–23.6 years, spanning both intermediate and chronic durations. A description of study methods and results is provided above under the discussion of Intermediate-Duration Inhalation MRL for Particulate Hexavalent Chromium Compounds and in Appendix A.



## 2. RELEVANCE TO PUBLIC HEALTH

The LOAEL of 0.002 mg chromium(VI)/m<sup>3</sup> was multiplied by 8 hour/24 hour and by 5 days/7 days to yield a duration-adjusted LOAEL (LOAEL<sub>ADJ</sub>) of 0.0005 mg chromium(VI)/m<sup>3</sup>. The chronic-duration MRL of 5x10<sup>-6</sup> was obtained by dividing the LOAEL<sub>ADJ</sub> (0.0005 mg chromium(VI)/m<sup>3</sup>) by an uncertainty factor of 100 (10 for human variability and 10 for extrapolating from a LOAEL).

Few studies have evaluated the effects of chronic inhalation exposure to particulate hexavalent chromium compounds. In workers chronically exposed to inhaled chromium(VI) compounds at 0.0042 mg chromium(VI)/m<sup>3</sup>, the prevalence of high urinary N-acetyl-β-glucosamidase was increased, indicating possible renal damage (Liu et al. 1998); however, since the chemical form of chromium(VI) was not reported, data from this study are not suitable as the basis for the chronic-duration inhalation MRL specific for particulate hexavalent chromium compounds. The chronic-duration database in animals consists of studies that either did not identify adverse effects of chronic inhalation exposure to particulate hexavalent chromium compounds (Glaser et al. 1986, 1988; Lee et al. 1989) or older studies that did not report sufficient experimental details (Nettesheim and Szakal 1972; Steffee and Baetjer 1965). Thus, due to inadequate data, a chronic-duration inhalation MRL for particulate hexavalent chromium compounds was not derived.

***Oral MRLs—Chromium(VI)***

***Acute.*** Studies on the acute toxicity of orally-administered chromium(VI) in humans are mostly limited to case reports on ingestion of fatal doses (Clochesy 1984; Iseron et al. 1983; Kaufman et al. 1970; Loubieres et al. 1999; Saryan and Reedy 1988). At lower doses (≥0.036 mg chromium (IV)/kg as potassium dichromate), oral exposure to chromium(VI) has been shown to enhance dermatitis in individuals with known chromium sensitivity (Goitre et al. 1982; Kaaber and Veien 1977).

In animals, acute-duration studies on oral exposure to chromium(VI) compounds have shown effects on hematology and clinical chemistry (NTP 2007, 2008a), male reproductive organs (Li et al. 2001) and development (Elsaieed and Nada 2002; Junaid et al. 1996b); however, the available studies did not evaluate comprehensive toxicological end points. Decreased MCV, MCH, and reticulocyte count were observed in rats exposed to ≥0.70 mg chromium (VI)/kg/day after 4–5 days of exposure (NTP 2007, 2008a); however, the magnitude of changes was small and may not yet represent an adverse effect of chromium(VI). Significant alterations in the serum activities of liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and creatine kinase were observed at ≥4.0–4.1 mg

## 2. RELEVANCE TO PUBLIC HEALTH

chromium(VI)/kg/day in rats exposed for 4–5 days (NTP 2007, 2008a). Effects on male reproductive organs, including decreased sperm count, increased percentage of abnormal sperm, and morphological change to seminiferous tubules (decreased diameter of seminiferous tubules and germ cell rearrangement) were observed in Wistar rats following a 6-day gavage administration of  $\geq 5.2$  mg chromium(VI)/kg/day as chromic acid; observations were made 6 weeks after the dosing period (Li et al. 2001). A NOAEL was not defined in this study.

Developmental effects, including increased pre- and postimplantation loss, resorptions, dead fetuses/litter, and skeletal (incomplete ossification of skull bone) and visceral (renal pelvis dilatation) malformations were observed in Wistar rats exposed to 8 mg chromium(VI)/kg/day (the only dose tested) as potassium chromate in drinking water (Elsaieed and Nada 2002). Other studies reported total litter loss, decreased viable fetuses and increased resorptions in rats (Bataineh et al. 2007) and increased resorptions in mice (Junaid et al. 1996b) exposed at higher doses.

Results of acute-duration studies in animals show that exposure to oral chromium(VI) compounds may cause hematological (NTP 2007, 2008a), reproductive (Li et al. 2001), and developmental effects (Elsaieed and Nada 2002; Junaid et al. 1996b). However, since the available studies did not evaluate comprehensive toxicological end points, data are inadequate for derivation of an acute-duration oral MRL for chromium(VI). Therefore, an acute-duration oral MRL for hexavalent chromium was not derived.

***Intermediate***

- An oral MRL of 0.005 mg chromium(VI)/kg/day has been derived for intermediate (15–364 days) exposure to hexavalent chromium compounds.

Hematological effects (microcytic, hypochromic anemia) in male rats and female mice observed after exposure for 22 days in the NTP (2008a) 2-year study were identified as the most sensitive effect of intermediate-duration oral exposure to chromium(VI) for the purpose of derivation of an intermediate-duration oral MRL for chromium(VI) compounds of 0.005 mg chromium(VI)/kg/day. The basis for this determination is as follows.

No human intermediate-duration studies on chromium(VI) were identified. Numerous animal studies examining systemic, neurological, reproductive, and developmental toxicity have reported effects following oral exposure to chromium(VI) compounds, with hematological effects (microcytic, hypochromic anemia) identified as the most sensitive. Microcytic, hypochromic anemia, characterized by

## 2. RELEVANCE TO PUBLIC HEALTH

decreased MCV, MCH, Hct, and Hgb, was observed in rats and mice exposed to chromium(VI) compounds in drinking water or feed for intermediate-duration exposures ranging from 22 days to 6 months (NTP 1996a, 1996b, 1997, 2007, 2008a). The lowest reported LOAEL values for hematological effects were 0.77 mg chromium(VI)/kg/day (with a NOAEL value of 0.21 mg chromium(VI)/kg/day) for decreased Hct, Hgb, MCV, and MCH in male rats; and 0.38 mg chromium(VI)/kg/day (a NOAEL was not established) for decreased MCV and MCH in female mice exposed to sodium dichromate dihydrate in drinking water for 22 days (NTP 2008a). Slightly higher LOAEL values were observed for hematological effects in rats and mice exposed to dietary potassium dichromate for 9 weeks (NTP 1996a, 1996b, 1997).

The duration-dependence of hematological effects was evaluated in rats and mice exposed to sodium dichromate dihydrate in drinking water from 23 days up to 6 months (NTP 2007, 2008a). Results of both studies show that the severity of microcytic, hypochromic anemia was dose-dependent, with maximum effects observed after 22–23 days of exposure. For all intermediate-duration exposures (22 days to 6 months), NOAEL and LOAEL values in male rats for hematological effects were 0.21 and 0.77 mg chromium(VI)/kg/day, respectively. In female mice, microcytic, hypochromic anemia was also observed, with LOAEL values of 0.38, 1.4, and 3.1 mg chromium(VI)/kg/day at the 22-day, 3-month, and 6-month assessments, respectively, with effects less severe than those observed in rats.

Studies examining systemic toxicity in animals have reported numerous effects, including hepatotoxicity (Achaya et al. 2001; Kumar and Rana 1982, Kumar et al. 1985; NTP 1996a, 2007), gastrointestinal effects (NTP 2007), renal toxicity (Acharya et al. 2001; Diaz-Mayans et al. 1986; Kumar and Rana 1982, 1984), lymphatic and immunological effects (NTP 2007; Snyder and Valle 1991), and decreased body weight (Bataineh et al. 1997; Chowdhury and Mitra 1995; Elbetieha and Al-Hamood 1997; Kanojia et al. 1996, 1998; NTP 2007; Quinteros et al. 2007; Trivedi et al. 1989). However, LOAEL values for these effects were higher than those producing hematopoietic effects. Studies on reproductive toxicity in animals identify the male reproductive system as a target for intermediate-duration exposure to oral chromium(VI) (Aruldas et al. 2004, 2005, 2006; Bataineh et al. 1997; Chowdhury and Mitra 1995; Subramanian et al. 2006; Yousef et al. 2006; Zahid et al. 1990), although these effects are less sensitive than hematological effects. In developmental studies in rats and mice, gestational exposure produced increased postimplantation loss, decreased number of live fetuses/litter, decreased fetal weight, internal and skeletal malformations, and delayed sexual maturation in offspring; however, these effects were observed high doses (e.g.,  $\geq 35$  mg chromium(VI)/kg/day) (Al-Hamood et al. 1998; Bataineh et al. 2007; Junaid et al. 1996a; Kanojia et al. 1998; Trivedi et al. 1989).

## 2. RELEVANCE TO PUBLIC HEALTH

Hematological effects (microcytic, hypochromic anemia) in male rats observed after exposure for 22 days in the NTP (2008a) 2-year study were identified as the most sensitive effect of intermediate-duration oral exposure to chromium(VI). In this study, male F344/N rats (6–7 weeks old) were exposed to sodium dichromate dihydrate in drinking water in a 2-year toxicology and carcinogenicity study, with hematological assessments conducted at 22 days, 3 months, 6 months, and 1 year (see Appendix A for a detailed description of study methods and results). To determine the point of departure for derivation of the intermediate-duration oral MRL, available continuous-variable models in the EPA Benchmark Dose (version 1.4.1) were fit to the data for Hct, Hgb, MCV, and MCH in male rats (NTP 2008a) (detailed results of the benchmark dose analysis are provided in Appendix A). Because several hematological parameters are used to define the clinical picture of anemia, the BMDL<sub>2sd</sub> values for hemoglobin, MCV, and MCH (none of the models provided an adequate fit for hematocrit) were averaged resulting in a BMDL<sub>2sd</sub> of 0.52 mg chromium(VI)/kg/day. The intermediate-duration MRL of 0.005 mg chromium(VI)/kg/day was derived by dividing the average BMDL<sub>2sd</sub> by a composite uncertainty factor of 100 (10 or extrapolation from animals to humans and 10 for human variability).

*Chronic*

- An oral MRL of 0.001 mg chromium(VI)/kg/day has been derived for chronic ( $\geq 1$  year) exposure to hexavalent chromium compounds.

Nonneoplastic lesions of the duodenum observed in mice in an chronic drinking water (NTP 2008a) was selected as the critical effect for derivation of a chronic-duration MRL for chromium(VI) compounds of 0.001 mg chromium(VI)/kg/day. The rationale for this determination is as follows.

The chronic-duration oral toxicity database in drinking water in humans consists of ecological studies of an area near a ferrochromium production plant in the Liaoning Province, China comparing cancer mortality in locations that had relatively high or low chromium concentrations in well water (Beaumont et al. 2008; Zhang and Li 1987). Evaluations of cancer mortality rates (cancers deaths per person-year in an 8-year observation period) show that the adjusted stomach cancer mortality rate was higher for the exposed population compared to the control population (Beaumont et al. 2008). However, it was not possible to estimate exposure levels based on the description of the pollution process. Thus, available human data are not adequate as the basis for the chronic-duration oral MRL.

## 2. RELEVANCE TO PUBLIC HEALTH

Chronic-duration oral toxicity studies have been conducted in rats and mice (Mackenzie et al. 1958; NTP 2008a). No hematological, hepatic, or renal effects or changes in body weight were observed in study in Sprague-Dawley rats exposed to 3.6 chromium(VI)/kg/day as potassium chromate in drinking water for 1 year (Mackenzie et al. 1958). NTP (2008a) exposed groups of F344/N rats (50/sex/group) and B6C3F1 mice (50/sex/group) to sodium dichromate dihydrate in drinking water in a 2-year toxicology and carcinogenicity study (see Appendix A for a detailed description of all study methods and results). Results of this study identify several chromium(VI)-induced effects, including microcytic, hypochromic anemia, and nonneoplastic lesions of the liver, duodenum, mesenteric and pancreatic lymph nodes, pancreas, and salivary gland. Based on comparison of LOAEL values, the lowest LOAELs were observed for histopathological changes of the liver (chronic inflammation in female rats and histiocytic cellular infiltration in female mice), duodenum (diffuse epithelial hyperplasia in male and female mice), mesenteric lymph node (histiocytic cellular infiltration in male and female mice), and pancreas (cytoplasm cellular alteration of acinar epithelial cells in female mice), with effects occurring in all treatment groups (see Appendix A for incidence data for all nonneoplastic lesions). Therefore, all effects with LOAEL values of the lowest dose tested were considered as the possible the critical effect for derivation of the chronic-duration oral MRL.

To determine the specific end point for derivation of the chronic-duration oral MRL, all available dichotomous models in the EPA Benchmark Dose Software (BMDS version 1.4.1) were fit to the incidence data for selected end points in female rats and male and female mice exposed to sodium dichromate dihydrate in drinking water for 2 years (NTP 2008a) (details of benchmark dose analysis are presented in Appendix A). Based on the lowest BMDL<sub>10</sub> value of 0.09 mg chromium(VI)/kg/day, diffuse epithelial hyperplasia of the duodenum in female mice was selected as the point of departure for derivation of the chronic-duration oral MRL. The chronic-duration MRL of 0.001 mg chromium(VI)/kg/day was derived by dividing the BMDL<sub>10</sub> by a composite uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). The chronic-duration oral MRL based on nonneoplastic lesions of the duodenum in female mice is expected to be protective for all other adverse effects observed in the 2-year drinking water study (e.g., hematological effects and lesions of the liver, lymph nodes, pancreas and salivary gland).

***Inhalation MRLs—Chromium(III)***

***Acute.*** Studies evaluating the effects of acute exposure of humans to chromium(III) compounds were not identified. Acute-duration exposure studies in rats and hamsters indicate that the respiratory tract is a

## 2. RELEVANCE TO PUBLIC HEALTH

target of inhaled chromium(III) compounds (Derelanko et al. 1999; Henderson et al. 1979). Derelanko et al. (1999) evaluated effects of acute exposure to chromium(III) as chromic oxide (insoluble) or basic chromium sulfate (soluble) in rats (5 rats/sex/group) on composition of BAL fluid. After exposure of rats for 5 days (6 hours/day) to 3, 10, or 30 mg chromium(III)/m<sup>3</sup> as chromic oxide (insoluble), analysis of BAL fluid revealed cytoplasmic accumulation of a yellow crystalline material in mononuclear cells of all exposure groups; however, it is not clear if this observation represents an adverse effect. No other BAL parameters were affected (nucleated cell count and differential, protein, and BAL fluid activities of  $\beta$ -glucuronidase, lactic dehydrogenase, and glutathione reductase). In rats treated for 5 days (6 hours/day) with 3, 10, or 30 mg chromium(III)/m<sup>3</sup> as basic chromium sulfate (soluble), BAL fluid analysis showed significant decreases in nucleated cells at all doses in males and females and decreases in the percentage of segmented neutrophils and mononuclear cells at 30 mg chromium(III)/m<sup>3</sup> in males. Increased amounts of cellular debris and lysed cells were present in BAL fluid of rats treated with  $\geq 3$  mg chromium(III)/m<sup>3</sup> as basic chromium sulfate (incidence data were not reported). In Syrian hamsters, changes in BAL fluid and lung tissue enzyme activities were observed following exposure to inhaled chromium trichloride for 30 minutes (Henderson et al. 1979); effects included “sporadic changes” in activities of acid phosphatase and alkaline phosphatase in the BAL fluid at 25 mg chromium(III)/m<sup>3</sup> and increased acid phosphatase activity in lung tissue at 0.9 mg chromium(III)/m<sup>3</sup>. In addition, histological examination of the lung revealed focal accumulations of macrophages and polymorphonuclear cells. However, it is not clear that the effects observed in this study are toxicologically significant. Thus, results of acute-duration studies in rats and hamsters show that inhaled chromium(III) compounds produce alterations in BAL fluid composition and lung tissue enzyme activities; however, data are not adequate to characterize the exposure-response relationship for respiratory effects. Therefore, an acute-duration inhalation MRL for trivalent chromium was not derived.

***Intermediate.*** Studies evaluating the effects of intermediate-duration exposure of humans to chromium(III) compounds were not identified. In animals exposed to inhaled chromium(III) compounds for intermediate durations, the respiratory tract has been identified as the primary target organ, based on results of a 13-week study in rats exposed to chromic oxide (insoluble) or basic chromium sulfate (soluble) (Derelanko et al. 1999). In this study, which examined comprehensive toxicological end points, male and female CDF rats (15/sex/group) were exposed by nose-only inhalation to 0, 3, 10, or 30 mg chromium(III)/m<sup>3</sup> as chromic oxide or as basic chromium sulfate for 6 hours/day, 5 days/week for 13 weeks. Of the 15 rats/sex/group, 10 rats/sex/group were sacrificed after 13 weeks of exposure and 5 rats/sex/group were sacrificed after an additional 13-week recovery period (e.g., no exposure). Assessments made in this study included mortality; clinical signs of toxicity; body weight; hematology;

## 2. RELEVANCE TO PUBLIC HEALTH

clinical chemistry; urinalysis; sperm morphology, count and motility; gross necropsy; microscopic examination of comprehensive tissues for all animals in the control and 30 mg chromium(III)/m<sup>3</sup> groups; and microscopic examination of respiratory tissues (nasal tissues, trachea, lungs, larynx, and mediastinal and mandibular lymph nodes) in all animals. Both chromic oxide and basic chromium sulfate produced adverse respiratory effects (histopathological changes to respiratory tissues and increased lung weights) in male and female rats, with no adverse effects in other tissues. However, differences between the two compounds were observed with respect to severity and location of respiratory effects; effects of chromic oxide were less severe and isolated to the lung and respiratory lymph tissues, whereas the effects of basic chromium sulfate were more severe and observed throughout the respiratory tract (e.g., nose, larynx, lung, and respiratory lymph tissues). The study authors suggested that differences in the respiratory toxicity of these compounds may be related to differences in chemical-physical properties (e.g., solubility, acidity). The only other intermediate-duration inhalation study in animals was conducted in rabbits exposed to 0.6 mg chromium(III)/m<sup>3</sup> as chromium nitrate for 4–6 weeks (6 hours/day, 5 days/week) (Johansson et al. 1986b). Results of this study showed effects on pulmonary macrophages (altered functional and metabolic activities); however, the toxicological significance of this finding is uncertain and animals were not examined for other effects. Thus, the 13-week inhalation study by Derelanko et al. (1999) was selected as the critical study for derivation of intermediate-duration inhalation MRLs for chromium(III) compounds. Based on the differences in respiratory toxicity between insoluble chromic oxide and soluble basic chromium sulfate, distinct intermediate-duration inhalation MRLs were derived for insoluble and soluble trivalent chromium particulate compounds. Additional details of respiratory effects produced by chromic oxide and basic chromium sulfate are described below under derivation of intermediate-duration inhalation MRLs for insoluble trivalent chromium compounds and for soluble trivalent chromium compounds, respectively.

- An inhalation MRL of 0.005 mg chromium(III)/m<sup>3</sup> has been derived for intermediate (15–364 days) exposure to insoluble trivalent chromium particulate compounds.

The lung and respiratory lymphatic tissues were identified as the target tissues for inhaled insoluble trivalent chromium particulate compounds, based on observations reported in the study by Derelanko et al. (1999) (as discussed above). Similar effects were observed in male and female rats exposed to chromic oxide for 13 weeks, with histopathological changes to the respiratory lymphatic tissue occurring at  $\geq 3$  mg chromium(III)/m<sup>3</sup> and to the lung at  $\geq 10$  mg chromium(III)/m<sup>3</sup>. Lymphoid hyperplasia of the mediastinal node was observed in rats of all treatment groups (severity not reported). In rats exposed to 10 and 30 mg chromium(III)/m<sup>3</sup>, trace-to-mild chronic interstitial inflammation of the lung, characterized by inflammatory cell infiltration, was observed in alveolar septa, and hyperplasia of Type II pneumocytes

## 2. RELEVANCE TO PUBLIC HEALTH

(severity not reported) were observed. Histopathological changes were isolated to the lungs and respiratory lymphatic tissues and were not observed in other tissues, including nasal tissues and the larynx.

For evaluations conducted at the end of the 13-week treatment period, a LOAEL of 3 mg chromium(III)/m<sup>3</sup> for hyperplasia of the mediastinal node was identified for both males and females; the severity of this effect was not reported. Following a 13-week posttreatment recovery period, trace-to-mild septal cell hyperplasia and trace-to-mild chronic interstitial inflammation of the lung were observed at  $\geq 3$  mg chromium(III)/m<sup>3</sup> in males and at  $\geq 10$  mg chromium(III)/m<sup>3</sup> in females. In addition, pigmented macrophages and black pigment in peribronchial lymphatic tissues and the mediastinal lymph node in animals from all treatment groups were also observed; this finding, although not considered adverse, indicates that the test material had not been completely cleared from the lung during the treatment-free recovery period. Thus, for evaluations conducted at the 13-week posttreatment recovery period, a minimal LOAEL (based on severity) of 3 mg chromium(III)/m<sup>3</sup> for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats was identified.

The LOAEL of 3 mg chromium(III)/m<sup>3</sup> for hyperplasia of the mediastinal node in males and females (observed at the end of the 13-week treatment period) and the minimal LOAEL of 3 mg chromium(III)/m<sup>3</sup> for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in males (observed at the end of the 13-week recovery period) were considered as potential critical effects for derivation of the intermediate-duration inhalation MRL for insoluble trivalent chromium particulate compounds. A benchmark concentration for these effects could not be determined since incidence data for lesions of the lung and respiratory lymphatic tissue were not reported; thus, a NOAEL/LOAEL approach was used. To determine the point of departure, the LOAEL value of 3 mg chromium(III)/m<sup>3</sup> was first adjusted for intermittent and converted to human equivalent concentrations (LOAEL<sub>HEC</sub>) (see Appendix A for details).

Based on the lowest LOAEL<sub>HEC</sub> of 0.43 mg chromium(III)/m<sup>3</sup>, trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats were selected as the critical effect. The intermediate-duration inhalation MRL for insoluble trivalent chromium particulate compounds of 0.005 mg chromium(III)/m<sup>3</sup> was derived by dividing the minimal LOAEL<sub>HEC</sub> of 0.43 mg chromium(III)/m<sup>3</sup> by a composite uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).



## 2. RELEVANCE TO PUBLIC HEALTH

- An inhalation MRL of 0.0001 mg chromium(III)/m<sup>3</sup> has been derived for intermediate (15–364 days) exposure to soluble trivalent chromium particulate compounds.

The lung and respiratory lymphatic tissues were identified as the target tissues for inhaled soluble trivalent chromium particulate compounds, based on observations reported in the study by Derelanko et al. (1999) (as discussed above). Similar effects were observed in male and female rats exposed to inhaled basic chromium sulfate for 13 weeks, with histopathological changes to the nose, larynx, lung, and respiratory lymphatic tissues and increased relative lung weight occurring at  $\geq 3$  mg chromium(III)/m<sup>3</sup>. Microscopic examination of the lung revealed the following changes in all treatment groups: chronic inflammation of the alveoli; alveolar spaces filled with macrophages, neutrophils, lymphocytes, and cellular debris; foci of “intense” inflammation and thickened alveolar walls; chronic interstitial inflammation with cell infiltration; hyperplasia of Type II pneumocytes; and granulomatous inflammation, characterized by infiltration of macrophages and multinucleated giant cells. Macrophage infiltration and granulomatous inflammation of the larynx, acute inflammation, and suppurative and mucoid exudates of nasal tissues and histiocytosis and hyperplasia of peribronchial lymphoid tissues and the mediastinal lymph node were also observed in all treatment groups. Thus, data for histopathological changes in various regions of the respiratory tract and increased relative lung weights were evaluated to determine the specific end point for derivation of the intermediate-duration MRL for soluble trivalent chromium particulate compounds.

Benchmark dose analysis could not be conducted for respiratory tract lesions, since incidence data were not reported by Derelanko et al. (1999); therefore, a NOAEL/LOAEL approach was used, with adjustment of the LOAEL for intermittent exposure and human equivalent concentrations (see Appendix A for details). Data for relative lung weights in males and females (presented in Appendix A) were modeled using all available continuous-variable models in the EPA Benchmark Dose program (version 1.4.1). The BMC and the 95% lower confidence limit (BMCL) calculated were estimated for doses associated with a change of 1 standard deviation from the control mean (BMDL<sub>1sd</sub>). The BMCL<sub>1sd</sub> values for the best fitting models in male and female rats were adjusted for intermittent exposure and human equivalent concentrations, yielding BMCL<sub>1sd, HEC</sub> values of 0.17 and 0.34 mg chromium(III)/m<sup>3</sup> in males and females, respectively (see Appendix A for detail of benchmark dose analysis).

Based on comparison of LOAEL<sub>HEC</sub> values for respiratory tract lesions and BMCL<sub>1sd, HEC</sub> values for increased lung weight, the lowest value of 0.04 mg chromium(III)/m<sup>3</sup> (the LOAEL<sub>HEC</sub> for lesions of the larynx and nose in female rats) was selected as the point of departure. The intermediate-duration inhalation MRL for soluble trivalent chromium particulate compounds of 0.0001 mg chromium(III)/m<sup>3</sup>

## 2. RELEVANCE TO PUBLIC HEALTH

was derived by dividing the LOAEL<sub>HEC</sub> of 0.04 mg chromium(III)/m<sup>3</sup> by a composite uncertainty factor of 300 (10 for use of a LOAEL, 3 for pharmacodynamic variability between animals to humans, and 10 for human variability). It should not be concluded from comparison of the intermediate-duration MRLs for soluble particulate chromium(VI) and soluble particulate chromium(III) compounds that chromium(III) is more toxic than chromium(VI).

The respiratory tract is the major target of inhalation exposure to chromium compounds in humans and animals. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. For chronic exposure of humans, the available occupational studies for exposure to chromium(III) compounds include or likely include concomitant exposure to chromium(VI) compounds and other compounds that may produce respiratory effects (Langård 1980; Mancuso 1951; Osim et al. 1999). Thus, while the available data in humans suggest that respiratory effects occur following inhalation exposure to chromium(III) compounds, the respiratory effects of inhaled chromium(VI) and other compounds are confounding factors in estimating exposure levels for these effects for the purpose of deriving MRLs.

**Chronic.** No studies evaluating the effects of chronic-duration inhalation exposure of animals to chromium(III) compounds alone were identified. Exposure to mixtures of chromium(VI) and chromium(III) compounds (3:2 mixture of chromium(VI) trioxide and chromium(III) oxide) have resulted in adverse respiratory effects in Wistar rats, including increased lung weight and histopathological changes to lung tissues (interstitial fibrosis and thickening of the septa of the alveolar lumens; Glaser et al. 1986, 1988). However, these data not appropriate as the basis for a chronic-duration inhalation MRL for chromium(III) compounds due to concomitant exposure to chromium(VI).

**Oral MRLs—Chromium(III)**

No acute-, intermediate-, or chronic-duration oral MRLs were derived for chromium(III) because studies evaluating the effects of chromium(III) in humans and animals following acute, intermediate, and chronic oral exposure were inadequate for establishing the exposure concentrations associated with adverse health effects (as discussed below). The IOM has recommended an adequate intake level of 20–45 µg chromium(III) for adolescents and adults, equivalent to 0.28–0.64 µg chromium(III)/kg/day (0.0003–0.0006 mg chromium(III)/kg/day), assuming a 70-kg body weight (IOM 2001).

## 2. RELEVANCE TO PUBLIC HEALTH

Little information is available on the effects of acute-duration oral exposure to chromium (III) compounds. Information on the effects of intermediate-duration oral exposure of humans is limited to case reports of renal failure (Wani et al. 2006; Wasser et al. 1997) and rhabdomyolysis (Martin and Fuller 1998) following ingestion of dietary supplements containing chromium(III). In animals, acute exposure of rats to dietary chromium(III) picolinate did not produce alterations in hematology or clinical chemistry. Following acute exposure of mated rats, an increase in total litter loss was observed in female rats (at 33.6 mg chromium(III)/kg/day) (Bataineh et al. 2007). In a study evaluating effects of chromium(III) on maturation of the reproductive system in mice (74 mg chromium(III)/kg/day), significant decreases in the relative weights of reproductive tissues (testes, seminal vesicles, and preputial glands in males; ovaries and uterus in females) and a significant delay in timing of vaginal opening in the female offspring were observed (Al-Hamood et al. 1998). However, gestational exposure studies on chromium(III) compounds were conducted at high daily doses and do not provide sufficient information to characterize the dose-response relationship for adverse developmental effects. Thus, the data are inadequate for derivation of an acute-duration oral MRL.

Information on adverse effects of intermediate-duration oral exposure of humans to chromium(III) compounds was not identified. Results of most animal studies show no adverse effects associated with intermediate-duration oral exposure to chromium(III) compounds (chromium chloride, chromium nicotinate, chromium oxide, chromium picolinate, and chromium potassium sulfate) (Anderson et al. 1997b; De Flora et al. 2006; Ivankovic and Preussmann 1975; NTP 2008b; Rhodes et al. 2005; Shara et al. 2005, 2007), even at very high daily doses. In the study conducted by NTP (2008b; Rhodes et al. 2005), daily doses of up to 506 and 1,415 mg chromium(III)/mg/day as chromium picolinate were evaluated in rats and mice, respectively, and in the Ivankovic and Preussmann (1975) study, daily doses up to 1,806 mg chromium(III)/kg/day as chromium oxide were evaluated in rats.

Adverse reproductive effects have been reported following intermediate-duration exposure of animals to chromium(III) as chromium chloride administered by gavage or in drinking water. A series of studies by the same research group evaluated reproductive effects of exposure to chromium(III) as chromium chloride in drinking water for 12 weeks (Al-Hamood et al. 1998; Bataineh et al. 1997, 2007; Elbetieha and Al-Hamood 1997). Reproductive effects observed included alterations in sexual behavior (reductions in the number of mounts, increased postejaculatory interval, and decreased rates of ejaculation), aggressive behavior toward other males, and significantly lower absolute weight of testes, seminal vesicles, and preputial glands in male Sprague-Dawley rats (40 mg chromium(III)/kg/day; only dose tested) (Bataineh et al. (1997); decreased number of pregnant female Swiss mice following the mating of

## 2. RELEVANCE TO PUBLIC HEALTH

unexposed females to exposed males (13 mg chromium(III)/kg/day) (Elbetieha and Al-Hamood 1997); impaired fertility in exposed female mice (5 mg chromium(III)/kg/day) mated to unexposed males (Elbetieha and Al-Hamood 1997); and increased testes and ovarian weights and decreased preputial gland and uterine weights in mice (5 mg chromium(III)/kg/day) (Elbetieha and Al-Hamood 1997). Results of the study by Elbetieha and Al-Hamood (1997) should be interpreted with caution due to concerns regarding experimental methods, including decreased water consumption in the higher concentration group (resulting in a potential overestimate of exposure and uncertainty regarding daily dose calculations); the study was not conducted using a standard mating protocol; sperm counts were not conducted; and the definition and classification of non-viable fetuses was not described. Decreased spermatogenesis was observed in BALB/c mice treated with 9.1 mg chromium(III)/kg/day as chromium sulfate in drinking water for 7 weeks (Zahid et al. 1990); however, sensitivity of methods used to evaluate spermatogonia in this study have been questioned by NTP (1996a). NOAEL values for reproductive effects were not identified in these studies. In studies designed to confirm or refute the findings of the Zahid et al. (1990) study, the reproductive effects of different concentrations of chromium(VI) as potassium dichromate in the diet on BALB/c mice and Sprague-Dawley rats were investigated (NTP 1996a, 1996b). Groups of 24 of each species were fed potassium dichromate(VI) in their feed continuously for 9 weeks followed by an 8-week recovery period. The average daily ingestions of chromium(VI) were 1.05, 3.5, 7.5, and 32.2 mg/kg/day for male mice and were 0.35, 1.05, 2.1, and 8.4 mg/kg/day for rats (NTP 1996b). Microscopic examinations of the testes and epididymis for Sertoli nuclei and preleptotene spermatocyte counts in stage X or XI tubules did not reveal any treatment-related effects. Similarly, exposure to sodium dichromate dihydrate in drinking water did not produce morphological changes to male reproductive organs of B6C3F1 mice exposed to 27.9 or 5.9 mg chromium(VI)/kg/day for 3 months or 2 years, respectively, or affect sperm count or motility in male B6C3F1, BALB/c, and C57BL/6N mice exposed to 8.7 mg chromium(VI)/kg/day for 3 months (NTP 2007, 2008a).

In contrast to the reproductive effects of chromium chloride in drinking water, dietary exposure to chromium(III) picolinate has not been associated with reproductive effects. Exposure to chromium picolinate in the diet for 3 months did not produce adverse effects on reproductive tissues, as assessed by organ weights, gross and histopathological examinations, sperm count, sperm motility, duration of estrous cycle stages and estrous cycle length at doses up to 505 and 506 mg chromium(III)/kg/day in male and female rats, respectively, or at doses up to 1,415 and 1,088 mg chromium(III)/kg/day in male and female mice (NTP 2008b). No morphological changes to reproductive organs, as assessed by histopathological examination, were observed in male and female Sprague-Dawley rats exposed to chromium nicotinate in

## 2. RELEVANCE TO PUBLIC HEALTH

the diet at 1.2 and 1.5 mg chromium(III)/kg/day, respectively for 2 months or at 0.22 and 0.25 mg chromium(III)/kg/day, respectively for 1 year (Shara et al. 2005, 2007). In summary, conflicting results on reproductive effects of chromium(III) compounds have been reported. It is unclear if differences in results are related to experimental methods, including exposure media (drinking water versus feed) or to differences in toxic potency of the specific chromium(III) compounds evaluated. Thus, available data are not sufficient to define the dose-response relationship for adverse reproductive effects of chromium(III) compounds.

Little information is available on the potential developmental effects of chromium(III) compounds. No developmental effects were observed in the offspring of rats fed 1,806 mg chromium(III)/kg/day as chromium oxide for 60 days before mating and throughout the gestational period (Ivankovic and Preussmann 1975).

Results of studies in animals exposed to oral chromium(III) compounds indicate that adverse reproductive effects may occur. However, the available data do not identify NOAEL values for effects and, therefore, are not sufficient to characterize the dose-response relationship. Thus, data are inadequate for derivation of an intermediate-duration oral MRL.

Chronic-duration studies on oral exposure of humans to chromium(III) compounds were not identified. Several animal studies show no adverse effects associated with chronic-duration oral exposure to chromium(III) compounds (chromium acetate, chromium chloride, chromium nicotinate, chromium oxide, chromium picolinate) (Ivankovic and Preussmann 1975; Mackenzie et al. 1958; Schroeder et al. 1965; Shara et al. 2007), even at very high daily doses. Thus, in the absence of data showing adverse effects of chronic oral exposure, a chronic-duration oral MRL for chromium(III) compounds was not derived.

2. RELEVANCE TO PUBLIC HEALTH

This page is intentionally blank.

### 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 chromium. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

Chromium is a naturally occurring element found in animals, plants, rocks, and soil and in volcanic dust and gases. Chromium has oxidation states (or "valence states") ranging from chromium(-II) to chromium(VI). Elemental chromium (chromium(0)) does not occur naturally. Chromium compounds are stable in the trivalent state and occur in nature in this state in ores, such as ferrochromite. The hexavalent (VI) form is the second-most stable state. However, chromium(VI) rarely occurs naturally, but is usually produced from anthropogenic sources (EPA 1984a).

Trivalent chromium compounds, except for acetate, nitrate, and chromium(III) chloride-hexahydrate salts, are generally insoluble in water. Some hexavalent compounds, such as chromium trioxide (or chromic acid) and the ammonium and alkali metal (e.g., sodium, potassium) salts of chromic acid are readily soluble in water. The alkaline metal (e.g., calcium, strontium) salts of chromic acid are less soluble in water. The zinc and lead salts of chromic acid are practically insoluble in cold water. Chromium(VI) compounds are reduced to chromium(III) in the presence of oxidizable organic matter. However, in natural waters where there is a low concentration of reducing materials, chromium(VI) compounds are more stable (EPA 1984a). For more information on the physical and chemical properties of chromium, see Chapter 4.

In humans and animals, chromium(III) is an essential nutrient that plays a role in glucose, fat, and protein metabolism by potentiating the action of insulin (Anderson 1981). The biologically active form of chromium, called chromodulin, is an oligopeptide complex containing with four chromic ions (Jacquemet et al. 2003). Both humans and animals are capable of converting inactive inorganic chromium(III) compounds to physiologically active forms. The nutritional role of chromium is further discussed in Section 3.4.3. Although chromium(III) has been reported to be an essential nutrient, exposure to high

### 3. HEALTH EFFECTS

levels via inhalation, ingestion, or dermal contact may cause some adverse health effects. Most of the studies on health effects discussed below involve exposure to chromium(III) and chromium(VI) compounds. In addition, chromium(IV) was used in an inhalation study to determine permissible exposure levels for workers involved in producing magnetic tape (Lee et al. 1989).

Several factors should be considered when evaluating the toxicity of chromium compounds. The purity and grade of the reagent used in the testing is an important factor. Both industrial- and reagent-grade chromium(III) compounds can be contaminated with small amounts of chromium(VI) (Levis and Majone 1979). Thus, interpretation of occupational and animal studies that involve exposure to chromium(III) compounds is difficult when the purity of the compounds is not known. In addition, it is difficult to distinguish between the effects caused by chromium(VI) and those caused by chromium(III) since chromium(VI) is rapidly reduced to chromium(III) after penetration of biological membranes and in the gastric environment (Petrilli et al. 1986b; Samitz 1970). However, whereas chromium(VI) can readily be transported into cells, chromium(III) is much less able to cross cell membranes. The reduction of chromium(VI) to chromium(III) inside of cells may be an important mechanism for the toxicity of chromium compounds, whereas the reduction of chromium(VI) to chromium(III) outside of cells is a major mechanism of protection.

#### 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



### 3. HEALTH EFFECTS

classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) are indicated in Tables 3-1 and 3-3 and Figures 3-1 and 3-3 for chromium(VI).

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**

Due to the extremely high boiling point of chromium, gaseous chromium is rarely encountered. Rather, chromium in the environment occurs as particle-bound chromium or chromium dissolved in droplets. As discussed in this section, chromium(VI) trioxide (chromic acid) and soluble chromium(VI) salt aerosols may produce different health effects than insoluble particulate compounds. For example, exposure to chromium(VI) trioxide results in marked damage to the nasal mucosa and perforation of the nasal septum, whereas exposure to insoluble(VI) compounds results in damage to the lower respiratory tract.

## 3. HEALTH EFFECTS

**3.2.1.1 Death**

No studies were located regarding death in humans after acute inhalation of chromium or chromium compounds. An increased risk of death from noncancer respiratory disease was reported in retrospective mortality studies of workers in a chrome plating plant (Sorahan et al. 1987) and chromate production (Davies et al. 1991; Taylor 1966) (see Section 3.2.1.2, Respiratory Effects). However, a number of methodological deficiencies in these studies prevent the establishment of a definitive cause-effect relationship. Retrospective mortality studies associating chromium exposure with cancer are discussed in Section 3.2.1.7.

Acute inhalation LC<sub>50</sub> values in rats for several chromium(VI) compounds (sodium chromate, sodium dichromate, potassium dichromate, and ammonium dichromate) ranged from 29 to 45 mg chromium(VI)/m<sup>3</sup> for females and from 33 to 82 mg chromium(VI)/m<sup>3</sup> for males (Gad et al. 1986). Acute inhalation LC<sub>50</sub> values for chromium trioxide were 87 and 137 mg chromium(VI)/m<sup>3</sup> for female and male rats, respectively (American Chrome and Chemicals 1989). Female rats were more sensitive than males to the lethal effects of most chromium(VI) compounds except sodium chromate, which was equally toxic in both sexes. Signs of toxicity included respiratory distress, irritation, and body weight depression (Gad et al. 1986). The LC<sub>50</sub> values for chromium(VI) are recorded in Table 3-1 and plotted in Figure 3-1.

**3.2.1.2 Systemic Effects**

No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to chromium or its compounds. Respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, endocrine, dermal, ocular, and body weight effects are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1 for chromium(VI) and recorded in Table 3-2 and plotted in Figure 3-2 for chromium(III).

**Respiratory Effects.** The respiratory tract in humans is a major target of inhalation exposure to chromium compounds. Chromate sensitive workers acutely exposed to chromium(VI) compounds may develop asthma and other signs of respiratory distress. Five individuals who had a history of contact dermatitis to chromium were exposed via a nebulizer to an aerosol containing 0.035 mg chromium(VI)/mL as potassium dichromate. A 20% decrease in the forced expiratory volume of the lungs was observed and was accompanied by erythema of the face, nasopharyngeal pruritus, nasal blocking, coughing, and wheezing (Olaguibel and Basomba 1989).

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation

Key to Figure	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
<b>ACUTE EXPOSURE</b>								
<b>Death</b>								
1	Rat (Fischer- 344)	4 hr				137 M (LC50) 87 F (LC50)	American Chrome and Chemicals 1989 CrO3 (VI)	
2	Rat (Fischer- 344)	4 hr				82 M (LC50) 45 F (LC50)	Gad et al. 1986 (NH4)2Cr2O7 (VI)	
3	Rat (Fischer- 344)	4 hr				35 M (LC50) 29 F (LC50)	Gad et al. 1986 K2Cr2O7 (VI)	
4	Rat (Fischer- 344)	4 hr				70 M (LC50) 31 F (LC50)	Gad et al. 1986 Na2Cr2O7.2H2O (VI)	
5	Rat (Fischer- 344)	4 hr				33 (LC50)	Gad et al. 1986 Na2CrO4 (VI)	
<b>Systemic</b>								
6	Rat (Sprague-Dawley)	10 d 5 d/wk 6 hr/d	Resp	0.49 M	1.15 M (nasal hemorrhage)		Kim et al. 2004 CrO3 (VI)	
<b>INTERMEDIATE EXPOSURE</b>								
<b>Systemic</b>								
7	Human	<90 d (occup)	Resp		0.025 M (irritated nasal septum)		Gibb et al. 2000a CrO3 (VI)	

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
8	Human	90 d- 1 yr (occup)	Resp		0.033 M perforated nasal septum		Gibb et al. 2000a CrO3 (VI)	
			Other		0.036 M perforated eardrum			
9	Human	<1 yr 5 d/wk 8 hr/d (occup)	Resp		0.1	(epitaxis rhinorrhea, nasal ulceration and perforation)	Gomes 1972 CrO3 (VI)	
10	Human	0.5-12 mo 6 mo avg 5 d/wk 8 hr/d (occup)	Resp		0.09 M	(epitaxis, rhinorrhea ulceration of nasal septum)	Kleinfield and Rosso 1965 CrO3 (VI)	
11	Human	0.2-23.6 yr avg 2.5 yr 5 d/wk 8 hr/d (occup)	Resp		0.002 <sup>b</sup>	(nasal mucosa atrophy and ulceration, mild decreased lung function)	Lindberg and Hedenstierna 1983 CrO3 (VI)	

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
12	Rat (Wistar)	28 d 7 d/wk 22 hr/d	Resp		0.025 M (increased percentage of lymphocytes in bronchoalveolar lavage fluid)		Glaser et al. 1985 Na <sub>2</sub> Cr <sub>2</sub> O <sub>7</sub> ·2H <sub>2</sub> O (VI)	
			Gastro	0.2 M				
			Hemato	0.2 M				
			Hepatic	0.2 M				
			Renal	0.2 M				
			Bd Wt	0.2 M				
13	Rat (Wistar)	90 d 7 d/wk 22 hr/d	Resp		0.025 M (increased percentage of lymphocytes in bronchial alveolar lavage fluid)		Glaser et al. 1985 Na <sub>2</sub> Cr <sub>2</sub> O <sub>7</sub> ·2H <sub>2</sub> O (VI)	
			Gastro	0.2 M				
			Hemato	0.2 M				
			Hepatic	0.1 M	0.2 M (increased levels of serum phospholipids and triglycerides)			
			Renal	0.2 M				
			Bd Wt	0.2 M				

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency/ (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
14	Rat (Wistar)	30 or 90 d 7 d/wk 22 hr/d	Resp		0.05 <sup>c</sup> M (increased lung weight, hyperplasia, macrophage infiltration, increased protein, albumin, lactate dehydrogenase in BAL fluid)		Glaser et al. 1990 Na <sub>2</sub> Cr <sub>2</sub> O <sub>7</sub> ·2H <sub>2</sub> O (VI)	
			Gastro	0.4 M				
			Hemato		0.05 M (increased white blood cell count)			
			Hepatic	0.4 M				
			Renal	0.4 M				
			Bd Wt	0.1 M	0.2 M (28% decreased body weight gain)			
15	Rat (Sprague- Dawley)	13 wk 5 d/wk 6 hr/d	Resp	0.23 M	0.49 M (inflammation and macrophage aggregation in alveolar regions of the lung)		Kim et al. 2004 CrO <sub>3</sub> (VI)	
			Cardio	1.15 M				
			Hemato		0.23 M (decreased hematocrit)			
			Hepatic	1.15 M				
			Renal	1.15 M				
			Endocr	1.15 M				
			Bd Wt	1.15 M				

































Figure 3-2 Levels of Significant Exposure to Chromium III - Inhalation  
Acute ( $\leq 14$  days)

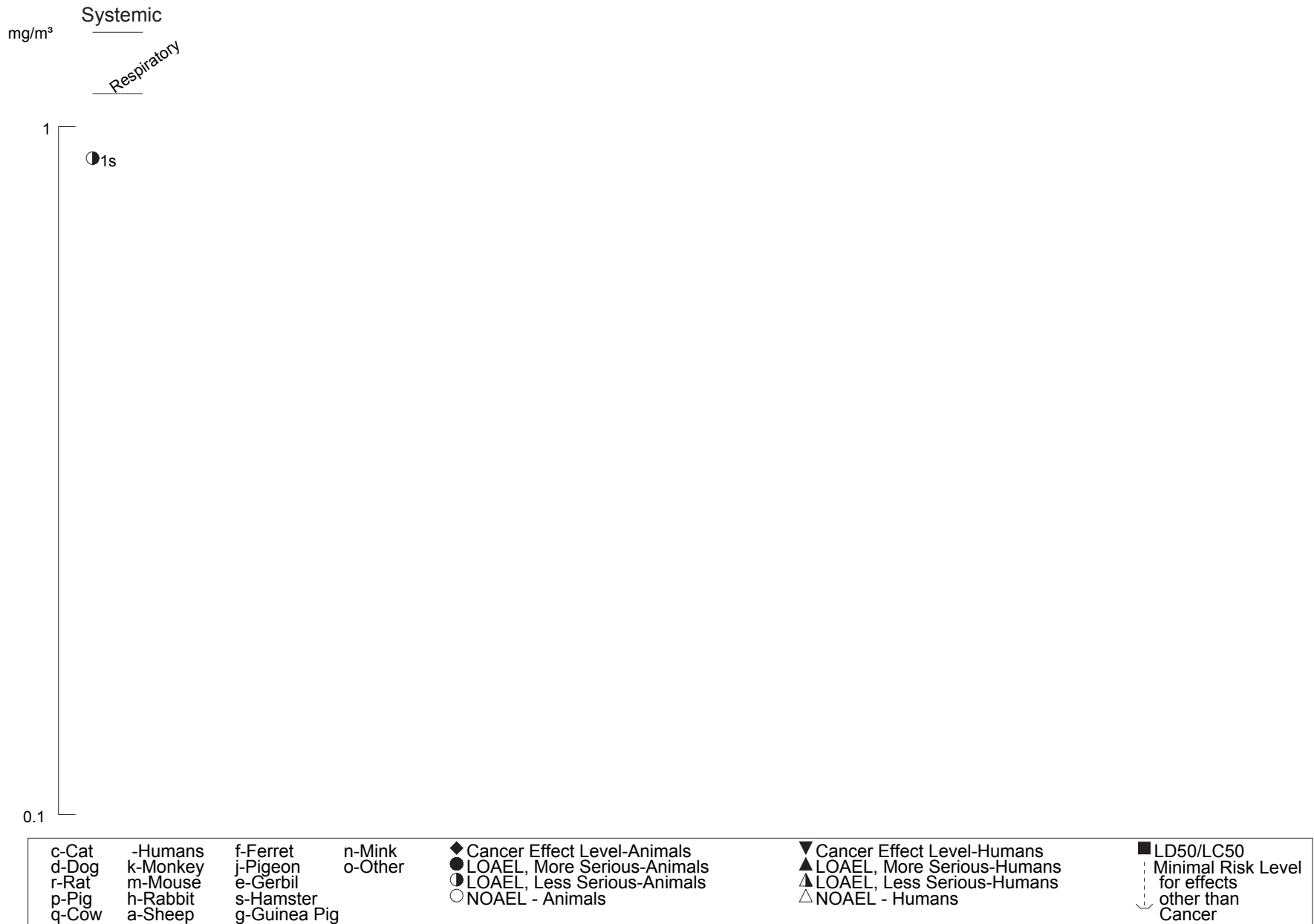
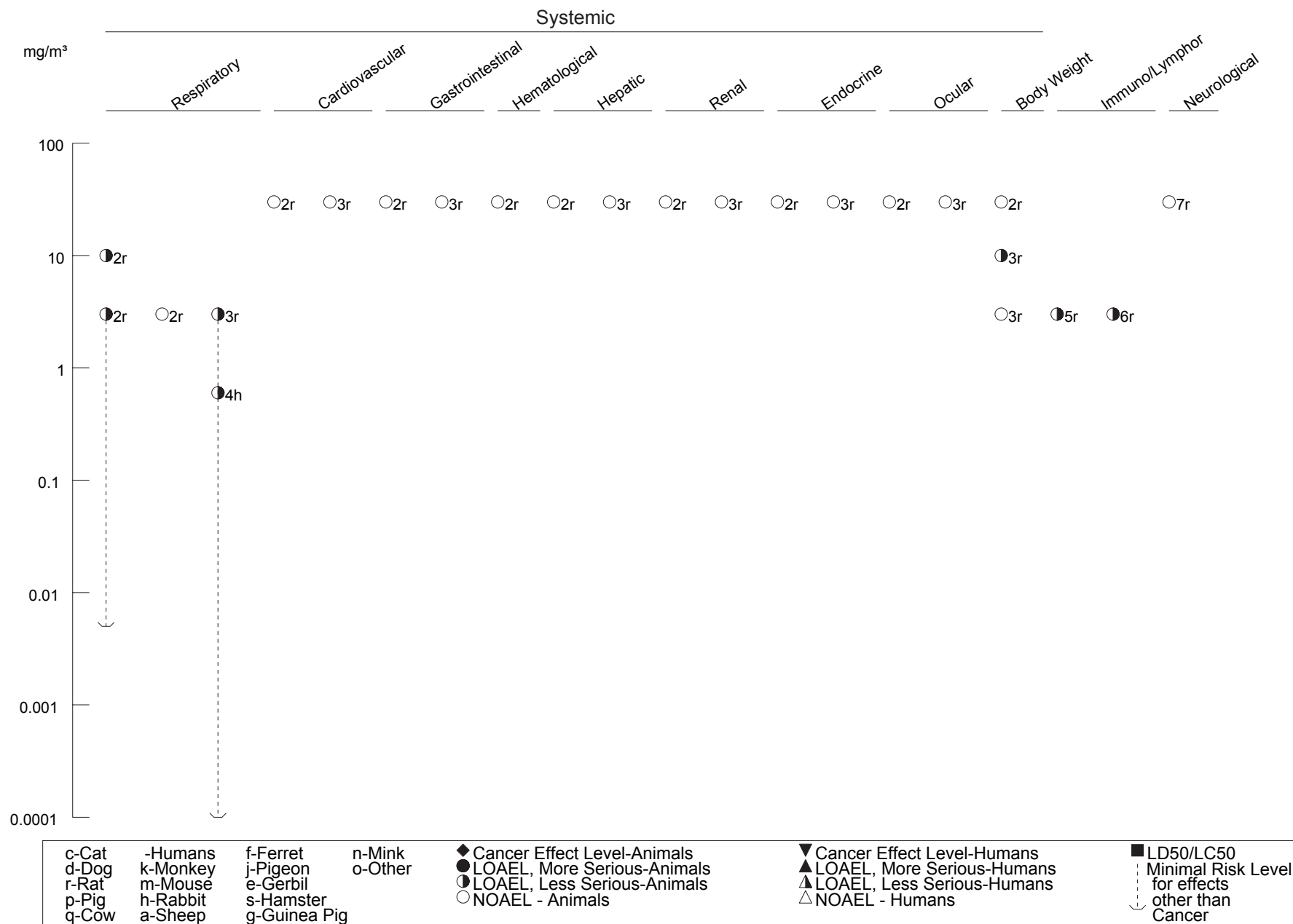


Figure 3-2 Levels of Significant Exposure to Chromium III - Inhalation (Continued)

Intermediate (15-364 days)









## 3. HEALTH EFFECTS

Dyspnea, cough, and wheezing were reported in two cases in which the subjects inhaled "massive amounts" of chromium(VI) trioxide. Marked hyperemia of the nasal mucosa without nasal septum perforation was found in both subjects upon physical examination (Meyers 1950). In a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes, workers experienced symptoms of sneezing, rhinorrhea, labored breathing, and a choking sensation when they were working over the chromate tanks. All five of the subjects had thick nasal and postnasal discharge and nasal septum ulceration or perforation after 2–3 months of exposure (Lieberman 1941). Asthma developed in a man who had been well until 1 week after beginning employment as an electroplater. When challenged with an inhalation exposure to a sample of chromium(III) sulfate, he developed coughing, wheezing, and decreased forced expiratory volume. He also had a strong asthmatic reaction to nickel sulfate (Novoy et al. 1983). Thus, chromium-induced asthma may occur in some sensitized individuals exposed to elevated concentrations of chromium in air, but the number of sensitized individuals is low and the number of potentially confounding variables in the chromium industry is high.

Intermediate- to chronic-duration occupational exposure to chromium(VI) may cause an increased risk of death due to noncancer respiratory disease. In a retrospective mortality study of 1,288 male and 1,401 female workers employed for at least 6 months in a chrome plating and metal engineering plant in the United Kingdom between 1946 and 1975, a statistically significant excess of death from diseases of the respiratory system (noncancer) were obtained for men (observed/expected [O/E]=72/54.8, standard mortality ratio [SMR]=131,  $p<0.05$ ) and men and women combined (O/E=97/76.4, SMR=127,  $p<0.05$ ), but not for women alone. Exposure was mainly to chromium trioxide, but exposure concentrations were not precisely known. The contribution of nickel exposure to the effects was found to be unimportant, while data on smoking habits were not available (Sorahan et al. 1987). Similarly, a high SMR was found for noncancer respiratory disease among 1,212 male chromate workers who were employed for at least 3 months in three chromate plants in the United States during the years 1937–1960 and followed for 24 years (O/E=19/7.843, SMR=242) (Taylor 1966). The increased risk of death from respiratory effects correlated with duration of employment in chromate production, but no information on exposure levels, smoking habits, or exposure to other chemicals was provided. The nature of the respiratory diseases was not further described in either of these reports. Chromate production workers in the United Kingdom who were first employed before 1945 had a high risk of death from chronic obstructive airways disease (O/E=41/28.66, SMR=143,  $p<0.05$ ) (Davies et al. 1991). Exposure concentrations were not known, and reliable smoking data were not available.

## 3. HEALTH EFFECTS

Occupational exposure to chromium(VI) as chromium trioxide in the electroplating industry caused upper respiratory problems. A case history of nine men in a chrome plating facility reported seven cases of nasal septum ulceration. Signs and symptoms included rhinorrhea, nasal itching and soreness, and epistaxis. The men were exposed from 0.5 to 12 months to chromium trioxide at concentrations ranging from 0.09 to 0.73 mg chromium(VI)/m<sup>3</sup> (Kleinfeld and Rosso 1965). Electroplating workers in Sao Paulo, Brazil, exposed to chromium trioxide vapors while working with hot chromium trioxide solutions had frequent incidences of coughing, expectoration, nasal irritation, sneezing, rhinorrhea, and nose-bleed and developed nasal septum ulceration and perforation. The workers had been employed for <1 year, and most of the workers had been exposed to concentrations >0.1 mg chromium(VI)/m<sup>3</sup> (Gomes 1972). Nose and throat irritation, rhinorrhea, and nose-bleed also occurred at higher incidence in chrome platers in Singapore than in controls (Lee and Goh 1988).

Numerous studies of workers chronically exposed to chromium(VI) compounds have reported nasal septum perforation and other respiratory effects. Workers at an electroplating facility exposed to 0.0001–0.0071 mg chromium(VI)/m<sup>3</sup> as chromium trioxide for an average of 26.9 months complained of excessive sneezing, rhinorrhea, and epistaxis. Many of the workers had ulcerations and/or perforations of the nasal mucosa (Cohen et al. 1974). A study using only questionnaires, which were completed by 997 chrome platers and 1,117 controls, found a statistically significant increase in the incidence of chronic rhinitis, rhinitis with bronchitis, and nasal ulcers and perforations in workers exposed to chromium(VI) in the chrome plating industry in 54 plants compared to the control population (Royle 1975b). The workers had been exposed to chromium(VI) in air and in dust. The air levels were generally <0.03 mg chromium(VI)/m<sup>3</sup>, and dust levels were generally between 0.3 and 97 mg chromium(VI)/g. The exposure levels at which effects first occurred could not be determined. A NIOSH Health Hazard Evaluation of an electroplating facility in the United States reported nasal septum perforation in 4 of 11 workers employed for an average of 7.5 years and exposed to mean concentrations of 0.004 mg chromium(VI)/m<sup>3</sup>. Many of the workers had epistaxis, rhinitis, and nasal ulceration (Lucas and Kramkowski 1975). Nasal mucosal changes ranging from irritation to perforation of the septum were found among 77 employees of eight chromium electroplating facilities in Czechoslovakia where the mean level in the breathing zone above the plating baths was 0.414 mg chromium(VI)/m<sup>3</sup> (Hanslian et al. 1967). The incidence of olfactory cleft obstruction, dry nose, feelings of nasal obstruction, and nasal crusting was significantly increased in workers employed at chromium plating factories (mean employment duration of 7.9 years) in An-San, Korea compared to an unexposed control group (Kitamura et al. 2003). Air concentrations of chromium(VI) ranged from 0.005 to 0.03 mg chromium(VI)/m<sup>3</sup> and of chromium(III) ranged from 0.005 to 0.06 mg chromium(III)/m<sup>3</sup>. Increased incidences of nasal septum

## 3. HEALTH EFFECTS

perforation, nasal septum ulcer, and nasal obstruction were observed in workers at chromium electroplating facilities exposed for a mean duration of 6.1 years, as compared to workers at zinc electroplating facilities (Kuo et al. 1997a). The chromium electroplating workers had 31.7 and 43.9 times greater risks of developing nasal septum ulcers or nasal perforations, respectively, than the zinc workers. A significant relationship between duration of exposure and the risk of nasal septum ulcers was also found; the chromium electroplating workers with a work duration of >9 years had a risk 30.8 times higher than those with a work duration of <2 years. Duration did not significantly affect the risk of nasal perforation. Statistically significant decreases in vital capacity, forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV<sub>1</sub>) were also observed in the chromium workers. Alterations in lung function were also reported in a study of 44 workers at 17 chromium electroplating facilities (Bovet et al. 1977). Statistically significant decreases in forced expiratory volume in 1 second and forced expiratory flow were observed; vital capacity was not altered. Lower lung function values were found among workers with high urinary chromium levels (exposure levels were not reported), and it was determined that cigarette smoking was not a confounding variable.

A study of respiratory effects, lung function, and changes in the nasal mucosa in 43 chrome plating workers in Sweden exposed to chromium(VI) as chromium trioxide for 0.2–23.6 years (median=2.5 years) reported respiratory effects at occupational exposure levels of 0.002 mg chromium(VI)/m<sup>3</sup>. Signs and symptoms of adverse nasal effects were observed and reported at mean exposure levels of 0.002–0.2 mg chromium(VI)/m<sup>3</sup>. Effects noted at ≤0.002 mg chromium(VI)/m<sup>3</sup> included a smeary and crusty septal mucosa and atrophied mucosa. Nasal mucosal ulceration and septal perforation occurred in individuals exposed at peak levels of 0.02–0.046 mg chromium(VI)/m<sup>3</sup>; nasal mucosal atrophy and irritation occurred in individuals exposed at peak levels of 0.0025–0.011 mg chromium(VI)/m<sup>3</sup>; and no significant nasal effects were observed in individuals exposed at peak levels of 0.0002–0.001 mg chromium(VI)/m<sup>3</sup>. Workers exposed to mean concentrations of 0.002–0.02 mg chromium(VI)/m<sup>3</sup> had slight, transient decreases in FVC, forced expired volume in 1 second (FEV<sub>1</sub>), and forced mid-expiratory flow during the workday. Workers exposed to <0.002 mg chromium(VI)/m<sup>3</sup> showed no effects on lung function (Lindberg and Hedenstierna 1983). The concentrations at which minor lung function changes were observed (0.002–0.02 mg chromium(VI)/m<sup>3</sup>) and those at which no changes were observed (<0.002 mg chromium(VI)/m<sup>3</sup>) are similar to those for nasal effects (0.0025–0.011 mg chromium(VI)/m<sup>3</sup>). The effects observed in this study may not have resulted from exposure levels actually measured, but may have resulted from earlier exposure under unknown conditions. Furthermore, poor personal hygiene practices resulting in transfer of chromium(VI) in chrome plating solutions from the hands to the nose could contribute to the development of nasal ulceration and

## 3. HEALTH EFFECTS

perforation (Cohen et al. 1974; Lucas and Kramkowski 1975), perhaps leading to an underestimation of airborne levels of chromium(VI) necessary to cause these effects. Despite these considerations, the study by Lindberg and Hedenstierna (1983) is useful because it indicates concentration-responses of chromium(VI) compounds that cause significant nasal and respiratory effects. The LOAEL of 0.002 mg chromium(VI)/m<sup>3</sup> for respiratory effects in humans was used to calculate an inhalation MRL of  $5 \times 10^{-6}$  mg chromium(VI)/m<sup>3</sup> for intermediate-duration exposure to chromium(VI) as chromium trioxide mists and other dissolved hexavalent chromium aerosols or mists as described in the footnotes in Table 3-1.

Occupational exposure to chromium(VI) and/or chromium(III) in other chromium-related industries has also been associated with respiratory effects. These industries include chromate and dichromate production, stainless steel welding, and possibly ferrochromium production and chromite mining.

In a survey of a facility engaged in chromate production in Italy, where exposure concentrations were  $\geq 0.01$  mg chromium(VI)/m<sup>3</sup>, high incidences of nasal septum perforation, septal atrophy and ulcerations, sinusitis, pharyngitis, and bronchitis were found among 65 men who worked in the production of dichromate and chromium trioxide for at least 1 year (Sassi 1956). Medical records of 2,307 male workers (all nonsmokers) employed at a chromate production plant in Baltimore, Maryland between 1950 and 1974 were evaluated to determine the percentage of workers reporting clinical symptoms, mean time of employment to first diagnosis of symptoms, and mean exposure to chromium(VI) at the time of first diagnosis (exposure for each worker was the annual mean in the area of employment during the year of first diagnosis) (Gibb et al. 2000a). The most frequently reported clinical symptoms were irritation and ulcerated nasal septum, occurring in 68.1 and 62.9% of the cohort, respectively. For irritation of the nasal septum, the mean time of employment to first diagnosis was 89 days and the mean annual exposure level during the year of first diagnosis was 0.025 mg chromium(VI)/m<sup>3</sup>; for nasal septal ulceration, the mean time of employment to first diagnosis was 86 days and the mean annual exposure level during the year of first diagnosis was 0.028 mg chromium(VI)/m<sup>3</sup>. Other nasal effects had a longer time to first diagnosis. The time to first diagnosis for perforated nasal septum was 313 days, occurring in 17.3% of the cohort at a mean exposure level of 0.033 mg chromium(VI)/m<sup>3</sup>, and for bleeding nasal septum, the time to first diagnosis was 418 days, occurring in 12.1% of the cohort at a mean exposure level of 0.025 mg chromium(VI)/m<sup>3</sup>. In a study of 97 workers from a chromate plant exposed to a mixture of insoluble chromite ore containing chromium(III) and soluble chromium(VI) as sodium chromate and dichromate, evaluation for respiratory effects revealed that 63% had perforations of the nasal septum, 86.6% had chemical rhinitis, 42.3% had chronic chemical pharyngitis, 10.35% had laryngitis, and 12.1% had sinus, nasal, or laryngeal polyps. The number of complaints and clinical signs increased as the exposure to

## 3. HEALTH EFFECTS

respirable chromium(VI) and chromium(III) compounds increased, but exposure levels at which effects first occurred were not clearly defined (Mancuso 1951). An extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants found that effects on the lungs consisted of bilateral hilar enlargement. Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m<sup>3</sup>); water-soluble hexavalent chromium compounds (0.005–0.17 mg chromium(VI)/m<sup>3</sup>); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent trivalent chromium (0–0.47 mg chromium/m<sup>3</sup>) (PHS 1953). Challenge tests with fumes from various stainless steel welding processes indicated that the asthma observed in two stainless steel welders was probably caused by chromium or nickel, rather than by irritant gases (Keskinen et al. 1980). In a study of 54 male miners in Zimbabwe exposed to chrome ore dust, decreases in pulmonary function, as indicated by measures of FVC, FEV<sub>1</sub>, peak expiratory flow rate (PEFR), and FEV<sub>1</sub>%, was observed compared to an unexposed control (e.g., non-mining) population (Osime et al. 1999). Exposure levels were reported only as respirable dust, not as chromium specifically, and the mining company did not employ industrial hygiene practices to reduce exposure. In this same study, no changes in lung function were observed in a group of 46 male miners working for a company following industrial hygiene procedures (again, specific chromium exposure levels were not reported). The analysis controlled for smoking and infectious respiratory diseases. In a report of 10 cases of pneumoconiosis in underground workers in chromite mines in South Africa, radiographic analysis revealed fine nodulation and hilar shadows. Chromium in the chromite ore in South Africa was in the form of chromium(III) oxide. The cause of the pneumoconiosis was considered to be deposition of insoluble radio-opaque chromite dust in the tissues, rather than fibrosis (Sluis-Cremer and du Toit 1968). In a case report of a death of a sandblaster in a ferrochromium department of an iron works, the cause of death was silicosis, but autopsy also revealed diffuse enlargement of alveolar septae and chemical interstitial and alveolar chronic pneumonia, which were attributed to inhalation of chromium(III) oxide (Letterer 1939). In an industrial hygiene survey of 60 ferrochromium workers exposed to chromium(III) and chromium(VI) (0.02–0.19 mg total chromium/m<sup>3</sup>) conducted in 1975, appreciably higher incidences of subjective symptoms of coughing, wheezing, and dyspnea were reported compared with controls. These workers had been employed at the plant for at least 15 years. The control group consisted of workers employed at the same plant for <5 years. Statistically significant decreased mean FVC (p<0.01) and FEV<sub>1</sub> (p<0.05) were found in the ferrochromium workers compared with controls. Two of the ferrochromium workers had nasal septum perforations, which were attributed to previous exposure to hexavalent chromium. A major limitation of this study is that the control group was significantly younger than the study cohort. In addition, the weekly amount of tobacco smoked by the control group was slightly greater than that

## 3. HEALTH EFFECTS

smoked by the study groups, and the controls began smoking 5 years earlier than the study groups. Therefore, the increase in subjective respiratory symptoms and decreased pulmonary function parameters cannot unequivocally be attributed to chromium exposure (Langård 1980). However, no increase in the prevalence of respiratory illness was found in a study of 128 workers from two factories that produced chromium(III) oxide or chromium(III) sulfate (Korallus et al. 1974b) or in 106 workers at a factory that produced these chromium(III) compounds where workroom levels were  $\leq 1.99$  mg chromium(III)/m<sup>3</sup> (Korallus et al. 1974a). Similar results were reported in a cross-sectional study that was conducted to determine whether occupational exposure to trivalent chromium or hexavalent chromium caused respiratory diseases, decreases in pulmonary function, or signs of pneumoconiosis in stainless steel production workers (Huvinen et al. 1996). The median personal exposure levels were 0.0005  $\mu\text{g}/\text{m}^3$  for chromium(VI) and 0.022  $\mu\text{g}/\text{m}^3$  for chromium(III); the 221 workers were employed for >8 years with an average potential exposure of 18 years. Spirometry measurements were taken and chest radiographic examinations were conducted. There were no significant differences in the odds ratios between the exposed workers and the 95 workers in the control group. The deficits in lung function shown in both populations could be explained by age and smoking habits. In a follow-up study of these workers (Huvinen et al. 2002a), no adverse respiratory effects were observed (as assessed by spirometry, chest x-ray, and self-reported symptoms) in workers in the chromium(VI) group (n=104) compared to controls (n=81). Workers exposed to chromium(III) in the sintering and crushing departments (n=68) reported an increase in respiratory symptoms (phlegm production, shortness of breath on exertion) compared to control, but no differences in spirometry or chest x-ray. Workers exposed to chromium(III) as chromite ore (n=31) had lower lung function tests, although smoking was a confounding factor. In addition to chromium, workers were also exposed to nickel and molybdenum. In a study of stainless steel workers (all nonsmokers) exposed for a minimum of 14 years to chromium(VI) (n=29), chromium(III) (n=14), or chromite(III) ore (n=5), no increase was observed in the incidence of nasal diseases or nasal symptoms in exposed chromium-exposed workers compared to a control population of 39 workers (Huvinen et al. 2002b). However, although an exposure-related increase in the incidence of clinical signs of nasal irritation was not observed, anterior rhinoscopy revealed a slight increase in the incidence of inflammatory changes in the nasal mucosa of workers exposed to chromium(VI) (risk ratio=2.4) or chromium(III) (risk ratio=2.3), compared to control. The mean exposure level for the chromium(VI) group was 0.5  $\mu\text{g Cr(VI)}/\text{m}^3$ , for the chromium(III) group was 248  $\mu\text{g total Cr}/\text{m}^3$  (concentration of chromium(III) not reported) and for the chromite ore group was 22  $\mu\text{g Cr(III)}/\text{m}^3$ .

The respiratory system in animals is also a primary target for acute- and intermediate-duration inhalation exposure to chromium(VI) and chromium(III). Rats exposed to sodium dichromate for 28 or 90 days had

## 3. HEALTH EFFECTS

increased lung weight but no histopathological abnormalities at concentrations  $\leq 0.2$  mg chromium(VI)/m<sup>3</sup>. The percentage of lymphocytes was increased in the bronchoalveolar lavage fluid at  $\geq 0.025$  mg/m<sup>3</sup>. A decrease in macrophage activity was observed in the 0.2 mg chromium(VI)/m<sup>3</sup> group exposed for 90 days. Clearance of iron oxide from the lungs decreased in rats exposed to 0.2 mg chromium(VI)/m<sup>3</sup> for 42 days prior to and 49 days after challenge with iron oxide particles when compared to controls. The decreased clearance of iron oxide correlated with the decrease in macrophage activity (Glaser et al. 1985). In a similar but more extensive study, obstructive respiratory dyspnea was observed in rats exposed to sodium dichromate at  $\geq 0.2$  mg chromium(VI)/m<sup>3</sup> for 30 or 90 days, and mean lung weight was increased at  $\geq 0.05$  mg chromium(VI)/m<sup>3</sup>. Slight hyperplasia was observed at high incidence in rats at  $\geq 0.05$  mg chromium(VI)/m<sup>3</sup>. Lung fibrosis occurred at low incidence in the rats exposed to  $\geq 0.1$  mg chromium(VI)/m<sup>3</sup> for 30 days, but not in the 0.05 mg/m<sup>3</sup> or the control groups. The incidence of both these lesions declined after longer exposure, indicating repair. Accumulation of macrophages and inflammation occurred at  $\geq 0.05$  mg chromium(VI)/m<sup>3</sup> regardless of duration. Results of bronchoalveolar lavage (BAL) analysis provided further evidence of an irritation effect that was reversible (Glaser et al. 1990). The data from the Glaser et al. (1990) study was used to develop benchmark concentrations (BMCs) (Malsch et al. 1994). The BMC of 0.016 mg chromium(VI)/m<sup>3</sup> for alterations in lactate dehydrogenase levels in BAL fluid was used to calculate an inhalation MRL of 0.0003 mg chromium(VI)/m<sup>3</sup> for intermediate-duration exposure to chromium(VI) as particulate hexavalent compounds as described in the footnote of Table 3-1.

Male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m<sup>3</sup> as chromium trioxide mist developed nasal hemorrhage after 10 days (lasting for 4 weeks) during a 90-day inhalation study (Kim et al. 2004). "Peculiar sounds" during respiration were noted starting after 1 week of exposure and resolving by week 8 in rats exposed to  $\geq 0.23$  mg chromium(VI)/m<sup>3</sup>; however, no additional information on this observation was reported. After 90 days, histopathological changes to respiratory tissue included macrophage aggregation and foamy cells, and inflammation of alveolar regions; however, no abnormalities were observed in nasal tissue at 0.49 mg chromium(VI)/m<sup>3</sup> (incidence data were not reported). Mice exposed to chromium trioxide mist at concentrations of 1.81 and 3.63 mg chromium(VI)/m<sup>3</sup> intermittently for  $\leq 12$  months developed perforations in the nasal septum, hyperplastic and metaplastic changes in the larynx, trachea, and bronchus, and emphysema (Adachi 1987; Adachi et al. 1986).

The respiratory effects of chromium(III) compounds were investigated in male and female CDF rats exposed to insoluble chromic oxide or soluble basic chromium sulfate by nose-only inhalation at 3, 10, or

## 3. HEALTH EFFECTS

30 mg chromium(III)/m<sup>3</sup> for 6 hours/day, 5 days/week for 13 weeks (Derelanko et al. 1999). After 5 days of exposure, BAL was conducted on a subgroup of animals. In rats treated with chromic oxide, a yellow crystalline material was observed in the cytoplasm of mononuclear cells of all exposure groups; however, it is not clear if this observation represents an adverse effect. No other BAL parameters were affected (nucleated cell count and differential, protein and BAL fluid activities of  $\beta$ -glucuronidase, lactic dehydrogenase, and glutathione reductase). In rats treated with basic chromium sulfate, BAL fluid analysis showed significant decreases in nucleated cells at all doses in males and females and decreases in the percentage of segmented neutrophils and mononuclear cells at 30 mg chromium(III)/m<sup>3</sup> in males. Increased amounts of cell debris and lysed cells were present in all basic chromium sulfate groups (incidence data were not reported). In rats exposed to chromic oxide for 13 weeks, absolute and relative lung weights were increased by 12 and 13%, respectively, in males exposed to 30 mg chromium(III)/m<sup>3</sup> as chromic oxide; no change was observed in females. Histopathological examination of respiratory tissues showed pigmented macrophages containing a dense black substance, presumably the test substance, throughout the terminal bronchioles and alveolar spaces in rats from all treatment groups; this finding is consistent with normal physiological clearance mechanisms for particulates deposited in the lung and is not considered to be adverse. At concentrations of 10 and 30 mg chromium(III)/m<sup>3</sup>, trace to mild chronic interstitial inflammation, characterized by inflammatory cell infiltrates, and septal cell hyperplasia was observed. No lesions were observed in the nasal cavity. Following a 13-week recovery period, microscopic examination of respiratory tissues of rats treated with chromic oxide showed pigmented macrophages and black pigment in peribronchial tissues and the mediastinal lymph node in all treatment groups and septal cell hyperplasia and chronic interstitial inflammation of the lung, both trace-to-mild in severity, in males of all treatment groups and in females exposed to 10 and 30 mg chromium(III)/m<sup>3</sup>. In rats treated with basic chromium sulfate, a dose-related increase in absolute and relative lungs weights was observed in all treatment groups. Histopathological examination of respiratory tract tissues revealed chronic inflammation of the lung (characterized by cell infiltration and debris in alveolar spaces and intense inflammation) and alveolar wall hyperplasia in all treatment groups. In addition, inflammation and suppurative and mucoid exudates of nasal tissues and granulomatous inflammation of the larynx were observed in all treatment groups. Incidence data for histopathological findings were not reported. Following the 13-week recovery period for rats treated with basic chromium sulfate, enlargement of the mediastinal lymph node was observed on gross necropsy in all treatment groups. Microscopic examination of respiratory tissues showed changes to the lung (chronic alveolar inflammation, interstitial inflammation, septal cell hyperplasia, and granulomatous inflammation) in all treatment groups, larynx (granulomatous inflammation) in the 10 and 30 mg chromium(III)/m<sup>3</sup> groups, nasal tissues (trace suppurative exudates) in one to two animals in each groups, and mediastinal lymph



## 3. HEALTH EFFECTS

node (histiocytosis and hyperplasia) in all treatment groups chromium(III)/m<sup>3</sup> groups. Results of this study demonstrate differences in the respiratory effects of inhaled chromium oxide and inhaled basic chromium sulfate. Effects of soluble basic chromium sulfate were more severe and were observed throughout the respiratory tract, while effects of chromic oxide were more mild and limited to the lung; these observations may be related to differences in chemical-physical properties of the test compounds. Data from the Derelanko et al. (1999) study was used as the basis for intermediate-duration inhalation MRLs for chromium(III) compounds. Since soluble and insoluble chromium(III) compounds exhibited different effects in the respiratory tract, distinct intermediate-duration MRLs were derived for insoluble and soluble trivalent chromium particulates. For insoluble chromium(III) compounds (chromic oxide), the minimal LOAEL of 3 mg chromium(III)/m<sup>3</sup> was used to calculate an intermediate-duration inhalation MRL of 0.005 mg chromium(III)/m<sup>3</sup> for exposure to trivalent chromium particulates as described in the footnote of Table 3-2. For soluble chromium(III) (basic chromium sulfate) compounds, the LOAEL of 3 mg chromium(III)/m<sup>3</sup> was used to calculate an intermediate-duration inhalation MRL of 0.0001 mg chromium(III)/m<sup>3</sup> for exposure to trivalent chromium particulates as described in the footnote of Table 3-2.

Pulmonary fluid from hamsters exposed to 0.9 or 25 mg chromium(III)/m<sup>3</sup> as chromium trichloride for 30 minutes revealed sporadic changes in activities of acid phosphatase and alkaline phosphatase in the lavage fluid at 25 mg chromium(III)/m<sup>3</sup>. In the lung tissue, a 75% increase in the acid phosphatase activity was found at 0.9 mg chromium(III)/m<sup>3</sup> and in the  $\beta$ -glucuronidase activity at an unspecified concentration. Histological examination revealed alterations representing mild nonspecific irritation but no morphological damage (Henderson et al. 1979). In rabbits exposed to 0.6 mg chromium(III)/m<sup>3</sup> as chromium nitrate intermittently for 4–6 weeks, changes in the lungs were confined to nodular accumulations of macrophages in the lungs. Macrophage morphology demonstrated black inclusions and large lysosomes. These changes represent normal physiological responses of the macrophages to the chromium particle. Phagocytosis and the reduction of nitroblue tetrazolium to formazan was impaired by chromium(III), indicating a decrease in the functional and metabolic activity of the macrophage (Johansson et al. 1986a, 1986b).

Chronic exposure to chromium(VI) compounds and mixtures of chromium(VI) and chromium(III) compounds have also resulted in adverse respiratory effects in animals. Experiments in which rats were exposed to either chromium(VI) alone as sodium dichromate or a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months showed similar loading of macrophages and increases in lung weight. However, histopathology of rats exposed to 0.1 mg/m<sup>3</sup> of chromium(III) and chromium(VI)

## 3. HEALTH EFFECTS

together revealed interstitial fibrosis and thickening of the septa of the alveolar lumens due to the large accumulation of chromium in the lungs, whereas histopathology of the lungs was normal in rats exposed only to chromium(VI) (Glaser et al. 1986, 1988). Mice exposed to 4.3 mg chromium(VI)/m<sup>3</sup> as calcium chromate dust intermittently for 18 months had epithelialization of alveoli. Histopathology revealed epithelial necrosis and marked hyperplasia of the large and medium bronchi, with numerous openings in the bronchiolar walls (Nettesheim and Szakal 1972). Significantly increased incidences of pulmonary lesions (lung abscesses, bronchopneumonia, giant cells, and granulomata) were found in rats exposed chronically to a finely ground, mixed chromium roast material that resulted in airborne concentrations of 1.6–2.1 mg chromium(VI)/m<sup>3</sup> compared with controls. In the same study, guinea pigs exposed chronically to the chromium roast material along with mists of potassium dichromate or sodium chromate solutions that also resulted in 1.6–2.1 mg chromium(VI)/m<sup>3</sup> had significantly increased incidences of alveolar and interstitial inflammation, alveolar hyperplasia, and interstitial fibrosis, compared with controls. Similarly, rabbits were also exposed and also had pulmonary lesions similar to those seen in the rats and guinea pigs, but the number of rabbits was too small for meaningful statistical analysis (Steffee and Baetjer 1965).

In the only study of chromium(IV) exposure, all rats treated with 0.31 or 15.5 mg chromium(IV)/m<sup>3</sup> as chromium dioxide dust for 2 years had discolored mediastinal lymph nodes and lungs, and dust laden macrophages. Lung weight was increased at 12 and 24 months in the 15.5 mg chromium(IV)/m<sup>3</sup> group (Lee et al. 1989). The increased lung weight and macrophage effects probably represent the increased lung burden of chromium dioxide dust and normal physiological responses of macrophages to dust.

**Cardiovascular Effects.** Information regarding cardiovascular effects in humans after inhalation exposure to chromium and its compounds is limited. In a survey of a facility engaged in chromate production in Italy, where exposure concentrations were  $\geq 0.01$  mg chromium(VI)/m<sup>3</sup>, electrocardiograms were recorded for 22 of the 65 workers who worked in the production of dichromate and chromium trioxide for at least 1 year. No abnormalities were found (Sassi 1956). An extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants found no association between heart disease or effects on blood pressure and exposure to chromates. Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m<sup>3</sup>); water-soluble chromium(VI) compounds (0.005–0.17 mg chromium(VI)/m<sup>3</sup>); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent trivalent chromium (0–0.47 mg chromium/m<sup>3</sup>) (PHS 1953). No excess deaths were observed from cardiovascular diseases and ischemic heart disease in a

## 3. HEALTH EFFECTS

cohort of 4,227 stainless steel production workers from 1968 to 1984 when compared to expected deaths based on national rates and matched for age, sex, and calendar time (Moulin et al. 1993). No measurements of exposure were provided. In a cohort of 3,408 individuals who had worked in four facilities that produced chromium compounds from chromite ore in northern New Jersey sometime between 1937 and 1971, where the exposure durations of workers ranged from <1 to >20 years, and no increases in atherosclerotic heart disease were evident (Rosenman and Stanbury 1996). The proportionate mortality ratios for white and black men were 97 (confidence limits 88–107) and 90 (confidence limits 72–111), respectively.

Cardiovascular function was studied in 230 middle-aged workers involved in potassium dichromate production who had clinical manifestations of chromium poisoning (96 with respiratory effects and 134 with gastrointestinal disorders) and in a control group of 70 healthy workers of similar age. Both groups with clinical manifestations had changes in the bioelectric and mechanical activity of the myocardium as determined by electrocardiography, kinetocardiography, rheocardiography, and ballistocardiography. These changes were more pronounced in the workers with respiratory disorders due to chromium exposure than in the workers with chromium-induced gastrointestinal effects. The changes in the myocardium could be secondary to pulmonary effects and/or to a direct effect on the blood vessels and myocardium (Kleiner et al. 1970).

For intermediate-duration exposures, no histopathological changes to the heart were observed in male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m<sup>3</sup> as chromium trioxide (Kim et al. 2004) or in male and female CDF rats exposed to 30 mg chromium(III)/m<sup>3</sup> as chromic oxide or basic chromium sulfate for 3 months, (Derelanko et al. 1999). No histopathological lesions were found in the hearts of rats exposed chronically to chromium dioxide at 15.5 mg chromium(IV)/m<sup>3</sup> (Lee et al. 1989). Additional information regarding cardiovascular effects in animals after exposure to chromium or chromium compounds was not located.

**Gastrointestinal Effects.** Gastrointestinal effects have been associated with occupational exposure of humans to chromium compounds. In a report of two cases of acute exposure to "massive amounts" of chromium trioxide fumes, the patients complained of abdominal or substernal pain, but further characterization was not provided (Meyers 1950).

In a NIOSH Health Hazard Evaluation of an electroplating facility in the United States, 5 of 11 workers reported symptoms of stomach pain, 2 of duodenal ulcer, 1 of gastritis, 1 of stomach cramps, and 1 of

## 3. HEALTH EFFECTS

frequent indigestion. The workers were employed for an average of 7.5 years and were exposed to mean concentrations of 0.004 mg chromium(VI)/m<sup>3</sup> (Lucas and Kramkowski 1975). These workers were not compared to a control group. An otolaryngological examination of 77 employees of eight chromium electroplating facilities in Czechoslovakia, where the mean level in the breathing zone above the plating baths was 0.414 mg chromium(VI)/m<sup>3</sup>, revealed 12 cases of chronic tonsillitis, 5 cases of chronic pharyngitis, and 32 cases of atrophy of the left larynx (Hanslian et al. 1967). In a study of 97 workers from a chromate plant exposed to a mixture of insoluble chromite ore containing chromium(III) and soluble chromium(VI) as sodium chromate and dichromate, gastrointestinal radiography revealed that 10 of the workers had ulcer formation, and of these, 6 had hypertrophic gastritis. Nearly all of the workers breathed through the mouth while at work and swallowed the chromate dust, thereby directly exposing the gastrointestinal mucosa. Only two cases of gastrointestinal ulcer were found in 41 control individuals, who had the same racial, social, and economic characteristics as the chromium-exposed group (Mancuso 1951). In a survey of a facility engaged in chromate production in Italy where exposure concentrations were  $\geq 0.01$  mg chromium(VI)/m<sup>3</sup>, 15.4% of the 65 workers who worked in the production of dichromate and chromium trioxide for at least 1 year had duodenal ulcers and 9.2% had colitis. The ulcers were considered to be due to exposure to chromium (Sassi 1956). Gastric mucosa irritation leading to duodenal ulcer was found in 21 of 90 workers engaged in the production of chromium salts. Symptoms of gastrointestinal pathology appeared about 3–5 years after the workers' initial contact (Stereckova et al. 1978). Most of these studies reporting gastrointestinal effects did not compare the workers with appropriate controls. Although the gastrointestinal irritation and ulceration due to exposure to chromium(VI) in air could be due to a direct action of chromium(VI) on the gastrointestinal mucosa from swallowing chromium as a result of mouth breathing (or transfer via hand-to-mouth activity), other factors, such as stress and diet, can also cause gastrointestinal effects. While occupational exposure to chromium(VI) may result in gastrointestinal effects, a lower than expected incidence of death from diseases of the digestive tract was found among a cohort of 2,101 employees who had worked for at least 90 days during the years 1945–1959 in a chromium production plant in Baltimore, Maryland, and were followed until 1977. The rate (O/E=23/36.16, SMR=64) is based on comparison with mortality rates for Baltimore (Hayes et al. 1979). In contrast to findings with chromium(VI) compounds, no indication was found that exposure to chromium(III) resulted in stomach disorders in workers employed in two factories that produced chromium(III) oxide or chromium(III) sulfate (Korallus et al. 1974b).

Information regarding gastrointestinal effects in animals after inhalation exposure to chromium or its compounds is limited. For intermediate-duration exposures, no histopathological changes to gastrointestinal tissues in male and female CDF rats exposed to 30 mg chromium(III)/m<sup>3</sup> as chromic

## 3. HEALTH EFFECTS

oxide or basic chromium sulfate for 3 months, (Derelanko et al. 1999). Histological examination of the stomachs of rats exposed to sodium dichromate dihydrate at  $\leq 0.2$  mg chromium(VI)/m<sup>3</sup> for 28 or 90 days revealed no abnormalities (Glaser et al. 1985). In mice exposed intermittently to 4.3 mg chromium(VI)/m<sup>3</sup> as calcium chromate for 18 months, small ulcerations in the stomach and intestinal mucosa were reported to occur occasionally, but the incidence in the treated mice or controls and other details regarding these lesions were not reported (Nettesheim et al. 1971). No treatment-related histopathological lesions were found in the stomach, large intestine, duodenum, jejunum, or ileum of rats chronically exposed to chromium dioxide at 15.5 mg chromium(IV)/m<sup>3</sup> (Lee et al. 1989).

**Hematological Effects.** Hematological evaluations of workers occupationally exposed to chromium compounds have yielded equivocal results. Ninety-seven workers from a chromate plant were exposed to a mixture of insoluble chromite ore containing chromium(III) and soluble sodium chromate and dichromate. Hematological evaluations revealed leukocytosis in 14.4% or leukopenia in 19.6% of the workers. The leukocytosis appeared to be related primarily to monocytosis and eosinophilia, but controls had slight increases in monocytes and occasional increases in eosinophils without leukocytosis. Decreases in hemoglobin concentrations and slight increases in bleeding time were also observed (Mancuso 1951). Whether these hematological findings were significantly different from those seen in controls was not stated, but the effects were attributed to chromium exposure. In a survey of a facility engaged in chromate production in Italy where exposure concentrations were  $\geq 0.01$  mg chromium(VI)/m<sup>3</sup>, hematological evaluation of workers who worked in the production of dichromate and chromium trioxide for at least 1 year were unremarkable or inconclusive (Sassi 1956). In an extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants, hematological evaluations revealed no effects on red blood cell counts, hemoglobin, hematocrit, or white blood cell counts. The sedimentation rate of red cells was higher than that of controls, but the difference was not statistically significant. Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m<sup>3</sup>); water-soluble chromium(VI) compounds (0.005–0.17 mg chromium(VI)/m<sup>3</sup>); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent chromium(III) (0–0.47 mg chromium/m<sup>3</sup>) (PHS 1953). Likewise, no effects on red blood cell counts, white blood cell counts, hemoglobin levels, or sedimentation rate were found in a case control study of 17 male manual metal arc stainless steel welders from six industries with mean occupational durations of 20 years (Littorin et al. 1984). The relationship between serum and urine chromium levels and blood hemoglobin was examined in workers exposed to chromium(III) at a tannery plant in Leon, Mexico (Kornhauser et al. 2002). Groups of workers were classified as unexposed (control; n=11), moderately

## 3. HEALTH EFFECTS

exposed (n=14) or highly exposed (n=11) based on job type; exposure levels were not reported. Blood chromium levels of 0.13, 0.25, and 0.39  $\mu\text{g/L}$  and urine chromium levels of 1.35, 1.43, and 1.71  $\mu\text{g/L}$  were observed in the control, moderate, and high exposure groups, respectively; statistically significant differences were observed between the control group and both chromium groups for blood chromium and between the control and the high exposure groups for urine chromium. An inverse relationship was observed between urine chromium and blood hemoglobin ( $r=-0.530$ ), serum chromium and urine iron ( $r=-0.375$ ) and the chromium/iron ratio in urine and hemoglobin ( $r=-0.669$ ;  $<0.05$ ). Results indicate a potential effect of chromium(III) exposure on hemoglobin; however, due to small group size, definitive conclusions cannot be made. No hematological disorders were found among 106 workers in a chromium(III) producing plant where workroom levels were  $\leq 1.99$  mg chromium(III)/ $\text{m}^3$  as chromium(III) oxide and chromium(III) sulfate (Korallus et al. 1974a).

Results from hematological evaluations in rats yielded conflicting results. Hematological effects were observed in male Sprague-Dawley rats exposed to chromium trioxide mist for 90 days; changes included significant decreases in hematocrit (at 0.23 and 1.15, but not 0.49 mg chromium(VI)/ $\text{m}^3$ ), hemoglobin (at 0.49 and 1.15 mg chromium(VI)/ $\text{m}^3$ ) and erythrocyte count (at 1.15 mg chromium(VI)/ $\text{m}^3$ ) (Kim et al. 2004). Hematological evaluations of rats exposed to sodium dichromate at 0.025–0.2 mg chromium(VI)/ $\text{m}^3$  for 28 or 90 days or 0.1 mg chromium(VI)/ $\text{m}^3$  for 18 months were unremarkable (Glaser et al. 1985, 1986, 1988). However, increased white blood cell counts were found in rats exposed to  $\geq 0.1$  mg chromium(VI)/ $\text{m}^3$  as sodium dichromate for 30 days and at  $\geq 0.05$  mg chromium(VI)/ $\text{m}^3$  for 90 days. The white blood cell counts were not increased 30 days postexposure (Glaser et al. 1990). Rats exposed to 0.1 mg chromium/ $\text{m}^3$  as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months had increased red and white blood cell counts, hemoglobin content, and hematocrit (Glaser et al. 1986, 1988).

No changes in hematological parameters were observed in rats exposed to 15.5 mg chromium(IV)/ $\text{m}^3$  as chromium dioxide for 2 years (Lee et al. 1989).

In male and female CDF rats exposed to insoluble chromic oxide or soluble basic chromium sulfate by nose-only inhalation at 3, 10, or 30 mg chromium(III)/ $\text{m}^3$  for 6 hours/day, 5 days/week for 13 weeks, no adverse effects on hematological parameters were observed (Derelanko et al. 1999).

**Musculoskeletal Effects.** No musculoskeletal effects have been reported in either humans or animals after inhalation exposure to chromium.

## 3. HEALTH EFFECTS

**Hepatic Effects.** Chromium(VI) has been reported to cause severe liver effects in four of five workers exposed to chromium trioxide in the chrome plating industry. Derangement of the cells in the liver, necrosis, lymphocytic and histiocytic infiltration, and increases in Kupffer cells were reported. Abnormalities in tests for hepatic dysfunction included increases in sulfobromophthalein retention, gamma globulin, icterus, cephalin cholesterol flocculation, and thymol turbidity (Pascale et al. 1952). In a cohort of 4,227 workers involved in production of stainless steel from 1968 to 1984, excess deaths were observed from cirrhosis of the liver compared to expected deaths (O/E=55/31.6) based on national rates and matched for age, sex, and calendar time having an SMR of 174 with confidence limits of 131–226 (Moulin et al. 1993). No measurements of exposure were provided. Based on limited information, however, the production of chromium compounds does not appear to be associated with liver effects. As part of a mortality and morbidity study of workers engaged in the manufacture of chromium(VI) compounds (84%) and chromium(III) compounds (16%) derived from chromium(VI) in Japan, 94 workers who had been exposed for 1–28 years were given a complete series of liver function tests 3 years after exposure ended. All values were within normal limits (Satoh et al. 1981). In a survey of a facility engaged in chromate production in Italy, where exposure concentrations were  $\geq 0.01$  mg chromium(VI)/m<sup>3</sup>, 15 of 65 men who worked in the production of dichromate and chromium trioxide for at least 1 year had hepatobiliary disorders. When the workers were given liver function tests, slight impairment was found in a few cases. These disorders could have been due to a variety of factors, especially heavy alcohol use (Sassi 1956). No indication was found that exposure to chromium(III) resulted in liver disorders in workers employed in two factories that produced chromium(III) oxide or chromium(III) sulfate (Korallus et al. 1974b).

The hepatic effects observed in animals after inhalation exposure to chromium or its compounds were minimal and not considered to be adverse. Rats exposed to as much as 0.4 mg chromium(VI)/m<sup>3</sup> as sodium dichromate for  $\leq 90$  days did not have increased serum levels of alanine aminotransferase or alkaline phosphatase, cholesterol, creatinine, urea, or bilirubin (Glaser et al. 1990). Triglycerides and phospholipids were increased only in the 0.2 mg chromium(VI)/m<sup>3</sup> group exposed for 90 days (Glaser et al. 1985). No histopathological changes to the liver were observed in male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m<sup>3</sup> as chromium trioxide (Kim et al. 2004) or in male and female CDF rats exposed to 30 mg chromium(III)/m<sup>3</sup> as chromic oxide or basic chromium sulfate for 3 months, (Derelanko et al. 1999). Chronic exposure of rats to 0.1 mg chromium(VI)/m<sup>3</sup> as sodium dichromate, to 0.1 mg total chromium/m<sup>3</sup> as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide, or to

## 3. HEALTH EFFECTS

15.5 mg chromium(IV)/m<sup>3</sup> as chromium dioxide did not cause adverse hepatic effects as assessed by histological examination and liver function tests (Glaser et al. 1986, 1988; Lee et al. 1989).

**Renal Effects.** No increases in genital/urinary disease were evident in a cohort of 3,408 workers from four former facilities that produced chromium compounds from chromite ore in northern New Jersey sometime between 1937 and 1971. The proportionate mortality ratios for white and black men were 71 (40–117) and 47 (15–111), respectively. Exposure durations ranged from <1 to >20 years (Rosenman and Stanbury 1996).

Renal function has been studied in workers engaged in chromate and dichromate production, in chrome platers, in stainless steel welders, in workers employed in ferrochromium production, in boilermakers, and in workers in an alloy steel plant. Workers exposed to chromium(VI) compounds in a chromate production plant were found to have higher levels of a brush border protein antigen and retinol binding protein in the urine compared with controls (Mutti et al. 1985a). A similar study was conducted in 43 male workers in the chromate and dichromate production industry, where occupational exposures were between 0.05 and 1.0 mg chromium(VI)/m<sup>3</sup> as chromium trioxide, and mean employment duration was 7 years. Workers with >15 µg chromium/g creatinine in the urine had increased levels of retinol binding protein and tubular antigens in the urine (Franchini and Mutti 1988). These investigators believe that the presence of low molecular weight proteins like retinol binding protein or antigens in the urine are believed to be early indicators of kidney damage. In an extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants, analysis of the urine revealed a higher frequency of white blood cell and red blood cell casts than is usually found in an industrial population (statistical significance not reported). Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m<sup>3</sup>); water-soluble chromium(VI) compounds (0.005–0.17 mg chromium(VI)/m<sup>3</sup>); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent chromium(III) (0–0.47 mg chromium/m<sup>3</sup>) (PHS 1953).

Some studies of renal function in chromate production workers found negative or equivocal results. In a survey of a facility engaged in chromate production in Italy, where exposure concentrations were ≥0.01 mg chromium(VI)/m<sup>3</sup>, results of periodic urinalyses of workers who worked in the production of dichromate and chromium trioxide for at least 1 year were generally unremarkable, with the exception of one case of occasional albuminuria and a few cases of slight urobilinuria (Sassi 1956). As part of a mortality and morbidity study of workers engaged in the manufacture of chromium(VI) compounds



## 3. HEALTH EFFECTS

(84%) and chromium(III) compounds (16%) derived from chromium(VI) in Japan, 94 workers who had been exposed for 1–28 years were given a complete series of kidney function tests (not further characterized) 3 years after exposure ended. All values were within normal limits (Satoh et al. 1981).

Studies of renal function in chrome platers, whose exposure is mainly to chromium(VI) compounds, have also yielded equivocal results. A positive dose-response for elevated urinary levels of  $\beta_2$ -microglobulin was found in chrome platers who were exposed to 0.004 mg chromium(VI)/m<sup>3</sup>, measured by personal air samplers, for a mean of 5.3 years. However, since no increase in  $\beta_2$ -microglobulin levels was found in ex-chrome platers who had worked for at least 1 year in an old chrome plating plant from 1940 to 1968, this effect may be reversible (Lindberg and Vesterberg 1983b). Liu et al. (1998) similarly found significantly higher urinary  $\beta_2$ -microglobulin and N-acetyl- $\beta$ -glucosaminidase levels in hard-chrome electroplaters exposed to 0.0042 mg chromium/m<sup>3</sup> for a mean of 5.8 years, as compared to aluminum anode-oxidation workers. The prevalence of elevated levels (higher than reference values) was significantly increased for N-acetyl- $\beta$ -glucosaminidase, but not for  $\beta_2$ -microglobulin. In another study, comparison of results of renal function tests between chrome platers and construction workers revealed that the chrome platers had significantly ( $p < 0.001$ ) increased levels of urinary chromium and increased clearance of chromium, but decreased ( $p < 0.05$ ) levels of retinol binding protein. However, no differences were found for blood urea nitrogen, serum and urinary  $\beta_2$ -microglobulin, serum immunoglobulin, total protein in the urine, urinary albumin, N-acetyl- $\beta$ -D-glucosamidase,  $\beta$ -galactosidase, or lysozyme (Verschoor et al. 1988).

Studies of renal function in stainless steel welders, whose exposure is mainly to chromium(VI) compounds, were negative. Stainless steel welders had significantly increased ( $p < 0.001$ ) levels of urinary chromium, increased clearance of chromium, and increased serum creatinine compared with controls, but no differences were found in the levels of retinol binding protein,  $\beta_2$ -microglobulin, or other indices of kidney damage (Verschoor et al. 1988). Similar negative results were found in another group of stainless steel welders (Littorin et al. 1984).

Occupational exposure to chromium(III) or chromium(0) does not appear to be associated with renal effects. No renal impairment based on urinary albumin, retinol binding protein, and renal tubular antigens was found in 236 workers employed in the ferrochromium production industry where ferrochromite is reduced with coke, bauxite, and quartzite. The mean airborne concentration of chromium in various sample locations was 0.075 mg chromium(III)/m<sup>3</sup>; chromium(VI) was below the detection limit of 0.001 mg chromium(VI)/m<sup>3</sup> at all locations (Foa et al. 1988). Workers employed in an alloy steel plant

## 3. HEALTH EFFECTS

with a mean exposure of 7 years to metallic chromium at 0.61 mg chromium(0)/m<sup>3</sup> and to other metals had normal urinary levels of total protein and  $\beta_2$ -microglobulin, enzyme activities of alanine-aminopeptidase, N-acetyl- $\beta$ -D-glucosaminidase, gammaglutamyl-transpeptidase, and  $\beta$ -galactosidase (Triebig et al. 1987). In boilermakers exposed to chromium(0), no increase in urinary levels of chromium, and no differences in the levels of retinol binding protein,  $\beta_2$ -microglobulin, or other indices of renal toxicity were found (Verschoor et al. 1988).

In a group of 30 men and 25 women who were lifetime residents of an area in northern New Jersey contaminated with chromium landfill, signs of preclinical renal damage were assessed by examining the urinary levels of four proteins, intestinal alkaline phosphatase, tissue nonspecific alkaline phosphatase, N-acetyl- $\beta$ -D-glucosaminidase, and microalbumin (Wedeen et al. 1996). The mean urinary chromium concentrations were 0.2 $\pm$ 0.1  $\mu$ g/g creatinine for the women and 0.3  $\mu$ g/g creatinine for the men. None of the four proteins exceeded normal urinary levels in either men or women. The authors concluded that long-term environmental exposure to chromium dust did not lead to tubular proteinuria or signs of preclinical renal damage.

Exposure of rats to sodium dichromate at  $\leq$ 0.4 mg chromium(VI)/m<sup>3</sup> for  $\leq$ 90 days did not cause abnormalities, as indicated by histopathological examination of the kidneys. Serum levels of creatinine and urea and urine levels of protein were also normal (Glaser et al. 1985, 1990). No changes in urinalysis parameters or histopathological changes to the kidneys were observed in male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m<sup>3</sup> as chromium trioxide (Kim et al. 2004) and no histopathological lesions were observed in the kidneys of male and female CDF rats exposed to 30 mg chromium(III)/m<sup>3</sup> as chromic oxide or basic chromium sulfate for 3 months (Derelanko et al. 1999). Furthermore, no renal effects were observed in rats exposed to 0.1 mg chromium/m<sup>3</sup> as sodium dichromate (chromium(VI)) or as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months, based on histological examination of the kidneys, urinalysis, and blood chemistry (Glaser et al. 1986, 1988). Rats exposed to 15.5 mg chromium(IV)/m<sup>3</sup> as chromium dioxide for 2 years showed no histological evidence of kidney damage or impairment of kidney function, as measured by routine urinalysis. Serum levels of blood urea nitrogen, creatinine, and bilirubin were also normal (Lee et al. 1989).

**Endocrine Effects.** Increased serum amylase activity (a marker for pancreatic function) was observed in a group of 50 chrome plating workers in Bangalore, India, compared to 50 workers with no history of chromium(VI) exposure. Employment duration of exposed workers ranged from 15 to 20 years; exposure levels were not reported (Kalasthi et al. 2007). Serum amylase activity in exposed workers was

## 3. HEALTH EFFECTS

significantly correlated to urine chromium ( $r=0.289$ ;  $p<0.05$ ). No studies were located regarding endocrine effects in humans following inhalation exposure to chromium(III) compounds.

For intermediate-duration exposures, no histopathological changes to the endocrine tissues were observed in male Sprague-Dawley rats exposed to  $1.15 \text{ mg chromium(VI)/m}^3$  as chromium trioxide (Kim et al. 2004) or in male and female CDF rats exposed to  $30 \text{ mg chromium(III)/m}^3$  as chromic oxide or basic chromium sulfate for 3 months (Derelanko et al. 1999). Male rats exposed 22 hours/day for 18 months to  $0.1 \text{ mg chromium(VI)/m}^3$  as sodium dichromate or exposed to a mixture of chromium(VI) and chromium(III) ( $0.06 \text{ mg chromium(VI)/m}^3$  plus  $0.04 \text{ mg chromium(III)/m}^3$ ) as chromium(VI) trioxide and chromium(III) oxide did not result in any histopathological changes in adrenal glands (Glaser et al. 1986, 1988). Rats exposed to  $15.5 \text{ mg chromium(IV)/m}^3$  as chromium dioxide for 2 years showed no histopathological abnormalities in adrenals, pancreas, and thyroid glands (Lee et al. 1989).

**Dermal Effects.** Acute systemic and dermal allergic reactions have been observed in chromium-sensitive individuals exposed to chromium via inhalation as described in Sections 3.2.3.2 and 3.2.3.3.

No studies were located regarding systemic dermal effects in animals after inhalation exposure to chromium(VI) or chromium(III) compounds.

**Ocular Effects.** Effects on the eyes due to direct contact of the eyes with airborne mists, dusts, or aerosols or chromium compounds are described in Section 3.2.3.2. Medical records of 2,307 male workers (all nonsmokers) employed at a chromate production plant in Baltimore, Maryland between 1950 and 1974 were evaluated to determine the percentage of workers reporting clinical symptoms, mean time of employment to first diagnosis of symptoms, and mean exposure to chromium(VI) at the time of first diagnosis (exposure for each worker was the annual mean in the area of employment during the year of first diagnosis) (Gibb et al. 2000a). Conjunctivitis was reported on 20.0% of the study population, at a mean exposure level of  $0.025 \text{ mg Cr(VI)/m}^3$  and a mean time-to-onset of 604 days.

Ophthalmoscopic examination did not reveal any changes in male and female CDF rats exposed to  $30 \text{ mg chromium(III)/m}^3$  as chromic oxide or basic chromium sulfate for 3 months (Derelanko et al. 1999).

Histopathologic examination of rats exposed to  $15.5 \text{ mg chromium(IV)/m}^3$  as chromium dioxide for 2 years revealed normal morphology of the ocular tissue (Lee et al. 1989).

### 3. HEALTH EFFECTS

**Body Weight Effects.** In a report of a case of acute exposure to "massive amounts" of chromium trioxide fumes, the patient became anorexic and lost 20–25 pounds during a 3-month period following exposure (Meyers 1950).

In rats exposed to an aerosol of sodium dichromate for 30 or 90 days or for 90 days followed by an additional 30 days of nonexposure, body weight gain was significantly decreased at 0.2 and 0.4 mg chromium(VI)/m<sup>3</sup> for 30 days (p<0.001), at 0.4 mg chromium(VI)/m<sup>3</sup> for 90 days (p<0.05), and at 0.2 (p<0.01) and 0.4 mg chromium(VI)/m<sup>3</sup> (p<0.05) in the recovery group (Glaser et al. 1990). There was no effect on body weight gain in rats exposed for 28 days to 0.2 mg/m<sup>3</sup> (Glaser et al. 1985) or for ≤18 months to 0.1 mg chromium(VI)/m<sup>3</sup> as sodium dichromate (Glaser et al. 1986, 1988, 1990) or 0.1 mg chromium(III and VI)/m<sup>3</sup> as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months (Glaser et al. 1986, 1988). Body weight was significantly decreased in male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m<sup>3</sup> as chromium trioxide mist for 90 days (Kim et al. 2004) and in male, but not female, rats exposed to 10 mg chromium(III)/m<sup>3</sup> as chromic oxide for 13 weeks (Derelanko et al. 1999). However, exposure of male and female rats to 30 mg chromium(III)/m<sup>3</sup> as basic chromium sulfate for 13 weeks did not produce body weight changes (Derelanko et al. 1999). Similarly, there was no effect on body weight gain in rats exposed to 15.5 mg chromium(IV)/m<sup>3</sup> as chromium dioxide for 2 years (Lee et al. 1989).

#### 3.2.1.3 Immunological and Lymphoreticular Effects

Sensitization of workers, resulting in respiratory and dermal effects, has been reported in numerous occupational exposure studies. Although the route of exposure for initial sensitization in an occupational setting is most likely a combination of inhalation, oral, and dermal routes, information on the exposure levels producing sensitization by the inhaled route was not identified. Additional information on contact dermatitis in sensitized workers is provided in Section 3.2.3.3 (Dermal Exposure, Immunological and Lymphoreticular Effects).

Acute reactions have been observed in chromium sensitive individuals exposed to chromium via inhalation as noted in several individual case reports. A 29-year-old welder exposed to chromium vapors from chromium trioxide baths and to chromium and nickel fumes from steel welding for 10 years complained of frequent skin eruptions, dyspnea, and chest tightness. Chromium sensitivity in the individual was measured by a sequence of exposures, via nebulizer, to chromium(VI) as sodium chromate. Exposure to 0.029 mg chromium(VI)/mL as sodium chromate caused an anaphylactoid

## 3. HEALTH EFFECTS

reaction, characterized by dermatitis, facial angioedema, bronchospasms accompanied by a tripling of plasma histamine levels, and urticaria (Moller et al. 1986). Similar anaphylactoid reactions were observed in five individuals who had a history of contact dermatitis to chromium, after exposure, via nebulizer, to an aerosol containing 0.035 mg chromium(VI)/mL as potassium dichromate. Exposure resulted in decreased forced expiratory volume, facial erythema, nasopharyngeal pruritus, nasal blocking, cough, and wheezing (Olaguibel and Basomba 1989). Challenge tests with fumes from various stainless steel welding processes indicated that the asthma observed in two stainless steel welders was probably caused by chromium or nickel, rather than by irritant gases produced by the welding process (Keskinen et al. 1980). A 28-year-old construction worker developed work-related symptoms of asthma, which worsened during periods when he was working with (and sawing) corrugated fiber cement containing chromium. A skin patch test to chromium was negative. Asthmatic responses were elicited upon inhalation challenge with fiber cement dust or nebulized potassium chromate (Leroyer et al. 1998). A 40-year-old woman exposed to chromium and nickel in a metalworks company developed occupational asthma and tested positive to skin prick tests and bronchial challenge tests with potassium dichromate (Cruz et al. 2006). In four male workers (two electroplating workers, one welder, and one cement worker) with work-related symptoms of asthma, two tested positive to skin prick tests with potassium dichromate and nickel sulfate and all tested positive to bronchial challenge tests with potassium dichromate and nickel sulfate (Fernandez-Nieto et al. 2006). Chromium-induced asthma may occur in some sensitized individuals exposed to elevated concentrations of chromium in air, but the number of sensitized individuals is low and the number of potentially confounding variables in the chromium industry is high.

Concentrations of some lymphocyte subpopulations (CD4+ helper-inducer, CD5--CD19+ B, CD3--CD25+ activated B, and CD3--HLA-DR+ activated B and natural killer lymphocytes) were significantly reduced (about 30–50%) in a group of 15 men occupationally exposed to dust containing several compounds (including hexavalent chromium as lead chromate) in a plastics factory. Worker blood lead and urine chromium levels were significantly higher than those of 15 controls not known to be occupationally exposed to toxic agents. Serum chromium concentrations and serum immunoglobulins IgA, IgG, and IgM were not significantly different between the two groups (Boscolo et al. 1997). The immunological effects of chromium were evaluated in a small group tannery workers (n=20) in Italy, compared to a matched group of unexposed controls (n=24) (Mignini et al. 2004). Exposure of individual workers was not reported, but monitoring of 20 factories with participating workers reported TWA concentrations of 0.09–0.10 mg total chromium/m<sup>3</sup> and 0.001–0.002 mg chromium(VI)/m<sup>3</sup>. The mean time of employment of the exposed group was 5.8 years. Urine chromium excretion was significantly

## 3. HEALTH EFFECTS

increased in workers, although no increased in plasma chromium was observed, compared to controls. In workers, proliferative response of peripheral blood mononucleocytes (PBMC) in response to concavalin A was increased approximately 24% compared to controls; no difference between workers and controls were observed for the percent distribution of lymphocyte subsets (e.g., T lymphocytes, T helper lymphocytes, T cytotoxic lymphocytes, B lymphocytes, and natural killer cells).

Immunological effects of exposure to chromic acid were evaluated in 46 electroplating workers in Taiwan (Kuo and Wu 2002). The entire group was employed for an average of 6.1 years. Workers were divided into low (n=19), moderate (n=17), and high (n=10) subgroups based on mean urine chromium excretion of <1.13, 1.14–6.40, and >6.40  $\mu\text{g}$  chromium/g creatinine, respectively. Airborne chromium was measured by personal samplers for all study participants for the duration of one 8-hour shift (data not reported); however, no information was reported on individual or group exposures over the time of employment. A negative correlation was observed between urine chromium and B cell percentage and a positive correlation was observed between urine chromium and blood IL-8 concentration. The study authors report that smoking was an important factor for lymphocyte subsets; thus, interpretation of these results is limited by confounding factors.

An animal study was designed to examine the immunotoxic effects of soluble and insoluble hexavalent chromium agents released during welding (Cohen et al. 1998). Rats exposed to atmospheres containing soluble potassium chromate at 0.36 mg chromium(VI)/ $\text{m}^3$  for 5 hours/day, 5 days/week for 2 or 4 weeks had significantly increased levels of neutrophils and monocytes and decreased alveolar macrophages in bronchoalveolar lavage than air-exposed controls. Significantly increased levels of total recoverable cells were noted at 2 (but not 4) weeks of exposure. In contrast, no alterations in the types of cells recovered from the bronchoalveolar lavage fluid were observed in rats exposed to 0.36 mg chromium(VI)/ $\text{m}^3$  as insoluble barium chromate, as compared to controls. However, the cell types recovered did differ from those recovered from rats exposed to soluble chromium. Changes seen in pulmonary macrophage functionality varied between the soluble and insoluble chromium(VI) exposure groups. The production of interleukin (IL)-1 and tumor necrosis factor (TNF)- $\alpha$  cytokines were reduced in the potassium chromate exposed rats; only TNF- $\alpha$  was decreased in the barium chromate rats. IL-6 levels were not significantly altered in either group. Barium chromate affected zymosan-inducible reactive oxygen intermediate formation and nitric oxide production to a greater degree than soluble chromium(VI). Insoluble chromium(VI) reduced the production of superoxide anion, hydrogen peroxide, and nitric oxide; soluble chromium(VI) only reduced nitric oxide production.

## 3. HEALTH EFFECTS

Rats exposed to 0.025–0.2 mg chromium(VI)/m<sup>3</sup> as sodium dichromate for 28 or 90 days had increased spleen weights at  $\geq 0.05$  mg chromium(VI)/m<sup>3</sup> and increased response to sheep red blood cells at  $\geq 0.025$  mg chromium(VI)/m<sup>3</sup>. In the 90-day study, serum immunoglobulin content was increased in the 0.05 and 0.1 mg chromium(VI)/m<sup>3</sup> groups but not in the 0.2 mg chromium(VI)/m<sup>3</sup> group. There was an increase in mitogen-stimulated T-cell response in the group exposed for 90 days to 0.2 mg chromium(VI)/m<sup>3</sup>. Bronchial alveolar lavage fluid had an increased percentage of lymphocytes in the groups exposed to 0.025 and 0.05 mg chromium(VI)/m<sup>3</sup> and an increased percentage of granulocytes in the groups exposed to 0.05 mg chromium(VI)/m<sup>3</sup> for 28 days. The phagocytic activity of macrophages was increased in the 0.05 mg chromium(VI)/m<sup>3</sup> group. A higher number of macrophages in telophase was observed in the 0.025 and 0.05 mg chromium(VI)/m<sup>3</sup> groups. Bronchial alveolar lavage fluid from rats exposed for 90 days had an increased percentage of lymphocytes in the 0.025, 0.05, and 0.2 mg chromium(VI)/m<sup>3</sup> groups and an increased percentage of granulocytes and number of macrophages in the 0.05 mg chromium(VI)/m<sup>3</sup> groups. The phagocytic activity of the macrophages was increased in the 0.025 mg and 0.05 mg chromium(VI)/m<sup>3</sup> groups and decreased in the 0.2 mg chromium(VI)/m<sup>3</sup> group. A greater number of macrophages in telophase and an increase in their diameter were observed in the 0.025, 0.05, and 0.2 mg chromium(VI)/m<sup>3</sup> groups (Glaser et al. 1985).

Low-level exposure to sodium dichromate seems to stimulate the humoral immune system (as indicated by the significant increase in total immunoglobulin levels); exposure to 0.2 mg chromium(VI)/m<sup>3</sup> ceases to stimulate the humoral immune system (significant decreases in total immunoglobulin levels) but still may have effects on the T lymphocytes. The depression in macrophage cell count and phagocytic activities correlated with a 4-fold lower rate of lung clearance for inhaled iron oxide in the 0.2 mg chromium(VI)/m<sup>3</sup> group (Glaser et al. 1985).

Intermediate-duration exposure of rats to inhaled chromium(III) compounds produces histopathological alterations to respiratory lymph nodes and tissues. In male and female CDF rats, exposure to 3, 10, and 30 mg chromium(III)/m<sup>3</sup> as soluble basic chromium sulfate for 13 weeks resulted in histiocytic cellular infiltration and hyperplasia of peribronchial lymphoid tissue and mediastinal lymph nodes; lymph node enlargement was also observed on necropsy (Derelanko et al. 1999). Following a 13-week recovery period, enlargement, histiocytosis, and hyperplasia of the mediastinal lymph node was observed in rats exposed to 3, 10, and 30 mg chromium(III)/m<sup>3</sup> as basic chromium sulfate. Hyperplasia of the mediastinal lymph node was observed in male and female CDF rats exposed to chromium oxide at concentrations of 3, 10, and 30 mg chromium(III)/m<sup>3</sup> for 13 weeks (Derelanko et al. 1999). Following a 13-week recovery

### 3. HEALTH EFFECTS

period, black pigment (trace-to-mild) in peribronchial lymphoid tissue and mediastinal lymph nodes was found in all treatment groups.

The LOAELs for immunological effects in rats are recorded in Table 3-1 and plotted in Figure 3-1 for chromium(VI) and recorded in Table 3-2 and plotted in Figure 3-2 for chromium(III).

#### 3.2.1.4 Neurological Effects

In a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes, workers experienced symptoms of dizziness, headache, and weakness when they were working over the chromate tanks (Lieberman 1941). Such poor working conditions are unlikely to still occur in the United States because improvements in industrial hygiene have been made over the years. Results of olfactory perceptions tests conducted in workers employed at chromium plating factories in An-San Korea (mean employment duration of 7.9 years) indicate that olfactory recognition thresholds were significantly higher in exposed workers compared to controls (Kitamura et al. 2003). Air concentrations of chromium(VI) ranged from 0.005 to 0.03 mg chromium(VI)/m<sup>3</sup> and of chromium(III) ranged from 0.005 to 0.06 mg chromium(III)/m<sup>3</sup>. Although the cause of this change was not determined, the study authors suggest that chromium may directly affect the olfactory nerve.

No increases in vascular lesions in the central nervous system were evident in a cohort of 3,408 workers from four former facilities that produced chromium compounds from chromite ore in northern New Jersey (Rosenman and Stanbury 1996). The proportionate mortality ratios for white and black men were 78 (61–98) and 68 (44–101), respectively. The subjects were known to have worked in the four facilities sometime between 1937 and 1971 when the last facility closed. Exposure durations ranged from <1 to >20 years.

No information was located regarding neurological effects in humans or animals after inhalation exposure to chromium(III) compounds or in animals after inhalation exposure to chromium(VI) compounds. No histopathological lesions were found in the brain of male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m<sup>3</sup> as chromium trioxide for 3 months or in male and female CDF rats exposed to 30 mg chromium(III)/m<sup>3</sup> as chromic oxide or basic chromium sulfate for 3 months (Derelanko et al. 1999; Kim et al. 2004) or in the brain, spinal cord, or nerve tissues of rats exposed to 15.5 mg chromium(IV)/m<sup>3</sup> as chromium dioxide for 2 years (Lee et al. 1989). No neurological or behavioral tests were conducted in these studies.



## 3. HEALTH EFFECTS

**3.2.1.5 Reproductive Effects**

Information regarding reproductive effects in humans after inhalation to chromium compounds is limited. Semen quality was evaluated in 61 workers in a chromium sulfate manufacturing plant in India (Kumar et al. 2005). Employment duration and chromium exposure levels were not reported. The study included a control group of 15 unexposed workers. Chromium blood levels in the exposed group were significantly increased compared to the control group. Although no effect was observed on semen volume, liquefaction time, or pH or on sperm viability, count, motility, or concentration, a significant increase was observed in the number of morphologically abnormal sperm in exposed workers. In the exposed group, 53% of subjects had less than 30% normal sperm; in the control group, only 10% of subject had <30% normal sperm. A significant positive correlation ( $r=0.301$ ;  $p=0.016$ ) was observed between blood chromium and the percentage of abnormal sperm in exposed workers. Sperm count and motility were significantly decreased by 47 and 15%, respectively in a group of 21 workers employed at a chrome plating plant in Henan, China, compared to age-matched, unexposed controls (Li et al. 2001). Serum follicle stimulating hormone (FSH) concentration was significantly increased by 204% and semen lactate dehydrogenase activity was significantly decreased by 30% in exposed compared to control workers, although no effect on serum luteinizing hormone (LH) concentration was observed. Serum chromium levels were 11% higher in the exposed workers compared to control; however, the increase was not statistically significant. Duration of employment for all study participants ranged from 1 to 15 years; no information on exposure levels or demographics of the exposed and control groups were reported.

The effect of chromium(VI) on the course of pregnancy and childbirth was studied in women employees at a dichromate manufacturing facility in Russia. Complications during pregnancy and childbirth (not further described) were reported in 20 of 26 exposed women who had high levels of chromium in blood and urine, compared with 6 of 20 women in the control group. Toxicosis (not further described) was reported in 12 exposed women and 4 controls. Postnatal hemorrhage occurred in four exposed and two control women (Shmitova 1980). Similar results were reported in a more extensive study of 407 women who worked at a factory producing chromium compounds (not otherwise specified) compared with 323 controls. The frequency of birth complications was 71.4% in a subgroup of highly exposed women, 77.4% in a subgroup of women with a lower level of exposure, and 44.2% in controls. Toxicosis in the first half of pregnancy occurred in 35.1% of the high exposure group, 33.3% of the low exposure group, and 13.6% of the controls. The frequency of postnatal hemorrhage was 19.0% for the high exposure group and 5.2% in controls (Shmitova 1978). Because these studies were generally of poor quality and

## 3. HEALTH EFFECTS

the results were poorly reported, no conclusions can be made regarding the potential for chromium to produce reproductive effects in humans.

The occurrence of spontaneous abortion among 2,520 pregnancies of spouses of 1,715 married Danish metal workers exposed to hexavalent chromium from 1977 through 1987 were examined (Hjollund et al. 1995). Occupational histories were collected from questionnaires and information on spontaneous abortion, live births, and induced abortion was obtained from national medical registers. The number of spontaneous abortions was not increased for pregnant women whose spouses worked in the stainless steel welding industry when compared to controls (odds ratio 0.78, 95% confidence interval [CI] 0.55–1.1). The authors believed that the risk estimate was robust enough that factors such as maternal age and parity and smoking and alcohol consumptions were not confounders. There was no association found in spontaneous abortions in women whose husbands were in the cohort subpopulations who were mild steel welders and metal-arc stainless steel welders, which would lead to higher exposures to welding fumes (workplace chromium exposures not provided). This more recent study does not corroborate earlier findings (Bonde et al. 1992) that showed that wives of stainless steel welders were at higher risk of spontaneous abortions. The current study was based on abortions recorded in a hospital register, while the earlier study was based on self-reporting data. The latter study probably included more early abortions and was biased because the job exposure of male metal workers is apparently modified by the outcome of their partners' first pregnancy.

Histopathological examination of the testes of rats exposed to 0.2 mg chromium(VI)/m<sup>3</sup> as sodium dichromate for 28 or 90 days (Glaser et al. 1985), to 0.1 mg chromium(VI)/m<sup>3</sup> as sodium dichromate for 18 months, or to 0.1 mg chromium/m<sup>3</sup> as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months (Glaser et al. 1986, 1988) revealed no abnormalities. For intermediate-duration exposures to chromium(III) compounds, no histopathological changes to the reproductive tissues in male and female CDF rats exposed to 30 mg chromium(III)/m<sup>3</sup> as chromic oxide or basic chromium sulfate for 3 months; treatment also had no effect on sperm count, motility, or morphology (Derelanko et al. 1999). No histopathological lesions were observed in the prostate, seminal vesicle, testes, or epididymis of male rats or in the uterus, mammary gland, or ovaries of female rats exposed to 15.5 mg chromium(IV)/m<sup>3</sup> as chromium dioxide for 2 years (Lee et al. 1989).

The NOAELs for reproductive effects in rats are recorded in Table 3-1 and plotted in Figure 3-1 for chromium(VI) and recorded in Table 3-2 and plotted in Figure 3-2 for chromium(III).

## 3. HEALTH EFFECTS

**3.2.1.6 Developmental Effects**

No studies were located regarding developmental effects in humans or animals after inhalation exposure to chromium or its compounds.

**3.2.1.7 Cancer**

Occupational exposure to chromium(VI) compounds in various industries has been associated with increased risk of respiratory system cancers, primarily bronchogenic and nasal. Among the industries investigated in retrospective mortality studies are chromate production, chromate pigment production and use, chrome plating, stainless steel welding, ferrochromium alloy production, and leather tanning. Compilations and discussion of many of these studies can be found in reviews of the subject (Goldbohm et al. 2006; IARC 1990; Steenland et al. 1996). Studies of chromium workers have varied considerably in strength of design for determining cancer risks related to chromium exposure. The strongest designs have provided estimates of chromium(VI) (or exposure to other chromium species) for individual members of the cohorts, enabling application of dose-response analysis to estimate the contribution of chromium exposure to cancer risk. Studies that do not provide estimates of chromium exposure have relied on surrogate dose metrics (e.g., length of employment at job titles associated with chromium exposure) for exploring attribution of cancer risk to chromium exposure. However, these surrogate measures are often strongly correlated with exposures to other work place hazards, making conclusions regarding possible associations with chromium exposures more uncertain. Chromium dose-response relationships have been reported for chromate production workers, but not for other categories of chromium workers. In studies of chromate production workers, increased risk of respiratory tract cancers have been found in association with increased cumulative exposure to chromium(VI) and several estimates of excess lifetime risk attributed to chromium exposure have been reported. Studies of chrome platers, who were exposed to chromium(VI) and other carcinogenic chemicals, including nickel, have found significant elevations in lung cancer risk in association with surrogate indicators of chromium exposure, such as duration of employment at jobs in which exposure to chromium occurred; however, estimates of risk attributable to specifically to chromium exposure have not been reported. Results of studies in stainless steel welders exposed to chromium(VI) and other chemicals, and in ferrochromium alloy workers, who were exposed mainly to chromium(0) and chromium(III), but also to some chromium(VI), have been mixed and are inconclusive with respect to work-associated elevations in cancer rates. Studies in leather tanners, who are exposed to chromium(III), have not found elevated cancer rates.

## 3. HEALTH EFFECTS

**Chromate Production.** Numerous studies of cancer mortality among chromate production workers have been reported (Alderson et al. 1981; Bidstrup and Case 1956; Buckell and Harvey 1951; Crump et al. 2003; Davies et al. 1991; Enterline 1974; Gibb et al. 2000b; Korallus et al. 1982; Mancuso 1997a; Ohsaki et al. 1978; Park and Stayner 2006; Park et al. 2004; Pastides et al. 1994; PHS 1953; Rosenman and Stanbury 1996; Sassi 1956; Satoh et al. 1994; Taylor 1966). Collectively, these studies provide evidence for associations between lung cancer mortality and employment in chromate production, with risks declining with improved industrial hygiene. Less consistently, nasal cancers have been observed (Alderson et al. 1981; Rosenman and Stanbury 1996; Sassi 1956; Satoh et al. 1994). Evidence for associations between exposure to chromium and cancer is strongest for lung cancer mortality, which has been corroborated and quantified in numerous studies. A meta-analysis of 49 epidemiology studies based on 84 papers of cancer outcomes, primarily among chromium workers, found SMRs ranging from 112 to 279 for lung cancer, with an overall SMR of 141 (95% CI 135–147; Cole and Rodu 2005). When limited to high-quality studies controlled for smoking, the overall SMR for lung cancer was 112 (95% CI 104–119). SMRs for other forms of cancer from studies that controlled for confounders were not elevated. Several studies have attempted to derive dose-response relationships for this association (Crump et al. 2003; Gibb et al. 2000b; Mancuso 1997a; Park and Stayner 2006; Park et al. 2004). These studies are particularly important because they have included individual exposure estimates to chromium for each member of the cohort based on work place monitoring; dose-response modeling to ascertain the contribution of changing exposures to chromium to risk (in workers who were also exposed to other work-place hazards that could have contributed to cancer risk); and evaluation of the impacts of potential co-variables and confounders (e.g., age, birth cohort, and smoking) on chromium-associated risk.

Gibb et al. (2000b) examined lung cancer mortality in a cohort of chromate production workers (n=2,357, males) in Baltimore, Maryland, who were first hired during the period 1950–1974, with mortality followed through 1992. This cohort was the subject of numerous earlier studies, which found significantly increased lung cancer mortality (i.e., standard mortality ratios) among workers at the plant (Baetjer 1950b; Braver et al. 1985; Hayes et al. 1979; Hill and Ferguson 1979). In the Gibb et al. (2000b) study, cumulative exposures to chromium(VI) or chromium(III) ( $\text{mg}/\text{m}^3\text{-year}$ ) were reconstructed for each member of the cohort from historical workplace air monitoring data and job title records (Gibb et al. 2000b). Lung cancer for the entire group had a relative risk of 1.80 (95% CI 1.49–2.14). Relative risk of lung cancer mortality (adjusted for smoking) increased by a factor to 1.38 (95% CI 1.20–1.63) in association with a 10-fold increase in cumulative exposure to chromium(VI). The analogous relative risk for cumulative exposure to chromium(III) was 1.32 (95% CI 1.15–1.51). Exposures to chromium(III) and chromium(VI) were highly correlated; therefore, discrimination of risks associated with either were

## 3. HEALTH EFFECTS

problematic. However, in a combined model that included cumulative exposure to both chromium species, relative risk for chromium(VI) exposure remained significant (1.66,  $p=0.045$ ), whereas relative risk for chromium(III) was negative ( $-0.17$ ,  $p=0.4$ ). This outcome suggests that exposure to chromium(VI), rather than chromium(III), was the dominant (if not sole) contributor to lung cancer risk (after adjustments for smoking). Park et al. (2004) reanalyzed the data for the Baltimore, Maryland cohort using a variety of dose-response models. In the preferred model (linear with cumulative chromium exposure and log-linear for age, smoking, race), cancer rate ratio for a 45-year cumulative exposure to  $1 \text{ mg/m}^3$ -year of chromium(VI) was estimated to be 2.44 (95% CI 1.54–3.83). This corresponded to an excess lifetime risk unit risk (i.e., additional lifetime risk from occupational exposure to  $1 \text{ } \mu\text{g CrO}_3/\text{m}^3$  or  $0.52 \text{ } \mu\text{g Cr(VI)/m}^3$ ) of 0.003 (95% CI 0.001–0.006) or to  $100 \text{ } \mu\text{g chromium(VI)/m}^3$  of 0.255 (95% CI 0.109–0.416). Subsequent analyses conducted by Park and Stayner (2006) attempted to estimate possible thresholds for increasing lung cancer risk. This analysis was able to exclude possible thresholds in excess of  $16 \text{ } \mu\text{g/m}^3$  chromium(VI) or  $0.4 \text{ mg/m}^3$ -year cumulative exposure to chromium(VI).

Several studies have examined cancer mortality in a cohort of chromate production workers in Painesville, Ohio, and have found increased lung cancer mortality (e.g., SMRs) among workers at the plant (Crump et al. 2003; Luippold et al. 2003; Mancuso 1997a; Mancuso and Hueper 1951). Mancuso (1997a) reconstructed cumulative exposure histories of individual members of the cohort ( $n=332$ ), hired during the period 1931–1937 and followed through 1993. The exposure estimations were based on historical workplace air monitoring data for soluble and insoluble chromium and job title records. Age-adjusted death rates from lung cancer were estimated for cumulative exposure strata, and increased with increasing cumulative exposure to total chromium, insoluble chromium, and soluble chromium (a dose response model was not reported). The highest rates were observed in soluble chromium strata  $>4 \text{ mg/m}^3$ -years (2,848 per 100,000). Death rates were not adjusted for smoking, which would have been a major contributor to lung cancer death rates in the cohort. Although the study discriminated exposures to soluble and insoluble chromium, these classifications are not adequate surrogates for exposures to trivalent or hexavalent chromium (Kimbrough et al. 1999; Mundt and Dell 1997); therefore, the study cannot attribute risk specifically to either species. More recent studies of this cohort have attempted to reconstruct individual exposure histories to chromium(VI), based on species-specific air monitoring data, and have attempted to quantify the potential contribution of smoking to lung cancer risk (Crump et al. 2003; Luippold et al. 2003). These studies included workers ( $n=482$ ) hired after 1940 and followed through 1997. Increasing lung cancer risk was significantly associated with increasing cumulative exposure to chromium(VI). Relative risk for lung cancer mortality was estimated to be 0.794 per  $\text{mg/m}^3$ -year (90% CI 0.518–1.120). The analogous additive risk was 0.00161 per  $\text{mg/m}^3$ -year per person year

## 3. HEALTH EFFECTS

(90% CI 0.00107–0.00225). These estimates correspond to unit risks (i.e., additional lifetime risk from occupational exposure to  $1 \mu\text{g}/\text{m}^3$ ) of 0.00205 (90% CI 0.00134–0.00291), based on the relative risk Poison model, and 0.00216 (90% CI 0.00143–0.00302), based on the additional risk Poison model. Risk estimates were not appreciably sensitive to birth cohort or to smoking designation (for the 41% of the cohort that could be classified). The latter outcome suggests that smoking did not have a substantial effect on chromium(VI) associated lung cancer risk (i.e., smoking and chromium appeared to contribute independently to cancer risk).

A meta-analysis of the Crump et al. (2003); Gibb et al. (2000b), and Mancuso (1997a) studies has also been reported (Goldbohm et al. 2006). Excess lifetime risk of lung cancers was estimated from a life table analysis (using Dutch population vital statistics) and estimates of relative risk from each study, or in the case of Mancuso (1997a), estimated in the meta-analysis (approximately 0.0015 per  $\text{mg}/\text{m}^3$ -year). Estimates of excess lifetime risks (deaths attributed to a 40-year occupational exposure to chromium(VI) at  $1 \mu\text{g}/\text{m}^3$ , for survival up to age 80 years) were 0.0025, 0.0048, and 0.0133, based on Crump et al. (2003), Mancuso et al. (1997a), and Gibb et al. (2000b), respectively.

In conclusion, despite limitations of some studies, occupational exposure to chromium(VI) in the chromate production industry is associated with increased risk of respiratory cancer. Estimates of excess lifetime occupational risks range from 0.002 to 0.005 per  $\mu\text{g}/\text{m}^3$  of chromium(VI). Changes in production process and industrial hygiene appear to have reduced overall risk over the past 30–40 years.

***Chromate Pigments Production and Use.*** Studies of workers engaged in the production of chromate pigments provide evidence for increased risk of lung cancer associated with employment in work areas where exposure to chromium compounds occurred. However, the contribution of chromium exposure to cancer risk in these cohorts remains uncertain for several reasons: (1) members of the cohorts experienced exposures to a variety of chemicals that may have contributed to cancer (e.g., nickel); (2) exposures of the individual cohort members to chromium were not quantified or subjected to exposure-response analysis; and (3) dose metrics used in dose-response analysis were measures of employment duration, which are highly correlated with exposures to chemical hazards other than chromium. Nevertheless, these studies have found elevated lung cancer rates in chromium pigment workers in comparison to reference populations (e.g., SMRs) and, in some studies, increased lung cancer rates in association with increased potential (e.g., job type, employment duration) for exposure to chromium (Dalager et al. 1980; Davies 1979, 1984; Franchini et al. 1983; Frentzel-Beyme 1983;

## 3. HEALTH EFFECTS

Haguenoer et al. 1981; Hayes et al. 1989; Langgård and Norseth 1975; Langgård and Vigander 1983; Sheffet et al. 1982).

**Chrome Plating.** Studies of chrome platers provide evidence for increased risk of lung cancer associated with employment in work areas where exposure to chromium compounds occurred. However, the contribution of chromium exposure to cancer risk in these cohorts remains uncertain for several reasons: (1) members of the cohorts experienced exposures to a variety of chemicals that may have contributed to cancer (e.g., nickel, sulfuric acid); (2) exposures of the individual cohort members to chromium were not quantified or subjected to exposure-response analysis; and (3) dose metrics used in dose-response analysis were measures of employment duration, which are highly correlated with exposures to chemical hazards other than chromium. Nevertheless, these studies have found elevated lung cancer rates in chrome bath workers in comparison to reference populations (e.g., standard mortality ratios) who were exposed primarily to soluble chromium(VI) (e.g., chromic acid mists) and, in some studies, increased lung cancer rates in association with increased potential (e.g., job type, employment duration) for exposure to chromium (Dalager et al. 1980; Guillemin and Berode 1978; Hanslian et al. 1967; Okubo and Tsuchiya 1977, 1979; Royle 1975a; Silverstein et al. 1981; Sorahan et al. 1987, 1998; Takahashi and Okubo 1990).

Sorahan et al. (1998) examined lung cancer risks in a cohort of nickel/chrome platters (n=1,762, hired during the period 1946–1975 with mortality follow-up through 1995). The same cohort was studied by Royle (1975a). Significant excess risks of lung cancer were observed among males and females working in the chrome bath area for <1 year (SMR=172; 95% CI 112–277; p<0.05) or >5 years (SMR=320; 95% CI 128–658; p<0.001), females working in the chrome bath area for <1 year (SMR=245; 95% CI 118–451; p<0.5), males starting chrome work in the period of 1951–1955 (SMR=210; 95% CI 132–317; p<0.01), and in male chrome workers 10–19 years after first chrome work (SMR=203; 95% CI 121–321; p<0.01). A significant (p<0.01) positive trend for lung cancer mortality and duration of exposure was found for the male chrome bath workers, but not for the female workers. Lung cancer mortality risks were also examined using an internal standard approach, in which mortality in chrome workers was compared to mortality in workers without chromium exposure. After adjusting for sex, age, calendar period, year of starting chrome work, period from first chrome work, and employment status, a significant positive trend (p<0.05) between duration of chrome bath work and lung cancer mortality risk was found.

**Stainless Steel Welding.** Workers in the stainless steel welding industry are exposed to chromium(VI) compounds, as well as other chemical hazards that could contribute to cancer (e.g., nickel); however, results of studies of cancer mortality in these populations have been mixed. Some studies have found

## 3. HEALTH EFFECTS

increased cancer mortality rates among workers; however, examinations of possible associations with exposures to chromium have not been reported. A study of 1,221 stainless steel welders in the former Federal Republic of Germany found no increased risk of lung cancer or any other specific type of malignancy compared with 1,694 workers involved with mechanical processing (not exposed to airborne welding fumes) or with the general population of the former Federal Republic of Germany (Becker et al. 1985). A follow-up study (Becker 1999) which extended the observation period to 1995, found similar results for lung (includes bronchus and trachea) cancer (SMR=121.5, 95% CI 80.7–175.6). An excess risk of pleura mesothelioma was observed (SMR=1,179.9; 95% CI=473.1–2430.5); however, this was attributed to asbestos exposure. A study of 234 workers from eight companies in Sweden, who had welded stainless steel for at least 5 years during the period of 1950–1965 and followed until 1984, found five deaths from pulmonary tumors, compared with two expected (SMR=249), based on the national rates for Sweden. The excess was not statistically significant. However, when the incidence of lung cancer in the stainless steel welders was compared with an internal reference group, a significant difference was found after stratification for age. The average concentration of chromium(VI) in workroom air from stainless steel welding, determined in 1975, was reported as 0.11 mg/m<sup>3</sup> (Sjogren et al. 1987). The cohort in this study was small, and stainless welders were also exposed to nickel fumes. Smoking was probably not a confounding factor in the comparisons with the internal reference group.

In a study of the mortality patterns in a cohort of 4,227 workers involved in the production of stainless steel from 1968 to 1984, information was collected from individual job histories, and smoking habits were obtained from interviews with workers still active during the data collection (Moulin et al. 1993). The observed number of deaths was compared to expected deaths based on national rates and matched for age, sex, and calendar time. No significant excess risk of lung cancer was noted among workers employed in melting and casting stainless steel (SMR=104). However, there was a significant excess among stainless steel foundry workers (SMR=229). The SMR increased for workers with length of employment over 30 years to 334 (119–705). No measurements of exposure were provided.

***Ferrochromium Production.*** Workers in the ferrochromium alloy industry are exposed to chromium(III) and chromium(VI) compounds, as well as other chemical hazards that could contribute to cancer; however, results of studies of cancer mortality in these populations have been mixed. No significant increase in the incidence of lung cancer was found among 1,876 employees who worked in a ferrochromium plant in Sweden for at least 1 year from 1930 to 1975 compared with the expected rates for the county in which the factory was located. The workers had been exposed mainly to metallic chromium and chromium(III), but chromium(VI) was also present. The estimated levels ranged from 0 to



## 3. HEALTH EFFECTS

2.5 mg chromium(0) and chromium(III)/m<sup>3</sup> and from 0 to 0.25 mg chromium(VI)/m<sup>3</sup> (Axelsson et al. 1980). An excess of lung cancer was found in a study of 325 male workers employed for >1 year in a ferrochromium producing factory in Norway between 1928 and 1977 (Langård et al. 1980), and whose employment began before 1960 (SMR=850, p=0.026); however, in a follow-up of this cohort (n=379, hired before 1965 and followed through 1985), the SMR for lung cancer was not significant (SMR=154; Langård et al. 1990). Workroom monitoring in 1975 indicated that the ferrochromium furnace operators worked in an atmosphere with 0.04–0.29 mg total chromium/m<sup>3</sup>, with 11–33% of the total chromium as chromium(VI) (Langård et al. 1980).

An ecological study examined the distribution of lung cancer cases in Dolný Kubin in the Slovak Republic where ferrochromium production facility was located. Cases were stratified into three groups (males): ferrochromium workers (n=59), workers (n=106) thought not to have been exposed to chromium, and residents (n=409) who were not thought to have had appreciable exposure to chromium. Lung cancer rates were higher in the chromium workers (320 per 1,000 per year, 95% CI 318–323) compared to workers (112, 95% CI 109–113) and residents (79, 95% CI 76–80) who were not thought to have been exposed to chromium (relative risk=4.04 for chromium workers compared to residents). Mean work shift air concentrations in the smelter were 0.03–0.19 mg/m<sup>3</sup> for total chromium and 0.018–0.03 mg/m<sup>3</sup> for chromium(VI). These estimates were not adjusted for smoking or other potential co-variables that might have contributed to cancer rates in the chromium workers.

**Leather Tanning.** Studies of workers in tanneries, where exposure is mainly to chromium(III), in the United States (0.002–0.054 mg total chromium/m<sup>3</sup>) (Stern et al. 1987), the United Kingdom (no concentration specified) (Pippard et al. 1985), and the Federal Republic of Germany (no concentration specified) (Korallus et al. 1974a) reported no association between exposure to chromium(III) and excess risk of cancer.

**Environmental Exposure.** In addition to the occupational studies, a retrospective environmental epidemiology study was conducted of 810 lung cancer deaths in residents of a county in Sweden where two ferrochromium alloy industries are located. No indication was found that residence near these industries is associated with an increased risk of lung cancer (Axelsson and Rylander 1980).

A retrospective mortality study conducted on a population that resided in a polluted area near an alloy plant that smelted chromium in the People's Republic of China found increased incidences of lung and stomach cancer. The alloy plant began smelting chromium in 1961 and began regular production in 1965,

## 3. HEALTH EFFECTS

at which time sewage containing chromium(VI) dramatically increased. The population was followed from 1970 to 1978. The size of the population was not reported. The adjusted mortality rates of the exposed population ranged from 71.89 to 92.66 per 100,000, compared with 65.4 per 100,000 in the general population of the district. The adjusted mortality rates for lung cancer ranged from 13.17 to 21.39 per 100,000 compared with 11.21 per 100,000 in the general population. The adjusted mortality rates for stomach cancer ranged from 27.67 to 55.17 per 100,000 and were reported to be higher than the average rate for the whole district (control rates not reported). The higher cancer rates were found for those who lived closer to the dump site (Zhang and Li 1987). Attempts to abate the pollution from chromium(VI) introduced in 1967 also resulted in additional pollution from sulfate and chloride compounds. It was not possible to estimate exposure levels based on the description of the pollution process. Exposure of this population was mainly due to chromium(VI) in drinking water, although air exposure cannot be ruled out.

The studies in workers exposed to chromium compounds clearly indicate that occupational exposure to chromium(VI) is associated with an increased risk of respiratory cancer. Using data from the Mancuso (1975) study and a dose-response model that is linear at low doses, EPA (1984a) derived a unit risk estimate of  $1.2 \times 10^{-2}$  for exposure to air containing  $1 \mu\text{g chromium(VI)/m}^3$  (or potency of  $1.2 \times 10^{-2} [\mu\text{g/m}^3]^{-1}$ ) (IRIS 2008).

Chronic inhalation studies provide evidence that chromium(VI) is carcinogenic in animals. Mice exposed to  $4.3 \text{ mg chromium(VI)/m}^3$  as calcium chromate had a 2.8-fold greater incidence of lung tumors, compared to controls (Nettesheim et al. 1971). Lung tumors were observed in 3/19 rats exposed to  $0.1 \text{ mg chromium(VI)/m}^3$  as sodium dichromate for 18 months, followed by 12 months of observation. The tumors included two adenomas and one adenocarcinoma. No lung tumors were observed in 37 controls or the rats exposed to  $\leq 0.05 \text{ mg chromium(VI)/m}^3$  (Glaser et al. 1986, 1988). The increased incidence of lung tumors in the treated rats was significant by the Fisher Exact Test ( $p=0.03$ ) performed by Syracuse Research Corporation.

Several chronic animal studies reported no carcinogenic effects in rats, rabbits, or guinea pigs exposed to  $\approx 1.6 \text{ mg chromium(VI)/m}^3$  as potassium dichromate or chromium dust 4 hours/day, 5 days/week (Baetjer et al. 1959b; Steffee and Baetjer 1965).

Rats exposed to  $\leq 15.5 \text{ mg chromium(IV)/m}^3$  as chromium dioxide for 2 years had no statistically significant increased incidence of tumors (Lee et al. 1989).

## 3. HEALTH EFFECTS

The Cancer Effect Levels (CELs) are recorded in Table 3-1 and plotted in Figure 3-1.

### 3.2.2 Oral Exposure

#### 3.2.2.1 Death

Cases of accidental or intentional ingestion of chromium that have resulted in death have been reported in the past and continue to be reported even in more recent literature. In many cases, the amount of ingested chromium was unknown, but the case reports provide information on the sequelae leading to death. For example, a 22-month-old boy died 18.5 hours after ingesting an unknown amount of a sodium dichromate solution despite gastric lavage, continual attempts to resuscitate him from cardiopulmonary arrest, and other treatments at a hospital. Autopsy revealed generalized edema, pulmonary edema, severe bronchitis, acute bronchopneumonia, early hypoxic changes in the myocardium, liver congestion, and necrosis of the liver, renal tubules, and gastrointestinal tract (Ellis et al. 1982). Another case report of a 1-year-old girl who died after ingesting an unknown amount of ammonium dichromate reported severe dehydration, caustic burns in the mouth and pharynx, blood in the vomitus, diarrhea, irregular respiration, and labored breathing. The ultimate cause of death was shock and hemorrhage into the small intestine (Reichelderfer 1968).

Several reports were available in which the amount of ingested chromium (VI) compound could be estimated. A 17-year-old male died after ingesting 29 mg chromium(VI)/kg as potassium dichromate in a suicide. Despite attempts to save his life, he died 14 hours after ingestion from respiratory distress with severe hemorrhages. Caustic burns in the stomach and duodenum and gastrointestinal hemorrhage were also found (Clochesy 1984; Iserson et al. 1983). A 35-year-old female died after ingesting approximately 25 g chromium(VI) (357 mg chromium(VI)/kg assuming 70 kg body weight) as chromic acid in a suicide (Loubieres et al. 1999). The patient died of multiple organ failure. Terminal laboratory analysis and autopsy revealed metabolic acidosis, gastrointestinal hemorrhage and necrosis, fatty degeneration of the liver, and acute renal failure and necrosis.

A few reports have described death of humans after ingesting lower doses of chromium(VI). In one case, a 14-year-old boy died 8 days after admission to the hospital following ingestion of 7.5 mg chromium(VI)/kg as potassium dichromate from his chemistry set. Death was preceded by gastrointestinal ulceration and severe liver and kidney damage (Kaufman et al. 1970). In another case, a

## 3. HEALTH EFFECTS

44-year-old man died of severe gastrointestinal hemorrhage 1 month after ingesting 4.1 mg chromium(VI)/kg as chromic acid (Saryan and Reedy 1988).

Acute oral LD<sub>50</sub> values in rats exposed to chromium(III) or chromium(VI) compounds varied with the compound and the sex of the rat. LD<sub>50</sub> values for chromium(VI) compounds (sodium chromate, sodium dichromate, potassium dichromate, and ammonium dichromate) range from 13 to 19 mg chromium(VI)/kg in female rats and from 21 to 28 mg chromium(VI)/kg in male rats (Gad et al. 1986). LD<sub>50</sub> values of 108 (female rats) and 249 (male rats) mg chromium(VI)/kg for calcium chromate were reported by Vernot et al. (1977). The LD<sub>50</sub> values for chromium trioxide were 25 and 29 mg chromium(VI)/kg for female and male rats, respectively (American Chrome and Chemicals 1989). An LD<sub>50</sub> of 811 mg chromium(VI)/kg as strontium chromate was reported for male rats (Shubochkin and Pokhodzie 1980). Twenty percent mortality was observed when female Swiss Albino mice were exposed to potassium dichromate(VI) in drinking water at a dose of 169 mg chromium(VI)/kg/day (Junaid et al. 1996a). Similar exposure to a dose level of 89 mg chromium(VI)/kg/day resulted in 15% mortality among female rats of the Druckrey strain (Kanojia et al. 1998). The disparity between this dose and the LD<sub>50</sub> identified in the Gad et al. (1986) study may be due to the route of administration, drinking water versus gavage. Chromium(III) compounds are less toxic than chromium(VI) compounds, with LD<sub>50</sub> values in rats of 2,365 mg chromium(III)/kg as chromium acetate (Smyth et al. 1969) and 183 and 200 mg chromium(III)/kg as chromium nitrate in female and male rats, respectively (Vernot et al. 1977). The lower toxicity of chromium(III) acetate compared with chromium(III) nitrate may be related to solubility; chromium(III) acetate is less soluble in water than is chromium(III) nitrate. Signs of toxicity included hypoactivity, lacrimation, mydriasis, diarrhea, and change in body weight. Treatment with the chromium(III) dietary supplement chromium nicotinate of male and female rats resulted in no mortality at doses up to >621.6 mg/kg/day (Shara et al. 2005). The LD<sub>50</sub> values for chromium(VI) or chromium(III) compounds indicate that female rats are slightly more sensitive to the toxic effects of chromium(VI) or chromium(III) than male rats. LD<sub>50</sub> values in rats are recorded in Table 3-3 and plotted in Figure 3-3 for chromium(VI) and recorded in Table 3-4 and plotted in Figure 3-4 for chromium(III).

Intermediate and chronic exposure of rats and mice to chromium(III) or chromium(VI) compounds did not decrease survival. Survival was not affected in rats and mice exposed to chromium(VI) as sodium dichromate dihydrate in drinking water at doses up to 20.9 and 27.9 mg chromium(VI)/kg/day, respectively, for 3 months (NTP 2007) or at doses up to 7.0 and 8.7 mg chromium(VI)/kg/day,

Table 3-3 Levels of Significant Exposure to Chromium VI - Oral

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
<b>ACUTE EXPOSURE</b>								
<b>Death</b>								
1	Human	once (IN)				29 M (death)	Clochesy 1984; Iserson et al. 1983 K2Cr2O7 (VI)	17-year-old, 60 kg boy ingested 5 g potassium dichromate [1,750 mg Cr(VI)]; dose = 29 mg Cr(VI)/kg.
2	Human	once (IN)				7.5 M (death)	Kaufman et al. 1970 K2Cr2O7 (VI)	14-year-old boy ingested 1.5 g potassium dichromate [0.53 mg Cr(VI)]. Assuming 70 kg body weight, dose = 7.5 mg Cr(VI)/kg.
3	Human	once (IN)				357 F (death)	Loubieres et al. 1999 CrO3 (VI)	35-year-old woman ingested chromic acid solution containing 25 g Cr(VI). Assuming 70 kg body weight, dose = 357 mg Cr(VI)/kg.
4	Human	once (IN)				4.1 M	Saryan and Reedy 1988 CrO3 (VI)	44-year-old man ingested ~2.8g Cr(VI) as chromium trioxide; ~4.1 mg Cr(VI)/kg body weight.
5	Rat (Fischer- 344) (G)	once				29 M (LD50) 25 F (LD50)	American Chrome and Chemicals 1989 CrO3 (VI)	





































































































## 3. HEALTH EFFECTS

respectively, for 2 years (NTP 2008a). Mortality was not increased in rats fed 2,040 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 2 years (Ivankovic and Preussmann 1975) or in rats and mice fed up to 313 and 781 mg chromium(III)/kg/day, respectively, as chromium picolinate in the diet for 2 years (NTP 2008b).

**3.2.2.2 Systemic Effects**

The systemic effects of oral exposure to chromium(III) and chromium(VI) compounds are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3 for chromium(VI) and recorded in Table 3-4 and plotted in Figure 3-4 for chromium(III).

**Respiratory Effects.** Case reports of humans who died after ingesting chromium(VI) compounds have described respiratory effects as part of the sequelae leading to death. A 22-month-old boy who ingested an unknown amount of sodium dichromate died of cardiopulmonary arrest. Autopsy revealed pleural effusion, pulmonary edema, severe bronchitis, and acute bronchopneumonia (Ellis et al. 1982). Autopsy of a 17-year-old male who committed suicide by ingesting 29 mg chromium(VI)/kg as potassium dichromate revealed congested lungs with blood-tinged bilateral pleural effusions (Clochesy 1984; Iserson et al. 1983). Respiratory effects were not reported at nonlethal doses. No information was identified on respiratory effects in humans after oral exposure to chromium(III) compounds.

No studies were identified regarding respiratory function in animals after oral exposure to chromium(VI) or chromium(III) compounds. The histopathology of lung and nasal tissue has been evaluated in rats and mice exposed to oral chromium(VI) (as sodium dichromate dihydrate) and chromium(III) (as chromium nicotinate, chromium oxide and chromium picolinate) for durations of 3 months to 2 years, with no abnormalities observed (Ivankovic and Preussmann 1975; NTP 2007, 2008a, 2008b; Shara et al. 2005, 2007). For chromium(VI) compounds, the highest doses tested for intermediate and chronic exposure durations were 27.9 and 8.7 chromium(VI)/kg/day, respectively, as sodium dichromate dihydrate in drinking water (NTP 2007, 2008a). For chromium(III) compounds, the highest doses tested for intermediate and chronic exposure durations were 1,806 and 2,040 mg chromium(III)/kg/day, respectively, as chromium oxide in the diet 5 days/week (Ivankovic and Preussmann 1975).

**Cardiovascular Effects.** Case reports of humans who died after ingesting chromium(VI) compounds have described cardiovascular effects as part of the sequelae leading to death. A 22-month-old boy who

## 3. HEALTH EFFECTS

ingested an unknown amount of sodium dichromate died of cardiopulmonary arrest. Autopsy revealed early hypoxic changes in the myocardium (Ellis et al. 1982). In another case, cardiac output, heart rate, and blood pressure dropped progressively during treatment in the hospital of a 17-year-old male who had ingested 29 mg chromium(VI)/kg as potassium dichromate. He died of cardiac arrest. Autopsy revealed hemorrhages in the anterior papillary muscle of the left ventricle (Clochesy 1984; Iserson et al. 1983). Cardiovascular effects have not been reported at nonlethal doses. No information was identified on cardiovascular effects in humans after oral exposure to chromium(III) compounds.

No studies were located regarding effects on cardiovascular function in animals after oral exposure to chromium(VI) compounds. Histopathological examination of the heart has been evaluated in rats and mice exposed to oral chromium(VI) (as sodium dichromate dihydrate and sodium acetate) and chromium(III) (as chromium nicotinate, chromium oxide and chromium picolinate) for durations of 3 months to 2 years, with no abnormalities observed (Ivankovic and Preussmann 1975; NTP 2007, 2008a, 2008b; Schroeder et al. 1965; Shara et al. 2005, 2007). For chromium(VI) compounds, the highest doses tested for intermediate and chronic exposure durations were 27.9 and 8.7 chromium(VI)/kg/day, respectively, as sodium dichromate dihydrate in drinking water (NTP 2007, 2008a). For chromium(III) compounds, the highest doses tested for intermediate and chronic exposure durations were 1,806 and 2,040 mg chromium(III)/kg/day, respectively, as chromium oxide in the diet 5 days/week (Ivankovic and Preussmann 1975). None of these studies assessed cardiovascular end points such as blood pressure or electrocardiograms.

**Gastrointestinal Effects.** Cases of gastrointestinal effects in humans after oral exposure to chromium(VI) compounds have been reported. In one study, a 14-year-old boy who died after ingesting 7.5 mg chromium(VI)/kg as potassium dichromate experienced abdominal pain and vomiting before death. Autopsy revealed gastrointestinal ulceration (Kaufman et al. 1970). In another study, a 44-year-old man died of gastrointestinal hemorrhage after ingesting 4.1 mg chromium(VI)/kg as chromic acid solution (Saryan and Reedy 1988). Gastrointestinal hemorrhage and extensive necrosis of all digestive mucous membranes were also observed on autopsy of a 35-year-old woman who died following ingestion of 357 mg chromium(VI)/kg as chromic acid (Loubieres et al. 1999). Gastrointestinal burns and hemorrhage have also been described as contributing to the cause of death of infants who ingested unknown amounts of sodium dichromate (Ellis et al. 1982) or ammonium dichromate (Reichelderfer 1968) and a 17-year-old male who ingested ~29 mg chromium(VI)/kg as potassium dichromate (Clochesy 1984; Iserson et al. 1983).

## 3. HEALTH EFFECTS

Some chromium(VI) compounds, such as potassium dichromate and chromium trioxide, are caustic and irritating to mucosal tissue. A 25-year-old woman who drank a solution containing potassium dichromate experienced abdominal pain and vomited (Goldman and Karotkin 1935). Two people who ate oatmeal contaminated with potassium dichromate became suddenly ill with severe abdominal pain and vomiting, followed by diarrhea (Partington 1950). Acute gastritis developed in a chrome plating worker who had accidentally swallowed an unreported volume of a plating fluid containing 300 g chromium trioxide/L. He was treated by hemodialysis, which saved his life (Fristedt et al. 1965). Nausea, hemetemesis, and bloody diarrhea were reported in a 24-year-old woman who ingested ammonium dichromate in a suicide attempt (Hasan 2007).

Ingestion of chromium compounds as a result of exposure at the workplace has occasionally produced gastrointestinal effects. In a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes, in addition to symptoms of labored breathing, dizziness, headache, and weakness from breathing the fumes during work, workers experienced nausea and vomiting upon eating on the premises (Lieberman 1941). Gastrointestinal effects were also reported in an epidemiology study of 97 workers in a chromate plant exposed to dust containing both chromium(III) and chromium(VI) compounds. Blocked nasal passages, as a result of working in the dust laden atmosphere, forced the individuals to breathe through their mouths, thereby probably ingesting some of the chromium dust. A 10.3% incidence of gastric ulcer formation and a 6.1% incidence of hypertrophic gastritis was reported. Epigastric and substernal pain were also reported in the chromate production workers (Mancuso 1951). Gastric mucosa irritation resulting in duodenal ulcer, possibly as a result of mouth breathing, has also been reported in other studies of chromate production workers (Sassi 1956; Sterekhova et al. 1978). Subjective symptoms of stomach pain, duodenal ulcers, gastritis, stomach cramps, and indigestion were reported by workers exposed to a mean concentration of 0.004 mg chromium(VI)/m<sup>3</sup> in an electroplating facility where zinc, cadmium, nickel, tin, and chromium plating were carried out (Lucas and Kramkowski 1975). An otolaryngological examination of 77 employees of eight chromium electroplating facilities in Czechoslovakia, where the mean level in the breathing zone above the plating baths was 0.414 mg chromium(VI)/m<sup>3</sup>, revealed 12 cases of chronic tonsillitis, 5 cases of chronic pharyngitis, and 32 cases of atrophic changes in the left larynx (Hanslian et al. 1967). These effects were probably also due to exposure via mouth breathing.

In a cross-sectional study conducted in 1965 of 155 villagers whose well water contained chromium(VI)/L as a result of pollution from an alloy plant in the People's Republic of China, associations were found between drinking the contaminated water and oral ulcer, diarrhea, abdominal

## 3. HEALTH EFFECTS

pain, indigestion, and vomiting. The alloy plant began chromium smelting in 1961 and began regular production in 1965. Similar results were found in two similar studies in other villages, but further details were not provided (Zhang and Li 1987). The highest concentration of chromium(VI) detected during sampling was 20 mg chromium(VI)/L, equivalent to a dose of 0.57 mg chromium(VI)/kg/day based on a default reference water consumption rate and body weight value of 2 L/day and 70 kg, respectively (note that these values may not be appropriate for the Chinese study population). However, exposure estimates for this population are uncertain and it is likely that exposure levels in many cases were to concentrations less than 20 mg chromium(VI)/L. At least some residents obtained drinking water from alternative sources (Sedman et al. 2006) and exposure may have been self-limiting due to lack of palatability of water (Beaumont et al. 2008). Thus, exposure levels associated with adverse effects are not well characterized.

No information was identified on gastrointestinal effects in humans after oral exposure to chromium(III) compounds.

Oral exposure of animals to chromium(VI), but not chromium(III), compounds results in irritation and histopathological changes to tissues of the gastrointestinal tract. Gastrointestinal hemorrhage was observed in rats given a lethal gavage dose of potassium dichromate (130 mg chromium(VI)/kg) (Samitz 1970). Histopathological changes were observed in rats and mice exposed to chromium(VI) as sodium dichromate dihydrate in drinking water for 3 months (NTP 2007) or 2 years (NTP 2008a). Following exposure for 3 months, duodenal histiocytic infiltration of the duodenum was observed in male and female F344/N rats exposed at  $\geq 3.5$  mg chromium(VI)/kg/day. At the highest daily dose (20.9 mg chromium(VI)/kg/day), ulcer and epithelial hyperplasia and metaplasia of the glandular stomach were observed. Epithelial hyperplasia and histiocytic cellular infiltration of the duodenum was observed at  $\geq 3.1$  and  $\geq 5.2$  mg chromium(VI)/kg/day, respectively, in male and female B6C3F1 mice. Similar nonneoplastic lesions of the duodenum were also reported in the 3-month comparative study in male B6C3F1, BALB/c, and C57BL/6 mice, with epithelial hyperplasia at  $\geq 2.8$  mg chromium(VI)/kg/day in B6C3F1 and BALB/c strains and  $\geq 5.2$  in the C57BL/6 strain, and histiocytic cellular infiltration at  $\geq 2.8$  mg chromium(VI)/kg/day in B6C3F1 and C57BL/6 strains and  $\geq 5.2$  mg chromium(VI)/kg/day in the BALB/c strain. After exposure for 2 years, duodenal histiocytic infiltration was observed in male and female rats exposed at 0.77 and 2.4 mg chromium(VI)/kg/day, respectively; in mice, duodenal epithelial hyperplasia was observed at 0.38 mg chromium(VI)/kg/day for 2 years and histiocytic cellular infiltration of the duodenum was also observed in males at 2.4 mg chromium(VI)/kg/day and females at 3.1 mg chromium(VI)/kg/day. In the 2-year study (NTP 2008a), neoplasms of the squamous epithelium of the

## 3. HEALTH EFFECTS

oral mucosa and tongue were observed in rats and of the small intestine (duodenum, jejunum and ileum) were observed in mice; these findings are discussed in Section 3.2.2.7 (Oral Exposure, Cancer). In female mice exposed to 0.38 mg chromium(VI)/kg/day and male mice exposed to 2.4 mg chromium(VI)/kg/day for 2 years, cytoplasmic alteration of the pancreas (depletion of cytoplasm zymogen granules) was observed; NTP stated that the biological significance of this finding was uncertain (NTP 2008a). In contrast to the findings in the NTP 3-month and 2-year drinking water studies of sodium dichromate dihydrate (NTP 2007, 2008a), no histopathological changes to the gastrointestinal tract were observed in BALB/c mice exposed to dietary potassium dichromate at doses up to 36.7 chromium(VI)/kg/day in a multigeneration continuous breeding study (NTP 1997). Differences in results of these studies could be attributed to difference in the exposure media (water versus feed). Data from the 2-year drinking water study on sodium dichromate dihydrate in mice (NTP 2008a) were used to develop the chronic-duration oral MRL for chromium(VI) compounds. The BMDL<sub>10</sub> value of 0.09 mg chromium(VI)/kg/day for diffuse epithelial hyperplasia of the duodenum in female mice was used to calculate an oral MRL of 0.001 mg chromium(VI)/kg/day for chronic-duration exposure to chromium(VI) a compounds as described in the footnote of Table 3-3.

No histopathological changes to the stomach or small intestine were observed in mice and rats exposed to oral chromium(III) (as chromium nicotinate, chromium oxide, and chromium picolinate) for 3 months or 2 years (Ivankovic and Preussmann 1975; NTP 2008b; Rhodes et al. 2005; Shara et al. 2005, 2007). The highest doses of chromium(III) tested were 1,415 mg chromium(III)/kg/day as chromium picolinate in the diet for 3 months (NTP 2008b; Rhodes et al. 2005) and 2,040 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 2 years (Ivankovic and Preussmann 1975).

**Hematological Effects.** Cases of hematological effects have been reported in humans after the ingestion of lethal or sublethal doses of chromium(VI) compounds. In a case of an 18-year-old woman who ingested a few grams of potassium dichromate, decreased hemoglobin content and hematocrit, and increased total white blood cell counts, reticulocyte counts, and plasma hemoglobin were found 4 days after ingestion. These effects were indicative of intravascular hemolysis (Sharma et al. 1978). A 25-year-old woman who drank a solution containing potassium dichromate had a clinically significant increase in leukocytes due to a rise in polymorphonuclear cells (Goldman and Karotkin 1935). In another study, a 44-year-old man had decreased hemoglobin levels 9 days after ingestion of 4.1 mg chromium(VI)/kg as chromic acid solution that probably resulted from gastrointestinal hemorrhage (Saryan and Reedy 1988). Inhibition of blood coagulation was described in a case of a 17-year-old male who died after ingesting ~29 mg chromium(VI)/kg as potassium dichromate (Clochesy 1984; Iserson et al. 1983). Anemia

## 3. HEALTH EFFECTS

following severe hemorrhaging developed in a chrome plating worker who had accidentally swallowed an unreported volume of a plating fluid containing 300 g chromium trioxide/L. He was treated by hemodialysis, which saved his life (Fristedt et al. 1965).

In a cross-sectional study conducted in 1965 of 155 villagers whose well water contained 20 mg chromium(VI)/L as a result of pollution from an alloy plant in the People's Republic of China, associations were found between drinking the contaminated water and leukocytosis and immature neutrophils. The alloy plant began chromium smelting in 1961 and began regular production in 1965. Similar results were found in two similar studies in other villages, but further details were not provided (Zhang and Li 1987). The highest concentration of chromium(VI) detected during sampling was 20 mg chromium(VI)/L, equivalent to a dose of 0.57 mg chromium(VI)/kg/day. However, exposure estimates for this population are uncertain and it is likely that exposure levels in many cases were to concentrations <20 mg chromium(VI)/L. At least some residents obtained drinking water from alternative sources (Sedman et al. 2006) and exposure may have been self-limiting due to lack of palatability of water at higher concentrations (Beaumont et al. 2008). Thus, exposure levels associated with adverse effects are not well characterized.

No reliable information was identified on hematological effects in humans of oral exposure to chromium(III) compounds.

Microcytic, hypochromic anemia, characterized by decreased mean cell volume (MCV), mean corpuscular hemoglobin (MCH), hematocrit (Hct), and hemoglobin (Hgb), was observed in F344/N rats and B6C3F1 mice exposed to chromium(III) compounds in drinking water for exposure durations ranging from 4 days to 1 year (NTP 2007, 2008a). Severity was dose-dependent. Maximum effects were observed after approximately 3 weeks of exposure; with increasing exposures durations (e.g., 14 weeks to 1 year), effects were less pronounced, presumably due to compensatory hematopoietic responses. In general, effects were more severe in rats than mice. Following acute exposure of male rats to sodium dichromate dihydrate in drinking water for 4 days, a slight, but statistically significant decrease (2.1%) in MCH was observed at 2.7 mg chromium(VI)/kg/day, but not at 0.7 mg chromium(VI)/kg/day. With increasing doses (7.4 mg chromium(VI)/kg/day and greater), additional decreases in MCH and decreased MCV were observed (NTP 2008a). Similar effects were observed in male and female rats exposed for 5 days, with effects observed at 4.0 and 4.1 chromium(VI)/kg/day, respectively (NTP 2007); a NOAEL was not established.

## 3. HEALTH EFFECTS

More severe microcytic, hypochromic anemia occurred in rats and mice following exposure to sodium dichromate dihydrate in drinking water for 22 or 23 days (NTP 2007, 2008a). Decreased Hct (6.1%), Hgb (8.4%), MCV (7.7%), and MCH (10.6%) occurred in male rats exposed for 22 days to 0.77 mg chromium(VI)/kg/day, with decreases exhibiting dose-dependence; effects were not observed at 0.21 mg chromium(VI)/kg/day (NTP 2008a). Similar hematological effects were observed in male and female rats exposed to 1.7 mg chromium(VI)/kg/day for 23 days (NTP 2007). In female mice exposed to 22 days, slight, but significant decreases in MCV (2.0%) and MCH (1.2%) were observed at 0.38 mg chromium(VI)/kg/day, with more severe effects at higher doses (NTP 2008a). After exposure for 3 months to 1 year, microcytic, hypochromic anemia in rats and mice was less severe than that observed after 22 or 23 days (NTP 2007, 2008a). For example in male rats exposed for 22 days, decreases in Hct (6.1%), Hgb (8.4%), MCV (7.7%), and MCH (10.6%) were observed at 0.77 mg chromium(VI)/kg/day, whereas after exposure to 0.77 mg chromium(VI)/kg/day for 1 year, decreased MCH (2.4%), but not MCV, Hct, or Hgb, were observed (NTP 2008a). Similar decreases in severity was also observed in female rats and in male and female mice exposed for 1 year compared to 22 days (NTP 2008a). In contrast, routine hematological examination revealed no changes in Sprague-Dawley rats exposed to 3.6 mg chromium(VI)/kg/day as potassium chromate in the drinking water for 1 year (MacKenzie et al. 1958); however, data on hematological parameters or statistical analyses were not presented in the report. Data from the 22-day evaluation in the 2-year NTP (2008a) drinking water study on sodium dichromate dihydrate in rats were used to develop the intermediate-duration oral MRL for chromium(VI) compounds. Because several hematological parameters are used to define the clinical picture of anemia, the intermediate-duration oral MRL was based on the average BMDL<sub>2sd</sub> value (e.g., the average of BMDL<sub>2sd</sub> values for Hgb, MCV, and MCH; BMD models did not provide adequate fit for hematocrit) of 0.52 mg chromium(VI)/kg/day, as described in the footnote of Table 3-3.

In feeding studies of potassium dichromate in Sprague-Dawley rats and BALB/c mice, slight microcytic hypochromic anemia, characterized by slightly reduced MCV and MCH values was observed (NTP 1996a, 1996b, 1997). In rats and mice fed potassium dichromate for 9 weeks, MCV and MCH values, were decreased at the highest concentration only, which was equivalent to 8.4 and 9.8 mg chromium(VI)/kg/day in male and female rats, respectively (NTP 1996b), and 32.2 and 48 mg chromium(VI)/kg/day in male and female mice, respectively (NTP 1996a). These effects did not occur at lower dietary concentrations equivalent to  $\leq 2.1$  or  $\leq 2.45$  mg chromium(VI)/kg/day for male and female rats, respectively, or to  $\leq 7.35$  or  $\leq 12$  mg chromium(VI)/day for male and female mice, respectively. In a multigeneration study of mice given potassium dichromate in the diet, F<sub>1</sub> males had decreased MCVs at dietary concentrations equivalent to 16 and 36.7 mg chromium(VI)/kg/day and decreased MCH values at



## 3. HEALTH EFFECTS

36.7 mg chromium(VI)/kg/day (NTP 1997). F<sub>1</sub> females had dose-related decreased MCV at concentrations equivalent to  $\geq 7.8$  mg chromium(VI)/kg/day. Since 7.8 mg chromium(VI)/kg/day was the lowest dose in the study, a no effect level was not identified. Compared to results of the drinking water studies on sodium dichromate dihydrate (NTP 2007, 2008a), hematological effects observed in the dietary studies on potassium dichromate (NTP 1996a, 1996b, 1997) occurred at higher daily doses. Differences may be related to differences in the exposure media (feed versus drinking water).

No hematological effects were observed in animals after oral exposure to chromium(III) compounds for exposure durations ranging from acute to chronic. Exposure of F344/N rats to chromium picolinate in the diet for 3 days at doses up to 506 mg chromium(III)/kg/day did not produce hematological effects (NTP 2008b). For intermediate duration exposure, no hematological effects were observed in rats exposed to chromic oxide in the diet at doses up to 1,806 mg chromium(III)/kg/day for 3 months (Ivankovic and Preussmann 1975), in rats and mice exposed to chromium picolinate in the diet at 506 and 1,415 mg chromium(III)/kg/day, respectively, for 3 months (NTP 2008b), or in rats chromium nicotinate in the diet at 1.5 or 0.25 mg chromium(III)/kg/day for 3 months or 38 weeks, respectively (Shara et al. 2005). For chronic exposure durations, no hematological abnormalities were found in rats exposed to 3.6 mg chromium(III)/kg/day as chromium trichloride in the drinking water for 1 year (MacKenzie et al. 1958), or in rats exposed to 0.25 mg chromium(III)/kg/day as chromium nicotinate for 2 years (Shara et al. 2007).

**Musculoskeletal Effects.** No information regarding musculoskeletal effects in humans exposed to oral chromium (VI) compounds was identified. The development of rhabdomyolysis was reported in a 24-year-old woman who ingested a dietary supplement containing chromium(III) picolinate (Martin and Fuller 1998). Over a 48-hour period, the patient ingested 1,200  $\mu\text{g}$  of chromium(III) picolinate, equivalent to 148.8  $\mu\text{g}$  of chromium(III) or 2.2  $\mu\text{g}$  of chromium(III)/kg body weight (based on a reported body weight of 67 kg) over a 48-hour period. Upon evaluation 4 days after initially ingesting the dietary supplement, she reported muscle pain on palpation and had muscular hypertrophy and elevated serum creatine kinase, although no myoglobin was detected in urine. In addition to chromium(III) picolinate, the dietary supplements contained numerous other substances.

Increases in serum creatine kinase (CK) activity were observed in F344/N rats following acute and intermediate exposure to sodium dichromate dihydrate in drinking water (NTP 2007). After exposure for 5 days, serum CK activity was increased in males by 31% at 31.8 mg chromium(VI)/kg/day and in females by 46% at 16.4 mg chromium(VI)/kg/day; after exposure for 13 weeks, serum CK activity was

## 3. HEALTH EFFECTS

increased by 70% and 50% in males and females, respectively, at 5.9 mg chromium(VI)/kg/day. Since serum CK activity increased with dose, NTP (2007) suggested that findings were consistent with muscle injury. After exposure of rats for 12 months to 2.4 mg chromium(VI)/kg/day as sodium dichromate dihydrate in drinking water, serum CK activity was increased by 64% (NTP 2008a). No information regarding musculoskeletal effects in animals exposed to oral chromium(III) compounds was identified.

**Hepatic Effects.** Effects on the liver have been described in case reports of humans who had ingested chromium(VI) compounds. Liver damage, evidenced by the development of jaundice, increased bilirubin, and increased serum lactic dehydrogenase, was described in a case of a chrome plating worker who had accidentally swallowed an unreported volume of a plating fluid containing 300 g chromium trioxide/L (Fristedt et al. 1965). In a 14-year-old boy who died after ingesting 7.5 mg chromium(VI)/kg as potassium dichromate, high levels of the liver enzymes, glutamic-oxaloacetic transaminase (aspartate aminotransferase) and glutamic-pyruvic transaminase (alanine aminotransferase), were found in the serum 24 hours after ingestion. Upon postmortem examination, the liver had marked necrosis (Kaufman et al. 1970). Fatty degeneration of the liver was observed on autopsy of a 35-year-old female who died after ingesting approximately 257 mg chromium(VI)/kg (assuming a 70-kg body weight) as chromic acid in a suicide (Loubieres et al. 1999).

Effects on the liver of rats and mice exposed to oral chromium(VI) compounds for acute, intermediate and chronic durations have been detected by biochemical and histochemical techniques. In male and female F344/N rats exposed to 4.0 and 4.1 mg chromium(VI)/kg/day, respectively, as disodium dichromate in drinking water for 5 days, serum alanine aminotransferase (ALT) activity was increased by 15 and 30%, respectively (NTP 2007). After 14 weeks of exposure, serum ALT activity was increased by 14% in male rats and by 30% in female rats and serum sorbital dehydrogenase (SDH) activity was increased by 77% in male rats and 359% in female rats at 1.7 mg chromium(VI)/kg/day (NTP 2007). In females, morphological changes to the liver included cellular histiocyte infiltration and chronic focal inflammation at doses of 3.5 and 20.9 mg chromium(VI)/kg/day, respectively; no morphological changes were observed in male rats, indicating that female rats may be more sensitive than males. However, similar exposure to B6C3F1 mice to 27.9 mg chromium(VI)/kg/day for 14 weeks produced no effects on serum liver enzymes or hepatic morphology (NTP 2007). Increased serum ALT and aspartate aminotransferase (AST) activities and hepatic morphological changes (vacuolization, increased sinusoidal space, and necrosis) were observed in rats exposed to 1.3 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 22 weeks (Acharya et al. 2001). Increased serum ALT (253%) and histopathological changes (focal necrosis and degeneration with changes in vascularization) were reported

## 3. HEALTH EFFECTS

in Wistar rats exposed to chromium(VI) (compound not specified) in drinking water for 10 weeks (Rafael et al. 2007). Rats treated by gavage with 13.5 mg chromium(VI)/kg/day as potassium chromate for 20 days had increased accumulations of lipids (Kumar and Rana 1982) and changes and relocalization of liver enzymes (alkaline phosphatase, acid phosphatase, glucose-6-phosphatase, cholinesterase, and lipase) (Kumar et al. 1985), as determined by histochemical means. In another study, no treatment-related histological changes in liver cells were observed in groups of Sprague-Dawley rats containing 24 males and 48 females that were exposed to chromium(VI) as potassium dichromate in the diet for 9 weeks followed by a recovery period of 8 weeks (NTP 1996b). Average daily ingestion of chromium(VI) for males was 1, 3, 6, and 24 mg/kg/day and 1, 3, 7, and 28 mg/kg/day for females. Although no indication of hepatic effects was found in mice exposed to  $\leq 36.7$  mg/kg/day in a multigeneration feeding study (NTP 1997), some indication of liver toxicity was found in a 9-week feeding study in BALB/c mice exposed to 1.1, 3.5, 7.4, and 32 mg chromium(VI)/kg/day for males and 1.8, 5.6, 12, and 48 mg chromium(VI)/kg/day for females (NTP 1996a). Hepatocyte cytoplasmic vacuolization occurred in 1/6 males at 3.5 mg/kg/day, 2/5 males at 7.4 mg/kg/day, and 2/6 males at 32 mg/kg/day, and in 1/12 control females, 0/12 females at 1.8 mg/kg/day, 3/12 females at 5.6 mg/kg/day, 2/12 females at 12 mg/kg/day, and 4/12 females at 48 mg/kg/day. The vacuoles were small, clear, and well demarcated, which is suggestive of lipid accumulation. The small number of animals and lack of a clear dose-response preclude a definitive conclusion as to whether this effect was toxicologically significant. For chronic exposure durations, adverse liver effects have been observed in F344/N rats and B6C3F1 mice exposed to chromium(VI) as sodium chromate dihydrate in drinking water (NTP 2008a). In male rats exposed for 1 year to 0.77 mg chromium(VI)/kg/day, serum ALT activity was increased by 156%. After exposure for 2 years, histopathological examination of the liver showed the following morphological changes, with females of both species appearing more sensitive than males: chronic inflammation (2.1 mg chromium(VI)/kg/day), histiocytic cellular infiltration (5.9 mg chromium(VI)/kg/day) and basophilic foci (0.77 mg chromium(VI)/kg/day) in male rats; chronic inflammation (0.24 mg chromium(VI)/kg/day), histiocytic cellular infiltration (0.94 mg chromium(VI)/kg/day) and fatty change (0.94 mg chromium(VI)/kg/day) in female rats; clear cell and eosinophilic foci in male mice (5.9 mg chromium(VI)/kg/day); and histiocytic cellular infiltration (0.38 mg chromium(VI)/kg/day) and chronic inflammation (3.1 mg chromium(VI)/kg/day) in female mice (NTP 2008a). No morphological changes, however, were detected in the livers of rats exposed to 3.6 mg chromium(VI)/kg/day as potassium chromate in the drinking water for 1 year (MacKenzie et al. 1958).

No evidence of liver damage has been observed in rats and mice treated with oral chromium(III) compounds for intermediate and chronic exposure durations, based on histopathological examination of

## 3. HEALTH EFFECTS

the liver. For intermediate-duration exposures, no morphological changes were observed in rats exposed to 1,806 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 90 days (Ivankovic and Preussmann 1975), rats exposed to 9 mg chromium(III)/kg/day as chromium chloride or chromium picolinate in the diet for 20 weeks (Anderson et al. 1997b), rats exposed to 506 mg chromium(III)/kg/day and mice exposed to 1,415 mg chromium(III)/kg/day as chromium picolinate in the diet for 14 weeks (NTP 2008b; Rhodes et al. 2005), or rats exposed to chromium nicotinate in the diet at 1.5 mg chromium(III)/kg/day for 14 weeks or 0.25 mg chromium(III)/kg/day as chromium nicotinate for 38 weeks (Shara et al. 2005, 2007). For chronic-duration exposures, histological examination revealed no morphological changes in the livers of rats exposed to chromium oxide in the diet 5 days/week at 2,040 mg chromium(III)/kg/day for 2 years (Ivankovic and Preussmann 1975), rats exposed to 3.6 mg chromium(III)/kg/day as chromium trichloride in the drinking water for 1 year (MacKenzie et al. 1958), of rats exposed to 513 mg chromium(III)/kg/day and mice exposed to 781 mg chromium(III)/kg/day as chromium picolinate in the diet for 2 years (NTP 2008b), rats exposed to 0.25 mg chromium(III)/kg/day as chromium nicotinate in the diet for 2 years (Shara et al. 2005, 2007), or rats exposed to 0.46 mg chromium(III)/kg/day as chromium acetate in the drinking water for 2–3 years (Schroeder et al. 1965).

**Renal Effects.** Case studies were located regarding renal effects in humans after oral exposure to chromium(VI) compounds. Acute renal failure, characterized by proteinuria, and hematuria, and followed by anuria, developed in a chrome plating worker who had accidentally swallowed an unreported volume of a plating fluid containing 300 g chromium trioxide/L. He was treated by hemodialysis (Fristedt et al. 1965). Necrosis of renal tubules was found upon autopsy of a 22-month-old boy who died after ingesting an unknown amount of sodium dichromate (Ellis et al. 1982) and of a 17-year-old boy who died after ingesting 29 mg chromium(VI)/kg as potassium dichromate (Clochesy 1984; Iserson et al. 1983). A fatal ingestion of 4.1 mg chromium(VI)/kg as a chromic acid solution in a 44-year-old man resulted in acute tubular necrosis and renal failure (Saryan and Reedy 1988). A 14-year-old boy who ingested 7.5 mg chromium(VI)/kg as potassium dichromate died from renal failure 8 days after he was admitted to the hospital. Upon postmortem examination, the kidneys were pale, enlarged, and necrotic with tubular necrosis and edema (Kaufman et al. 1970). Acute renal failure and necrosis also observed on autopsy of a 35-year-old woman who died following ingestion of 357 mg chromium(VI)/kg as chromic acid (Loubieres et al. 1999). Another case study of an 18-year-old woman who ingested a few grams of potassium dichromate reported proteinuria, oliguria, and destruction of the tubular epithelium of the kidneys. She regained renal function following dialysis (Sharma et al. 1978). Proteinuria and oliguria were also observed after ingestion of potassium dichromate by a 25-year-old woman (Goldman and Karotkin 1935).

## 3. HEALTH EFFECTS

Acute renal failure was reported in a 24-year-old man who ingested the an unknown quantity of a dietary supplement (Arsenal X<sup>®</sup>) containing chromium picolinate daily for 2 weeks (Wani et al. 2006). Serum creatinine was elevated approximately 3 times above the normal range, blood urea nitrogen was elevated slightly above normal range, urinalysis was positive for protein, and renal biopsy showed acute tubular necrosis. The patient developed severe impairment of renal function that required hemodialysis. Renal function improved within 4 weeks of discontinuation of treatment with the supplement. Chemical analysis of the dietary supplement was not conducted and the patient's plasma chromium levels were not obtained. Adverse renal effects were reported in a 49-year-old woman who ingested 600 µg of chromium(III) picolinate (equivalent to 74.4 µg chromium(III)/day or 1.1 µg chromium(III)/kg/day, assuming a body weight of 70 kg) daily for 6 weeks (Wasser et al. 1997). The patient was evaluated approximately 5 months after initiating the 6-week treatment. Serum creatinine levels were approximately 6 times above the normal range, blood urea nitrogen was approximately 4 times above the normal range, and trace amounts of blood were found in the urine. Renal biopsy showed severe chronic active interstitial nephritis. After 2 months of treatment with prednisone, serum creatinine levels were approximately 4 times above the normal range (other values were not reported) Chemical analysis of the dietary supplement was not conducted and the patient's plasma chromium levels were not obtained.

Renal effects have been observed in animals following oral exposure to chromium(VI), but not chromium(III), compounds. Effects on the kidneys of rats exposed to potassium chromate have been detected by biochemical and histochemical techniques. Rats treated by gavage with 13.5 mg chromium(VI)/kg/day for 20 days had increased accumulation of lipids and accumulated triglycerides and phospholipids in different regions of the kidney than controls (Kumar and Rana 1982). Similar treatment of rats also resulted in inhibition of membrane and lysosomal enzymes (alkaline phosphatase, acid phosphatase, glucose-6-phosphatase, and lipase) in the kidneys (Kumar and Rana 1984). Histopathological changes to the kidneys, including vacuolization in glomeruli, degeneration of basement membrane of Bowman's capsule, and renal tubular epithelial degeneration, were observed in Wistar rats exposed to 1.3 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 22 weeks (Acharya et al. 2001). Oliguria and proteinuria were observed in Wistar rats exposed to 100 mg chromium(VI)/kg/day as sodium chromate in drinking water for 28 days (Diaz-Mayans et al. 1986). However, histological examination revealed no morphological changes in the kidneys of rats exposed to 3.6 mg chromium(VI)/kg/day as potassium chromate in drinking water for 1 year (MacKenzie et al. 1958). Results of studies in rats and mice conducted by NTP (1996a, 1996b, 1997, 2007, 2008a) also show no histopathological changes in kidneys following intermediate-or chronic-duration exposure to

## 3. HEALTH EFFECTS

chromium(VI) compounds in the diet or drinking water. The respective highest doses of chromium(VI) tested for intermediate and chronic exposure durations were 48 mg chromium(VI)/kg/day in mice exposed to dietary potassium dichromate for 9 weeks (NTP 1996a) and 8.7 chromium(VI)/kg/day, as sodium dichromate dihydrate in drinking water (NTP 2007, 2008a).

Exposure of mice and rats to chromium(III) compounds (chromium acetate, chromium nicotinate, chromium oxide, chromium picolinate, and chromium trichloride) in food or drinking water for up to 2 years did not result in renal damage, based on histopathological examination of kidneys (Anderson et al. 1997b; Ivankovic and Preussmann 1975; MacKenzie et al. 1958; NTP 2008b; Schroeder et al. 1965; Shara et al. 2005, 2007). The respective highest doses of chromium(III) tested for intermediate and chronic exposure durations were 1,806 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 3 months and 2,040 mg chromium(III)/kg/day chromium oxide in the diet 5 days/week for 2 years (Ivankovic and Preussmann 1975). Renal function was not assessed in these studies.

**Endocrine Effects.** No studies were located regarding endocrine effects in humans following oral exposure to chromium(VI) or (III) compounds. Serum prolactin levels were decreased by 59% in male Wistar rats exposed to 74 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 30 days (Quinteros et al. 2007). Histopathological examination of the endocrine tissues (including adrenal gland, parathyroid, and thyroid) has been evaluated in rats and mice exposed to oral chromium(VI) (as sodium dichromate dihydrate) and chromium(III) (as chromium nicotinate and chromium picolinate) for durations of 3 months to 2 years, with no abnormalities observed (NTP 2007, 2008a, 2008b; Shara et al. 2005, 2007). For chromium(VI) compounds, the highest doses tested for intermediate and chronic exposure durations were 27.9 and 8.7 chromium(VI)/kg/day, respectively, as sodium dichromate dihydrate in drinking water (NTP 2007, 2008a). For chromium(III) compounds, the highest doses tested for intermediate and chronic exposure durations were 1,415 and 781 mg chromium(III)/kg/day, respectively, as chromium picolinate in the diet for 3 months and 2 years, respectively (NTP 2008b; Rhodes et al. 2005). Endocrine function was not assessed in these studies.

**Dermal Effects.** Administration of 0.04 mg chromium(VI)/kg as potassium dichromate in an oral tolerance test exacerbated the dermatitis of a building worker who had a 20-year history of chromium contact dermatitis. A double dose led to dyshidrotic lesions (vesicular eruptions) on the hands (Goitre et al. 1982). Dermatitis in 11 of 31 chromium-sensitive individuals worsened after ingestion of 0.036 mg chromium(VI)/kg as potassium dichromate (Kaaber and Veien 1977). The sensitizing exposures were not

## 3. HEALTH EFFECTS

discussed or quantified. No information regarding dermal effects of oral exposure of humans to chromium(III) compounds was identified.

No studies were located regarding noncancer dermal effects in animals after oral exposure to chromium(VI) or chromium(III) compounds. The effect of oral exposure to chromium(VI) compounds on increased susceptibility of hairless mice to ultraviolet light-induced skin cancer is discussed in Section 3.2.2.7 (Oral Exposure, Cancer).

**Ocular Effects.** No studies were located regarding ocular effects in humans after oral exposure to chromium(VI) or chromium(III) compounds. Histopathologic examination of rats and mice exposed to sodium dichromate dihydrate in drinking water at 20.9 and 27.9 mg chromium(IV)/kg/day, respectively, for 3 months or at 7.0 and 8.7 mg chromium(IV)/kg/day, respectively, for 2 years revealed normal morphology of the ocular tissue (NTP 2007, 2008a). Similar negative findings were observed in rats and mice exposed to chromium(III) as dietary chromium picolinate at 506 and 1415 mg chromium(III)/kg/day, respectively, for 3 months or at 313 and 781 mg chromium(III)/kg/day, respectively, for 2 years (NTP 2008b).

**Body Weight Effects.** Studies reporting body weight effects in humans exposed to chromium(VI) were not identified. The potential beneficial effect of dietary supplementation with chromium(III) (as chromium picolinate or other chromium(III) compounds) to aid in weight loss and increase lean body mass has been reported. Although the role of chromium(III) in the regulation of lean body mass, percentage body fat, and weight reduction is highly controversial with negative and positive results being reported in the literature, studies assessing these effects were not designed to evaluate weight loss as a toxicological end point (Anderson 1998b). Thus, body weight effects associated with dietary supplementation with chromium(III) compounds is not considered adverse (see Section 2.2 for additional information).

Significant decreases in body weight have been reported in several intermediate-duration oral chromium(VI) studies in animals (Bataineh et al. 1997; Chowdhury and Mitra 1995; De Flora et al. 2006; Elbetieha and Al-Hamood 1997; NTP 1996a, 1996b, 2007; Quinteros et al. 2007; Yousef et al. 2006). However, it should be noted that high concentrations of chromium in drinking water decrease palatability of water, resulting in decreased water consumption; thus, decreased body weight may, in part, be due to decreased water consumption, in addition to other causes. In male rats exposed to 73 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 30 days, body weight was decreased

## 3. HEALTH EFFECTS

by 11.6% (Quinteros et al. 2007). A 19% decrease in body weight gain was observed male rats exposed to 42 mg chromium(VI)/kg/day (Bataineh et al. 1997) and a 10% decrease was reported in male mice exposed to 6 mg chromium(VI)/kg/day (Elbetieha and Al-Hamood 1997) as potassium dichromate in drinking water for 12 weeks. Note that daily doses in the study by Elbetieha and Al-Hamood (1997) may be overestimated, due to decreased water consumption in the higher concentration group (decrease was not quantified by study authors). Final body weight was decreased in rats and mice exposed to sodium dichromate dihydrate in drinking water for 14 weeks (NTP 2007). In rats, body weight was decreased in males by 11% at 11.2 mg chromium(VI)/kg/day and in females by 6% at 20.9 mg chromium(VI)/kg/day; in mice, body weight was decreased by 6% in males at 3.1 mg chromium(VI)/kg/day and by 8% in females at 5.2 mg chromium(VI)/kg/day. Decreases in body weight were also observed in male mice (9.3%) and female (13.5%) mice exposed to 165 and 14 mg chromium(VI)/kg/day as sodium dichromate dihydrate in drinking water for 210 days (De Flora et al. 2006). Gavage administration of 40 or 60 mg chromium(VI)/kg/day as sodium dichromate for 90 days resulted in 57 and 59% decreases in body weight gain, respectively (Chowdhury and Mitra 1995). In contrast, no changes in body weight gain were seen in rats or mice exposed to 9.8 or 48 mg chromium(VI)/kg/day, respectively, as potassium dichromate in the diet for 9 weeks (NTP 1996a, 1996b) or in rabbits administered 3.6 mg chromium(VI)/kg/day by gavage as potassium dichromate (Yousef et al. 2006). No alterations in body weight gain were observed in rats chronically exposed (1 year) to 3.6 mg chromium(VI)/kg/day as potassium chromate in drinking water (Mackenzie et al. 1958). In contrast, final body weight was decreased by 12% decrease male rats at 5.9 mg chromium(VI)/kg/day and by 11% in female rats at 7.0 mg chromium(VI)/kg/day as sodium dichromate dihydrate in drinking water for 2 years (NTP 2008a).

Several studies have examined the effect of exposure to potassium dichromate in drinking water on maternal body weight gain. An acute exposure (9 days) resulted in 8 and 24% decreases in body weight gain in pregnant mice exposed to 101 or 152 mg chromium(VI)/kg/day, respectively (Junaid et al. 1996b). Similarly, a decrease in maternal body weight gain was observed in pregnant mice exposed to 98 mg chromium(VI)/kg/day as potassium dichromate for 19 days (Trivedi et al. 1989). Reduced maternal body weight gains of 8, 14, and 21% were observed in rats exposed to 37, 70, or 87 mg chromium(VI)/kg/day for 20 days prior to mating (Kanojia et al. 1996). Similar decreases in body weight gain (18 and 24%) were observed in rats exposed to 89 or 124 mg chromium(VI)/kg/day, respectively, for 3 months prior to mating (Kanojia et al. 1998). However, no alterations in maternal body weight gain were observed in a continuous breeding study in which rats were exposed to 36.7 mg chromium(VI)/kg/day as potassium dichromate in the diet (NTP 1997).



## 3. HEALTH EFFECTS

Conflicting results have been reported for alterations in body weight in rats and mice exposed to oral chromium(III) compounds for intermediate and chronic exposure durations. Dietary exposure to 9 mg chromium(III)/kg/day as chromium chloride or chromium picolinate for 20 weeks (Anderson et al. 1997b) or 3.6 mg chromium(III)/kg/day as chromium chloride (Mackenzie et al. 1958) did not result in significant alterations in body weight gain. No alterations on body weight were observed in rats or mice exposed to dietary chromium picolinate for 14 weeks at doses up to 506 and 1,415 mg chromium(III)/kg/day, respectively (NTP 2008b; Rhodes et al. 2005) or in male and female mice exposed to chromic potassium sulfate in drinking water for 210 days at doses of 165 and 140 mg chromium(III)/kg/day, respectively (De Flora et al. 2006). No change in body weight was observed in male and female rats exposed to dietary chromium nicotinate for 90 days at 1.5 and 1.2 mg chromium(III)/kg/day, respectively (Shara et al. 2005); however, body weight was decreased by 8.1% in males at 0.22 mg chromium(III)/kg/day and by 11.4% in females at 0.25 mg chromium(III)/kg/day following exposure to dietary chromium nicotinate for 38 weeks (Shara et al. 2007). Exposure to chromium chloride in drinking water resulted in 14 and 24% decreases in body weight gain in rats exposed to 40 mg chromium(III)/kg/day for 12 weeks (Bataineh et al. 1997) and male mice exposed to 5 mg chromium(III)/kg/day for 12 weeks (Elbetieha and Al-Hamood 1997), respectively. Note that daily doses in the study by Elbetieha and Al-Hamood (1997) may be overestimated, due to decreased water consumption in the higher concentration group (decrease was not quantified by study authors). No alterations in body weight gain were observed in rats or mice exposed to 0.46 or 0.48 mg chromium(III)/kg/day, respectively, as chromium acetate for a lifetime (Schroeder et al. 1964, 1965), or in mice and rats exposed to dietary chromium picolinate for 2 years at doses up to 313 and 781 mg chromium(III)/kg/day, respectively (NTP 2008b). However, exposure to dietary chromium nicotinate for 2 years resulted in a 14.9% decrease in male rats at 0.22 mg chromium(III)/kg/day and a 9.6% decrease in female rats at 0.25 mg chromium(III)/kg/day (Shara et al. 2007).

**Metabolic Effects.** Metabolic acidosis was observed in a 35-year-old female died after ingesting approximately 257 mg chromium(VI)/kg (assuming a 70-kg body weight) as chromic acid in a suicide (Loubieres et al. 1999). No information on adverse metabolic effects of chromium(III) compounds in humans was identified. Serum glucose was elevated by 65% in male Wistar rats exposed to 3.7 mg chromium(VI)/kg/day (compound not specified) in drinking water for 10 weeks (Rafael et al. 2007). No changes in serum glucose were reported in rats and mice exposed to sodium dichromate dihydrate in drinking water for 3 months at doses up to 27.9 mg chromium(VI)/kg/day or for 2 years at doses up to 8.7 mg chromium(VI)/kg/day (NTP 2007, 2008a); however, data on serum glucose were not presented in

## 3. HEALTH EFFECTS

the study reports. No information on adverse metabolic effects of chromium(III) compounds in animals was identified.

**3.2.2.3 Immunological and Lymphoreticular Effects**

The only reported effect of orally exposed humans on the immune system was the exacerbation of chromium dermatitis in chromium-sensitive individuals, as noted for dermal effects in Section 3.2.2.2. Sensitization of workers, resulting in respiratory and dermal effects, has been reported in numerous occupational exposure studies. Although the route of exposure for initial sensitization in an occupational setting is most likely a combination of inhalation, oral, and dermal routes, information on the exposure levels producing sensitization by the oral route was not identified. Additional information on contact dermatitis in sensitized workers is provided in Section 3.2.3.3 (Dermal Exposure, Immunological and Lymphoreticular Effects).

Oral exposure of animals to chromium(VI), but not chromium (III), compounds resulted in functional and histopathological changes to the immune system (NTP 2007, 2008a; Snyder and Valle 1991). Splenocytes prepared from rats given potassium chromate in drinking water at 16 mg chromium(VI)/kg/day for 3 weeks showed an elevated proliferative response of T- and B-lymphocytes to the mitogens, concanavalin A and liposaccharide, compared with splenocytes from control rats. A 5-fold enhancement of the proliferative response to mitomycin C was also seen when splenocytes from rats exposed for 10 weeks were incubated with splenocytes from nonexposed rats and additional chromium (0.1 mg chromium(VI)/L) was added to the incubation compared to the system without added chromium. It was suggested that these increased proliferative responses represent chromium-induced sensitization (Snyder and Valle 1991). Microscopic changes to lymphatic tissues, including histiocytic cellular infiltration of mesenteric and/or pancreatic nodes, were observed in rats and mice exposed to sodium dichromate dihydrate in drinking water for 3 months or 2 years (NTP 2007, 2008a). Following 3 months of exposure, histiocytic cellular infiltration was observed in male and female rats at 1.7 and 20.9 mg chromium(VI)/kg/day, respectively, and in mice at 3.1 mg chromium(VI)/kg/day (NTP 2007). After 2 years of exposure, histiocytic cellular infiltration and hemorrhage of mesenteric lymph nodes were observed in male rats at 0.77 mg chromium(VI)/kg/day (NTP 2008a). Histiocytic cellular infiltration of lymph nodes, but not hemorrhage, was observed at 2.4 mg chromium(VI)/kg/day in female rats and at 0.38 mg chromium(VI)/kg/day in mice (NTP 2008a). No abnormal histopathological changes were observed in lymphatic tissues of rats and mice exposed to oral chromium(III) (as chromium nicotinate and chromium picolinate) for 3 months or 2 years (NTP 2008b; Rhodes et al. 2005; Shara et al. 2005, 2007).

## 3. HEALTH EFFECTS

These highest doses of chromium(III) tested for intermediate and chronic exposure durations were 1,415 mg chromium(III)/kg/day as chromium picolinate in feed for 3 months and 781 mg chromium(III)/kg/day as chromium picolinate in feed for 2 years. The NOAEL and LOAEL values are recorded in Table 3-3 and plotted in Figure 3-3 for chromium(VI) and recorded in Table 3-4 and plotted in Figure 3-4 for chromium(III).

**3.2.2.4 Neurological Effects**

The only information regarding neurological effects in humans after oral exposure to chromium(VI) is the report of an enlarged brain and cerebral edema upon autopsy of a 14-year-old boy who died after ingesting 7.5 mg chromium(VI)/kg as potassium dichromate. These effects may be the result of accompanying renal failure (Kaufman et al. 1970). No information was identified on neurological effects in humans after oral exposure to chromium(III) compounds.

A decrease in motor activity and balance was reported in rats given 98 mg chromium(VI)/kg/day as sodium chromate in drinking water for 28 days (Diaz-Mayans et al. 1986). No additional studies were identified evaluating neurological function in laboratory animals following oral exposure to chromium(VI) or chromium(III) compounds. Histopathological examination of the brain and nervous system tissues has been evaluated in rats and mice exposed to oral chromium(VI) (as sodium dichromate dihydrate) and chromium(III) (as chromium nicotinate, chromium oxide, and chromium picolinate) for durations of 3 months to 2 years, with no abnormalities observed (Ivankovic and Preussmann 1975; NTP 2007, 2008a, 2008b; Shara et al. 2005, 2007). For chromium(VI) compounds, the highest doses tested for intermediate and chronic exposure durations were 27.9 and 8.7 chromium(VI)/kg/day, respectively, as sodium dichromate dihydrate in drinking water (NTP 2007, 2008a). For chromium(III) compounds, the highest doses tested for intermediate and chronic exposure durations were 1,806 and 2,040 mg chromium(III)/kg/day, respectively, as chromium oxide in the diet 5 days/week (Ivankovic and Preussmann 1975). None of these studies conducted more sensitive neurological, neurochemical, or neurobehavioral tests.

The NOAEL and LOAEL values are recorded in Table 3-3 and plotted in Figure 3-3 for chromium(VI) and recorded in Table 3-4 and plotted in Figure 3-4 for chromium(III).

## 3. HEALTH EFFECTS

**3.2.2.5 Reproductive Effects**

No studies were located regarding reproductive effects in humans after oral exposure to chromium(VI) or chromium(III) compounds.

A number of studies have reported reproductive effects in animals orally exposed to chromium(VI). Functional and morphological effects on male reproductive organs have been reported in monkeys, rats, mice, and rabbits. In a series of studies in male bonnet monkeys (*Macaca radiate*) (Aruldas et al. 2004, 2005, 2006; Subramanian et al. 2006), decreased testes weight, histopathological changes of the epididymis, disrupted spermatogenesis, and decreased sperm count and motility were observed following exposure to 2.1, 4.1, and 8.3 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 180 days. Histopathological changes, characterized by ductal obstruction and development of microcanals, germ cell depletion, hyperplasia of Leydig cells, and Sertoli cell fibrosis, increased in severity with dose. Sperm count and motility were significantly decreased, with effects exhibiting duration- and dose-dependence (Subramanian et al. 2006). After exposure for 2 months, significant decreases in sperm count (by 13%) and motility (by 12%) were observed only in monkeys treated with 8.3 mg chromium(VI)/kg/day, whereas after 6 months, dose-dependent decreases in sperm count and motility were observed at doses of  $\geq 2.1$  mg chromium(VI)/kg/day. No effects on sperm count or motility were observed in monkeys treated with 1.1 mg chromium(VI)/kg/day, although histopathological assessment of male reproductive tissues was not conducted in this dose group.

Exposure of male Wistar rats to 5.2 and 10.4 mg chromium(VI)/kg/day administered as chromic acid by gavage for 6 days produced decreased sperm count and histopathological changes to the testes (Li et al. 2001). Similar effects occurred at both doses, with sperm count decreased by 75.5 and 79.6% at 5.2 and 10.4 mg chromium(VI)/kg/day, respectively, and the "level of abnormal sperm" was increased 2.4-fold and 2.8-fold at 5.2 and 10.4 mg chromium(VI)/kg/day, respectively. Histopathological assessment of testes showed decreased diameter of seminiferous tubules and germ cell rearrangement within the tubules. In contrast, exposure of F344/N male rats to chromium(VI) as sodium dichromate dihydrate in drinking water at doses up to 20.9 mg chromium(VI)/kg/day for 3 months or 5.9 mg chromium(VI)/kg/day for 2 years did not produce histopathological changes to male reproductive tissues (NTP 2007, 2008a).

Male reproductive effects were observed in groups of 10 mature male Charles Foster strain rats administered 20, 40, and 60 mg chromium(VI)/kg/day as sodium dichromate(VI) by gavage for 90 days (Chowdhury and Mitra 1995). Testis weight, population of Leydig cells, seminiferous tubular diameter,

## 3. HEALTH EFFECTS

testicular protein, DNA, and RNA were all significantly reduced at 40 and 60 mg chromium(VI)/kg/day. The number of spermatogonia was not affected by treatment; however, resting spermatocytes (high dose), pachytene spermatocytes (high dose, intermediate dose) and stage-7 spermatid (high and intermediate doses) counts were significantly reduced and were treatment related. Testicular activity of succinic dehydrogenase was significantly lowered in the two high-dose groups, testicular cholesterol concentrations were elevated in the highest-dosed group, and both serum testosterone and testicular levels of  $3\beta\text{-}\Delta^5\text{-hydroxysteroid dehydrogenase}$  were significantly lowered. The authors also determined that the total testicular levels of ascorbic acid in the two higher-dosing groups was about twice that of the control values whereas, in the highest-treated group the total ascorbic acid levels were about half those of controls. At the low dose (20 mg/kg/day), testicular protein,  $3\beta\text{-}\Delta^5\text{-hydroxysteroid dehydrogenase}$ , and serum testosterone were decreased. The authors indicated that chromium enhanced levels of the vitamin, but at the highest dose, testicular levels became exhausted, thus decreasing the ability of the cells to reduce chromium(VI).

Significant alterations in sexual behavior and aggressive behavior were observed in male Sprague-Dawley rats exposed to 42 mg chromium(VI)/kg/day as potassium dichromate in the drinking water for 12 weeks (Bataineh et al. 1997). The alterations in sexual behavior included decreased number of mounts, lower percentage of ejaculating males, and increased ejaculatory latency and postejaculatory interval. The adverse effects on aggressive behavior included significant decreases in the number of lateralizations, boxing bouts, and fights with the stud male and ventral presenting. No significant alterations in fertility were observed when the exposed males were mated with unexposed females.

Reduced sperm count and degeneration of the outer cellular layer of the seminiferous tubules were observed in BALB/c mice exposed for 7 weeks to 15.2 mg chromium(VI)/kg/day as potassium dichromate in the diet (Zahid et al. 1990). Morphologically altered sperm occurred in mice given diets providing 28 mg chromium(VI)/kg/day as potassium dichromate. No effect was found on testis or epididymis weight, and reproduction function was not assessed. In contrast, an increase in testes weight was observed in Swiss mice exposed in drinking water to 6 mg chromium(VI)/kg/day as potassium dichromate for 12 weeks. At the next highest dose (14 mg chromium(VI)/kg/day), decreases in seminal vesicle and preputial gland weights were observed, although no information of sperm count was reported (Elbetieha and Al-Hamood 1997). At the higher exposure level, mice consumed less water (data on water consumption were not included in the study report); thus, the daily chromium(VI) dose may be overestimated for this exposure group. In studies designed to confirm or refute the findings of the Zahid et al. (1990) study, the reproductive effects of different concentrations of chromium(VI) as potassium

## 3. HEALTH EFFECTS

dichromate in the diet on BALB/c mice and Sprague-Dawley rats were investigated (NTP 1996a, 1996b). Groups of 24 of each species were fed potassium dichromate(VI) in their feed continuously for 9 weeks followed by an 8-week recovery period. For mice, the average daily ingestions of chromium(VI) were 1.05, 3.5, 7.5, and 32.2 mg/kg/day for males and for rats were 0.35, 1.05, 2.1, and 8.4 mg/kg/day (NTP 1996b). Microscopic examinations of the testes and epididymis for Sertoli nuclei and preleptotene spermatocyte counts in stage X or XI tubules did not reveal any treatment-related effects. Similarly, exposure to sodium dichromate dihydrate in drinking water did not produce morphological changes to male reproductive organs of B6C3F1 mice exposed to 27.9 or 5.9 mg chromium(VI)/kg/day for 3 months or 2 years, respectively, or affect sperm count or motility in male B6C3F1, BALB/c and C57BL/6N mice exposed to 8.7 mg chromium(VI)/kg/day for 3 months (NTP 2007, 2008a).

Reduced sperm count and plasma testosterone were observed in male New Zealand rabbits administered 3.6 mg chromium(VI)/kg/day as potassium dichromate for 10 weeks by gavage (Yousef et al. 2006). Sperm count was decreased by 18%, total sperm output was decreased by 25.9%, total number of mobile sperm was decreased by 34.3%, and number of dead sperm increased by 23.9%. In addition, relative weight of testes and epididymis were decreased by 22.2% and plasma testosterone was decreased by 20.8%.

Effects of chromium(VI) on the female reproductive system have been reported in rats and mice. Murthy et al. (1996) reported a number of reproductive effects in female Swiss albino mice exposed to potassium dichromate in drinking water for 20 days. The observed effects included a significant reduction in the number of follicles at different stages of maturation at  $\geq 60$  mg chromium(VI)/kg/day, reduction in the number of ova/mice at  $\geq 120$  mg chromium(VI)/kg/day, significant increase in estrus cycle duration at 180 mg chromium(VI)/kg/day, and histological alterations in the ovaries (e.g., proliferated, dilated, and congested blood vessels, pyknotic nuclei in follicular cells, and atretic follicles) at  $\geq 120$  mg chromium(VI)/kg/day. The severity of the reproductive effects appeared to be dose-related. In an ancillary study, electron microscopy of selected ovarian tissues revealed ultrastructural changes (disintegrated cell membranes of two-layered follicular cells and altered villiform cristae of mitochondria and decreased lipid droplets in interstitial cells) in mice exposed to 1.2 mg chromium(VI)/kg/day for 90 days; the toxicological significance of these alterations is not known. The study authors suggest that the effects observed in the interstitial cells may be due to a reduction in lipid synthesizing ability, which could lead to decreased steroid hormone production. An increase in relative ovarian weight was observed in female Swiss mice exposed for 12 weeks to 14 mg chromium(VI)/kg/day as potassium dichromate (Elbetieha and Al-Hamood 1997), although the calculated daily dose may be overestimated, due to

## 3. HEALTH EFFECTS

decreased water consumption in the higher concentration group (decrease was not quantified by study authors). In contrast, microscopic examinations of the ovaries showed no treatment-related effects in female BALB/c mice and Sprague-Dawley rats fed up to 9.8 and 48 mg chromium(VI)/kg/day, respectively, as potassium dichromate(VI) in the diet continuously for 9 weeks followed by an 8-week recovery period (NTP 1996b). Similarly, exposure of female F344/N rats and B6C3F1 mice to sodium dichromate dihydrate in drinking water at doses up to 20.9 and 27.9 mg chromium(VI)/kg/day, respectively, for 3 months or at doses up to 7.0 and 8.6 mg chromium(VI)/kg/day, respectively, for 2 years did not produce histopathological changes to the ovaries (NTP 2007, 2008a).

Several studies have reported increases in preimplantation losses and resorptions in rats and mice exposed to chromium(VI). However, for studies evaluating high concentration of chromium, it is possible that effects may, in part, be secondary to maternal toxicity. In addition, high concentration of chromium in food and water decrease palatability and can result in decreased food and drinking water consumption. Exposure of pregnant mice to 46 mg chromium(VI)/kg/day as potassium dichromate in drinking water during gestation resulted in increased preimplantation and postimplantation loss, and decreased litter size. Maternal body weight gain decreased at doses  $\geq 98$  mg chromium(VI)/kg/day (Trivedi et al. 1989). In female Swiss albino mice exposed for 20 days prior to mating to potassium dichromate in drinking water at concentrations that resulted in doses of 0, 52, 98, or 169 mg chromium(VI)/kg/day and then mated, the number of corpora lutea was decreased at 169 mg/kg/day, preimplantation loss and resorptions were increased at  $\geq 98$  mg/kg/day, and placental weights were decreased at  $\geq 57$  mg/kg/day (Junaid et al. 1996a). Increases in the number of resorptions were also found in female Swiss albino rats exposed to 37, 70, or 87 mg chromium(VI)/kg/day (as potassium dichromate in the drinking water) for 20 days prior to mating (Kanojia et al. 1996). Additional reproductive effects observed at 70 or 87 mg chromium(VI)/kg/day include decreased number of corpora lutea, decreased number of implantations, and increased number of preimplantation losses. A treatment-related increase in the length of estrus cycle was significantly different from controls only in the 87 mg chromium(VI)/kg/day group. Decreased mating, decreased fertility, and increased pre- and postimplantation loss were observed in female Druckrey rats receiving doses of 45, 89, and 124 mg chromium(VI)/kg/day (as potassium dichromate in the drinking water) for 3 months prior to mating; the 89 and 124 mg chromium(VI)/kg/day groups exhibited increased resorptions as well (Kanojia et al. 1998). A decrease in fertility (decreased number of implantations and viable fetuses) was observed in male and female Swiss mice that were exposed to 6 mg chromium(VI)/kg/day as potassium dichromate for 12 weeks and then were mated with unexposed males and females; however, the classification of non-viable fetuses was not presented in this report (Elbetieha and Al-

## 3. HEALTH EFFECTS

Hamood 1997). An increase in the number of mice with resorptions was also observed in the exposed females.

No reproductive effects were observed in a multigeneration reproductive assessment by continuous breeding study of BALB/c mice were fed a diet containing potassium dichromate(VI). Males and females were exposed to chromium for 7 days and then 20 pairs ( $F_0$ ) in each dose group were allowed to continuously mate for 85 days (NTP 1997). The mean doses of chromium(VI) in  $F_0$  animals were 6.8, 13.5, and 30.0 mg/kg/day. Litters produced during the 85-day mating period were examined at postnatal day 1. There were no treatment related changes in average litters/pair, number of live and dead pups per litter, sex ratios, pup weights, or changes in gestational time. There were no dose related gross pathological organ differences observed for both  $F_0$  males and females, nor any differences in organ to body weight ratios. At the highest dose the  $F_0$  females had lower mean body weights than control animals by about 7%. There were no effects on sperm number or motility, nor were there any increases in abnormal sperm morphology. Histopathological examination of livers and kidneys from  $F_0$  males and females showed no changes that were treatment related.  $F_1$  litters produced after 85 days were reared by the dam until weaning on postnatal day 21 then separated and allowed to mature for about 74 days. At that time, 20 pairs were allowed to mate and produce  $F_2$  progeny. Mean exposures to chromium(VI) to  $F_1$  animals were determined to be 7.8, 16.0, and 36.7 mg/kg/day.  $F_2$  litters were reared by the dam until weaning on postnatal day 21 before being sacrificed. There were no differences in  $F_2$  average litters/pair, number of live and dead pups per litter, sex ratios, pup weights, or changes in gestational time between exposed groups and controls. There were no dose-related gross pathological organ differences observed for both  $F_1$  males and females, nor any differences in organ to body weight ratios. No histological lesions were observed in liver and kidney cells that were dose related, nor did chromium(VI) have any effects on estrous cycling.

Studies on the reproductive effects of chromium(III) yield conflicting results. Exposure to chromium(III) as chromium oxide did not cause reproductive effects in rats. Male and female rats fed 1,806 mg chromium(III)/kg/day as chromium oxide 5 days/week for 60 days before gestation and throughout the gestational period were observed to have normal fertility, gestational length, and litter size (Ivankovic and Preussmann 1975). A study by Bataineh et al. (1997) found significant alterations in sexual behavior (reductions in the number of mounts, increased postejaculatory interval, and decreased rates of ejaculation), aggressive behavior toward other males, and significantly lower absolute weight of testes, seminal vesicles, and preputial glands in male Sprague-Dawley rats exposed to 40 mg chromium(III)/kg/day as chromium chloride in the drinking water for 12 weeks. Male fertility indices (assessed by



## 3. HEALTH EFFECTS

impregnation, number of implantations, and number of viable fetuses) did not appear to be adversely affected by exposure to chromium chloride, although the untreated females mated to treated males exhibited an increase in the total number of resorptions (Bataineh et al. 1997). In contrast, a decrease in the number of pregnant females was observed following the mating of unexposed females to male Swiss mice exposed to 13 mg chromium(III)/kg/day as chromium chloride (Elbetieha and Al-Hamood 1997). Impaired fertility (decreased number of implantations and viable fetuses) was also observed in females exposed to 5 mg chromium(III)/kg/day mated to unexposed males; however, no information on sperm count was reported and the definition and classification of viable fetuses were not provided (Elbetieha and Al-Hamood 1997). This study also found increased testes and ovarian weights and decreased preputial gland and uterine weights at 5 mg chromium(III)/kg/day. At lower concentrations of chromium chloride (9 mg chromium(III)/kg/day in the diet for 20 weeks), no alterations in testes or epididymis weights were observed in rats (Anderson et al. 1997b). A similar exposure to chromium(III) picolinate also did not result in testes or epididymis weight alterations (Anderson et al. 1997b). This study did not assess reproductive function. Mice exposed for 7 weeks to 9.1 mg chromium(III)/kg/day as chromium sulfate in the diet had reduced sperm count and degeneration of the outer cellular layer of the seminiferous tubules. Morphologically altered sperm occurred in BALB/c mice given diets providing 42.4 mg chromium(III)/kg/day as chromium sulfate (Zahid et al. 1990).

Exposure of rats and mice to high doses of chromium(III) compounds (chromium nicotinate and chromium picolinate) in the diet for 3 months or 2 years did not produce histopathological changes to male or female reproductive organs (NTP 2008b; Rhodes et al. 2005; Shara et al. 2005, 2007). In the 3-month studies on chromium picolinate, doses up to 505 and 506 mg chromium(III)/kg/day were evaluated in male and female F344/N rats, respectively, and doses up to 1,415 and 1,088 mg chromium(III)/kg/day were evaluated in male and female B6C3F1 mice, respectively; in the 2-year studies, doses up to 286 and 313 mg chromium(III)/kg/day were evaluated in male and female rats, respectively and doses up to 781 and 726 mg chromium(III)/kg/day, were evaluated in male and female mice, respectively (NTP 2008b; Rhodes et al. 2005). In addition, the 3-month study in rats and mice did not find any treatment-related effects on sperm count and motility or on estrous cycle (percentage of time spent in various estrous cycle stages or estrous cycle length, based on evaluation of vaginal cytology (NTP 2008b; Rhodes et al. 2005). Although the 3-month and 2-year studies on chromium nicotinate did not reveal any morphological changes to reproductive tissues of male and female Sprague-Dawley rats, only low doses were evaluated (up to 1.5 mg chromium(III)/kg/day for 3 months and up to 0.25 mg chromium(III)/kg/day for 2 years) (Shara et al. 2005, 2007).

### 3. HEALTH EFFECTS

As discussed in greater detail in Section 3.2.2.6, the reproductive system is also a target in the developing organism. Delayed vaginal opening and decreased relative weights of the uterus, ovaries, testis, seminal vesicle, and preputial glands were observed in mouse offspring exposed to potassium dichromate or chromium(III) chloride on gestational day 12 through lactation day 20 (Al-Hamood et al. 1998). Impaired fertility was observed in the chromium(III) chloride-exposed female offspring when they were mated with unexposed males (Al-Hamood et al. 1998); no effect on fertility was observed in the male offspring.

The highest NOAEL value and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3 for chromium(VI) and recorded in Table 3-4 and plotted in Figure 3-4 for chromium(III).

#### **3.2.2.6 Developmental Effects**

No studies were located regarding developmental effects in humans after oral exposure to chromium or its compounds.

Several animal studies provide evidence that chromium(VI) is a developmental toxicant in rats and mice. A series of studies (Junaid et al. 1996a; Kanojia et al. 1996, 1998) were conducted to assess whether pre-mating exposure to potassium dichromate would result in developmental effects. In the first study, groups of 15 female Swiss albino mice were exposed to 0, 52, 98, or 169 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 20 days (Junaid et al. 1996a) and then mated with untreated males. At 52 mg chromium(VI)/kg/day, there was a 17.5% postimplantation loss over controls and a 30% decrease in fetal weight. At 98 mg/kg/day, there were decreases in the number of implantation sites, number of live fetuses, and fetal weight. There were also increases in the number of resorptions and number of pre- and postimplantation losses. At 169 mg chromium(VI)/kg/day, there was 100% preimplantation loss. The fetuses in the 98 mg/kg/day group had higher numbers of subdermal hemorrhagic patches and kinky short tails and decreased fetal body weight and crown rump length. Although there were no major skeletal abnormalities in any other treated animals, there was a significant reduction in ossification at 52 mg chromium(VI)/kg/day (53% compared to 12% for controls) and significant reduction in ossification in caudal, parietal and interparietal bones of fetuses at 98 mg chromium(VI)/kg/day. There were no significant soft tissue deformities in any of the treated fetuses. Although dosing occurred prior to mating, internal chromium levels remaining in females after mating may have been toxic to the conceptus that caused adverse developmental effects.

## 3. HEALTH EFFECTS

In the second study, female Swiss albino rats were exposed to potassium dichromate concentrations in the drinking water resulting in doses of 37, 70, or 87 mg chromium(VI)/kg/day for 20 days prior to mating (Kanojia et al. 1996). Lower gestational weight gain, increased postimplantation loss, and decreased number of live fetuses were observed in all treatment groups, relative to controls. Increased incidences of reduced fetal ossification in fetal caudal bones were reported at the 70 and 87 mg chromium(VI)/kg/day dose levels; additionally, the 87 mg chromium(VI)/kg/day dose group of fetuses exhibited increased incidences of reduced ossification in parietal and interparietal bones, as well as significant incidences of subdermal hemorrhagic thoracic and abdominal patches (42%), kinky tails (42%), and short tails (53%), relative to 0% in controls. No treatment-related gross visceral abnormalities were seen.

In the third study, groups of 10 female Druckrey rats were exposed to potassium dichromate in the drinking water for 3 months pre-mating at concentrations yielding dose levels of 45, 89, or 124 mg chromium(VI)/kg/day (Kanojia et al. 1998). Reduced maternal gestational weight gain, increased pre- and postimplantation loss, reduced fetal weight, fetal subdermal hemorrhagic thoracic and abdominal patches, increased chromium levels in maternal blood, placenta, and fetuses, and increased incidences of reduced ossification in fetal caudal bones were observed in all treatment groups. In addition, the 89 and 124 mg chromium(VI)/kg/day dose groups exhibited increased resorptions, reduced numbers of corpora lutea and fetuses per litter, reduced implantations, reduced placental weight, increased incidences of reduced ossification in fetal parietal and interparietal bones, and reduced fetal crown-rump length. No treatment-related gross visceral abnormalities were seen. A decreased number of pregnancies were observed in mated female rats administered 35.7 mg chromium(VI)/mg/day as potassium dichromate by gavage on gestational days 1–3; exposure on gestational days 4–6 decreased the number of viable fetuses and increased the number of resorptions, but did not alter the number of pregnancies (Bataineh et al. 2007).

Exposure of pregnant mice to 57 mg chromium(VI)/kg/day as potassium dichromate in drinking water during gestation resulted in embryo lethal effects (i.e., increased resorptions and increased post-implantation loss), gross abnormalities (i.e., subdermal hemorrhage, decreased cranial ossification, tail kinking), decreased crown-rump length, and decreased fetal weight. The incidence and severity of abnormalities increased at higher doses. Maternal toxicity, evidenced by decreased body weight gain, occurred at doses  $\geq 120$  mg chromium(VI)/kg/day. No implantations were observed in the dams given 234 mg chromium(VI)/kg/day (Trivedi et al. 1989).

## 3. HEALTH EFFECTS

Groups of 10 female Swiss albino mice received chromium(VI) as potassium dichromate in drinking water during organogenesis on days 6–14 at levels that provided 0, 53.2, 101.1, and 152.4 mg chromium(VI)/kg/day (Junaid et al. 1996b). No notable changes in behavior or clinical signs were observed in control or treated animals. Reduction of gestational weight gains of 8.2 and 30% were observed for the animals in the intermediate- and high-dose groups. The number of dead fetuses was higher in the high-dose group and fetal weight was lower in both intermediate- and high-dose groups (high dose=1.06 g, intermediate dose=1.14 g) as compared to the control value of 1.3 g. The number of resorption sites was 0.31 for controls, 1.00 for the low dose, 1.70 for the intermediate dose, and 2.30 for the high dose, demonstrating a dose-response relationship. The studies also showed that there was a significantly greater incidence of postimplantation loss in the two highest-dose groups of 21 and 34.60% as compared to control value of 4.32%. No significant gross structural abnormalities in any of the treated dosed groups were observed except for drooping of the wrist (carpal flexure) and subdermal hemorrhagic patches on the thoracic and abdominal regions in 16% in the offspring of the high-dose group. Significant reduced ossification in nasal frontal, parietal, interparietal, caudal, and tarsal bones were observed only in the 152.4 mg chromium(VI)/kg/day-treated animals.

Impaired development of the reproductive system was observed in the offspring of female BALB/c mice exposed to 66 mg chromium(VI)/kg/day as potassium chromate in the drinking water on gestation day 12 through lactation day 20 (Al-Hamood et al. 1998). A significant delay in vaginal opening was observed. Significant decreases in the numbers of pregnant animals, of implantations, and of viable fetuses were also observed when the female offspring were mated at age 60 days with unexposed males. No developmental effects were observed in the male offspring. In pregnant rats exposed to 8 mg chromium(VI)/kg/day as potassium chromate in drinking water on gestational days 6 through 15, pre- and postimplantation losses and the number of resorbed and dead fetuses per litter were increased compared to controls (Elsaieed and Nada 2002). Fetal weight was significantly decreased by 67% and the number of visceral (renal pelvis dilatation) and skeletal (incomplete ossification of skull bone) anomalies per litter were significantly increased. No effects on fetal body weight or the number of fetuses per litter were observed in mice exposed to 4.8 mg chromium(VI)/kg/day as sodium dichromium dihydrate or 2.4 mg chromium(VI)/kg/day as potassium dichromate in drinking water on gestational days 0 through 18; however, no additional assessments on fetal development were conducted in this study (De Flora et al. 2006).

Three studies examined the developmental toxicity of chromium(III) following oral maternal exposure. In the first study, no developmental effects were observed in offspring of rats fed 1,806 mg

## 3. HEALTH EFFECTS

chromium(III)/kg/day as chromium oxide 5 days/week for 60 days before mating and throughout gestation (Ivankovic and Preussmann 1975). In contrast, reproductive effects have been observed in the offspring of mice exposed to chromium(III) chloride. Significant decreases in the relative weights of reproductive tissues (testes, seminal vesicles, and preputial glands in males; ovaries and uterus in females) were observed in the offspring of BALB/c mice exposed to 74 mg chromium(III)/kg/day as chromium(III) chloride in the drinking water on gestation day 12 through lactation day 20 (Al-Hamood et al. 1998). A significant delay in timing of vaginal opening was also noted in the female offspring. At age 60 days, the male and female offspring were mated with unexposed animals. No significant alterations in fertility (number of pregnant animals, number of implantations, number of viable fetuses, and total number of resorptions) were observed in the exposed males. A significant decrease in the number of pregnant females (62.5 versus 100% in controls) was observed among the female offspring mated with untreated males. The conflicting results between the Ivankovic and Preussmann (1975) study and the Al-Hamood et al. (1998) study may be a reflection on the developmental end points examined or the differences in the species tested. In rats administered 33.6 mg chromium(III)/kg/day (only dose tested) by gavage as chromium chloride on gestational days 1–3, a decreased number of pregnancies were observed; however, when exposed on gestational days 4–6, no effects on pregnancy rates, implantations, viable fetuses, or resorptions were observed (Bataineh et al. 2007).

The NOAEL and LOAEL values for developmental effects in each species are recorded in Table 3-3 and plotted in Figure 3-3 for chromium(VI) and recorded in Table 3-4 and plotted in Figure 3-4 for chromium(III).

### 3.2.2.7 Cancer

Studies of associations between environmental exposures to chromium and cancer outcomes in humans are limited to several ecological studies (Beaumont et al. 2008; Fryzek et al. 2001; Zhang and Li 1987). These types of studies investigate possible associations between rates of selected diseases (e.g., cancer deaths) within a geographic population and some measure of average exposure to chromium (e.g., drinking water chromium concentrations or location with respect to potential sources of exposure). Actual exposures to individuals are not determined and therefore, exposure misclassification bias often contributes to uncertainty regarding associations between outcomes and exposure. Findings from ecological studies are mixed and do not strongly support associations between cancer mortality and exposures to chromium. One study did find significantly higher stomach cancer death rates in areas where well water chromium levels had been elevated (Beaumont et al. 2008).

## 3. HEALTH EFFECTS

An ecological study of an area near a ferrochromium production plant in the Liaoning Province, China compared cancer mortality in locations that had relatively high or low chromium concentrations in well water (Beaumont et al. 2008; Zhang and Li 1987). The most recent study of the area estimated cancer mortality rates (cancers deaths per person-year in an 8-year observation period) based on mortality records for the period 1970–1978 (Beaumont et al. 2008). The province was divided into nine areas, four of which were designated as no (or low) chromium (groundwater concentration <0.001 mg Cr/L) and five which were designated as high chromium. The main sources of chromium in well water were from discharges from the plant to surface water and groundwater, which began operating in 1961. Chromium levels in well water from samples collected in the contaminated areas in 1965 (by this time, full-scale production was occurring) ranged from 0.6 to 20 mg/L with 15% of wells having concentrations >2 mg/L. Total number of cancer deaths were 80 (of 98,458 person-years) in the high chromium areas and 182 (of 252,277 person-years) in the comparison areas. Age-adjusted cancer mortality rate ratios (rate in high regions/rate in low regions) were 1.82 (95% CI 1.11–2.91) for stomach cancer, 1.15 (95% CI 0.62–2.05) for lung cancer, 0.86 (95% CI 0.53–1.36) for other cancers, and 1.13 (95% CI 0.86–1.46) for all cancer.

An ecological study of areas in Kings County and San Bernardino County, California compared cancer mortality in locations near natural gas compressor plants with areas not located near the plants (Fryzek et al. 2001). Hexavalent chromium compounds had been used as additives in cooling tower water at the gas plants during the period 1950 to approximately 1980. Mortality records for zip codes for the cities of Kettleman City (in Kings County), and Hinkely and Topock (in San Bernadino County), in which natural gas compressor plants were located, were compared to records from zip codes in Kings County and San Bernadino County, other than those encompassing these three cities.. The study included mortality records for the period 1989–1998, during which time 2,226,214 deaths were recorded. Age-adjusted cancer mortality rate ratios (rate in areas near the plant/rate in comparison areas) were 1.03 (95% CI 0.90–1.17) for lung cancer death, 0.93 (95% CI 0.87–1.00) for all cancer deaths, and 0.98 (95% CI 0.95–1.02) for all deaths.

An ecological study compared levels of chromium (and other chemicals) in drinking water in 453 Nebraska communities with death rates in these areas (Bednar and Kies 1991). Data on chromium in drinking water were obtained for the year period 1986–1987, and mortality data was obtained for the year 1986. Mean chromium concentration in drinking water was 0.002 mg/L (range <0.001–0.01). Linear correlation (Pearson) between chromium levels and death from chronic lung disease was -0.101 (p=0.03).

## 3. HEALTH EFFECTS

Chronic exposure to chromium(VI) as sodium dichromate in drinking water resulted in increased incidence of neoplasms of the digestive tract in mice and rats (NTP 2008a). Groups of 50 male and 50 female F344/N rats were exposed to drinking water containing 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dihydrate for 2 years. NTP (2008a) calculated 2-year mean daily doses of 0, 0.6, 2.2, 6, or 17 mg sodium dichromate dihydrate/kg/day (equivalent to 0, 0.21, 0.77, 2.1 or 5.9 mg chromium(VI)/kg/day) in male rats and, 0, 0.7, 2.7, 7, or 20 mg sodium dichromate dihydrate/kg/day (equivalent to 0, 0.24, 0.94, 2.4, and 7.0 mg chromium(VI)/kg/day) in female rats. Incidences of squamous epithelial neoplasms of the oral mucosa and tongue were elevated in rats exposed to sodium dichromate compared to controls, with significant increased mortality-adjusted incidence in males at the 5.9 mg chromium(VI)/kg/day dose (15.7 versus 0% in controls,  $p=0.007$ ), and in females at the 7.0 mg chromium(VI)/kg/day (23.9 versus 2.2% in controls,  $p<0.001$ ). In both male and female rats, there was a significant dose trend for digestive tract neoplasms ( $p<0.001$ ). Groups of 50 male B6C3F1 mice were exposed to 0, 14.3, 28.6, 85.7, or 257.4 mg sodium dichromate dihydrate/L, and 50 female B6C3F1 mice were exposed to drinking water concentrations of 0, 14.3, 57.3, 172, or 516 mg sodium dichromate dihydrate/L. NTP (2008a) calculated 2-year mean daily doses of sodium dichromate dihydrate in male mice of 1.1, 2.6, 7 or 17 mg/kg/day (equivalent to 0, 0.38, 0.91, 2.4 and 5.9 mg chromium(VI)/kg/day); and in female mice of 0, 1.1, 3.9, 9, or 25 mg/kg/day (equivalent to 0, 0.38, 1.4, 3.1, or 8.7 mg chromium(VI)/kg/day). Incidences of neoplasms of the of the small intestine (duodenum, jejunum, or ileum) were elevated in mice exposed to sodium dichromate compared to controls, with significant increased mortality-adjusted incidence in males at the 2.4 (15.1 versus 2.2% in controls,  $p=0.032$ ) or 5.9 mg chromium(VI)/kg/day dose (43.8 versus 2.2% in controls,  $p=0.001$ ), and in females at the 3.1 (36.3 versus 2.2% in controls) or 8.7 mg chromium(VI)/kg/day (45.9 versus 2.2% in controls,  $p<0.001$ ). In both male and female mice, there was a significant dose trend for digestive tract neoplasms ( $p<0.001$ ). NTP (2008a) concluded that the results of these studies provided clear evidence of carcinogenic activity of sodium dichromate dihydrate in male and female F344/N rats based on increased incidences of squamous cell neoplasms of the oral cavity; and clear evidence of carcinogenic activity of in male and female B6C3F1 mice based on increased incidences of neoplasms of the small intestine (duodenum, jejunum, or ileum).

The carcinogenicity of chromium(VI) was evaluated in mice exposed potassium chromate in drinking water at 9 mg chromium(VI)/kg/day for three generations (880 days) (Borneff et al. 1968). In treated mice, 2 of 66 females developed forestomach carcinoma and 9 of 66 females and 1 of 35 males developed forestomach papilloma. The vehicle controls also developed forestomach papilloma (2 of 79 females, 3 of 47 males) but no carcinoma. The incidence of forestomach tumors in the treated mice was not significantly higher than controls. Although study authors concluded that evidence of carcinogenicity

## 3. HEALTH EFFECTS

was equivocal, statistical analysis of these data (performed by Syracuse Research Corporation) using Fischer's exact test shows statistically significant increases in the incidence of adenoma or carcinomas (forestomach) ( $p=0.0067$ ) and in the incidence of adenomas (forestomach) alone ( $p=0.027$ ), compared to control. In this same study, coexposure to both potassium chromate and 3,4-benzpyrene in a similar protocol showed that potassium chromate did not potentiate the carcinogenicity of 3,4-benzpyrene (Borneff et al. 1968). Exposure of female hairless mice to ultraviolet light in combination with chromium(VI) as potassium chromate in drinking water at concentrations of 2.5 or 5.0 mg potassium chromate(VI)/L (approximately 0.18, or 0.35 mg chromium(VI)/kg/day) for 182 days, or in the diet at concentrations of 0, 2.5, or 5.0 mg potassium chromate(VI)/kg food (approximately 0.13, or 0.26 mg chromium(VI)/kg/day) for 26 weeks, produced an increased incidence of skin tumors compared to animals exposed to UV light alone or chromium(VI) alone (Davidson et al. 2004; Uddin et al. 2007). Exposure to chromium(VI) alone did not result in neoplasms.

Chronic exposure to chromium(III) as chromium picolinate dihydrate in the diet resulted in increased incidence of neoplasms of the preputial gland in male rats; however, no increased neoplasms were observed in female rats, or in male or female mice (NTP 2008b). Groups of 50 male and 50 female F344/N rats were fed a diet containing 0, 2,000, 10,000, or 50,000 ppm chromium picolinate monohydrate for 2 years. NTP (2008b) calculated 2-year mean daily doses of chromium picolinate monohydrate of 0, 90, 460, and 2,400 mg/kg/day (equivalent to 0, 11, 55, or 286 mg chromium(III)/kg/day) in male rats and 0, 100, 510, and 2,630 mg/kg/day (equivalent to 0, 12, 61, or 313 mg chromium(III)/kg/day) in female rats. Mortality-adjusted incidence of adenoma of the preputial gland of male rats was significantly elevated in rats that received 55 mg chromium(III)/kg/day (14.9 versus 2.2% in controls,  $p=0.031$ ), but not in rats exposed to lower dose or the higher dose (286 mg chromium(III)/kg/day), and there was no significant dose trend for the neoplasm. Incidences of neoplasms were not significantly different from controls in females, including neoplasms of the clitoral gland. Groups of 50 male and 50 female F6C3F1 mice were fed a diet containing 0, 2,000, 10,000, or 50,000 ppm chromium picolinate monohydrate for 2 years. NTP (2008b) calculated 2-year mean daily doses of chromium picolinate monohydrate of 0, 250, 1,200, and 6,565 mg/kg/day (equivalent to 0, 30, 143, 2.1, or 781 mg chromium(III)/kg/day) in male mice and 100, 510, and 2,630 mg/kg/day (equivalent to 0, 29, 143, or 726 mg chromium(III)/kg/day) in female mice. No neoplasms or lesions were attributed to exposure to chromium picolinate monohydrate in male or female mice. NTP (2008b) concluded that evidence for carcinogenicity of chromium picolinate in male rats was equivocal and that the study provided no evidence of carcinogenicity in mice.



### 3. HEALTH EFFECTS

No evidence of carcinogenicity was observed in male or female rats fed diets containing chromium oxide at 2,040 mg chromium(III)/kg/day 5 days/week for 2 years. Moreover, no evidence of carcinogenicity was found in the offspring of these rats after 600 days of observation (Ivankovic and Preussmann 1975).

The Cancer Effect Levels (CELs) for chromium(VI) are recorded in Table 3-3 and plotted in Figure 3-3.

#### 3.2.3 Dermal Exposure

Some chromium(VI) compounds, such as chromium trioxide (chromic acid), potassium dichromate, potassium chromate, sodium dichromate, and sodium chromate, are very caustic and can cause burns upon dermal contact. These burns can facilitate the absorption of the compound and lead to systemic toxicity.

##### 3.2.3.1 Death

A 49-year-old man with an inoperable carcinoma of the face was treated with chromic acid crystals. Severe nephritis occurred following the treatment with the chromium(VI) compounds. Death occurred 4 weeks after exposure (Major 1922). Twelve individuals died as a result of infection to necrotic areas of the skin that were caused by application of a salve made up with potassium chromate used to treat scabies. Renal failure was observed. Autopsies revealed fatty degeneration of the heart, hyperemia and necrosis of kidney tubules, and hyperemia of the gastric mucosa (Brieger 1920).

Single-dose dermal LD<sub>50</sub> values in New Zealand rabbits exposed to chromium(VI) as sodium chromate, sodium dichromate, potassium dichromate, and ammonium dichromate were determined by Gad et al. (1986). LD<sub>50</sub> values ranged from 361 to 553 mg chromium(VI)/kg for females and from 336 to 763 mg chromium(VI)/kg for males. Signs of toxicity included dermal necrosis, eschar formation, dermal edema and erythema, diarrhea, and hypoactivity. The dermal LD<sub>50</sub> value for chromium trioxide was 30 mg chromium(VI)/kg for combined sexes (American Chrome and Chemicals 1989). In male and female Sprague-Dawley rats, no mortalities were observed following a single dermal application of 621.6 mg chromium(III)/kg as chromium nicotinate (Shara et al. 2005).

The LD<sub>50</sub> values are recorded in Table 3-5 for chromium(VI) and Table 3-6 for chromium(III).

















## 3. HEALTH EFFECTS

**3.2.3.2 Systemic Effects**

Several reports of health effects in individuals treated with potassium dichromate are discussed below (Brieger 1920; Major 1922; Smith 1931). The results of these studies should be interpreted cautiously because pre-existing conditions may have contributed to the observed effects. The highest NOAEL value and all reliable LOAEL values for dermal effects in each species and duration category are recorded in Table 3-5 for chromium(VI) and Table 3-6 for chromium(III).

**Respiratory Effects.** Occupational exposure to chromium compounds results in direct contact of mucocutaneous tissue, such as nasal and pharyngeal epithelium, due to inhalation of airborne dust and mists of these compounds. Such exposures have led to nose and throat irritation and nasal septum perforation. Because exposure is to airborne chromium, studies noting these effects are described in Section 3.2.1.2.

A case report of a man who was admitted to a hospital with skin ulcers on both hands due to dermal exposure to ammonium dichromate in a planographic printing establishment where he had worked for a few months noted that he also had breathing difficulties. However, because he also had many previous attacks of hay fever and asthma, it was not possible to distinguish whether his breathing difficulties were caused by or exacerbated by dermal exposure to ammonium dichromate (Smith 1931).

No studies were located regarding respiratory effects in animals after dermal exposure to chromium or its compounds.

**Cardiovascular Effects.** Information regarding cardiovascular effects in humans after dermal exposure to chromium or its compounds is limited. Weak, thready, and markedly dicrotic pulse developed  $\approx 1.5$  hours after a salve made up with potassium chromate to treat scabies was applied to skin of an unspecified number of individuals. Some of the people died as a result of infection to the exposed area, and autopsy revealed degeneration of the heart (Brieger 1920).

No studies were located regarding cardiovascular effects in animals after dermal exposure to chromium or its compounds.

**Gastrointestinal Effects.** Vomiting occurred soon after application of a salve made up of potassium chromate to the skin of an unspecified number of individuals for the treatment of scabies. Some of these

### 3. HEALTH EFFECTS

individuals died as a result of infection of the exposed area, and autopsy revealed hyperemia of the gastric mucosa (Brieger 1920).

Diarrhea was reported in New Zealand rabbits exposed to lethal concentrations of chromium(VI) compounds (Gad et al. 1986).

**Hematological Effects.** Severe leukocytosis, with notable increases in immature polymorphonuclear cells, myelocytes, and myeloblasts and nucleated red cells and Howell-Jolly bodies, indicative of hemolytic anemia were observed in individuals after application of a salve that contained potassium chromate to treat scabies (Brieger 1920). Leukocytosis was also described in a case report of a man who was admitted to a hospital with skin ulcers on both hands due to dermal exposure to ammonium dichromate in a planographic printing establishment, where he had worked for a few months (Smith 1931). It should be noted that the man had a history of asthma.

No studies were located regarding hematological effects in animals after dermal exposure to chromium compounds.

**Musculoskeletal Effects.** Information regarding musculoskeletal effects in humans after dermal exposure to chromium or its compounds is limited to a case report. A man was admitted to a hospital with skin ulcers on both hands due to dermal exposure to ammonium dichromate in a planographic printing establishment, where he had worked for a few months. He also had tenderness and edema of the muscles of the extremities (Smith 1931).

No studies were located regarding musculoskeletal effects in animals after dermal exposure to chromium or its compounds.

**Hepatic Effects.** No reliable studies were located regarding hepatic effects in humans after dermal exposure to chromium compounds.

Information regarding liver effects in animals after dermal exposure to chromium or its compounds is limited. A single application of 0.5% potassium dichromate (0.175% chromium(VI)) to the shaved skin of rats resulted in increased levels of serotonin in the liver, decreased activities of acetylcholinesterase and cholinesterase in the plasma and erythrocytes, increased levels of acetylcholine in the blood, and increased glycoprotein hexose in the serum. These effects may indicate alterations in carbohydrate

## 3. HEALTH EFFECTS

metabolism (Merkur'eva et al. 1982). Application of 50 mg chromium/kg/day (specific chemical or valence state not reported) for 30 days to clipped skin under occluded conditions to female guinea pigs produced small increases in enzyme activities in liver tissue, specifically aspartate aminotransferase (17%), alanine aminotransferase (2%), acid phosphatase (16%), and gamma glutamyl transpeptidase (54%), compared to untreated controls (Mathur 2005). Microscopic evaluation of the liver showed “shrunk” hepatocytes and thickening of the walls of hepatic arteries.

**Renal Effects.** Acute nephritis with albuminuria and oliguria, polyuria, and nitrogen retention were observed in individuals after application of a salve that contained potassium chromate. These effects disappeared in individuals who survived. Autopsy of people who died revealed hyperemia and tubular necrosis (Brieger 1920). Acute nephritis with polyuria and proteinuria were also described in a man who was admitted to a hospital with skin ulcers on both hands due to dermal exposure to ammonium dichromate in a planographic printing establishment where he had worked for a few months (Smith 1931). A 49-year-old man with an inoperable carcinoma of the face was treated with chromic acid crystals. Severe nephritis occurred after treatment with the chromium(VI) compound. Urinalysis revealed marked protein in the urine. Death resulted 4 weeks after exposure. A postmortem examination of the kidneys revealed extensive destruction of the tubular epithelium (Major 1922).

Application of 50 mg chromium/kg/day (specific chemical or valence state not reported) for 30 days to clipped skin under occluded conditions to female guinea pigs produced increases in enzyme activities in renal tissue, specifically aspartate aminotransferase (8%), alanine aminotransferase (96%), and acid phosphatase (4%), compared to untreated controls (Mathur 2005). Microscopic evaluation of the kidney showed lobularization of the glomerular tuft and congestion of capillaries. No additional information on renal effects of dermal exposure to chromium(VI) or chromium(III) compounds was identified.

**Dermal Effects.** Occupational exposure to airborne chromium compounds has been associated with effects on the nasal septum, such as ulceration and perforation. These studies are discussed in Section 3.2.1.2 on Respiratory Effects. Dermal exposure to chromium compounds can cause contact allergic dermatitis in sensitive individuals, which is discussed in Section 3.2.3.3. Skin burns, blisters, and skin ulcers, also known as chrome holes or chrome sores, are more likely associated with direct dermal contact with solutions of chromium compounds, but exposure of the skin to airborne fumes and mists of chromium compounds may contribute to these effects.

## 3. HEALTH EFFECTS

Acute dermal exposure of humans to chromium(VI) compounds causes skin burns. Necrosis and sloughing of the skin occurred in individuals at the site of application of a salve containing potassium chromate. Twelve of 31 people died as a result of infection of these areas (Brieger 1920). In another case, a man who slipped at work and plunged his arm into a vat of chromic acid had extensive burns and necrosis on his arm (Cason 1959).

Longer-term occupational exposure to chromium compounds in most chromium-related industries can cause deep penetrating holes or ulcers on the skin. A man who had worked for a few months in a planographic printing establishment, where he handled and washed sheets of zinc that had been treated with a solution of ammonium dichromate, had skin ulceration on both hands (Smith 1931).

In an extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants, 50% of the chromate workers had skin ulcers or scars. In addition, inflammation of oral structures, keratosis of the lips, gingiva, and palate, gingivitis, and periodontitis due to exposure of these mucocutaneous tissues to airborne chromium were observed in higher incidence in the chromate workers than in controls. Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m<sup>3</sup> air); water-soluble chromium(VI) compounds (0.005–0.17 mg chromium(VI)/m<sup>3</sup>); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent chromium(III) (0–0.47 mg chromium/m<sup>3</sup> air) (PHS 1953). Among 258 electroplating workers exposed to chromium trioxide fumes at 0.1 mg chromium(VI)/m<sup>3</sup> for <1 year, 5% developed dental lesions, consisting of yellowing and wearing down of the teeth (Gomes 1972).

Chronic exposure of chrome chemical production workers produced dermal symptoms, including irritated and ulcerated skin, dermatitis, and burns (Gibb et al. 2000a). Medical records of 2,307 male workers (all nonsmokers) employed at a chromate production plant in Baltimore, Maryland between 1950 and 1974 were evaluated to determine the percentage of workers reporting clinical symptoms, mean time of employment to first diagnosis of symptoms, and mean exposure to chromium(VI) at the time of first diagnosis (exposure for each worker was the annual mean in the area of employment during the year of first diagnosis). Ulcerated skin occurred in 31.6% of workers, at a mean exposure of 0.029 mg Cr(VI)/m<sup>3</sup> and a mean time to first diagnosis of 373 days. Ulcerated skin was significantly associated with chromium(VI) exposure (p=0.004), with a relative risk of 1.11. Burns were observed in 31.4% of workers, with a mean exposure and time to onset of 0.027 mg/m<sup>3</sup> and 409 days, respectively. Dermatitis was observed in 18.5% of workers, with a mean exposure and time to onset of 0.029 mg/m<sup>3</sup> and 624 days,

## 3. HEALTH EFFECTS

respectively. Irritated skin was observed in 15.1% of workers, with a mean exposure and time to onset of  $0.025 \text{ mg/m}^3$  and 719 days, respectively.

Irritation and ulceration of the buccal cavity, as well as chrome holes on the skin, were also observed in workers in a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes (Lieberman 1941). Electroplaters in Czechoslovakia exposed to an average of  $0.414 \text{ mg chromium(VI)/m}^3$  above the plating baths also had high incidences of buccal cavity changes, including chronic tonsillitis, pharyngitis, and papilloma (Hanslian et al. 1967). In a study of 303 electroplating workers in Brazil, whose jobs involve working with cold chromium trioxide solutions, >50% had ulcerous scars on the hands, arms, and feet. Air monitoring revealed that most workers were exposed to  $\geq 0.1 \text{ mg chromium(VI)/m}^3$ , but even those exposed to  $< 0.1 \text{ mg chromium(VI)/m}^3$  developed lesions (Gomes 1972). Chrome holes were also noted at high incidence in chrome platers in Singapore, while controls had no skin ulcers (Lee and Goh 1988). The incidence of skin ulcers was significantly increased in a group of 997 chrome platers compared with 1,117 controls. The workers had been exposed to chromium(VI) in air and in dust. The air levels were generally  $< 0.3 \text{ mg chromium(VI)/m}^3$ , and dust levels were generally between 0.3 and 97 mg chromium(VI)/g (Royle 1975b). In a NIOSH Health Hazard Evaluation of an electroplating facility in the United States, seven workers reported past history of skin sores, and nine had scars characteristic of healed chrome sores. The workers had been employed for an average of 7.5 years and were exposed to a mean concentration of  $0.004 \text{ mg chromium(VI)/m}^3$  in air. In addition, spot tests showed widespread contamination of almost all workroom surfaces and hands (Lucas and Kramkowski 1975).

An early report of cases of chrome ulcers in leather tanners noted that the only workmen in tanneries who suffered chrome holes were those who handled dichromate salts. In one of these cases, the penetration extended into the joint, requiring amputation of the finger (Da Costa et al. 1916). In a medical survey of a chemical plant that processed chromite ore, 198 of 285 workers had chrome ulcers or scars on the hands and arms. These workers had been exposed to one or more chromium(VI) compounds in the form of chromium trioxide, potassium dichromate, sodium dichromate, potassium chromate, sodium chromate, and ammonium dichromate (Edmundson 1951).

Similar dermal effects have been observed in animals. Dermal application of chromium(VI) compounds to the clipped, nonabraded skin of rabbits at 42–55 mg/kg resulted in skin inflammation, edema, and necrosis. Skin corrosion and eschar formation occurred at lethal doses (see Section 3.2.3.1) (Gad et al. 1986). Application of 0.01 or 0.05 mL of 0.34 molar solution of potassium dichromate (0.35 mg

## 3. HEALTH EFFECTS

chromium(VI) or 1.9 mg chromium(VI)/kg) to the abraded skin of guinea pigs resulted in skin ulcers (Samitz 1970; Samitz and Epstein 1962). Similar application of 0.01 mL of a 1 molar solution of chromium sulfate (1 mg chromium(III)/kg) however, did not cause skin ulcers in guinea pigs (Samitz and Epstein 1962). In a primary dermal irritation test, application of 88 mg chromium(III) as chromium nicotinate in corn oil to clipped skin of male and female New Zealand albino rabbits produced very slight erythema after 1 hour after application, with no signs of dermal irritation 48 hours after application (Shara et al. 2005).

Dermal sensitization due to hypersensitivity to chromium is discussed in Section 3.2.3.3.

**Ocular Effects.** Medical records of 2,307 male workers (all nonsmokers) employed at a chromate production plant in Baltimore, Maryland between 1950 and 1974 were evaluated to determine the percentage of workers reporting clinical symptoms, mean time of employment to first diagnosis of symptoms, and mean exposure to chromium(VI) at the time of first diagnosis (exposure for each worker was the annual mean in the area of employment during the year of first diagnosis) (Gibb et al. 2000a). Conjunctivitis was reported on 20.0% of the study population, at a mean exposure level of 0.025 mg Cr(VI)/m<sup>3</sup> and a mean time-to-onset of 604 days.

Direct contact of the eyes with chromium compounds also causes ocular effects. Corneal vesication was described in a worker who accidentally got a crystal of potassium dichromate or a drop of a potassium dichromate solution in his eye (Thomson 1903). In an extensive study of chromate workers in seven U.S. chromate production plants, eyes were examined because accidental splashes of chromium compounds into the eye had been observed in these plants. Congestion of the conjunctiva was found in 38.7% of the 897 workers, discharge in 3.2%, corneal scarring in 2.3%, any abnormal finding in 40.8%, and burning in 17.0%, compared with respective frequencies of 25.8, 1.3, 2.6, 29.0, and 22.6% in 155 nonchromate workers. Only the incidences of congestion of the conjunctiva and any abnormal findings were significantly higher in the exposed workers than in the controls (PHS 1953).

Instillation of 0.1 mL of a 1,000 mg chromium(VI)/L solution of sodium dichromate and sodium chromate (pH 7.4) was not irritating or corrosive to the eyes of rabbits (Fujii et al. 1976). Histological examination of the eyes of rats exposed to chromium dioxide (15.5 mg chromium(IV)/m<sup>3</sup>) in air revealed no lesions (Lee et al. 1989). In a primary eye irritation test, direct conjunctival instillation of 5.2 mg chromium(III) as chromium nicotinate in water to male and female New Zealand albino rabbits produced

## 3. HEALTH EFFECTS

conjunctivitis within 1 hour of application, although no corneal opacity or iritis was observed (Shara et al. 2005).

**3.2.3.3 Immunological and Lymphoreticular Effects**

In addition to the irritating and ulcerating effects, direct skin contact with chromium compounds elicits an allergic response, characterized by eczema or dermatitis, in sensitized individuals. Chromium-induced allergic contact dermatitis is typically isolated to areas at the site of contact, rarely occurring in areas remote to the point of contact (Winder and Carmody 2002). Following an induction phase during which the patient becomes sensitized, subsequent dermal exposure results in an allergic response. The acute response phase lasts for a few days to a few weeks and is characterized by erythema, edema, and small and large blisters; the chronic phase exhibits similar clinical features, but may also include thickened, scaly, and fissured skin (Winder and Carmody 2002). Evaluation by light and electron microscopy of skin biopsies of individuals with active dermatitis due to chromium shows increased intracellular edema of lower epidermal keratinocytes, formation of vacuoles in cells of the lower epidermis and dendritic, spindle-shaped cells in the upper dermis (Shah and Palmer 2002).

Studies using dermal patch testing as a technique to diagnose chromium sensitivity show that challenge with small amounts of chromium(VI) or chromium(III) can induce a response in sensitized individuals. A series of studies conducted by Hansen et al. (2003, 2006a, 2006b) show that patients with chromium-induced dermatitis associated with exposure to leather products responded to both low-dose and high-dose chromium(VI) and chromium(III) challenge using skin patch tests. In a group of 18 patients previously diagnosed with chromium sensitivity, the concentration of chromium(VI) as potassium dichromate required to elicit a positive response on skin patch challenge was 6 mg chromium(VI)/L and 1 mg chromium(III)/L as chromium trichloride (Hansen et al. 2003). Using higher doses in 2,211 patients with suspected contact dermatitis, 71 (3.2%) tested positive to 0.5% potassium dichromate (0.18% chromium(VI)) on skin patch challenge; of these 71 chromium(VI)-positive patients, 31 also produce a positive result when challenged with 13% chromium trichloride (3.7% chromium(III)) (Hansen et al. 2006b). The positive response to both chromium(VI) and chromium(III) challenge may indicate that exposure to both compounds may induced sensitivity or that there is cross-sensitivity between chromium(VI) and chromium(III) compounds on challenge. Similar results have been reported with high-dose chromium(III), showing that patch testing of chromium(VI)-sensitive patients with chromium(III) compounds can elicit an allergic reaction (Fregert and Rorsman 1964, 1966; Mali et al. 1966).

## 3. HEALTH EFFECTS

A study was performed on 54 volunteers who with chromium-induced allergic contact dermatitis to determine a dose-response relationship and to determine a minimum-elicitation threshold concentration (MET) that produces an allergic response in sensitive individuals (Nethercott et al. 1994). Patch testing was performed on the subjects in which the concentration of potassium chromate(VI) was varied up to 4.4  $\mu\text{g}/\text{cm}^2$ . Two percent (1/54) had a MET of 0.018. About 10% were sensitized at 0.089  $\mu\text{g}/\text{cm}^2$  and all were sensitized at 4.4  $\mu\text{g}/\text{cm}^2$ . Comparable studies were performed with chromium(III) chloride, however, only 1 showed a positive response at 33  $\mu\text{g}/\text{cm}^2$ , and upon retesting was negative. Based on these findings the authors concluded that soil concentrations of chromium(VI) and chromium(III) of 450 and 165,000 ppm, respectively, should not pose a hazard of allergic contact dermatitis to 99.99% of people who might be exposed to chromium through soil-skin contact.

Numerous studies have investigated the cause of dermatitis in patients and in workers in a variety of occupations and industries and have determined that chromium compounds are the sensitizing agents. In these studies, patch tests were conducted with chromium(VI) or chromium(III) compounds using various concentrations. In one study using 812 healthy volunteers, patch testing with a 0.5% solution of potassium dichromate chromium(VI) revealed chromium sensitivity in 14 of the volunteers (1.7% of the test population). Of the 14 positive reactions, 10 occurred in a group of 110 offset printers, lithographers, and printing plant cleaners with concurrent exposure to chromium (Peltonen and Fraki 1983). Subjects with a sensitivity to chromium and challenged with a 0.001% solution potassium dichromate had increased skin thickness and blood flow (Eun and Marks 1990). Studies conducted on chromium(VI) sensitive printers and lithographers indicate that chromium(VI) compounds elicit reactions more frequently than do chromium(III) compounds (Levin et al. 1959; Mali et al. 1966; Samitz and Shrager 1966). The authors attributed this to a greater degree of permeation of the hexavalent form than the trivalent form through the skin (see Section 3.4.1.3).

In a study of skin disease among workers at an automobile factory, 230 workers with skin disease and 66 controls were patch tested with potassium dichromate (0.175% chromium(VI)). Sensitivity to potassium dichromate was seen in 24% of the patients and 1% of the controls. Most of the sensitive patients were assemblers who handled nuts, bolts, screws, and washers, which were found to have chromate on the surfaces as a result of a chromate dip used in the engine assembly process.

Discontinuation of use of the chromate dip resulted in a significant decrease in the prevalence of dermatitis 6 months later (Newhouse 1963). Among 300–400 men directly exposed to cement dust, 8 had clinical symptoms of cement eczema. All eight tested positive with potassium dichromate, while only



## 3. HEALTH EFFECTS

four tested positive with cement (Engebrigtsen 1952). Patch testing of employees of the Baltimore and Ohio Railroad system with a variety of chemicals revealed that in 32 of 98 cases of dermatitis, the antirust diesel-engine coolant compound, which contained sodium chromate, was the etiological agent (Kaplan and Zeligman 1962). Among 200 employees who worked in a diesel locomotive repair shop, 6 cases of chromate dermatitis were diagnosed by positive patch tests to samples of radiator fluid and to 0.25% sodium dichromate (0.09% chromium(VI)). The radiator fluid to which the workers were occupationally exposed contained 66% sodium dichromate (Winston and Walsh 1951). A search for the source of chromium exposure in workers who developed contact dermatitis in wet sandpapering of primer paint on automobiles revealed that the paint contained zinc chromate (Engel and Calnan 1963).

In a study of 1,752 patients considered to have occupational dermatoses, contact dermatitis was the main diagnosis in 1,496 patients (92% women, 83% men). The allergic type, as opposed to the irritant type, was more prevalent in men (73%) than in women (51%). Positive patch tests to chromium (not otherwise specified) occurred in 8% of the women and 29% of the men. Among 280 chromium-sensitized men, 50% were employed in building and concrete work, 17% in metal work, and 12% in tanneries. In the 42 chromium-sensitized women, 20% were in cement work, 19% in metal work, 28% in cleaning, and 15% in laboratory work (Fregert 1975). A survey study of 335 construction workers (including tile setters, painters, construction and cement workers, and wood processors) with occupational dermatitis showed that 152 workers (approximately 45%) were sensitized to chromium based on positive to patch test to potassium dichromate (Bock et al. 2003).

Chromate sensitivity has also been reported in women who frequently used dichromate-containing detergent and bleach (Basketter et al. 2001; Wahba and Cohen 1979).

Other industries and sources of chromium that have resulted in chromium sensitivity include welding, printing, glues, wood ash, foundry sand, match heads, machine oils, timber preservative, boiler linings, making of television screens, magnetic tapes, tire fitting, chrome plating, wood and paper industry, leather tanning, cement working, and milk testing (Burrows 1983; Chen et al. 2008; Gass and Todd 2007; Lockman 2002; Wong et al. 1998).

Animals can also be sensitized to chromium compounds. Contact sensitivity was induced in mice by rubbing a solution of 1% potassium dichromate (0.35% chromium(VI))  $\approx$ 50 times on the shaved abdomens. Challenge with potassium dichromate on the ear resulted in significant induction of

### 3. HEALTH EFFECTS

sensitivity, measured by ear thickness and histologically observed infiltration of nucleophilic leukocytes (Mor et al. 1988).

Guinea pigs can be sensitized to chromium(VI) and chromium(III) compounds by a series of intradermal injections of 0.009 mg chromium(VI)/kg as potassium dichromate or of 0.004 mg chromium(III)/kg as chromium trichloride. Regardless of the compound used to sensitize the guinea pigs, subsequent patch testing with chromium(VI) or chromium(III) yielded the same erythmatic reaction. The response, however, was greater when chromium(VI) was used as the sensitizer (Gross et al. 1968). Similarly, the same erythmatic response to chromium(VI) and chromium(III) compounds was noted in guinea pigs sensitized to 0.04 mg chromium(VI)/kg as potassium dichromate or 0.03 mg chromium(III)/kg as chromium sulfate (Jansen and Berrens 1968).

Results of skin testing to demonstrate or diagnose chromium sensitization are recorded in Table 3-5 for chromium(VI) and Table 3-6 for chromium(III).

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

#### **3.2.3.4 Neurological Effects**

#### **3.2.3.5 Reproductive Effects**

#### **3.2.3.6 Developmental Effects**

#### **3.2.3.7 Cancer**

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

### **3.3 GENOTOXICITY**

*In vivo* studies of chromium compounds are summarized in Table 3-7. *In vitro* studies on the genotoxicity of chromium(VI) and chromium(III) compounds are summarized in Tables 3-8 and 3-9, respectively. Chromium(VI) compounds rapidly (within seconds to minutes) enter cells by facilitated diffusion, while chromium(III) compounds enter much more slowly (within days) by simple diffusion; therefore, chromium(VI) compounds are of greater concern with regard to health effects. Available genotoxicity studies on occupationally exposed humans typically evaluate effects in blood cells since blood is easily accessible, whereas evaluation of effects in cells from cancer target tissues (e.g., lung,

## 3. HEALTH EFFECTS

**Table 3-7. Genotoxicity of Chromium *In Vivo***

Species (test system)	End point	Results	Reference	Valence	Compound
<i>Drosophila melanogaster</i>	Gene mutation	+	Gava et al. 1989b; Rasmuson 1985; Rodriguez-Arnaiz and Martinez 1986; Zimmering et al. 1985	(VI)	Potassium dichromate, sodium dichromate, chromium trioxide, calcium chromate
<i>D. melanogaster</i>	Gene mutation	+	Olvera et al. 1993	(VI)	Chromium trioxide
<i>D. melanogaster</i>	Gene mutation	+	Kaya et al. 2002	(VI)	Potassium dichromate
<i>D. melanogaster</i>	Gene mutation	+	Amrani et al. 1999	(VI)	Potassium chromate, potassium dichromate
<i>D. melanogaster</i>	Gene mutation	-	Amrani et al. 1999	(III)	Chromium chloride
Human lymphocytes	Chromosomal aberrations	+	Koshi et al. 1984; Sarto et al. 1982	(VI)	Stainless steel, welding fumes, chromium trioxide
Human lymphocytes	Chromosomal aberrations	-	Hamamy et al. 1987	(III)	Chrome alum (primarily chromium sulfate)
Human lymphocytes	Chromosomal aberrations	-	Husgafvel- Pursiainen et al. 1982	(VI)	Stainless steel, welding fumes
Human lymphocytes	Sister chromatid exchanges	+	Koshi et al. 1984; Lai et al. 1998; Sarto et al. 1982; Stella et al. 1982	(VI)	Chromium plating, stainless steel, welding fumes, chromium trioxide
Human lymphocytes	DNA strand breaks, hydroxylation of deoxyquanosine	-	Gao et al. 1994	(VI)	Production of bichromate
Human lymphocytes	Sister chromatid exchanges	-	Nagaya et al. 1991	(VI)	Chromium plating
Human lymphocytes	Sister chromatid exchanges, DNA strand breaks	+	Werfel et al. 1998	(VI)	Welding fumes
Human lymphocytes	Sister chromatid exchanges	-	Nagaya 1986	(VI)	Chromium plating

## 3. HEALTH EFFECTS

**Table 3-7. Genotoxicity of Chromium *In Vivo***

Species (test system)	End point	Results	Reference	Valence	Compound
Human peripheral lymphocytes	Micronuclei	+	Vaglenov et al. 1999	(VI)	Chromium electroplating
Human peripheral lymphocytes	Micronuclei	+	Benova et al. 2002	(VI)	Chromium plating
Human buccal mucosa	Micronuclei	+	Benova et al. 2002	(VI)	Chromium plating
Human peripheral lymphocytes	Chromosome aberrations, sister chromatid exchanges	–	Benova et al. 2002	(VI)	Chromium plating
Human peripheral lymphocytes	DNA strand breaks	+	Gambelunghe et al. 2003	(VI)	Chromium plating
Human buccal mucosa	Chromosome aberrations, sister chromatid exchanges	–	Benova et al. 2002	(VI)	Chromium plating
Human whole blood cells	Sister chromatid exchanges	+	Wu et al. 2001	(VI)	Chromium electroplating
Human peripheral lymphocytes	Micronuclei, DNA-protein crosslinks	+	Medeiros et al. 2003a	(III)	Tanners
Human peripheral lymphocytes	Micronuclei	–	Medeiros et al. 2003a	(VI)	Welders
Human peripheral lymphocytes	DNA-protein crosslinks	+	Medeiros et al. 2003a	(VI)	Welders
New polychromatic erythrocytes	Micronuclei	+	LeCurieux et al. 1992	(VI)	Potassium chromate
Rat lung (intratracheal exposure)	DNA alterations	+	Izzotti et al. 1998	(VI)	Sodium dichromate
Rat liver (intratracheal exposure)	DNA alterations	–	Izzotti et al. 1998	(VI)	Sodium dichromate
Rat liver (oral exposure)	DNA-protein crosslinks	+	Coogan et al. 1991a	(VI)	Potassium chromate
Rat liver and kidney nuclei (intraperitoneal exposure)	DNA crosslinks, DNA-protein crosslinks, DNA strand breaks	–	Cupo and Wetterhahn 1985	(III)	Chromium oxide
Rat liver, kidney, and lung nuclei (intraperitoneal exposure)	DNA-protein crosslinks	+	Tsapalos et al. 1983b	(VI)	Sodium dichromate
Rat hepatocytes (oral exposure)	Unscheduled DNA synthesis	–	Mirsalis et al. 1996	(VI)	Potassium chromate
Rat (F344/N) bone marrow cells (oral exposure)	Micronuclei	–	NTP 2008b	(III)	Chromium picolinate

## 3. HEALTH EFFECTS

**Table 3-7. Genotoxicity of Chromium *In Vivo***

Species (test system)	End point	Results	Reference	Valence	Compound
Rat (Sprague-Dawley) hepatic	DNA fragmentation	–	Shara et al. 2005	(III)	Niacin-bound chromium
Mouse erythrocytes (oral exposure)	Micronuclei	–	Shindo et al. 1989	(VI)	Potassium chromate
Mouse (B <sub>6</sub> C <sub>3</sub> F <sub>1</sub> , BALB/c) erythrocytes (oral exposure)	Micronuclei	–	NTP 2007	(VI)	Sodium dichromate dihydrate
Mouse (am3-C57BL/6) erythrocytes (oral exposure)	Micronuclei	+	NTP 2007	(VI)	Sodium dichromate dihydrate
Mouse B <sub>6</sub> C <sub>3</sub> F <sub>1</sub> (oral exposure)	Micronuclei	–	NTP 2008b	(III)	Chromium picolinate monohydrate
Mouse (B <sub>6</sub> C <sub>3</sub> F <sub>1</sub> ) erythrocytes (oral exposure)	Micronuclei	–	NTP 2008b	(III)	Chromium picolinate monohydrate
Mouse (transplacental exposure)	DNA deletions	+	Kirpnick-Sobol et al. 2006	(III)	Chromium (III) chloride salt
Mouse (transplacental exposure)	DNA deletions	+	Kirpnick-Sobol et al. 2006	(VI)	Potassium dichromate
Mouse (BDF1) bone marrow cells (drinking water exposure)	Micronuclei	–	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (BDF1) peripheral blood cells (drinking water exposure)	Micronuclei	–	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (BDF1) bone marrow cells (drinking water exposure)	Micronuclei	–	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (BDF1) peripheral blood cells (drinking water exposure)	Micronuclei	–	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (BDF1) peripheral blood cells (drinking water exposure)	Micronuclei	–	De Flora et al. 2006	(III)	Chromic potassium sulfate dodecahydrate
Mouse (BDF1) bone marrow cells (drinking water exposure)	Micronuclei	–	De Flora et al. 2006	(III)	Chromic potassium sulfate dodecahydrate
Mouse (BDF1) bone marrow cells (gavage exposure)	Micronuclei	–	De Flora et al. 2006	(VI)	Potassium dichromate

## 3. HEALTH EFFECTS

**Table 3-7. Genotoxicity of Chromium *In Vivo***

Species (test system)	End point	Results	Reference	Valence	Compound
Mouse (BDF1) bone marrow cells (intraperitoneal exposure)	Micronuclei	+	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) bone marrow—dams (drinking water exposure)	Micronuclei	—	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (Swiss) bone marrow—dams (drinking water exposure)	Micronuclei	—	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) bone marrow—dams (intraperitoneal exposure)	Micronuclei	+	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (Swiss) bone marrow—dams (intraperitoneal exposure)	Micronuclei	+	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) fetal liver cells (transplacental exposure from drinking water)	Micronuclei	—	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (Swiss) fetal liver cells (transplacental exposure from drinking water)	Micronuclei	—	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) fetal peripheral blood cells (transplacental exposure from drinking water)	Micronuclei	—	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (Swiss) fetal peripheral blood cells (transplacental exposure from drinking water)	Micronuclei	—	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) fetal liver cells (transplacental exposure from intraperitoneal injection)	Micronuclei	+	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (Swiss) fetal liver cells (transplacental exposure from intraperitoneal injection)	Micronuclei	+	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) fetal peripheral blood cells (transplacental exposure from intraperitoneal injection)	Micronuclei	+	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate

## 3. HEALTH EFFECTS

**Table 3-7. Genotoxicity of Chromium *In Vivo***

Species (test system)	End point	Results	Reference	Valence	Compound
Mouse (Swiss) fetal peripheral blood cells (transplacental exposure from intraperitoneal injection)	Micronuclei	+	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse leukocytes	DNA damage	+	Devi et al. 2001	(VI)	Potassium dichromate
Mouse erythrocytes (intraperitoneal exposure)	Micronuclei	–	Shindo et al. 1989	(VI)	Potassium chromate
Mouse erythrocytes (intraperitoneal exposure)	Micronuclei	+	Itoh and Shimada 1997; Wild 1978	(VI)	Potassium chromate
Mouse erythrocytes (intraperitoneal exposure)	Micronuclei	–	Itoh and Shimada 1996	(III)	Chromium chloride
Mouse erythrocytes (intraperitoneal exposure)	Micronuclei	+	Itoh and Shimada 1996	(VI)	Potassium chromate
Mouse peripheral lymphocytes	DNA damage	+	Wang et al. 2006	(VI)	Potassium chromate
Mouse bone marrow cells (oral exposure)	Micronuclei	–	Mirsalis et al. 1996	(VI)	Potassium chromate
Mouse bone marrow cells (gavage)	Chromosomal aberrations	+	Sarkar et al. 1993	(VI)	Chromium trioxide
Mouse bone marrow (intraperitoneal exposed)	Cell mutation	+	Itoh and Shimada 1998	(VI)	Potassium dichromate
Mouse hepatocytes (intraperitoneal exposed)	Cell mutation	+	Itoh and Shimada 1997, 1998	(VI)	Potassium dichromate
Mouse bone marrow (intraperitoneal exposed)	Micronuclei	+	Chorvatovičová et al. 1993; Wrońska-Nofer et al. 1999	(VI)	Potassium dichromate
Mouse (intraperitoneal exposure)	Dominant lethality	+	Paschin et al. 1982	(VI)	Potassium dichromate
Mouse liver and kidney cells (intraperitoneal exposure)	Single strand breaks	+	Ueno et al. 2001	(VI)	Potassium dichromate
Mouse spleen, lung, and brain cells (intraperitoneal exposure)	Single strand breaks	–	Ueno et al. 2001	(VI)	Potassium dichromate

– = negative results; + = positive results; (0) = 0 valence; (III) = trivalent; (VI) = hexavalent; DNA = deoxyribonucleic acid;

## 3. HEALTH EFFECTS

**Table 3-8. Genotoxicity of Chromium(VI) *In Vitro***

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
Subcellular targets:					
<i>Escherichia coli</i> DNA	DNA-protein crosslinks	No data	–	Fornance et al. 1981	Potassium chromate
Nuclei of mouse L1210 leukemia cells	DNA fragmentation	No data	–	Fornance et al. 1981	Potassium chromate
Double-standed M13mp2 bacteriophage DNA transferred to <i>E. coli</i>	Forward mutations	No data	+	Snow and Xu 1989	Potassium chromate
Puc 19 plasmid DNA	Gene mutation	No data	+	Kortenkamp et al. 1996b	Potassium chromate
Papilloma virus	Gene mutation	No data	+	Kowalski et al. 1996	Potassium chromate
PSV2neo-based plasmid DNA	DNA polymerase arrest	+	–	Bridgewater et al. 1994b, 1998	Sodium dichromate
Prokaryotic organisms:					
<i>Bacillus subtilis</i>	Recombinations	No data	+	Kanematsu et al. 1980; Nakamuro et al. 1975	Potassium chromate, potassium dichromate
<i>E. coli</i> PQ37, PQ35	Induction of SOS response	–	+	Olivier and Marzin 1987	Potassium chromate, potassium dichromate
<i>E. coli</i> AB1157, GC2375, UA4202, PQ30	Induction of SOS response	No data	+	Llagostera et al. 1986	Chromium chromate, potassium dichromate, chromium trioxide
<i>E. coli</i> Wp2, Hs30R, B/rWP2	Reverse mutations	No data	+	Kanematsu et al. 1980; Nakamuro et al. 1978; Venitt and Levy 1974	Potassium dichromate, potassium chromate, sodium chromate



## 3. HEALTH EFFECTS

**Table 3-8. Genotoxicity of Chromium(VI) *In Vitro***

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
<i>E. coli</i> , WP2/pKM101, WP2 uvrA/pKM101	Reverse mutations	No data	+	Watanabe et al. 1998a	Chromium trioxide, sodium dichromate
<i>E. coli</i> , WP2 uvrA/pKM101	Reverse mutations	+	+	NTP 2007	Sodium dichromate dihydrate
<i>Salmonella typhimurium</i> TA100, TA98	Reverse mutations	+	+	NTP 2007	Sodium dichromate dihydrate
<i>S. typhimurium</i> TA100	Base pair substitutions	No data	+	DeFlora 1978	Sodium dichromate
<i>S. typhimurium</i> TA100	Base pair substitutions	No data	+	Bennicelli et al. 1983	Sodium dichromate
<i>S. typhimurium</i> TA102	Base pair substitutions	No data	+	Bennicelli et al. 1983	Sodium dichromate
<i>S. typhimurium</i> TA92	Base pair substitutions	No data	+	Bennicelli et al. 1983	Sodium dichromate
<i>S. typhimurium</i> TA1535	Base pair substitutions	No data	-	Bennicelli et al. 1983	Sodium dichromate
<i>S. typhimurium</i> TA97	Frame shift mutations	No data	+	Bennicelli et al. 1983	Sodium dichromate
<i>S. typhimurium</i> TA1537, TA1538	Frame shift mutations	No data	-	Bennicelli et al. 1983	Sodium dichromate
<i>S. typhimurium</i> TA1978	Frame shift mutations	No data	±	Bennicelli et al. 1983	Sodium dichromate
<i>S. typhimurium</i> TA1535	Base pair substitutions	-	±	Nakamura et al. 1987	Potassium dichromate
<i>S. typhimurium</i> TA100	Base pair substitutions	+	+	Venier et al. 1982	Potassium dichromate
<i>S. typhimurium</i> TA1538	Frame shift mutations	-	-	Venier et al. 1982	Potassium dichromate
<i>S. typhimurium</i> TA98	Frame shift mutations	-	±	Venier et al. 1982	Potassium dichromate
<i>S. typhimurium</i> TA97a, TA98	Frame shift mutations	+	+	Tagliari et al. 2004	Potassium dichromate
<i>S. typhimurium</i> TA100, TA102	Base pair substitutions	+	+	Tagliari et al. 2004	Potassium dichromate

## 3. HEALTH EFFECTS

**Table 3-8. Genotoxicity of Chromium(VI) *In Vitro***

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
<i>S. typhimurium</i> TA100	Base pair substitutions	–	–	DeFlora 1981	Sodium dichromate, potassium chromate, calcium chromate, ammonium chromate, chromium trioxide
<i>S. typhimurium</i> TA1535	Base pair substitutions	No data	+	DeFlora 1981	Sodium dichromate, potassium chromate, calcium chromate, ammonium chromate, chromium trioxide
<i>S. typhimurium</i> TA100, TA1535	Base pair substitutions	No data	+	Haworth et al. 1983	Calcium chromate
<i>S. typhimurium</i> TA98, TA1537	Frame shift mutations	No data	+	Haworth et al. 1983	Calcium chromate
<i>S. typhimurium</i> TA100, TA1535	Base pair substitutions	No data	–	Kanematsu et al. 1980	Potassium dichromate
<i>S. typhimurium</i> TA100, TA1537, TA1538	Frame shift mutations	No data	–	Kanematsu et al. 1980	Potassium dichromate
<i>S. typhimurium</i> TA 1535 pSK1002	Mutations	+	+	Yamamoto et al. 2002	Potassium dichromate
<i>S. typhimurium</i> TA102, TA2638	Reverse mutations	No data	+	Watanabe et al. 1998a	Chromium trioxide, sodium dichromate
Eukaryotic organisms:					
Yeasts:					
<i>Saccharomyces cerevisiae</i> D7	Mitotic gene conversions	No data	+	Fukunaga et al. 1982; Singh 1983	Chromium trioxide
<i>S. cerevisiae</i> D7	Reverse mutations	No data	+	Singh 1983	Potassium dichromate
<i>S. cerevisiae</i> D7	Mitotic cross-over	No data	+	Fukunaga et al. 1982	Chromium trioxide
<i>S. cerevisiae</i>	DNA deletions	No data	+	Kirpnick-Sobol et al. 2006	Potassium dichromate

## 3. HEALTH EFFECTS

**Table 3-8. Genotoxicity of Chromium(VI) *In Vitro***

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
<i>Schizosacharomyces pombe</i>	Mitotic gene conversion	No data	+	Bonatti et al. 1976	Potassium dichromate
<i>S. pombe</i>	Forward mutations	No data	+	Bonatti et al. 1976	Potassium dichromate
Chickens:					
Chick embryos	DNA damage cross links, strand breaks, DNA-protein crosslinks	No data	+	Tsapakos et al. 1983a	Sodium chromate
Mammalian cells:					
Human embryonic lung fibroblasts (IMR-90)	DNA-protein crosslinks, DNA fragmentation	No data	+	Fornance et al. 1981	Potassium chromate
Human bronchial epithelial cells	DNA fragmentation	No data	+	Fornance et al. 1981	Potassium chromate
Human lymphocytes	Single strand breaks	No data	+	Depault et al. 2006	Potassium chromate
Human lymphocytes	DNA damage	No data	+	Blasiak and Kowalik 2000	Potassium dichromate
Human dermal fibroblasts (GM03440 cells)	DNA double-strand breaks	No data	+	Ha et al, 2003, 2004	Sodium chromate
Human bronchial fibroblasts (WTHBF-6 cells)	chromosome aberrations	No data	+	Holmes et al. 2006	Sodium chromate
Human bronchial fibroblasts (WTHBF-6 cells)	Disruption of mitosis	No data	+	Wise et al. 2006a	Sodium chromate
Human bronchial epithelial cells (BEP2D cells)	chromosome aberrations	No data	+	Wise et al. 2006b	Sodium chromate
Human lung fibroblasts	DNA polymerase arrest, DNA-DNA crosslinks	No data	+	Xu et al. 1996	Sodium chromate
Chinese hamster lung DON cells	Sister chromatid exchange, chromosomal aberrations	No data	+	Koshi 1979, Koshi and Iwaski 1983	chromium trioxide, zinc bromate, calcium chromate, potassium chromate
Chinese hamster ovary cells	Chromosomal aberrations, DNA fragmentation	No data	+	Blankenship et al. 1997	sodium chromate

## 3. HEALTH EFFECTS

**Table 3-8. Genotoxicity of Chromium(VI) *In Vitro***

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
Mouse L1210 leukemia cells	DNA fragmentation, DNA-protein crosslinks	No data	+	Fornace et al. 1981	Potassium chromate
Mouse embryo fibroblast cells	Chromosomal aberrations	No data	+	Sugiyama et al. 1986a	Calcium chromate
Mouse A18BcR cells	Unscheduled DNA synthesis	No data	+	Raffetto et al. 1977	Potassium dichromate
Mouse primary fetal cells	Transformations, chromosomal aberrations	No data	+	Raffetto et al. 1977	Potassium dichromate
Human gastric mucosa	DNA damage	No data	+	Trzeciak et al. 2000	Potassium dichromate
Human peripheral blood lymphocytes	DNA damage	No data	+	Trzeciak et al. 2000	Potassium dichromate
Human fibroblasts	Double strand breaks	No data	+	Ha et al. 2004	Sodium chromate
Human primary bronchial fibroblasts	Chromosomal aberrations	No data	+	Wise et al. 2002, 2004	Sodium chromate
Chinese hamster ovary cells	Chromosomal damage	No data	+	Seoane and Dulout 1999	Potassium dichromate
Mouse mammary FM3A carcinoma cells	Chromosomal aberrations	No data	+	Umeda and Nishmura 1979	Potassium dichromate, potassium chromate, chromium trioxide
Rat liver epithelial cells	Transformations	No data	+	Briggs and Briggs 1988	Potassium chromate

- = negative results; + = positive results; ± = weakly positive results; (VI) = hexavalent; DNA = deoxyribonucleic acid

## 3. HEALTH EFFECTS

**Table 3-9. Genotoxicity of Chromium(III) *In Vitro***

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
Subcellular targets:					
<i>Escherichia coli</i> DNA	DNA-protein crosslinks	No data	+	Fornace et al. 1981	Chromium trichloride
Nuclei of mouse L1210 leukemia cells	DNA fragmentation	No data	+	Fornace et al. 1981	Chromium trichloride
Single-stranded M13mp2 bacteriophage DNA	Replication assay: increased nucleotide incorporation	No data	+	Snow 1991; Snow and Xu 1989	Chromium trichloride
Double-stranded M13mp2 bacteriophage DNA transferred to <i>E. coli</i>	Forward mutations	No data	+	Snow 1991; Snow and Xu 1989	Chromium trichloride
pSV2neoTS DNA	DNA polymerase arrest	No data	+	Bridgewater et al. 1994b	Chromium trichloride
Prokaryotic organisms:					
<i>Bacillus subtilis</i>	Recombinations	No data	–	Kanematsu et al. 1980	Chromium sulfate, chromium potassium sulfate
<i>B. subtilis</i>	Recombinations	No data	–	Matsui 1980; Nakamuro et al. 1978; Nishioka 1975	Chromium trichloride
<i>B. subtilis</i>	Recombinations	No data	±	Nakamuro et al. 1978	Chromium nitrate
<i>B. subtilis</i>	Recombinations	No data	±	Nakamuro et al. 1978	Chromium acetate
<i>E. coli</i>	Gene mutations	No data	+	Sugden et al. 1990	cis-Dichlorobis (2,2'-bipyridyl) chromium(III)
<i>E. coli</i> WP2 <i>uvrA</i> /pKM101	Gene mutations	–	–	NTP 2008b	Chromium picolinate monohydrate
<i>E. coli</i> AB1157, GC275, VA4202, PQ30	Induction of SOS response	No data	–	Llagostera et al. 1986	Chromium trichloride, chromium nitrate, chromium acetate
<i>E. coli</i> PQ37, PQ35	Induction of SOS response	–	–	Olivier and Marzin 1987	Chromium trichloride hexahydrate
<i>E. coli</i> PQ37	Induction of SOS response	–	–	Venier et al. 1989	Chromium trichloride, chromium nitrate

## 3. HEALTH EFFECTS

**Table 3-9. Genotoxicity of Chromium(III) *In Vitro***

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
<i>E. coli</i> PQ37	Induction of SOS response	–	±	Venier et al. 1989	Chromium acetate
<i>Salmonella typhimurium</i> TA100, TA1535	Reverse mutations	–	–	De Flora 1981; Petrilli and De Flora 1978b	Chromium trichloride hexahydrate, chromium nitrite, monohydrate, chromium potassium sulfate, chromium acetate, neochromium, chromium alum, chromite
TA98, TA1537, TA1538	Base pair substitutions	–	–		
	Frame shift mutations	–	–		
<i>S. typhimurium</i> TA102	Base pair substitutions	–	–	Bennicelli et al. 1983	Chromium nitrate
<i>S. typhimurium</i> TA100, TA1535	Base pair substitutions	–	–	Venier et al. 1982	Chromium chloride hexahydrate, chromium nitrate monohydrate
TA98, TA1538	Frame shift mutations	–	–		
<i>S. typhimurium</i> TA100, TA98	Reverse mutations	–	–	NTP 2008b	Chromium picolinate monohydrate
<i>S. typhimurium</i> TA102, TA104, TA100, TA1535, TA97, TA98	Reverse mutations	–	–	NTP 2008b	Chromium picolinate
<i>S. typhimurium</i> TA92, TA98, TA100	Reverse mutations	No data	+	Warren et al. 1981	Chromium complexes with 2,2'-bipyridine and 1,10-phenanthroline
<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537	Reverse mutations	–	–	Whittaker et al. 2005	Chromium picolinate
<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537	Reverse mutations	–	–	Whittaker et al. 2005	Chromium chloride
<i>S. typhimurium</i> TA1535, TA97a, TA98, TA100, TA102	Reverse mutations	–	–	Shara et al. 2005	Niacin-bound chromium
<i>S. typhimurium</i> TA 1535 pSK1002	Mutations	–	–	Yamamoto et al. 2002	Chromium nitrate

## 3. HEALTH EFFECTS

**Table 3-9. Genotoxicity of Chromium(III) *In Vitro***

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
Eukaryotic organisms:					
Yeasts:					
<i>Saccharomyces cerevisiae</i>	Reverse mutations, mitotic gene conversions	No data	+	Bronzetti et al. 1986	Chromium trichloride
<i>S. cerevisiae</i>	DNA deletions	No data	+	Kirpnick-Sobol et al. 2006	Chromium (III) chloride salt
Chickens:					
Chick embryos	DNA damage (crosslinks, strand breaks)	No data	-	Tsapakos et al. 1983a	Chromium nitrate
Mammalian cells:					
Human lymphocytes	DNA damage	No data	+	Blasiak and Kowalik 2000	Chromium chloride
Human skin fibroblasts	Unscheduled DNA synthesis	No data	-	Whiting et al. 1979	Chromium trichloride
Human skin fibroblasts	DNA fragmentation	No data	-	Whiting et al. 1979	Chromium trichloride
Human leukocytes	Chromosomal aberrations	No data	±	Nakamuro et al. 1978	Chromium trichloride, chromium nitrate, chromium acetate
Human lymphocytes	Chromosomal aberrations	No data	±	Stella et al. 1982	Chromium trichloride hexahydrate
Human lymphocytes	Chromosomal aberrations	No data	-	Sarto et al. 1980	Chromium trichloride
Human lymphocytes	Sister chromatid exchange	No data	-	Stella et al. 1982	Chromium trichloride hexahydrate
Chinese hamster V79 cells	Chromosomal aberrations	No data	-	Newbold et al. 1979	Chromium acetate
Syrian hamster embryonal cells	Chromosomal aberrations	No data	-	Tsuda and Kato 1977	Chromium trichloride hexachloride, chromium sulfate tetrahydrate
Chinese hamster lung DON cells	Chromosomal aberrations	No data	-	Ohno et al. 1982	Chromium trichloride hexahydrate, chromium sulfate tetrahydrate

## 3. HEALTH EFFECTS

**Table 3-9. Genotoxicity of Chromium(III) *In Vitro***

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
Chinese hamster ovary cells	aberrations		±	Levis and Majone 1979	Chromium trichloride hexachloride, chromium nitrate monohydrate, chromium potassium sulfate, chromium acetate
Chinese hamster ovary cells	Sister chromatid exchange	No data	–	Levis and Majone 1979; MacRae et al. 1979; Venier et al. 1982	Chromium trichloride hexachloride, chromium nitrate, monohydrate, chromium potassium sulfate, chromium acetate
Chinese hamster ovary cells ( <i>hprt</i> locus)	Mutations	No data	+	Coryell and Stearns 2006; Stearns et al. 2002	Chromium trispicolinate
Mouse L5178Y+/- lymphoma	Mutations	–	–	Shara et al. 2005	Niacin-bound chromium
Mouse L5178Y lymphoma	Mutations	+	+	Whittaker et al. 2005	Chromium picolinate
Mouse L5178Y lymphoma	Mutations	–	±	Whittaker et al. 2005	Chromium chloride
Mouse leukemia cells	Chromosomal aberrations	No data	–	Fornace et al. 1981	Chromium trichloride
Mouse mammary carcinoma	Chromosomal aberrations	No data	–	Umeda and Nishimura 1979	Chromium sulfate
Fm3A cells:					
Mouse fetal cells	Chromosomal aberrations	No data	±	Raffetto et al. 1977	Chromium trichloride
Mouse fetal cells	Morphological transformations	No data	+	Raffetto et al. 1977	Chromium trichloride
Mouse A18BcR cells	Unscheduled DNA synthesis	No data	–	Raffetto et al. 1977	Chromium trichloride

– = negative results; + = positive results; ± = weakly positive results; (III) = trivalent; DNA = deoxyribonucleic acid



## 3. HEALTH EFFECTS

gastrointestinal tract) are not easily obtained for analysis. However, negative genotoxicity results in tissues that are not cancer targets (e.g., blood) should not be extrapolated to cancer target tissues.

Occupational exposure studies have yielded mixed results on the genotoxic potential of chromium compounds. Studies involving workers exposed to chromium(VI) in stainless steel welding and electroplating (Husgafvel-Pursiainen et al. 1982; Littorin et al. 1983; Nagaya 1986; Nagaya et al. 1991), and to chromium(III) in tanneries (Hamamy et al. 1987) did not report increases in the number of chromosomal aberrations or sister chromatid exchanges in peripheral lymphocytes of these workers. No elevations in DNA strand breaks or hydroxylation of deoxyguanosine were detected in lymphocytes of workers exposed to chromium(VI) involved in the production of bichromate (Gao et al. 1994), while DNA strand breaks were reported in the peripheral lymphocytes of 19 chromium platers (Gambelunghe et al. 2003). In contrast, other studies involving electroplaters and stainless steel welders reported higher levels of chromosomal aberrations or sister chromatid exchanges in workers exposed to chromium(VI) compared to controls (Deng et al. 1988; Koshi et al. 1984; Lai et al. 1998; Sarto et al. 1982; Stella et al. 1982; Werfel et al. 1998).

Urine samples from six workers working in chromium plating factories were tested for the induction of unscheduled DNA synthesis (UDS) in pleural mesothelial cells (Pilliere et al. 1992). The mean chromium concentration in the urine samples was  $11.7 \pm 8.8$   $\mu\text{g/L}$ . The urine from five of the workers showed a significant elevated in UDS over control subjects who were nonsmokers, with a trend toward increasing amounts of urine being tested. However, there was no correlation between UDS and chromium concentrations in urine.

An epidemiology study of stainless steel welders, with mean exposure levels of 0.055 mg chromium(VI)/ $\text{m}^3$  or 0.081 mg chromium (total)/ $\text{m}^3$ , did not report increases in the number of sister chromatid exchanges in the lymphocytes of exposed workers. The welders were also exposed to nickel and molybdenum from the welding rods (Littorin et al. 1983). A similar study was conducted to detect genotoxic effects of chromium(VI) on workers in electroplating factories. Of the 24 workers examined, none showed significant differences in sister chromatid exchange frequency (Nagaya 1986). Similarly, no correlation was found between excretion of chromium in the urine and the frequency of sister chromatid exchanges in 12 male chromium platers whose mean urinary chromium level was 17.9  $\mu\text{g/g}$  creatinine (Nagaya et al. 1991). In chrome platers ( $n=15$ ) in low (0.0075 mg Cr(VI)/ $\text{m}^3$ ) and high (0.0249 mg Cr(VI)/ $\text{m}^3$ ) exposure groups, no significant differences in the frequency of sister chromatid exchanges and chromosomal aberrations in peripheral lymphocytes and buccal mucosa cells were observed

## 3. HEALTH EFFECTS

compared to controls ( $0.0004 \text{ mg Cr(VI)/m}^3$ ;  $n=15$ ) (Benova et al. 2002). No increase in chromosomal aberrations was observed in 17 tannery workers exposed primarily to chromium(III) as compared with 13 controls (Hamamy et al. 1987). However, parallel measurements in these tannery workers showed that the average chromium levels in plasma ( $0.115 \text{ } \mu\text{g/L}$ ) and urine ( $0.14 \text{ } \mu\text{g/100 L}$ ) did not differ from the nonexposed workers. In addition, stainless steel welders occupationally exposed to chromium(VI) for a mean of 21 years did not have any increase in chromosomal aberrations or sister chromatid exchanges compared to a control group. No actual exposure levels were provided (Husgafvel-Pursiainen et al. 1982). Yet, other studies involving electroplaters and welders report a higher incidence of chromosomal aberrations or sister chromatid exchanges in lymphocytes of workers than in controls. In one study, a causal relationship between chromium exposure and the observed effects could not be established because the exposure was confounded by co-exposure to nickel and manganese (Elias et al. 1989a). In another study, although chromium workers were found to have higher rates of sister chromatid exchanges than workers exposed to nickel-chromium or controls (after adjusting for potential confounding factors), the differences were not significantly correlated to chromium concentrations in blood or urine (Lai et al. 1998). The frequency of sister chromatid exchanges was also higher in the blood of 35 chromium platers in Taiwan when compared to controls (Wu et al. 2001). The frequency of sister chromatid exchanges in the lymphocytes of 12 workers exposed to chromium(VI) as chromic acid fumes in a chrome plating industry was significantly increased (Stella et al. 1982). Significantly increased incidences of chromosomal aberrations in peripheral lymphocytes were found in workers exposed to chromium(VI) as chromium trioxide in two of four electroplating plants. Of the two plants where the increases were significant, one was a "bright" plating plant, where exposure involved nickel as well as chromium, and one was a "hard" plating plant, where exposure involved only chromium. However, the increase in chromosomal aberrations correlated poorly with urinary chromium levels, and only the increase in the "bright" platers showed a significant correlation with duration of exposure. A significantly increased incidence of sister chromatid exchanges was found in "hard" platers compared with controls (sister chromatid exchange was not evaluated in "bright" platers), and smoking appeared to enhance the increase (7 of 8 smokers and 7 of 11 nonsmokers had incidences significantly higher than controls). Moreover, the increased incidence of sister chromatid exchange showed a positive correlation with urinary chromium levels (Sarto et al. 1982). Repeated cytogenetic analysis of peripheral lymphocytes for 3 years revealed an increased frequency of chromosomal aberrations and sister chromatid exchanges in a group of stainless steel welders compared to controls. The workers were exposed to unreported chromium(VI) concentrations for a mean of 12.1 years, but exposure to ultraviolet rays and small amounts of manganese, nickel, iron, and magnesium could not be ruled out (Koshi et al. 1984). Compared to 39 controls, significantly elevated sister chromatid exchange values in lymphocytes and significantly higher rates of

## 3. HEALTH EFFECTS

DNA single-strand breakages were found in a group of 39 welders exposed to unreported chromium(VI) and nickel concentrations (Werfel et al. 1998). Only one study was located regarding the average levels of exposure for electroplating workers: workers exposed to an average level of 0.008 mg chromium(VI)/m<sup>3</sup> had increases in chromosomal aberrations and sister chromatid exchanges. However, high levels of nickel as well as chromium were found in hair and stool samples when compared to controls (Deng et al. 1988). Increased frequencies of micronuclei were reported in the peripheral lymphocytes and buccal mucosa cells in two studies of chromium electroplating workers in Bulgaria (Benova et al. 2002; Vaglenov et al. 1999). In chrome platers (n=15), significant increases in micronuclei in peripheral lymphocytes and buccal mucosa cells were observed in low (0.0075 mg Cr(VI)/m<sup>3</sup>) and high (0.0249 mg Cr(VI)/m<sup>3</sup>) exposure groups compared to controls (0.0004 mg Cr(VI)/m<sup>3</sup>; n=15) (Benova et al. 2002). Increased micronuclei frequency and DNA-protein crosslinks were observed in the peripheral lymphocytes of tanners primarily exposed to chromium(III) compounds, while welders, who are primarily exposed to chromium(VI) compounds had evidence of DNA-protein crosslinks, but not increased micronuclei frequency in peripheral lymphocytes (Medeiros et al. 2003a). No elevated levels of DNA strand breaks or hydroxylation of deoxyguanosine in lymphocytes were found in 10 workers occupationally exposed in the production of bichromate when compared with 10 nonoccupationally-exposed workers at the same facility Gao et al. (1994). From general background monitoring levels of chromium(VI), exposures were estimated to be between 0.001 and 0.055 mg/m<sup>3</sup>. In contrast, DNA strand breaks were reported in the peripheral lymphocytes of 19 chromium platers with a mean postshift urinary concentration of 7.31 µg/g creatinine when compared to non-exposed control subjects (Gambelunghe et al. 2003).

Chromium(VI) and chromium(III) have been shown to be genotoxic in human cell lines. S phase-dependent DNA double-strand breaks were observed in cultured human dermal fibroblasts exposed to sodium chromate (chromium(VI)) (Ha et al. 2003, 2004). Sodium chromate also induced concentration-dependent chromosome damage in cultured human bronchial fibroblasts and bronchial epithelial cells (Holmes et al. 2006; Wise et al. 2006b). Exposure of cultured human bronchial fibroblasts to sodium chromate produced disruption of mitosis, most likely through spindle assembly checkpoint bypass (Wise et al. 2006a). Weakly positive responses were observed for chromium(III) (Nakamuro et al. 1978; Stella et al. 1982). However, it should be noted that in positive studies, the genotoxic potency of chromium(III) compounds was several orders lower than that of chromium(VI) compounds tested in the same systems. Positive results for increased micronuclei and DNA damage were also observed in lymphocytes exposed to chromium(III) chloride (Blasiak and Kowalik 2000). Positive results of chromium(III) in intact cells could be due to contamination of the test compounds with traces of chromium(VI) (De Flora et al. 1990;

## 3. HEALTH EFFECTS

IARC 1990), nonspecific effects at very high doses, experimental conditions that would increase the penetration of chromium(III) into cells (e.g., detergents), or a technical artifact formed during the extraction procedures (De Flora et al. 1990). In one case, chromium(III) compounds showed genotoxicity that was linked to redox cycling of a chromium-DNA complex (Sugden et al. 1990). Although chromium(III) compounds are less toxic than chromium(VI) compounds because of its relative inability to cross cell membranes, chromium(III) causes more DNA damage and mutations when it is formed by intracellular reduction from chromium(VI) or it is reacted with DNA in subcellular systems (Bridgewater et al. 1994a, 1994b, 1998; Fornace et al. 1981; Snow 1991; Snow and Xu 1989).

Thus, results of studies in occupationally exposed humans and in human cell lines indicate that chromium(VI) and chromium(III) are genotoxic; however, studies in humans were limited in several aspects. Generally, the levels of exposure to chromium(VI) were not known and co-exposure to other potentially active compounds (namely ultraviolet rays and other potentially genotoxic metals) occurred in several studies. Some negative results (Hamamy et al. 1987) were probably due to low exposure, because the chromium levels in plasma and urine of exposed and unexposed workers did not differ. Furthermore, some of the studies (Deng et al. 1988; Hamamy et al. 1987; Stella et al. 1982) used groups that were too small (<20 individuals) to have the statistical power to reliably assess the cytogenetic changes in workers. Although most older occupational exposure studies gave negative or equivocal results, most recent studies have identified chromosomal effects in exposed workers (Benova et al. 2002; Gambelunghe et al. 2003; Wu et al. 2001). Furthermore, results of studies in human cell lines provide evidence of the genotoxic activity of chromium compounds. Thus, the available studies support that chromium compounds, particularly chromium(VI), have carcinogenic potential because interactions with DNA have been linked with the mechanism of carcinogenicity. No studies were located regarding genotoxic effects in humans after oral exposure to chromium or its compounds.

Numerous studies have evaluated the genotoxicity of chromium compounds in animals by several exposure routes, including oral, inhalation, and parenteral routes. No increased incidence of micronuclei in polychromatic erythrocytes was observed in mice given single gavage doses of potassium chromate at  $\leq 86$  mg chromium(VI)/kg (Shindo et al. 1989) or in mice exposed to potassium chromate via drinking water at 1–20 ppm for 48 hours or to bolus doses up to 4  $\mu\text{g}/\text{kg}$  for 2 days (Mirsalis et al. 1996). Similarly, no UDS in hepatocytes was found in rats. However, an increase in DNA-protein crosslinking was found in the livers of rats exposed to potassium chromate in the drinking water at  $\geq 6$  mg chromium(VI)/kg/day for 3 or 6 weeks (Coogan et al. 1991a).

## 3. HEALTH EFFECTS

The clastogenic effects of male Swiss albino mice fed chromium(VI) trioxide (20 mg/kg body weight) by gavage were studied; after 24 hours, bone marrow cells were isolated and 500 metaphase plates were scored for chromosomal aberrations (Sarkar et al. 1993). The treated cells showed a significant increase in aberrations per cell over controls by 4.4-fold. When animals were treated simultaneously with chlorophyllin (1.5 mg/kg), a sodium-copper derivative of chlorophyll and an antioxidant, numbers of aberrations were reduced to nearly background levels.

An increase in DNA-protein crosslinking was found in the livers of rats that had been exposed to potassium chromate in the drinking water at  $\geq 6$  mg chromium(VI)/kg/day for 3 or 6 weeks (Coogan et al. 1991a). Bone marrow cells from male mice fed chromium(VI) trioxide at 20 mg chromium(VI)/kg by gavage had a 4.4-fold increase in chromosomal aberration over controls (Sarkar et al. 1993). Significant DNA alterations were seen in the lung, but not the liver, of rats exposed to chromium (VI) by intratracheal instillation of sodium dichromate (Izzotti et al. 1998). DNA damage was also reported in leukocytes and peripheral lymphocytes of mice orally exposed to chromium(VI) as potassium chromate (Devi et al. 2001; Wang et al. 2006), and transplacental exposure of potassium dichromate resulted in DNA deletions the retinal pigment epithelium of mice (Kirpnick-Sobol et al. 2006). Intraperitoneal exposure to chromium(VI) as potassium dichromate caused single strand breaks in mouse liver and kidney cells, but did not in spleen, lung, or brain cells (Ueno et al. 2001). Micronucleated polychromatic erythrocytes were found in mice following intraperitoneal exposure to chromium(VI) as potassium dichromate (Chorvatovičová et al. 1993; De Flora et al. 2006; Itoh and Shimada 1996, 1997; Wild 1978; Wrońska-Nofer et al. 1999), though one study reported negative results following intraperitoneal exposure to potassium chromate (Shindo et al. 1989). In contrast, oral exposure of mice to chromium(VI), as potassium dichromate or sodium dichromate dihydrate, did not induce micronuclei in bone marrow or in peripheral blood cells (De Flora et al. 2006; Mirsalis et al. 1996; NTP 2008a). Similar to chromium(VI) compounds, oral exposure of chromium(III) compounds also did not induce micronuclei in mouse erythrocytes (NTP 2008b), bone marrow cells (De Flora et al. 2006; NTP 2008b), or in peripheral blood cells (De Flora et al. 2006). Transplacental exposure to fetuses from dams exposed to chromium(VI) as either sodium dichromate dihydrate or potassium dichromate through drinking water did not result in micronuclei in fetal liver or peripheral blood cells (De Flora et al. 2006), while transplacental exposure to fetuses from dams exposed by intraperitoneal injection to these same chromium(VI) compounds did result in micronuclei in both fetal liver and peripheral blood cells (De Flora et al. 2006).

No unscheduled DNA synthesis was found in rat hepatocytes after the rats were exposed to potassium chromate in drinking water (Mirsalis et al. 1996). The contrasting results may relate to route-specific

## 3. HEALTH EFFECTS

differences in absorption or metabolic fate of chromate *in vivo*. Furthermore, intraperitoneal exposure to chromium(VI) as potassium dichromate induced dominant lethality in mice (Paschin et al. 1982) and a significant increase in mutant frequency within mouse hepatocytes (Itoh and Shimada 1997, 1998) and bone marrow cells (Itoh and Shimada 1998). Intraperitoneal injection in rats with sodium dichromate chromium(VI) resulted in DNA crosslinks in liver, kidney, and lung nuclei (Tsapakos et al. 1983b), while similar injection in rats with chromium(III) trichloride did not cause DNA interstrand crosslinks, DNA-protein crosslinks, or DNA strand breaks in liver and kidney nuclei (Cupo and Wetterhahn 1985). Oral exposure to niacin-bound chromium(III) did not cause DNA fragmentation in rats after 90 days of dietary exposure at doses >621.6 mg Cr(III)/kg/day (Shara et al. 2005). In addition, studies in *Drosophila melanogaster* showed an induction of gene mutations after exposure to chromium(VI) (Amrani et al. 1999; Gava et al. 1989a; Kaya et al. 2002; Rasmuson 1985; Rodriguez-Arnaiz and Martinez 1986; Olvera et al. 1993; Zimmering et al. 1985), but not after exposure to chromium(III) (Amrani et al. 1999).

The vast majority of studies reported genotoxic effects of chromium(VI) in mammalian cells *in vitro* (Blasiak and Kowalik 2000; Briggs and Briggs 1988; Depault et al. 2006; DiPaolo and Casto 1979; Douglas et al. 1980; Elias et al. 1989b; Fornace et al. 1981; Gomez-Arroyo et al. 1981; Ha et al. 2004; Koshi 1979; Koshi and Iwasaki 1983; Kowalski et al. 1996; Levis and Majone 1979; MacRae et al. 1979; Majone and Levis 1979; Montaldi et al. 1987; Nakamuro et al. 1978; Newbold et al. 1979; Ohno et al. 1982; Raffetto et al. 1977; Sarto et al. 1980; Seoane and Dulout 1999; Stella et al. 1982; Sugiyama et al. 1986a; Trzeciak et al. 2000; Tsuda and Kato 1977; Umeda and Nishimura 1979; Venier et al. 1982; Whiting et al. 1979; Wise et al. 2002, 2003; Yang et al. 1992). Chromium(VI) also induced DNA damage (DNA interstrand crosslinks, DNA strand breaks, DNA-protein crosslinks) in cultured chick embryo hepatocytes (Tsapakos et al. 1983a). In contrast, mostly negative results were reported for chromium(III) in mammalian cells (Fornace et al. 1981; Levis and Majone 1979; MacRae et al. 1979; Newbold et al. 1979; Ohno et al. 1982; Raffetto et al. 1977; Sarto et al. 1980; Shara et al. 2005; Stella et al. 1982; Tsuda and Kato 1977; Umeda and Nishimura 1979; Venier et al. 1982; Whiting et al. 1979) and chick embryo hepatocytes (Tsapakos et al. 1983a). Positive results were obtained in Chinese hamster ovary cells (Coryell and Stearns 2006; Levis and Majone 1979; Stearns et al. 2002), mouse fetal cells (Raffetto et al. 1977), and mouse lymphoma cells (Whittaker et al. 2005). Chromium(III) picolinate caused chromosome damage (Stearns et al. 1995b) and mutations in cultured mammalian cells (Stearns et al. 2002).

## 3. HEALTH EFFECTS

Chromium(VI) was genotoxic in *Saccharomyces cerevisiae* (Fukunaga et al. 1982; Kirpnick-Sobol et al. 2006; Singh 1983) and *Schizosaccharomyces pombe* (Bonatti et al. 1976). Two studies demonstrated the genotoxicity of chromium(III) in *S. cerevisiae* (Bronzetti et al. 1986; Kirpnick-Sobol et al. 2006).

*In vitro* studies indicated that soluble chromium(VI) compounds are mutagenic in *Salmonella typhimurium* reverse mutation assays (Bennicelli et al. 1983; De Flora 1978, 1981; Haworth et al. 1983; Nakamura et al. 1987; NTP 2007a; Venier et al. 1982; Watanabe et al. 1998a; Yamamoto et al. 2002), and in a *Salmonella* microsuspension bioassay (Tagliari et al. 2004). Only one study reported negative results with chromium(VI) in all tested strains (Kanematsu et al. 1980). In contrast, studies with chromium(III) did not report the induction of reverse mutations in *S. typhimurium* (Bennicelli et al. 1983; De Flora 1981; NTP 2008b; Petrilli and De Flora 1978b; Shara et al. 2005; Venier et al. 1982; Whittaker et al. 2005; Yamamoto et al. 2002). After preincubation with mammalian microsomes, the mutagenicity of chromium(VI) compounds was reduced or abolished due to concentrations of the reductant glutathione, cysteine, or NADPH capable of converting chromium(VI) to chromium(III) compounds (Bennicelli et al. 1983; De Flora 1978, 1981). Chromium(VI) compounds caused gene mutations in *Bacillus subtilis* (Kanematsu et al. 1980; Nakamuro et al. 1978; Nishioka 1975) and *Escherichia coli* (Kanematsu et al. 1980; Kortenkamp et al. 1996b; Llagostera et al. 1986; Nakamuro et al. 1978; NTP 2007; Olivier and Marzin 1987; Venitt and Levy 1974; Watanabe et al. 1998a). Negative or weakly positive results were reported in *B. subtilis* with chromium(III) (Kanematsu et al. 1980; Matsui 1980; Nakamuro et al. 1978; Nishioka 1975) and mostly negative results were reported in *E. coli* (Llagostera et al. 1986; NTP 2008b; Olivier and Marzin 1987; Venier et al. 1989). However, hydrophobic ligands such as 2,2'-bipyridine, 1,10-phenanthroline, or picolinic acid form complexes with chromium(III), which are able to penetrate cell membranes and to cause genotoxicity. Complexes of chromium(III) with 2,2'-bipyridine or 1,10-phenanthroline were mutagenic in *S. typhimurium* (Warren et al. 1981). Chromium(III) picolinate was not mutagenic in *S. typhimurium* or *E. coli* (NTP 2008b).

A chromium(IV) ester was synthesized with 2,4-dimethyl-pentane-2,4-diol to examine its ability to cause DNA double strand breaks (Luo et al. 1996). Calf thymus DNA was reacted with the chromium(IV) complex (1.3 mg/mL) in the presence of 2 mM hydrogen peroxide for 6 days at pH 6.8. The results showed that the complex in the presence of hydrogen peroxide significantly damaged DNA by causing double strand breaks. Neither chromium(IV) or hydrogen peroxide alone damaged DNA. The kinetics of the reaction of chromium(IV) with hydrogen peroxide showed the formation of proportional amounts of hydroxyl radical with chromium(V). Use of a free radical scavenger prevented DNA strand breaks. Other studies have shown that chromium(IV) is a better Fenton reagent than chromium(V) for

### 3. HEALTH EFFECTS

reducing hydrogen peroxide, and thus, chromium(IV)-type damage by generating hydroxyl radicals may also be a contributor of *in vivo* genotoxicity.

In conclusion, chromium(VI) compounds were positive in the majority of tests reported, and their genotoxicity was related to the solubility and, therefore, to the bioavailability to the targets. Results of occupational exposure studies in humans, although somewhat compromised by concomitant exposures to other potential genotoxic compounds, provide evidence of chromium(VI)-induced DNA strand breaks, chromosome aberrations, increased sister chromatid exchange, unscheduled DNA synthesis, and DNA-protein crosslinks. Findings from occupational exposure studies are supported by results of *in vivo* studies in animals, *in vitro* studies in mammalian cells, yeast and bacteria, and studies in cell-free systems. Compared to chromium(VI), chromium(III) was more genotoxic in subcellular targets, but lost this ability in cellular systems. The reduction of chromium(VI) in the cells to chromium(III) and its subsequent genotoxicity may be greatly responsible for the final genotoxic effects (Beyersmann and Koster 1987; Zhitkovich et al. 2005). Reduction of chromium(VI) can also result in the formation of chromium(V), which is highly reactive and capable of interaction with DNA (Jennette 1982; Norseth 1986).

#### 3.4 TOXICOKINETICS

The toxicokinetics of a given chromium compound depend on the valence state of the chromium atom and the nature of its ligands. Naturally occurring chromium compounds are generally in the trivalent state (chromium(III)), while hexavalent chromium compounds (chromium(VI)) are produced industrially by the oxidation of chromium(III) compounds.

The amount and location of deposition of inhaled chromium will be determined by factors that influence convection, diffusion, sedimentation, and interception of particles in the airways. These factors include air flow velocities, which are affected by breathing rate and tidal volume; airway geometry; and aerosol particle size (ICRP 1994). In general, deposition in the thoracic and pulmonary regions of the respiratory tract increase (as a fraction of the total deposited dose) as particle sizes decrease. Larger particles (e.g., >10 µm in diameter) deposit in the extrathoracic region. Chromium that deposits in the respiratory tract are subject to three general clearance processes: (1) mucociliary transport to the gastrointestinal tract for the ciliated airways (i.e. trachea, bronchi, and proximal bronchioles); (2) phagocytosis by lung macrophages and cellular transport to thoracic lymph nodes; or (3) absorption and transfer by blood and/or lymph to other tissues. The above processes apply to all forms of deposited chromium, although



## 3. HEALTH EFFECTS

the relative contributions of each pathway and rates associated with each pathway may vary with the physical characteristics (e.g., particle size), chemical form (degree of water solubility), and chemotactic properties of the chromium particles. In general, less water-soluble chromium compounds that deposit in the pulmonary region can be expected to have a longer retention time in the lung than more soluble forms. In addition, lung concentrations of chromium increase with increasing age.

Most quantitative studies of the gastrointestinal absorption of chromium in humans have estimated the absorption fraction to be <10% of the ingested dose. In general, these studies suggest that the absorption fraction of soluble chromium compounds is higher than insoluble forms (e.g.,  $\text{CrCO}_3$ ), and is higher for soluble chromium(VI) compounds (e.g.,  $\text{K}_2\text{Cr}_2\text{O}_7$ ) than soluble chromium(III) (e.g.,  $\text{CrCl}_3$ ). Chromium(VI) is reduced in the stomach to chromium(III), which lowers the absorbed dose from ingested chromium(VI). Absorption is also affected by the nutritional status of chromium(III); the absorption fraction is higher when dietary intakes are lower. Peak plasma concentrations of chromium occur within 2 hours following an oral dose of soluble chromium, suggesting that absorption occurred. Chromium absorption occurs in the upper small intestine.

Chromium(III) and chromium(VI) can penetrate human skin to some extent, especially if the skin is damaged. Few quantitative estimates of dermal absorption in humans have been reported. A 3-hour immersion in a warm aqueous bath of 22 mg Cr(VI)/L (as  $\text{K}_2\text{Cr}_2\text{O}_7$ ) resulted in absorption (based on urine measurements) of approximately  $3.3 \times 10^{-5}$ – $4.1 \times 10^{-4}$   $\mu\text{g Cr/cm}^2\text{-hour}$  (Corbett et al. 1997).

Absorbed chromium distributes to nearly all tissues, with the highest concentrations found in kidney and liver. Bone is also a major depot and may contribute to long-term retention kinetics of chromium. Chromium(VI) is unstable in the body and is reduced to chromium(V), chromium(IV), and ultimately to chromium(III) by many substances including ascorbate and glutathione. Reduction of chromium(VI) to chromium(III) can give rise to reactive intermediates, chromium adducts with proteins and DNA, and secondary free radicals. Chromium(VI) in blood is taken up into red blood cells, where it undergoes reduction and forms complexes with hemoglobin and other intracellular proteins that are sufficiently stable to retain chromium for a substantial fraction of the red blood cell lifetime. Absorbed chromium can be transferred to fetuses through the placenta and to infants via breast milk. Absorbed chromium is excreted predominantly in urine. Studies in animals have shown that chromium can be secreted in bile following parenteral (e.g., intravenous) injection of chromium(VI) or chromium(III) compounds. Chromium can also be eliminated by transfer to hair and nails. Chromium absorbed following ingestion of chromium(VI) (as  $\text{K}_2\text{Cr}_2\text{O}_7$ ) appears to have a slower elimination rate ( $t_{1/2}$  approximately 40 hours)

## 3. HEALTH EFFECTS

than when chromium is absorbed following ingestion of soluble chromium(III) (as  $\text{CrCl}_3$ ;  $t_{1/2}$  approximately 10 hours).

### 3.4.1 Absorption

#### 3.4.1.1 Inhalation Exposure

The absorption of inhaled chromium compounds depends on a number of factors, including physical and chemical properties of the particles (oxidation state, size, solubility) and the activity of alveolar macrophages.

The identification of chromium in urine, serum and tissues of humans occupationally exposed to soluble chromium(III) or chromium(VI) compounds in air indicates that chromium can be absorbed from the lungs (Cavalleri and Minoia 1985; Gylseth et al. 1977; Kiilunen et al. 1983; Mancuso 1997b; Minoia and Cavalleri 1988; Randall and Gibson 1987; Tossavainen et al. 1980). In most cases, chromium(VI) compounds are more readily absorbed from the lungs than chromium(III) compounds, due in part to differences in the capacity to penetrate biological membranes. Nevertheless, workers exposed to chromium(III) lignosulfonate dust at 0.005–0.23 mg chromium(III)/m<sup>3</sup> had clearly detectable concentrations of chromium in the urine at the end of their shifts. Based on a one-compartment kinetic model, the biological half-life of chromium(III) from the lignosulfonate dust was 4–10 hours, which is the same order of magnitude as the half-life for chromium(VI) compounds (Kiilunen et al. 1983).

Rats exposed to 2.1 mg chromium(VI)/m<sup>3</sup> as zinc chromate 6 hours/day achieved steady-state concentrations in the blood after ~4 days of exposure (Langård et al. 1978). Rats exposed for a single inhalation of chromium(VI) trioxide mist from electroplating at a concentration of 3.18 mg chromium(VI)/m<sup>3</sup> for 30 minutes rapidly absorbed chromium from the lungs. The content of chromium in the lungs declined from 13.0 mg immediately after exposure to 1.1 mg at 4 weeks in a triphasic pattern with an overall half-life of 5 days (Adachi et al. 1981). Based on a study in rats exposed to chromium(VI) as potassium dichromate or to chromium(III) as chromium trichloride, the pulmonary clearance of both valence states was dependent on particle size, and chromium(VI) was more rapidly and extensively transported to the bloodstream than chromium(III). The rats had been exposed to 7.3–15.9 mg chromium(VI)/m<sup>3</sup> as potassium dichromate for 2–6 hours or to 8 or 10.7 mg chromium(III)/m<sup>3</sup> as chromium trichloride for 6 or 2 hours, respectively. Chromium(VI) particles of 1.5 or 1.6 µm had a two-compartment pulmonary clearance curve with half-lives of 31.5 hours for the first phase and 737 hours for the second phase. Chromium(VI) particles of 2 µm had a single component curve with a half-life

## 3. HEALTH EFFECTS

between 151 and 175 hours. Following exposure to chromium(VI), the ratio of blood chromium/lung chromium was 1.44 at 0.5 hours, 0.81 at 18 hours, 0.85 at 48 hours, and 0.96 at 168 hours after exposure. Chromium(III) particles of 1.5–1.8  $\mu\text{m}$  had a single component pulmonary clearance curve with a half-life of 164 hours. Following exposure to chromium(III), the ratio of blood chromium/lung chromium was 0.39 at 0.5 hours, 0.24 at 18 hours, 0.22 at 48 hours, and 0.26 at 168 hours after exposure. Therefore, the amount of chromium(VI) transferred to the blood from the lungs was always at least 3 times greater than the amount of chromium(III) transferred (Suzuki et al. 1984). Other studies reporting absorption from the lungs are intratracheal injection studies (Baetjer et al. 1959b; Bragt and van Dura 1983; Visek et al. 1953; Wiegand et al. 1984, 1987). These studies indicate that 53–85% of chromium(VI) compounds (particle size  $<5 \mu\text{m}$ ) are cleared from the lungs by absorption into the bloodstream or by mucociliary clearance in the pharynx; the rest remain in the lungs. Absorption by the bloodstream and mucociliary clearance was only 5–30% for chromium(III) compounds.

The kinetics of three chromium(VI) compounds, sodium chromate, zinc chromate, and lead chromate, were compared in rats in relation to their solubility. The rats received intratracheal injections of the  $^{51}\text{chromium}$ -labeled compounds (0.38 mg chromium(VI)/kg as sodium chromate, 0.36 mg chromium(VI)/kg as zinc chromate, or 0.21 mg chromium(VI)/kg as lead chromate). Peak blood levels of  $^{51}\text{chromium}$  were reached after 30 minutes for sodium chromate (0.35  $\mu\text{g chromium/mL}$ ), and 24 hours for zinc chromate (0.60  $\mu\text{g chromium/mL}$ ) and lead chromate (0.007  $\mu\text{g chromium/mL}$ ). At 30 minutes after administration, the lungs contained 36, 25, and 81% of the respective dose of the sodium, zinc, and lead chromate. On day 6,  $>80\%$  of the dose of all three compounds had been cleared from the lungs, during which time, the disappearance from lungs followed linear first-order kinetics. The residual amounts left in the lungs on day 50 or 51 were 3.0, 3.9, and 13.9%, respectively. The results indicate that zinc chromate, which is  $\sim 1,000$  times less soluble than sodium chromate, is more slowly absorbed from the lungs, but peak blood levels are higher than sodium chromate. Lead chromate was more poorly and slowly absorbed, as indicated by very low levels in blood and other tissues, and greater retention in the lungs (Bragt and van Dura 1983).

The fate of lead chromate(VI), chromium(VI) trioxide, chromium(III) oxide and chromium(III) sulfate were examined when solutions or suspensions of these chemicals were slowly infused into the tracheal lobe bronchus of sheep via bronchoscopic catheterization (Perrault et al. 1995). At 2, 3, 5, and 30 days, the samples of bronchoalveolar lavage were taken, and on day 31, the animals were sacrificed and lung specimens were examined for chromium particulates. There was no difference in lung particle concentrations among the four different compounds. The values ranged from  $0.14 \times 10^5$  to

### 3. HEALTH EFFECTS

$1.02 \times 10^5$  particles/g dry tissue compared to control values of  $0.03 \times 10^5$ . The alveolar clearance of slightly soluble chromium(III) oxide and chromium(III) sulfate was calculated to be 11 and 80 days, respectively. The insoluble lead chromate particles appeared to break up, forming isometric particles of lead chromate as well as lead-containing particulates that may have retarded clearance. Retention of chromium particulates from exposure to soluble chromium trioxide may have resulted in the formation of a less-soluble hydroxyl complex and/or chemical interaction between chromium and protein that prolongs the retention of the metal. Analyses of the particulates in lavage samples indicate that these diameters increase with time for lead chromate, decrease with time for chromium sulfate and chromium trioxide, and are unchanged for chromium(III) oxide. The authors state that their findings indicate that slightly soluble chromium(III) oxide and chromium sulfate that are chemically stable can be cleared from lungs at different rates, depending on the nature and morphology of the compound.

Amounts of total chromium were measured in lymphocytes, blood, and urine after intratracheal administration of either sodium dichromate(VI) or chromium(III) acetate hydroxide (a water-soluble chromium(III) compound) to male Wistar rats (Gao et al. 1993). The total amount of chromium administered was 0.44 mg chromium/kg body weight for each compound. The highest concentrations in tissues and urine occurred at 6 hours after treatment, the first time point examined. Mean chromium concentrations (n=4 rats per time point) from treatment with chromium(III) were 56.3 µg/L in whole blood, 96 µg/L in plasma,  $0.44 \mu\text{g}/10^{10}$  in lymphocytes, and 4,535.6 µg/g creatinine in urine. For treatment with chromium(VI) the levels were 233.2 µg/L for whole blood, 138 µg/L for plasma,  $2.87 \mu\text{g}/10^{10}$  for lymphocytes, and 2,947.9 µg/g creatinine in urine. The levels in lymphocytes in the chromium(III) treated animals were no different than in untreated animals. However, for chromium(VI) the lymphocyte levels were about 6-fold higher than control values. After 72 hours, the chromium levels were significantly reduced. These results suggest that absorbed chromium(III) compounds may be excreted more rapidly than absorbed chromium(VI) compounds because of a poorer ability to enter cells.

#### 3.4.1.2 Oral Exposure

Chromium(III) is an essential nutrient required for normal energy metabolism. The Institute of Medicine (IOM 2001) of the NAS determined an adequate intake (e.g., a level typically consumed by healthy individuals) of 20–45 µg chromium(III)/day for adolescents and adults (IOM 2001). Currently, the biological target for the essential effects of chromium(III) is unknown. Chromodulin, also referred to as glucose tolerance factor (GTF), has been proposed as one possible candidate (Jacquamet et al. 2003). The function of chromodulin, an oligopeptide complex containing with four chromic ions, has not been

## 3. HEALTH EFFECTS

established; however, a possible mechanism is that chromodulin facilitates the interaction of insulin with its cellular receptor sites, although this has not been proven (Anderson 1998a, 2003; IOM 2001). Chromium(III) picolinate is a common form of chromium(III) nutritional supplementation.

Trivalent chromium is very poorly absorbed from the gastrointestinal tract. Typically,  $\leq 1\%$  of an orally administered dose of trivalent chromium has been recovered in the urine of experimental animals of humans (Aitio et al. 1984; Anderson et al. 1983; Doisy et al. 1971; Donaldson and Barreras 1966; Gargas et al. 1994; Garcia et al. 2001; Kerger et al. 1996a) or experimental animals (Donaldson and Barreras 1966; Febel et al. 2001). Oral absorption of trivalent chromium complexed with an organic ligand is similarly low and not higher than inorganic forms (Anderson et al. 1996; Gonzalez-Vergara et al. 1981). Bypassing the stomach by infusing trivalent chromium into the duodenum or jejunum resulted in at most 1–2% of the dose being absorbed in humans (Donaldson and Barreras 1966), or 1% (Febel et al. 2001) to 4% in the rat (Donaldson and Barreras 1966).

Approximately 0.5–2.0% of dietary chromium(III) is absorbed via the gastrointestinal tract of humans (Anderson 1986; Anderson et al. 1983) as inferred from urinary excretion measurements. The absorption fraction is dependent on the dietary intake. At low levels of dietary intake (10  $\mu\text{g}$ ),  $\sim 2.0\%$  of the chromium was absorbed. When intake was increased by supplementation to  $\geq 40 \mu\text{g}$ , the absorption decreased to  $\sim 0.5\%$  (Anderson 1986; Anderson et al. 1983). Net absorption of chromium(III) by a group of 23 elderly subjects who received an average of 24.5  $\mu\text{g}/\text{day}$  (0.00035 mg chromium(III)/kg/day) from their normal diets was calculated to be 0.6  $\mu\text{g}$  chromium(III)/day, based on an excretion of 0.4  $\mu\text{g}$  chromium/day in the urine and 23.9  $\mu\text{g}$  chromium/day in the feces, with a net retention of 0.2  $\mu\text{g}/\text{day}$ . Thus, about 2.4% was absorbed. The retention was considered adequate for their requirements (Bunker et al. 1984).

The absorption fraction of soluble chromium(III), as chromium picolinate, is greater than  $\text{CrCl}_3$  (DiSilvestro and Dy 2007; Gargas et al. 1994). Following ingestion of 400  $\mu\text{g}$  chromium(III)/day as chromium picolinate (in a capsule) for 3 consecutive days, mean absorption fraction in eight healthy adults was 2.8% ( $\pm 1.4\%$  standard deviation [SD]; Gargas et al. 1994). Based on urinary excretion following oral administration of a single dose (200  $\mu\text{g}$  chromium(III)) of four different chromium(III) supplements to healthy women (n=24; cross-over design), the absorption of chromium picolinate was higher than that of chromium chloride, chromium polynicotinate, and chromium nicotinate-glucinate; estimates of oral absorption were not reported (DiSilvestro and Dy 2007). Urinary excretion of chromium following administration of chromium picolinate was approximately 16-fold higher than that following

## 3. HEALTH EFFECTS

administration of chromium chloride and approximately 2-fold greater than that following administration of the two nicotinate complexes.

Association of chromium with chelating agents, which may be naturally present in feed, can alter the bioavailability from food. In rats that were given  $^{51}\text{Cr}$ -chromium(III) trichloride mixed with chelating agents, either oxalate or phytate, phytate significantly ( $p < 0.05$ ) decreased the levels of radioactivity in blood, whole body, and urine achieved with chromium(III) trichloride alone (Chen et al. 1973). Oxalate, however, greatly increased the levels in blood, whole body, and urine. The oxalate served as a strong ligand to protect against the tendency of chromium(III) to form insoluble macromolecular chromium oxides at physiological pH. Fasted rats absorbed significantly more  $^{51}\text{Cr}$  chromium than did nonfasted rats, indicating that the presence of food in the gastrointestinal tract slows the absorption of chromium. Results of an *in vitro* experiment in this study indicated that the midsection had greater uptake than the duodenum or ileum and that oxalate significantly ( $p < 0.05$ ) increased, while phytate significantly ( $p < 0.05$ ) decreased the transport of chromium(III) across all three sections, paralleling the *in vivo* results. Ethylenediamine tetraacetic acid (EDTA) and citrate were also tested in the *in vitro* system, but were found to have no effect on chromium(III) intestinal transport; therefore, these chelating agents were not tested *in vivo* (Chen et al. 1973).

The absorption fraction of soluble chromium(VI) is higher than that of soluble chromium(III) (Anderson et al. 1983; Donaldson and Barreras 1966; Kerger et al. 1996a). Average absorption fractions, determined from cumulative urinary excretion in 8 healthy adults who ingested 5 mg chromium (in 10 mg Cr/L drinking water) as  $\text{CrCl}_3$  or  $\text{K}_2\text{Cr}_2\text{O}_7$  were 0.13% ( $\pm 0.04$ , standard error [SE]) and 6.9% ( $\pm 3.7$ , SE), respectively. Chromium(VI) can be reduced to chromium(III) when placed in an ascorbic acid solution (Kerger et al. 1996a). When  $\text{K}_2\text{Cr}_2\text{O}_7$  was ingested in orange juice (where it was reduced and may have formed complexes with constituents of the juice), the mean absorption fraction was 0.60% ( $\pm 0.11$ , SE; Kerger et al. 1996a). Plasma concentrations generally peaked around 90 minutes following exposure for all three chromium mixtures tested. Based on measurements of urinary excretion of chromium in 15 female and 27 male subjects who ingested 200  $\mu\text{g}$  chromium(III) as  $\text{CrCl}_3$ , the absorption fraction was estimated to be approximately 0.4% (Anderson et al. 1983). The absorption fraction of chromium(VI) (as sodium chromate) was substantially higher when administered directly into the duodenum (approximately 10%) compared to when it is ingested (approximately 1.2%), whereas the absorption fraction for  $\text{CrCl}_3$  was similar when administered into the small intestine (0.5%; Donaldson and Barreras 1966). These results are consistent with studies that have shown that gastric juice can reduce chromium(VI) to chromium(III) (De Flora et al. 1987a).

## 3. HEALTH EFFECTS

The absorption of chromium(VI) and chromium(III) was measured in four male and two female volunteers (ages ranging from 25 to 39 years) treated orally with potassium chromate (chromium(VI)) or chromic oxide (chromium(III)) in capsules at doses of 0.005 and 1.0 mg/kg/day, respectively (Finley et al. 1996b). Subjects were exposed to each compound for 3 days. Based on urinary excretion data, the mean absorption of potassium chromate was 3.4% (range 0.69–11.9%). No statistically significant increase in urinary chromium was observed during chromic oxide dosing, indicating that little, if any, was absorbed. In a follow-up study by the same group (Finley et al. 1997), five male volunteers ingested a liter, in three volumes of 333 mL, of deionized water containing chromium(VI) concentrations ranging from 0.1 to 10.0 mg/L (approximately 0.001–0.1 mg chromium(VI)/kg/day) for 3 days. A dose-related increase in urinary chromium was seen in all subjects and the percent of the dose excreted ranged from <2 to 8%. Dose-related increases in plasma and erythrocyte chromium levels were also observed.

In a repeated dose study, three healthy adults ingested chromium(VI) (as  $K_2Cr_2O_7$ ) in water at 5 mg chromium/day for 3 consecutive days (Kerger et al. 1997). Three divided doses were taken at approximately 6-hour intervals over a 5–15-minute period. After at least 2 days without dosing, the 3-day exposure regimen was repeated at 10 mg chromium/day. Estimated doses based on body weight were 0.05 and 0.1 mg/kg/day, respectively. Bioavailability based on 4-day urinary excretion was 1.7% (range 0.5–2.7%) at 0.05 mg chromium(VI)/kg/day and 3.4% (range 0.8–8.0%) at 0.1 mg chromium(VI)/kg/day. Absorption of 0.05 mg chromium(VI)/kg appeared to be somewhat lower when given as three divided doses rather than when given as a single bolus dose (1.7 versus 5.7%).

Uptake of potassium dichromate was determined in a man who was given 0.8 mg of chromium(VI) in drinking water 5 times each day for 17 days (Paustenbach et al. 1996). Steady-state concentrations of chromium in blood were attained after 7 days. Red blood cell and plasma levels returned to background levels within a few days after exposure was stopped. The data are consistent with a bioavailability of 2% and a plasma elimination half-life of 36 hours.

Studies with  $^{51}$ chromium in animals indicate that chromium and its compounds are also poorly absorbed from the gastrointestinal tract after oral exposure. When radioactive sodium chromate (chromium(VI)) was given orally to rats, the amount of chromium in the feces was greater than that found when sodium chromate was injected directly into the jejunum. Since chromium(III) is absorbed less readily than chromium(VI) by the gastrointestinal tract, these results are consistent with evidence that the gastric environment has a capacity to reduce chromium(VI) to chromium(III). Furthermore, the administration

## 3. HEALTH EFFECTS

of radioactive chromium(III) or chromium(VI) compounds directly into the jejunum decreased the amount of chromium recovery in the feces indicating that the jejunum is the absorption site for chromium (Donaldson and Barreras 1966). Absorption of either valence state was  $\leq 1.4\%$  of the administered oral dose in rats (Sayato et al. 1980) and hamsters (Henderson et al. 1979). Based on distribution (see Section 3.3.2.2) and excretion (see Section 3.3.4.2) studies in rats administered chromium by gavage for 2–14 days from various sources, that is, from sodium chromate (chromium(VI)), from calcium chromate (chromium(VI)), or from soil contaminated with chromium (30% chromium(VI) and 70% chromium(III)), the low gastrointestinal absorption of chromium from any source was confirmed. Chromium appeared to be better absorbed from the soil than from chromate salts, but  $<50\%$  of the administered chromium could be accounted for in these studies, partly because not all tissues were examined for chromium content and excretion was not followed to completion (Witmer et al. 1989, 1991). Adult and immature rats given chromium(III) chloride absorbed 0.1 and 1.2% of the oral dose, respectively (Sullivan et al. 1984). This suggests that immature rats may be more susceptible to potential toxic effects of chromium(III) compounds.

Treatment of rats by gavage with a nonencapsulated lead chromate pigment or with a silica-encapsulated lead chromate pigment resulted in no measurable blood levels of chromium (detection limit=10  $\mu\text{g/L}$ ) after 2 or 4 weeks of treatment or after a 2-week recovery period. However, kidney levels of chromium were significantly higher in the rats that received the nonencapsulated pigment than in the rats that received the encapsulated pigment, indicating that silica encapsulation reduces the gastrointestinal bioavailability of chromium from lead chromate pigments (Clapp et al. 1991).

The issue of whether or not chromium(VI) absorption occurs only when or principally when the reducing capacity of the gastrointestinal tract is exhausted is a factor to consider in evaluating and interpreting oral dosing bioassays in animals and human epidemiology studies of health outcomes related to ingestion exposures to chromium. Potentially, tumor responses could be enhanced if the reducing capacities of saliva and stomach fluid were exhausted. This is more likely to occur at the relatively high doses of chromium(VI) administered in animal bioassays than at doses experienced by humans from environmental exposures. However, results of experimental studies of chromium absorption in humans have not found evidence for an effect of limited of reducing capacity on absorption of chromium. The range of doses of chromium administered to humans in these different studies was considerable and demonstrated oral bioavailability at all doses. Donaldson and Barreras (1996) administered 20 ng of radiolabeled chromium(VI), Kerger et al. (1996a) administered 5 mg of chromium(VI), Finley et al. (1996b) administered 0.005 mg/kg-day of chromium(VI) for 3 days, and Finley et al. (1997) administered



## 3. HEALTH EFFECTS

0.1, 0.5, 1.0, 5.0 or 10 mg/day of chromium(VI) for 4 days. In the Finley et al. (1997) study, the percent of the administered dose of chromium(VI) recovered in the urine did not increase with dose. The results of these studies do not indicate that oral absorption of administered chromium(VI) only begins to occur when the reducing capacity of the stomach is exhausted, and are consistent with estimates of gastrointestinal reducing capacity (De Flora 2000; Proctor et al. 2002).

**3.4.1.3 Dermal Exposure**

Both chromium(III) and chromium(VI) can penetrate human skin to some extent, especially if the skin is damaged. Systemic toxicity has been observed in humans following dermal exposure to chromium compounds, indicating significant cutaneous absorption (see Section 3.2.3). Fourteen days after a salve containing potassium chromate was applied to the skin of an individual to treat scabies, appreciable amounts of chromium were found in the blood, urine, feces, and stomach contents (Brieger 1920) (see Section 3.4.2.3). It should be noted that the preexisting condition of scabies or the necrosis caused by the potassium chromate (see Section 3.2.3) could have facilitated dermal absorption of potassium chromate. Potassium dichromate (chromium(VI)), but not chromium(III) sulfate, penetrated the excised intact epidermis of humans (Mali et al. 1963). Dermal absorption by humans of chromium(III) sulfate in aqueous solution was negligible, with slightly larger amounts of chromium(III) nitrate in aqueous solution absorbed. The absorption of chromium(III) chloride was similar to potassium dichromate(VI) (Samitz and Shrager 1966). Chromium(III) from a concentrated chromium sulfate solution at pH 3 penetrated cadaverous human skin at a rate of  $5 \times 10^{-11}$  cm/sec, compared with a rate for chromium(VI) (source unspecified) of  $5 \times 10^{-7}$  cm/second (Spruit and van Neer 1966). In contrast, both chromium(VI) from sodium chromate and chromium(III) from chromium trichloride penetrated excised human mammary skin at similar rates, but the rate was generally slightly faster for chromium(VI). Absolute rates of absorption in nmol chromium/hour/cm<sup>2</sup> increased with increasing concentration of both chromium(VI) and chromium(III) (Wahlberg 1970). The average rate of systemic uptake of chromium in four volunteers submersed up to the shoulders in a tub of chlorinated water containing a 22 mg chromium(VI)/L solution of potassium dichromate for 3 hours was measured to be  $1.5 \times 10^{-4}$  µg/cm<sup>2</sup>-hour based on urinary excretion of total chromium (Corbett et al. 1997).

The influence of solvent on the cutaneous penetration of potassium dichromate by humans has been studied. The test solutions of potassium dichromate in petrolatum or in water were applied as occluded circular patches of filter paper to the skin. Results with dichromate in water revealed that chromium(VI) penetrated beyond the dermis and penetration reached steady state with resorption by the lymph and

### 3. HEALTH EFFECTS

blood vessels by 5 hours. About 10 times more chromium penetrated when potassium dichromate was applied in petrolatum than when applied in water. About 5 times more chromium penetrated when potassium dichromate was applied than when a chromium trichloride glycine complex was applied (Liden and Lundberg 1979). The rates of absorption of solutions of sodium chromate from the occluded forearm skin of volunteers increased with increasing concentration. The rates were 1.1  $\mu\text{g chromium(VI)/cm}^2/\text{hour}$  for a 0.01 M solution, 6.4  $\mu\text{g chromium(VI)/cm}^2/\text{hour}$  for a 0.1 M solution, and 10  $\mu\text{g chromium(VI)/cm}^2/\text{hour}$  for a 0.2 M solution (Baranowska-Dutkiewicz 1981).

Chromium and its compounds are also absorbed dermally by animals. The dermal absorption of sodium chromate (chromium(VI)) by guinea pigs was somewhat higher than that of chromium(III) trichloride, but the difference was not significant. At higher concentrations (0.261–0.398 M), absorption of sodium chromate was statistically higher than that of chromium trichloride. The peak rates of absorption were 690–725 and 315–330  $\text{nmol}/\text{hour}/\text{cm}^2$  for sodium chromate at 0.261–0.398 M and chromium trichloride at 0.239–0.261 M, respectively. Percutaneous absorption of sodium chromate was higher at  $\text{pH} \geq 6.5$  compared with  $\text{pH} \leq 5.6$  (Wahlberg and Skog 1965).

#### 3.4.2 Distribution

##### 3.4.2.1 Inhalation Exposure

Examination of tissues from Japanese chrome platers and chromate refining workers at autopsy revealed higher chromium levels in the hilar lymph node, lung, spleen, liver, kidney, and heart, compared to normal healthy males (Teraoka 1981). Analysis of the chromium concentrations in organs and tissues at autopsy of a man who died of lung cancer 10 years after his retirement from working in a chromate producing plant for 30 years revealed measurable levels in the brain, pharyngeal wall, lung, liver, aorta, kidney, abdominal rectal muscle, suprarenal gland, sternal bone marrow, and abdominal skin. The levels were significantly higher than in five controls with no occupational exposure to chromium. The man had been exposed mainly to chromium(VI), with lesser exposure to chromium(III) as the chromite ore (Hyodo et al. 1980). The levels of chromium were higher in the lungs, but not in the liver or kidneys, of autopsy specimens from 21 smeltery and refinery workers in North Sweden compared with that for a control group of 8 individuals. The amount of enrichment in the lungs decreased as the number of elapsed years between retirement and death increased (Brune et al. 1980). Tissues from three individuals having lung cancer who were industrially exposed to chromium were examined by Mancuso (1997b). One was employed for 15 years as a welder, a second worked for 10.2 years, and a third for 31.8 years in ore milling and preparations and boiler operations. The three cumulative chromium exposures for the three

## 3. HEALTH EFFECTS

workers were 3.45, 4.59, and 11.38 mg/m<sup>3</sup> years, respectively. Tissues from the first worker were analyzed 3.5 years after last exposure, the second worker 18 years after, and the third worker 0.6 years after last exposure. All tissues from the three workers had elevated levels of chromium with the possible exception of neural tissues. Levels were orders of magnitude higher in lungs than other tissues. The highest lung level reported was 456 mg/10 g tissue in the first worker, 178 in the second worker, and 1,920 for the third worker. There were significant chromium levels in the tissue of the second worker even though he had not been exposed to chromium for 18 years. Chromium concentrations in lung tissues from autopsy samples were 5 times higher in subjects who originated from the Ruhr and Dortmund regions of Germany, where emissions of chromium are high, than in subjects from Munster and vicinity. The lung concentrations of chromium increased with increasing age. Men had twice as high concentrations of chromium in the lungs than did women, which may reflect the greater potential for occupational exposure by men, the higher vital capacity of men, and possibly a greater history of smoking (Kollmeier et al. 1990).

Chromium may be transferred to fetuses through the placenta and to infants via breast milk. Analysis of chromium levels in women employees of a dichromate manufacturing facility in Russia during and after pregnancy revealed that the exposed women had significantly higher levels of chromium in blood and urine during pregnancy, in umbilical cord blood, placentae, and breast milk at child birth, and in fetuses aborted at 12 weeks than did nonexposed controls (Shmitova 1980). The reliability of this study is suspect because the levels of chromium reported in the blood and urine of the control women were much higher than usual background levels of chromium in these biological fluids (see Section 6.5), perhaps due to problems with analytical methods. Measurement of the chromium content in 255 samples from 45 lactating American women revealed that most samples contained <0.4 µg/L, and the mean value was 0.3 µg/L (Casey and Hambidge 1984). While these probably represent background levels in women whose main exposure to chromium is via the diet, the findings indicate that chromium may be transferred to infants via breast milk.

The distribution of radioactivity in rats given <sup>51</sup>chromium as sodium dichromate intratracheally was followed for 40 days by autoradiography and scintillation counting. Three days after the administration of 0.01 mg chromium(VI)/m<sup>3</sup> as radioactive sodium dichromate, the tissue distribution based on the relative concentrations in the tissue was lung > kidney > gastrointestinal tract > erythrocytes > liver > serum > testis > skin. Twenty-five days after dosing, the tissue distribution was lung > kidney > erythrocytes > testis > liver > serum > skin > gastrointestinal tract. Kidney, erythrocytes, and testis maintained their chromium levels for a period of 10–15 days before decreasing (Weber 1983). The

### 3. HEALTH EFFECTS

distribution of chromium(VI) compared with chromium(III) was investigated in guinea pigs after intratracheal instillation of potassium dichromate or chromium trichloride. At 24 hours after instillation, 11% of the original dose of chromium from potassium dichromate remained in the lungs, 8% in the erythrocytes, 1% in plasma, 3% in the kidney, and 4% in the liver. The muscle, skin, and adrenal glands contained only a trace. All tissue concentrations of chromium declined to low or nondetectable levels in 140 days with the exception of the lungs and spleen. After chromium trichloride instillation, 69% of the dose remained in the lungs at 20 minutes, while only 4% was found in the blood and other tissues, with the remaining 27% cleared from the lungs and swallowed. The only tissue that contained a significant amount of chromium 2 days after instillation of chromium trichloride was the spleen. After 30 and 60 days, 30 and 12%, respectively, of the chromium(III) was retained in the lungs, while only 2.6 and 1.6%, respectively, of the chromium(VI) dose was retained in the lung (Baetjer et al. 1959a).

#### 3.4.2.2 Oral Exposure

Autopsy studies in the United States indicate that chromium concentrations in the body are highest in kidney, liver, lung, aorta, heart, pancreas, and spleen at birth and tend to decrease with age. The levels in liver and kidney declined after the second decade of life. The aorta, heart, and spleen levels declined rapidly between the first 45 days of life and 10 years, with low levels persisting throughout life. The level in the lung declined early, but increased again from mid life to old age (Schroeder et al. 1962).

The distribution of chromium in human body tissue after acute oral exposure was determined in the case of a 14-year-old boy who ingested 7.5 mg chromium(VI)/kg as potassium dichromate. Despite extensive treatment by dialysis and the use of the chelating agent British antilewisite, the boy died 8 days after admission to the hospital. Upon autopsy, the chromium concentrations were as follows: liver, 2.94 mg/100 cc (normal, 0.016 mg/100 cc); kidneys, 0.64 and 0.82 mg/100 cc (normal, 0.06 mg/100 cc); and brain, 0.06 mg/100 cc (normal, 0.002 mg/100 cc) (Kaufman et al. 1970). Although these data were obtained after extensive treatment to rid the body of excess chromium, the levels of chromium remaining after the treatment clearly demonstrate that these tissues absorbed at least these concentrations after an acute, lethal ingestion of a chromium(VI) compound.

Chromium may be transferred to infants via breast milk as indicated by breast milk levels of chromium in women exposed occupationally (Shmitova 1980) or via normal levels in the diet (Casey and Hambidge 1984). It has been demonstrated that in healthy women, the levels of chromium measured in breast milk are independent of serum chromium levels, urinary chromium excretion, or dietary intake of chromium

## 3. HEALTH EFFECTS

(Anderson et al. 1993, Mohamedshah et al. 1998), but others (Engelhardt et al. 1990) have disputed this observation.

The tissue distribution of chromium was studied in rats administered chromium from a variety of sources. In one experiment, sodium chromate in water was administered by gavage for 7 days at 0, 1.2, 2.3, or 5.8 mg chromium(VI)/kg/day. Very little chromium (generally  $<0.5$   $\mu\text{g}/\text{organ}$ ) was found in the organs analyzed (liver, spleen, lung, kidney, and blood) after administration of the two lower doses. The levels were generally comparable to those in controls. After 5.8 mg/kg/day, the largest amount of chromium (expressed as  $\mu\text{g}$  chromium/whole organ) was found in the liver ( $\approx 22$   $\mu\text{g}$ ), followed by the kidney ( $\approx 7.5$   $\mu\text{g}$ ), lung ( $\approx 4.5$   $\mu\text{g}$ ), blood ( $\approx 2$   $\mu\text{g}$ ), and spleen ( $\approx 1$   $\mu\text{g}$ ). The total amount of chromium in these tissues represented only 1.7% of the final dose of 5.8 mg/kg/day, but not all organs were analyzed. In the next experiment, rats were exposed by gavage to 7 mg chromium/kg/day for 7 days from various sources: (1) sodium chromate; (2) calcium chromate; (3) soil containing chromium (30% chromium(VI), 70% chromium(III)); or (4) a mixture of calcium chromate and the contaminated soil. The highest levels of chromium were found in liver, spleen, kidney, lung, blood, brain, and testes after dosing with sodium chromate, but the relative levels in these tissues after the other treatments followed no consistent pattern. Rats gavaged for 14 days with 13.9 mg chromium/kg/day from the four different sources had higher levels of chromium in the tissues after they were dosed with the contaminated soil or the mixture of calcium chromate and the contaminated soil than with either of the chromate salts alone. Thus, the relative organ distribution of chromium depends on the source of chromium (Witmer et al. 1989, 1991). Components in soil may affect the oxidation state and the binding of chromium to soil components, and pH of the soil may also affect the bioavailability from soil.

The chromium content in major organs (heart, lung, kidney, liver, spleen, testes) of mice receiving drinking water that provided doses of 4.8, 6.1, or 12.3 mg chromium(III)/kg/day as chromium trichloride or 4.4, 5.0, or 14.2 mg chromium(VI)/kg/day as potassium dichromate was determined after 1 year of exposure. Chromium was detected only in the liver in the chromium(III)-treated mice. Mice treated with chromium(VI) compounds had accumulation in all of the above organs, with the highest levels reported in the liver and spleen. Liver accumulation of chromium was 40–90 times higher in the chromium(VI)-treated group than in the chromium(III)-treated group (Maruyama 1982). Chromium levels in tissue (bone, kidney liver, spleen) were 9 times higher in rats given chromium(VI) as potassium chromate in drinking water for 1 year than in rats given the same concentration of chromium(III) as chromium trichloride (MacKenzie et al. 1958). In rats exposed to potassium chromate in the drinking water for 3 or 6 weeks, a general trend of increasing chromium concentration with time of exposure was apparent in the

## 3. HEALTH EFFECTS

liver and kidneys, but only the kidneys showed a difference in the concentration after exposure to 100 and 200 ppm. Blood concentrations were almost saturated by 3 weeks with little further accumulation by 6 weeks. No chromium was detected in the lungs after drinking water exposure (Coogan et al. 1991a). After acute oral dosing with radiolabeled chromium trichloride (1  $\mu\text{Ci}$  for immature rats, 10  $\mu\text{Ci}$  for adults), adult and neonatal rats accumulated higher levels of chromium in the kidneys than in the liver. At 7 days after dosing, the liver and kidney contained 0.05 and 0.12% of the dose, respectively, in the neonates and 0.002 and 0.003% of the dose, respectively, in the adult rats. The carcass contained 0.95% of the dose in the neonates and 0.07% of the dose in adult rats. The lungs contained 0.0088% of the dose in neonates and 0.0003% of the dose in adult rats. No chromium(III) was detected in the skeleton or muscle. Approximately 35 and 0.2% of the administered dose of chromium(III) at day 7 was retained in the gut of neonates and adults, respectively (Sullivan et al. 1984).

The distribution of potassium chromate(VI) was compared in male Fisher rats and C57BL/6J mice exposed either by drinking water (8 mg chromium(VI)/kg/day for 4 and 8 weeks) or by intraperitoneal injection (0.3 and 0.8 mg chromium(VI)/kg/day for 4 or 14 days) (Kargacin et al. 1993). The concentrations of chromium ( $\mu\text{g/g}$  wet tissue) after drinking water exposures for 8 weeks in mice were: liver 13.83, kidney 4.72, spleen 10.09, femur 12.55, lung 1.08, heart 1.02, muscle 0.60, and blood 0.42. These concentrations were not markedly different than for 4-week exposures. For rats, the concentrations were: liver 3.59, kidney 9.49, spleen 4.38, femur 1.78, lung 0.67, heart 1.05, muscle 0.17, and blood 0.58. These results demonstrate that considerable species differences exist between mice and rats and need to be factored into any toxicological extrapolations across species even if the routes of administration are the same. In the drinking water experiments, blood levels in rats and mice were comparable, but in intraperitoneal injection experiments, rats' levels were about 8-fold higher than mice after 4 days of exposure. This difference appeared to be due to increased sequestering by rat red blood cells, since accumulation in white blood cells was lower in rats than mice. The higher incidence of red cell binding was also associated with greater binding of chromium to rat hemoglobin.

The feeding of five male Wistar rats at 0.49 mg chromium(III)/kg/day as chromium(III) chloride for 10 weeks resulted in increased chromium levels in liver, kidney, spleen, hair, heart, and red blood cells (Aguilar et al. 1997). Increases were highest in kidney (0.33  $\mu\text{g/g}$  wet tissue in controls versus 0.83  $\mu\text{g/g}$  in treated animals) and erythrocytes (1.44  $\mu\text{g/g}$  wet tissue in controls versus 3.16  $\mu\text{g/g}$  in treated animals).

The higher tissue levels of chromium after administration of chromium(VI) than after administration of chromium(III) (MacKenzie et al. 1958; Maruyama 1982; Witmer et al. 1989, 1991) reflect the greater

## 3. HEALTH EFFECTS

tendency of chromium(VI) to traverse plasma membranes and bind to intracellular proteins in the various tissues, which may explain the greater degree of toxicity associated with chromium(VI). In an experiment to determine the distribution of chromium in red and white blood cells, rats were exposed orally to 0.0031 mg/kg of <sup>51</sup>chromium(VI) as sodium chromate. The <sup>51</sup>chromium content of the fractionated blood cells was determined either 24 hours or 7 days after exposure. After 24 hours, the white blood cells contained much more <sup>51</sup>chromium (≈250 pg chromium/billion cells) than did the red blood cells (≈30 pg chromium/billion cells). After 7 days, the <sup>51</sup>chromium content of the white blood cells was reduced only 2.5-fold, while that of the red blood cells was reduced 10-fold. Thus, white blood cells preferentially accumulated chromium(VI) and retained the chromium longer than did the red blood cells. As discussed in Section 3.4.2.4, a small amount of chromium(III) entered red blood cells of rats after intravenous injection of <sup>51</sup>chromium trichloride, but no <sup>51</sup>chromium was detectable in white blood cells (Coogan et al. 1991b).

Twelve pregnant female albino rats (Druckrey strain) and 13 Swiss albino mice were exposed to 500 ppm potassium dichromate(VI) in their drinking water during pregnancy up to 1 day before delivery (Saxena et al. 1990a). The chromium(VI) daily intake was calculated to be 11.9 mg chromium(VI)/day for the rats and 3.6 mg chromium(VI)/day for mice which were considered to be maximal nontoxic doses for both species. In rats, concentrations of chromium were 0.067, 0.219, and 0.142 µg/g fresh weight in maternal blood, placenta, and fetuses, respectively, and 0.064, 0.304, and 0.366 µg/g fresh weight in mice, respectively. In treated rats, chromium levels were 3.2-fold higher in maternal blood, 3-fold higher in placenta, and 3.1-fold higher in fetal tissue when compared to control values. In treated mice, chromium levels were 2.5-fold higher in maternal blood, 3.2-fold higher in placenta, and 9.6-fold higher in fetuses when compared to control values. In treated mice, there was a significant elevation in chromium levels in placental and fetal tissues over maternal blood levels, and a significant increase in chromium levels in fetal tissue over placental concentrations when compared to controls. These differences were not observed in rats, indicating that the distribution patterns in mice and rats are different.

A study of transplacental transfer of chromium(III) in different forms indicated that placental transport varies with the chemical form. Male and female rats were fed either a commercial diet that contained 500 ppb chromium or a 30% Torula yeast diet that contained <100 ppb chromium. They were also given drinking water with or without 2 ppm chromium(III) added as chromium acetate monohydrate. The rats were mated and immediately after delivery, the neonates were analyzed for chromium content. The neonates whose dams were fed the commercial diet contained almost twice as much chromium as those whose dams were fed the chromium-deficient yeast diet. Addition of chromium(III) acetate to the

## 3. HEALTH EFFECTS

drinking water of the yeast-fed rats (2 ppm) did not increase the levels of chromium in the neonates. Administration of chromium(III) trichloride intravenously or by gavage before mating, during mating, or during gestation resulted in no or only a small amount of chromium in the neonates. Administration of chromium(III) in the form of GTF from Brewer's yeast by gavage during gestation resulted in chromium levels in the litters that were 20–50% of the dams' levels. The results indicate that fetal chromium is derived from specific chromium complexes in the diet (e.g., GTF) (Mertz et al. 1969).

**3.4.2.3 Dermal Exposure**

The findings of toxic effects in the heart, stomach, blood, muscles, and kidneys of humans who were dermally exposed to chromium compounds is suggestive of distribution to these organs (see Section 3.2.3.2). Fourteen days after a salve containing potassium chromate(VI) was applied to the skin of an individual to treat scabies, appreciable amounts of chromium were found in the blood (2–5 mg/100 mL), urine (8 mg/L), feces (0.61 mg/100 g), and stomach contents (0.63 mg/100 mL) (Brieger 1920). The preexisting condition of scabies or the necrosis caused by the potassium chromate could have facilitated its absorption. A transient increase in the levels of total chromium in erythrocytes and plasma was observed in subjects immersed in a tank of chlorinated water containing potassium dichromate(VI) (Corbett et al. 1997).

Chromium compounds are absorbed after dermal administration by guinea pigs. Measurement of <sup>51</sup>chromium in the organs and body fluids revealed distribution, due to dermal absorption of chromium(III) and chromium(VI) compounds, to the blood, spleen, bone marrow, lymph glands, urine, and kidneys. Absorption was greater for chromium(VI) than for chromium(III) (see Section 3.4.1.3) (Wahlberg and Skog 1965).

**3.4.2.4 Other Routes of Exposure**

The distribution of chromium(III) in humans was analyzed using a whole-body scintillation scanner, whole-body counter, and plasma counting. Six individuals given an intravenous injection of <sup>51</sup>chromium(III) as chromium trichloride had >50% of the blood plasma chromium(III) distributed to various body organs within hours of administration. The liver and spleen contained the highest levels. After 3 months, the liver contained half of the total body burden of chromium. The study results indicated a three-compartment model for whole-body accumulation and clearance of chromium(III). The half-lives were 0.5–12 hours for the fast component, 1–14 days for the medium component, and 3–12 months for the slow component (Lim et al. 1983).



## 3. HEALTH EFFECTS

An *in vitro* study in human blood showed that chromium(VI) was rapidly cleared from the plasma (Corbett et al. 1998). The reduction capacity appears to be concentration dependent and is overwhelmed at spike concentrations between 2,000 and 10,000 µg/L. High chromium(VI) concentrations (10,000 µg/L spike concentration) resulted in an accumulation of chromium(VI) in the erythrocytes and a lower plasma:erythrocyte ratio of total chromium. This study also found that the plasma reduction capacity was enhanced by a recent meal.

Both human and rat white blood cells accumulated more <sup>51</sup>chromium per cell than red blood cells after *in vitro* exposure of whole blood to <sup>51</sup>chromium(VI). The uptake of chromium by rat blood cells was also measured after intravenous exposure to <sup>51</sup>chromium(VI) as sodium chromate. After intravenous exposure, the white blood cells contained significantly more <sup>51</sup>chromium (≈30 pg chromium/billion cells) than the red blood cells (≈4 pg chromium/billion cells), and the amount of <sup>51</sup>chromium in the cells was the same after 24 hours as it was after 1 hour. The amount of <sup>51</sup>chromium in the white blood cells, but not in the red blood cells, decreased by approximately 1.7-fold after 7 days. When rats were injected intravenously with 20 ng of radiolabeled sodium chromate (chromium(VI)) or radiolabeled chromium trichloride (chromium(III)), the amount of chromium was ≈2 pg/billion red blood cells but not detectable in white blood cells after injection of chromium(III) chloride. The amount of chromium was ≈5 pg/billion red blood cells and ≈60 pg/billion white blood cells after injection of sodium chromate (Coogan et al. 1991b).

The distribution pattern in rats treated with sodium chromite (chromium(III)) by intravenous injection revealed that most of the chromium was concentrated in the reticuloendothelial system, which, together with the liver, accumulated 90% of the dose. The accumulation in the reticuloendothelial system was thought to result from colloid formation by chromite at physiological pH. Organs with detectable chromium levels 42 days postinjection were: spleen > liver > bone marrow > tibia > epiphysis > lung > kidney. Chromium trichloride given to rats by intravenous injection also concentrated in the liver, spleen, and bone marrow (Visek et al. 1953). In rats administered chromium(III) nitrate intraperitoneally for 30 or 60 days, the highest levels of chromium were found in the liver, followed by the kidneys, testes, and brain. The levels increased with increased doses but not linearly. The levels in the kidneys, but not the other organs, increased significantly with duration (Tandon et al. 1979).

Whole-body analysis of mice given a single intraperitoneal injection of 3.25 mg chromium(III)/kg as chromium trichloride showed that chromium trichloride was released very slowly over 21 days: 87% was

## 3. HEALTH EFFECTS

retained 3 days after treatment, 73% after 7 days treatment, and 45% after 21 days. In contrast, mice given a single intraperitoneal injection of 3.23 chromium(VI)/kg as potassium dichromate retained only 31% of the chromium(VI) dose at 3 days, 16% at 7 days and 7.5% at 21 days. Mice injected weekly with chromium(III) compounds at 17% of the LD<sub>50</sub> retained 6 times the amount of chromium as mice injected with chromium(VI) compounds at 17% of the LD<sub>50</sub>. The retention of chromium(III) was attributed to its ability to form coordination complexes with tissue components such as proteins and amino acids (Bryson and Goodall 1983).

In rats injected intraperitoneally with 2 mg chromium(VI)/kg/day as potassium chromate 6 days/week for 45 days, the mean levels of chromium (µg chromium/g wet weight) were 25.68 in the liver, 40.61 in the kidney, 7.56 in the heart, and 4.18 in the brain (Behari and Tandon 1980).

In rats injected subcutaneously with 5.25 mg chromium(VI)/kg as potassium dichromate, most of the chromium in the tissues analyzed was found in the red blood cells with a peak level (63 µg chromium/g) achieved 24 hours after dosing. White blood cells were not analyzed for chromium content. Whole plasma contained 2.7–35 µg/mL and the plasma ultrafiltrate contained 0.15–0.79 µg/mL. Tissue distribution 48 hours after dosing was as follows: 221.2 µg/g in renal cortex, 110.0 µg/g in liver, 103.0 µg/g in spleen, 86.8 µg/g in lung, 58.9 µg/g in renal medulla, and 8.8 µg/g in bone, compared with 2.28–5.98 µg/g in any tissues in controls. When rats were given repeated subcutaneous injections of 1.05 mg chromium(VI)/kg/day, every other day for 2, 4, 8, 10, or 12 weeks, most of the chromium was again found in the red blood cells. However, while red blood cell levels rose progressively during treatment, levels as high as those seen after a single dose were never achieved, even when the total dose exceeded the dose in the single injection experiment 10-fold. The tissue levels of chromium determined 48 hours after the last dose in the rats injected for 12 weeks were of the same order of magnitude as those seen after a single injection. These results suggest little tendency of soluble chromium(VI) compounds to accumulate in tissues with repeated exposure (Mutti et al. 1979).

In an *in vitro* study, whole blood samples were spiked with water-soluble chromium(VI) or chromium(III) compounds. The results showed a greater level of chromium inside erythrocytes after treatment with chromium(VI) compounds, compared to chromium(III) compounds. The investigators reported that only chromium(VI) compounds are taken up by erythrocytes and, presumably after reduction to chromium(III), form complexes with intracellular proteins that could not be eliminated (Lewalter et al. 1985).

## 3. HEALTH EFFECTS

The distribution of radioactivity was compared in mouse dams and fetuses following the intravenous injection of the dams with  $^{51}\text{Cr}$ Chromium labelled-sodium dichromate(VI) or  $^{51}\text{Cr}$ chromium labelled-chromium(III) trichloride. In the maternal tissues, the highest levels of radioactivity from both treatments were achieved in the renal cortex, but the concentration of radioactivity in the tissues of dams given the hexavalent form was much higher than that of the dams given the trivalent form. The patterns of distribution of radioactivity in other tissues were identical regardless of administered valence state, with the skeleton, liver, kidneys, and ovaries accumulating the highest levels and the brain and muscle accumulating the lowest levels. The serum concentration of radioactivity after treatment with chromium(III) was 3 times higher than that after treatment with chromium(VI). Radioactivity after treatment with both valence forms crossed the placenta, but the radioactivity from the hexavalent form crossed more readily. For chromium(VI),  $\approx 12\%$  of the maternal serum concentration of radioactivity was found in the fetuses when the dams were administered sodium dichromate in mid-gestation (days 12–15). When the dams were injected in late gestation (days 16–18),  $\approx 19\%$  of the radioactivity in maternal serum was found in the fetuses. For chromium(III), the fetal concentration of radioactivity was only  $\approx 0.4\%$  of the maternal serum concentration when the dams were injected with radiolabeled chromium trichloride in mid-gestation and  $0.8\%$  of the maternal serum radioactivity concentration when injected in late gestation. Radioactivity from both treatments accumulated in fetal skeletons in calcified areas and in the yolk sac placenta (Danielsson et al. 1982). Danielsson et al. (1982) noted that the radioactivity after administration of chromium(VI) may represent chromium(III) after reduction in the tissues. Chromium(III) also crossed the placenta of mice injected intraperitoneally with chromium trichloride (Iijima et al. 1983). While the results indicate that both chromium(VI) and chromium(III) may pose developmental hazards, they cannot be used to indicate that exposure of pregnant animals to chromium(III) by inhalation or oral routes would result in significant placental transfer because chromium(III) compounds are not well absorbed by these routes (see Section 3.4.1).

Tissue distribution in rats and mice after 14 days of intraperitoneal injection of  $0.8\text{ mg chromium(VI)/day}$  as potassium chromate were: liver  $6.00\text{ }\mu\text{g/g}$  wet weight in rats and  $8.89$  in mice, kidney  $24.14$  and  $11.77$ , spleen  $15.26$  and  $6.92$ , femur  $6.53$  and  $6.30$ , lung  $3.99$  and  $2.89$ , heart  $3.13$  and  $1.75$ , muscle  $1.10$  and  $0.51$ , and blood  $4.52$  and  $1.56$ . (Kargacin et al. 1993). Kidney and blood chromium concentrations were 2- and 4-fold higher, respectively, in rats compared to mice. Red blood cell concentrations were 3-fold higher in rats than mice and hemoglobin binding of chromium was twice as high in rats. By contrast, after oral exposure levels, in blood for rats and mice were similar. The authors ascribed this to faster entry into the blood after intraperitoneal injection and thus a greater likelihood that chromium(VI) could be sequestered in rat erythrocytes by reduction.

## 3. HEALTH EFFECTS

**3.4.3 Metabolism**

Chromium(III) compounds are essential to normal glucose, protein, and fat metabolism. In addition, chromium(III) is capable of forming complexes with nucleic acids and proteins. Chromium(III) may also participate in intracellular reduction and oxidation reactions. Chromium(VI) is unstable inside the body and is ultimately reduced to chromium(III) *in vivo* by a variety of reducing agents. Chromium(V) and chromium(IV) are transient intermediates in this process.

Currently, the biological target for the essential effects of chromium(III) is unknown. Chromodulin, also referred to as GTF, has been proposed as one possible candidate (Jacquamet et al. 2003). The function of chromodulin, an oligopeptide complex containing with four chromic ions, has not been established; however, a possible mechanism is that chromodulin facilitates the interaction of insulin with its cellular receptor sites, although this has not been proven (Anderson 1998a, 2003; IOM 2001).

*In vivo* and *in vitro* experiments in rats indicated that, in the lungs, chromium(VI) can be reduced to chromium(III) by ascorbate. The reduction of chromium(VI) by ascorbate results in a shorter residence time of chromium in the lungs and constitutes the first defense against oxidizing reagents in the lungs. When ascorbate is depleted from the lungs, chromium(VI) can also be reduced by glutathione. The level of ascorbic acid in the adult human lung has been estimated as approximately 7 mg/100 g wet tissue (Hornig 1975). The reduction of chromium(VI) by glutathione is slower and results in greater residence time of chromium in the lungs, compared to reduction by ascorbate (Suzuki and Fukuda 1990). Other studies reported the reduction of chromium(VI) to chromium(III) by epithelial lining fluid (ELF) obtained from the lungs of 15 individuals by bronchial lavage. The average reduction accounted for 0.6 µg chromium(VI)/mg of ELF protein. In addition, cell extracts made from pulmonary alveolar macrophages derived from five healthy male volunteers were able to reduce an average of 4.8 µg chromium(VI)/10<sup>6</sup> cells or 14.4 µg chromium(VI)/mg protein (Petrilli et al. 1986b). Metabolism of the chromium(VI) to chromium(III) by these cell fractions significantly reduced the mutagenic potency of the chromium when tested in the Ames reversion assay. Postmitochondrial (S12) preparations of human lung cells (peripheral lung parenchyma and bronchial preparations) were also able to reduce chromium(VI) to chromium(III) (De Flora et al. 1984). Moreover, large individual differences were observed (De Flora et al. 1984, 1987b), and extracts from pulmonary alveolar macrophages of smokers reduced significantly more chromium(VI) to chromium(III) than extracts from cells of nonsmokers. Because chromium(III) does not readily enter cells, these data suggest that reduction of chromium(VI) by the ELF may constitute the first

## 3. HEALTH EFFECTS

line of defense against toxicity of inhaled chromium compounds. Furthermore, uptake and reduction of chromium compounds by the pulmonary alveolar macrophages may constitute a second line of defense against pulmonary toxicity of chromium(VI) compounds. Microsomal reduction of chromium(VI) occurs in the lungs mainly as it does in the liver, as discussed below.

The first defense against chromium(VI) after oral exposure is the reduction of chromium(VI) to chromium(III) in the gastric environment where gastric juice (De Flora et al. 1987a) and ascorbate (Samitz 1970) play important roles. Studies using low-frequency electron paramagnetic resonance (EPR) spectrometry have shown that chromium(VI) is reduced to chromium(V) *in vivo* (Liu et al. 1994, 1995, 1997a, 1997b; Ueno et al. 1995b). *In vitro*, low concentrations of ascorbate favor the formation of chromium(V), whereas higher concentrations of ascorbate favor the formation of the reduced oxidation state, chromium(III) (Liu et al. 1995). EPR spectrometric monitoring also showed that chromium(VI) was rapidly reduced to chromium(V) on the skin of rats, with a 3-fold greater response when the stratum corneum was removed (Liu et al. 1997a). Thus, dermal effects from direct skin contact with chromium(VI) compounds may be mediated by rapid reduction to chromium(V). In whole blood and plasma, increasing ascorbate levels led to an increased oxidation of chromium(VI) to chromium(III) (Capellmann and Bolt 1992).

For humans, the overall chromium(VI)-reducing/sequestering capacities were estimated to be 0.7–2.1 mg/day for saliva, 8.3–12.5 mg/day for gastric juice, 11–24 mg for intestinal bacteria eliminated daily with feces, 3,300 mg/hour for liver, 234 mg/hour for males and 187 mg/hour for females for whole blood, 128 mg/hour for males and 93 mg/hour for females for red blood cells, 0.1–1.8 mg/hour for ELF, 136 mg/hour for pulmonary alveolar macrophages, and 260 mg/hour for peripheral lung parenchyma. Although these *ex vivo* data provide important information in the conversion of chromium(VI) to reduced states, the values may over- or underestimate the *in vivo* reducing capabilities (De Flora et al. 1997).

Reduction of chromium(VI) in the red blood cell occurs by the action of glutathione. Since the red blood cell membrane is permeable to chromium(VI) but not chromium(III), the chromium(III) formed by reduction of chromium(VI) by glutathione is essentially trapped within the erythrocyte for the life-span of the cell (Paustenbach et al. 2003), with approximately 1% of chromium eluting from the erythrocyte daily (ICSH 1980). Eventually, the diffusion of chromium(VI), the reduction to chromium(III), and complexing to nucleic acids and proteins within the cell will cause the concentration equilibrium to change so that more chromium(VI) is diffused through the membrane. Thus, there is a physiological drag so that increased diffusion results in greater chromium concentrations in the cell (Aaseth et al. 1982). It

## 3. HEALTH EFFECTS

appears that the rate of uptake of chromium(VI) by red blood cells may not exceed the rate at which they reduce chromium(VI) to chromium(III) (Corbett et al. 1998). *In vitro* incubation of red blood cells with an excess of sodium chromate(VI) (10 mM) decreased glutathione levels to 10% of the original amount (Wiegand et al. 1984). The above concepts are applicable to the uptake and reduction of chromium(VI) in other cell types.

The effect of glutathione-depleting agents on the amounts of cellular chromium(III) and chromium(V) was determined in Chinese hamster V-79 cells treated with sodium chromate (Sugiyama and Tsuzuki 1994). Buthionine sulfoximine at 25  $\mu$ M reduced glutathione levels to about 1% of control values, and increased chromium(V) levels by about 67%. The total chromium uptake was decreased by about 20% and chromium(III) levels were decreased by 20%. Diethylmaleate (1 mM) decreased glutathione levels to <1%, decreased chromium(V) levels by 27% and chromium(III) levels by 31%. However, the cellular uptake of total chromium was decreased to nearly 46%. The authors explained that the reason that the diethylmaleate inhibited the reduction of chromium(VI) to both chromium(III) and chromium(V) was not due to the decreased uptake, but involved the inhibition of the chromate-reducing enzymes in the cell.

In addition to the reduction of chromium(VI) by ascorbate or glutathione, *in vitro* studies have demonstrated reduction of chromium(VI) by microsomal enzymes. Hepatic microsomal proteins from male Sprague-Dawley rats pretreated with chromium(VI) reduced chromium(VI) to chromium(III). The rate of reduction varied both with the concentration of microsomal protein and the concentration of nicotinamide adenine dinucleotide phosphate (NADPH). In the absence of NADPH, microsomes did not reduce significant amounts of chromium(VI) over the 24-hour observation period. Therefore, the reduction of chromium(VI) in rat hepatic microsomes is NADPH-dependent (Gruber and Jennette 1978). Another study followed the kinetics of chromium(VI) reduction in hepatic microsomes from rats (Garcia and Jennette 1981). Induction of cytochrome P448 enzymes had no effect on the kinetics of the reaction, while induction of cytochrome P450 and NADPH-cytochrome P450 reductase resulted in a decrease in the apparent chromate-enzyme dissociation constant, and an increase in the apparent second-order rate constant, and no change in the apparent turnover number. Inhibition of NADPH-cytochrome P450 reductase and NADH-cytochrome  $b_5$  reductase inhibited the rate of microsomal reduction of chromium(VI), as did the addition of specific inhibitors of cytochrome P450. The results demonstrate the involvement of cytochrome P450, NADPH-dependent-cytochrome P450 reductase, and to a lesser extent cytochrome  $b_5$  and NADH-dependent-cytochrome  $b_5$  reductase, in the reduction of chromate by rat hepatic microsomes. The conversion of chromium(VI) to chromium(III) in rats can occur by electron transfer through cytochrome P450 and cytochrome  $b_5$ . Both oxygen and carbon monoxide were found to

## 3. HEALTH EFFECTS

inhibit the *in vitro* cytochrome P450 and cytochrome b<sub>5</sub>-dependent reduction of chromium(VI) (Mikalsen et al. 1989). The assertion that cytochrome P450 is involved in the reduction of chromium(VI) to chromium(III) has been further strengthened by Petrilli et al. (1985), who demonstrated that inducers of cytochrome P450 can increase the conversion of chromium(VI) to chromium(III) in S-9 mixtures prepared from the liver and lungs of exposed rats. Furthermore, it was observed that chromium(VI) can induce pulmonary cytochrome P450 and thus its own reduction in the lungs (Petrilli et al. 1985). Chromium(VI) apparently can alter the P450 activity in isolated rat microsomes. Witmer et al. (1994) demonstrated that hepatic microsomes from male rats treated with chromium(VI) resulted in a significant decrease in hydroxylation of testosterone at the 6 $\beta$ , 16 $\alpha$ , and 2 $\alpha$  positions, indicating a decrease in the activity of P4503A1 and 3A2. In lung microsomes, an increased hydroxylation was observed at the 16 $\alpha$  and 16 $\beta$  positions, indicating an increase in P450IIB1 activity. However, hepatic microsomes from treated females showed a 4-to5-fold increase in hydroxylation activity of testosterone at the 6 $\beta$  position, which demonstrated that the metabolic effects of chromium differ between males and females.

Two studies have examined possible species differences in the ability of microsomes to reduce chromium(VI) (Myers and Myers 1998; Pratt and Myers 1993). Chromium(VI) reduction was enzymatic and NADPH-dependent, and the rates were proportional to the amount of microsome added. In humans, the K<sub>m</sub> for chromium(VI) was 1–3 orders of magnitude lower than K<sub>m</sub> values in rats, although the V<sub>max</sub> was similar. This suggests that the human liver has a much greater capacity to reduce chromium(VI) than the rat liver. Also contrary to the rodent data, oxygen and cytochrome P450 inhibitors (carbon monoxide, piperonyl butoxide, metyrapone, and aminopyrine) did not inhibit chromium(VI) reduction. These differences indicate that, in humans, cytochrome P450 does not play a significant role in the reduction process, but that other microsomal flavoproteins are responsible for reducing chromium(VI). Inhibition of flavoproteins by TiCl<sub>3</sub> decreased chromium(VI) reduction by 96–100%, while inhibition of cytochrome c reductase (P450 reductase) by bromo-4'-nitroacetophenone resulted in an 80–85% inhibition of chromium(VI) reduction. Combined, these observations implicate P450 reductase, working independently of cytochrome P450, as a major contributor in the reduction of chromium(VI) in human microsomes. These findings suggest that metabolism of chromium(VI) in rodent systems may not readily be extrapolated to humans.

Microsomal reduction of chromium(VI) can also result in the formation of chromium(V), which involves a one-electron transfer from the microsomal electron-transport cytochrome P450 system in rats. The chromium(V) complexes are characterized as labile and reactive. These chromium(V) intermediates persist for 1 hour *in vitro*, making them likely to interact with deoxyribonucleic acid (DNA), which may

## 3. HEALTH EFFECTS

eventually lead to cancer (Jennette 1982). Because chromium(V) complexes are labile and reactive, detection of chromium(V) after *in vivo* exposure to chromium(VI) was difficult in the past. More recently, Liu et al. (1994) have demonstrated that chromium(V) is formed *in vivo* by using low-frequency electron paramagnetic resonance (EPR) spectroscopy on whole mice. In mice injected with sodium dichromate(VI) intravenously into the tail vein, maximum levels of chromium(V) were detected within 10 minutes and declined slowly with a life-time of about 37 minutes. The time to reach peak *in vivo* levels of chromium(V) decreased, in a linear manner as the administered dose levels of sodium dichromate decreased. The relative tissue distributions of chromium(V) indicated that most was found in the liver and much lesser amounts in blood. None was detected in kidney, spleen, heart, or lung. When the mice were pretreated with metal ion chelators, the intensity of the EPR signal decreased demonstrating that the formation of chromium(V) was inhibited. Reactions of chromium(VI) with glutathione produced two chromium(V) complexes and a glutathione thiyl radical. Reactions of chromium(VI) with DNA in the presence of glutathione produced chromium-DNA adducts. The level of chromium-DNA adduct formation correlated with chromium(V) formation. The reaction of chromium(VI) with hydrogen peroxide produced hydroxyl radicals. Reactions of chromium(VI) with DNA in the presence of high concentrations of hydrogen peroxide (millimolar compared to  $10^{-7}$ – $10^{-9}$  M inside cells) produced significant DNA strand breakage and the 8-hydroxy guanosine adduct, which correlated with hydroxyl radical production (Aiyar et al. 1989, 1991). Very little chromium(V) was generated by this pathway. It was postulated that the reaction of chromium(VI) with hydrogen peroxide produces tetraperoxo-chromium(V) species that act as a catalyst in a Fenton-type reaction producing hydroxyl radicals in which chromium(V) is continuously being recycled back to chromium(VI). The regeneration of chromium(VI) through interactions with chromium(V) and hydrogen peroxide is consistent with the findings of Molyneux and Davies (1995) (see Section 3.5.2). As discussed above, chromium(VI) is ultimately reduced to chromium(III) within the cell. Chromium(III) can form stable complexes with DNA and protein (De Flora and Wetterhahn 1989), which is discussed further in Section 3.5.2.

The mechanism for clearance of chromium(VI) once reduced inside the liver cell may involve a chromium(III)-glutathione complex. The glutathione complex would be soluble through the cell membrane and capable of entering the bile (Norseth et al. 1982). The complexing of chromium(III) to other ligands has been shown to make them more permeable to the cell membrane (Warren et al. 1981).



## 3. HEALTH EFFECTS

**3.4.4 Elimination and Excretion****3.4.4.1 Inhalation Exposure**

Normal urinary levels of chromium in humans have been reported to range from 0.22 to 1.8 µg/L (0.00024–0.0018 mg/L) with a median level of 0.4 µg/L (0.0004 mg/L) (IOM 2001; Iyengar and Woittiez 1988). Humans exposed to 0.05–1.7 mg chromium(III)/m<sup>3</sup> as chromium sulfate and 0.01–0.1 mg chromium(VI)/m<sup>3</sup> as potassium dichromate (8-hour TWA) had urinary excretion levels of 0.0247–0.037 mg chromium(III)/L. Workers exposed mainly to chromium(VI) compounds had higher urinary chromium levels than workers exposed primarily to chromium(III) compounds. An analysis of the urine did not detect the hexavalent form of chromium, indicating that chromium(VI) was rapidly reduced before excretion (Cavalleri and Minoia 1985; Minoia and Cavalleri 1988). Chromium(III) compounds were excreted rapidly in the urine of workers, following inhalation exposure to chromium(III) as chromium lignosulfonate. Workers exposed to 0.005–0.23 mg chromium(III)/m<sup>3</sup> had urine concentrations of 0.011–0.017 mg chromium(III)/L. The half-time for urinary excretion of chromium was short, 4–10 hours, based on an open, one-compartment kinetic model (Kiilunen et al. 1983). Tannery workers had higher urinary chromium(III) concentrations in postshift urine samples taken Friday afternoon and in preshift urine samples taken Monday, compared to controls. These workers also had hair concentrations of chromium that correlated with urinary levels. Analysis of workroom air revealed no detectable chromium(VI) and 0.0017 mg chromium(III)/m<sup>3</sup> (time-weighted average) (Randall and Gibson 1987). Elimination of chromium(III) from hair, serum, and urine has been studied in a group of 5 men who had ceased working in a leather tannery 9 months earlier (Simpson and Gibson 1992). Compared to levels recorded during employment, the mean level of chromium in hair was reduced from 28.5 to 2.9 µmol/g; serum levels were reduced from 9.4 to 3.8 nmol/L. These levels are comparable to those in the general population. Urine levels were unchanged (13.8 nmol/L while working and 14.4 nmol/L 9 months later); the authors stated that this was probably caused by consumption of beer (a source of chromium) the night before sampling. Data from autopsy studies indicate that chromium can be retained in the lung for decades following cessation of occupational exposures (Brune et al. 1980; Hyodo et al. 1980; Mancuso 1997b).

Peak urinary chromium concentrations were observed at 6 hours (the first time point examined) in rats exposed intratracheally to 0.44 mg/kg chromium(III) as chromium acetate hydroxide or chromium(VI) as sodium dichromate (Gao et al. 1993). Chromium urinary concentrations decreased rapidly, falling from 4,535 µg chromium/g creatinine at 6 hours to 148 µg chromium/g at 72 hours for the chromium acetate

## 3. HEALTH EFFECTS

hydroxide and from 2,947 µg chromium/g creatinine at 6 hours to 339 µg chromium/g at 72 hours for sodium dichromate.

Elimination of chromium was very slow in rats exposed to 2.1 mg chromium(VI)/m<sup>3</sup> as zinc chromate 6 hours/day for 4 days. Urinary levels of chromium remained almost constant for 4 days after exposure and then decreased, indicating that chromium bound inside the erythrocyte is released slowly (Langård et al. 1978).

#### 3.4.4.2 Oral Exposure

Given the low absorption of chromium compounds by the oral route, the major pathway of excretion after oral exposure is through the feces.

An acute, oral dose of radioactive chromium(III) as chromium chloride or chromium(VI) as sodium chromate was administered to humans after which feces and urine were collected for 24 hours and 6 days, respectively, and analyzed for chromium. The amount of chromium in the 6-day fecal collection was 99.6 and 89.4% of the dose for chromium(III) and chromium(VI) compounds, respectively. The amount of chromium in the 24-hour urine collection was 0.5 and 2.1% of the dose for chromium(III) and chromium(VI) compounds, respectively (Donaldson and Barreras 1966). In subjects drinking 0.001–0.1 mg chromium(VI)/kg/day as potassium chromate in water for 3 days, <2–8% of the dose was excreted in the urine (Finley et al. 1997). The percentage of the dose excreted appeared to increase with increasing dose.

Urinary excretion rates have been measured in humans after oral exposure to several chromium compounds (Finley et al. 1996b). A group of four male and two female volunteers ingested capsules containing chromium(III) picolinate at a dose of 200 µg/day for 7 days, to ensure that chromium deficiency was not a confounding factor. They then ingested 0.005 mg/kg/day chromium(VI) as potassium chromate (3 days), and 1.0 mg/kg/day chromium(III) as chromic oxide (3 days), with 3 days without dosing between the potassium chromate and chromic oxide doses. Urinary excretion rates of chromium were significantly elevated compared to postdosing control levels after seven daily doses of chromium(III) picolinate (2.4±0.8 versus 0.75±0.53 µg/day). The excretion rate increased sharply on the first of 3 days of potassium chromate dosing (11±17 µg/day) and remained steady over the next 2 days (13–14 µg/day). Excretion rates fell to 2.5±0.72 during 2 days without dosing and continued to fall during the 3 days of chromic oxide dosing, reaching rates similar to those seen postdosing. Mean pooled

## 3. HEALTH EFFECTS

urinary concentrations during the dosing periods were 2.4 µg chromium/g creatinine from exposure to chromium(VI) and 0.4 µg chromium/g creatinine from exposure to chromium(III) as compared to 0.23 µg chromium/g creatinine during the postdosing time periods. The lower urinary excretion of chromium(III) after exposure to chromic oxide reflects the poorer absorption of inorganic chromium(III) compounds compared to inorganic chromium(VI) compounds.

The half-life for chromium urinary excretion after administration in drinking water as potassium dichromate has been estimated in humans (Kerger et al. 1997). Ingestion of 0.05 mg chromium(VI)/kg resulted in an extended time course of excretion. Approximately 76–82% of the 14-day total amount of chromium in the urine was excreted within the first 4 days (mean peak concentration 209 µg chromium/g creatinine; range 29–585 µg chromium/g creatinine). The average urinary excretion half-life for four of the volunteers was 39 hours at this dose. All subjects had returned to background concentrations (0.5–2.0 µg chromium/g creatinine) by 14 days postdosing. About 87% of the total amount of chromium in the urine measured over 8 days was excreted during the first 4 days for one volunteer ingesting 0.03 mg chromium(VI)/kg (peak 97 µg chromium/g creatinine on day of ingestion). Urinary chromium concentrations had returned to an average of 2.5 µg chromium/g creatinine within 7 days postdosing, the last time point measured. Urinary excretion half-life in this volunteer was 37 hours. Similar time courses of excretion were observed when volunteers took the same doses as daily doses over 3-day periods. An earlier study by this group (Kerger et al. 1996a) examined urinary excretion half-lives following a bolus dose of 10 ppm (approximately 0.06 mg chromium/kg) chromium(III) chloride, potassium dichromate reduced with orange juice (presumably, the juice reduced the potassium dichromate to chromium(III)-organic complexes and chromium(III) ions), or potassium dichromate. The calculated urinary excretion half-lives for the three chromium solutions were 10.3, 15, and 39.3 hours, respectively. The potassium dichromate half-life is consistent with the results from the Kerger et al. (1997) study. If, in these studies, all of the absorbed chromium(VI) was rapidly and completely converted to chromium(III), there should be no difference in urinary half-life. The difference in excretion half-lives following dosing with chromium(III) and chromium(VI) appears to reflect incomplete reduction of absorbed chromium(VI) to chromium(III) as well as longer retention of chromium(VI) in tissues. The prolonged half-life following dosing with chromium(VI) appears to be a composite of the half-lives the chromium(VI) and chromium(III) derived from the reduction of chromium(VI) in the blood. Given that most is converted to chromium(III), the half-life for the sequestered chromium is quite long (much longer than 40 hours) and reflects the half-life of chromium observed in the red blood cells. Pretreatment of chromium(VI) with orange juice apparently did not convert all chromium(VI) to chromium(III), as indicated by a half-life of 15 hours.

## 3. HEALTH EFFECTS

The urinary excretion kinetics of chromium have also been examined in eight adults that were administered chromium(III) at 400 µg/day as chromium(III) picolinate for 3 consecutive days (Gargas et al. 1994). The mean time to peak urinary concentration was  $7.18 \pm 2.11$  hours (range 2.9–13.0 hours), the mean peak concentration being  $7.92 \pm 4.24$  µg chromium/g creatinine (range 3.58–19.13 µg/g creatinine). Excretion diminished rapidly after the peak, but did not appear to return to background in most of the volunteers before the next daily dose.

Pharmacokinetic models were used to predict the retention and excretion of ingested chromium(III) picolinate (Stearns et al. 1995a). A single dose of 5.01 mg (assuming 2.8% or 140 µg of the chromium(III) picolinate is absorbed) resulted in 11 µg (7.9%) retained after 1 year. The model predicted that about 1.4 µg would still be present in body tissues 10 years after dosing, and continuous dosing over a 1-year period would result in 6.2 mg of chromium(III) picolinate being retained, requiring about 20 years to reduce the retained level to 0.046 mg. These projected retention estimates may be 2–4-fold lower than results obtained from actual clinical findings. The authors caution that accumulative daily intake of chromium(III) may result in tissue concentrations that could be genotoxic.

Daily urinary excretion levels of chromium were nearly identical in men and women (averages of 0.17 and 0.20 µg/L, respectively; 0.18 µg/L combined) who ate normal dietary levels of chromium ( $\approx 60$  µg chromium(III)/day). When the subjects' normal diets were supplemented with 200 µg chromium(III)/day as chromium trichloride to provide intakes of  $\approx 260$  µg chromium(III)/day, urinary excretion of chromium rose proportionately to an average of 0.98 µg/L combined. Thus a 5-fold increase in oral intake resulted in about a five-fold increase in excretion, indicating absorption was proportional to the dose regardless of whether the source was food or supplement (Anderson et al. 1983). A group of 23 elderly subjects who received an average of 24.5 µg/day (0.00035 mg chromium(III)/kg/day) from their normal diets excreted 0.4 µg chromium/day in the urine (1.6%) and 23.9 µg chromium/day in the feces (97.6%), with a net retention of 0.2 µg/day (0.8%). Based on the 1980 daily requirement for absorbable chromium of 1 µg/day by the National Academy of Science Food and Nutrition Board, the retention was considered adequate for their requirements (Bunker et al. 1984).

An estimate of the half-life of elimination from plasma has been reported in humans. Uptake of potassium dichromate was determined in a man who was given 0.8 mg of chromium(VI) in drinking water 5 times each day for 17 days (Paustenbach et al. 1996). Steady-state concentrations of chromium in blood were attained after 7 days and a plasma elimination half-life of 36 hours was estimated.

## 3. HEALTH EFFECTS

Measurement of the chromium content in 255 milk samples from 45 lactating American women revealed that most samples contained  $<0.4 \mu\text{g/L}$  with a mean value of  $0.3 \mu\text{g/L}$  (Casey and Hambidge 1984). Another study (Anderson et al. 1993) measured chromium levels in the breast milk of 17 women 60 days postpartum, and reported mean levels of  $\sim 0.2 \mu\text{g/L}$ . Lactation, therefore, represents a route of excretion of chromium and a potential route of exposure to the nursing infant. However, the precise relationship between maternal chromium levels and levels in breast milk is unclear, if such a relationship exists at all (Anderson et al. 1993; Engelhardt et al. 1990; Mohamedshah et al. 1998).

Chromium can be excreted in hair and fingernails. Mean trace levels of chromium detected in the hair of individuals from the general population of several countries were as follows: United States, 0.23 ppm; Canada, 0.35 ppm; Poland, 0.27 ppm; Japan, 0.23 ppm; and India, 1.02 ppm (Takagi et al. 1986). Mean levels of chromium in the fingernails of these populations were: United States, 0.52 ppm; Canada, 0.82 ppm; Poland, 0.52 ppm; Japan, 1.4 ppm; and India, 1.3 ppm (Takagi et al. 1988).

Rats given 18 mg chromium(VI)/kg as potassium dichromate by gavage excreted about 25  $\mu\text{g}$  chromium in the first 24 hours after dosing and  $\approx 10 \mu\text{g}$  chromium in each of the next 24-hour periods (Banner et al. 1986).

In rats and hamsters fed chromium compounds, fecal excretion of chromium varied slightly from 97 to 99% of the administered dose. Urinary excretion of chromium varied from 0.6 to 1.4% of the dose administered as either chromium(III) or chromium(VI) compounds (Donaldson and Barreras 1966; Henderson et al. 1979; Sayato et al. 1980). The urinary and fecal excretion over 2-day periods in rats treated for 8 days by gavage with 13.92 mg chromium/kg/day in corn oil was higher when soil containing 70% chromium(III) and 30% chromium(VI) was the source of chromium than when chromium(VI) as calcium chromate was the source (see Section 3.4.2.2). Total urinary and fecal excretion of chromium on days 1 and 2 of dosing were 1.8 and 19%, respectively, of the dose from soil and  $<0.5$  and 1.8%, respectively, of the dose from calcium chromate. Total urinary and fecal excretion of chromium on days 7 and 8 of dosing were higher than on days 1 and 2. For contaminated soil, urinary excretion was 1.12% and fecal excretion was 40.6% of the dose. For calcium chromate, urinary excretion was 0.21% and fecal excretion was 12.35% of the dose (Witmer et al. 1991). Whether the higher excretion of chromium after dosing with soil than with the chromate salt represents greater bioavailability from soil could not be determined because about 50% of the administered dose could not be accounted for from the excretion and distribution data (see Section 3.4.2.2). Excretion of chromium(III) in dogs was approximately equal

## 3. HEALTH EFFECTS

to the clearance of creatinine, indicating little tubular absorption or reabsorption of chromium in the kidneys (Donaldson et al. 1984).

**3.4.4.3 Dermal Exposure**

Information regarding the excretion of chromium in humans after dermal exposure to chromium or its compounds is limited. Fourteen days after application of a salve containing potassium chromate(VI), which resulted in skin necrosis and sloughing at the application site, chromium was found at 8 mg/L in the urine and 0.61 mg/100 g in the feces of one individual (Brieger 1920). A slight increase (over background levels) in urinary chromium levels was observed in four subjects submersed in a tub of chlorinated water containing 22 mg chromium(VI)/L as potassium dichromate(VI) for 3 hours (Corbett et al. 1997). For three of the four subjects, the increase in urinary chromium excretion was <1 µg/day over the 5-day collection period.

<sup>51</sup>Chromium was detected in the urine of guinea pigs after radiolabeled sodium chromate(VI) or chromium(III) trichloride solutions were placed over skin depots that were monitored by scintillation counting to determine the dermal absorption (Wahlberg and Skog 1965).

**3.4.4.4 Other Routes of Exposure**

Elevated levels of chromium in blood, serum, urine, and other tissues and organs have been observed in patients with cobalt-chromium knee and hip arthroplasts (Michel et al. 1987; Sunderman et al. 1989). Whether corrosion or wear of the implant can release chromium (or other metal components) into the systemic circulation depends on the nature of the device. In one study, the mean postoperative blood and urine levels of chromium of nine patients with total hip replacements made from a cast cobalt-chromium-molybdenum alloy were 3.9 and 6.2 µg/L, respectively, compared with preoperative blood and urine levels of 1.4 and 0.4 µg/L, respectively. High blood and urinary levels of chromium persisted when measured at intervals over a year or more after surgery. These data suggest significant wear or corrosion of the metal components. No significant difference was found for patients with hip replacements made from the alloy and articulated with polyethylene (Coleman et al. 1973). Similarly, serum and urinary levels of chromium in patients with implants made from a porous coated cobalt chromium alloy with polyethylene components (to prevent metal-to-metal contact) were not significantly different from patients with implants made without chromium (Sunderman et al. 1989).

## 3. HEALTH EFFECTS

A number of factors have been shown to alter the rate of excretion of chromium in humans. Intravenous injection of calcium EDTA resulted in a rapid increase in the urinary excretion of chromium in metal workers (Sata et al. 1998). Both acute and chronic exercises have been shown to increase chromium excretion in the urine, though the increased excretion did not appear to be accompanied with decreased levels of total native chromium (Rubin et al. 1998). An increased rate of chromium excretion has been reported in women in the first 26 weeks of pregnancy (Morris et al. 1995b). Chromium supplementation did not appear to alter the rate of excretion into breast milk in postpartum women (Mohamedshah et al. 1998).

The urinary excretion of chromium after a single or during repeated subcutaneous injections of potassium dichromate was followed in rats. Following a single dose of 5.35 mg chromium(VI)/kg, chromium was excreted rapidly in two phases and was essentially complete at 48 hours. The filtered chromium load rose considerably during the first few hours after dosing and exceeded the tubular reabsorption rate. This increase was followed by a decrease that paralleled the urinary excretion of chromium. During repeated injections with 1.05 mg chromium(VI)/kg/day, every other day for 12 weeks, urinary excretion and diffusible chromium renal clearance rose at relatively high parallel rates, and reached plateaus at 10 ng/min for urinary excretion and 550  $\mu$ L/minute for renal clearance. The filtered load increased slightly. Since high levels of chromium were found in the renal cortex (see Section 3.4.2.4), the tubular reabsorption appeared to be limited by the accumulation of chromium in the tubular epithelium (Mutti et al. 1979).

Rats given a subcutaneous injection of potassium dichromate (chromium(VI)) and chromium nitrate (chromium(III)) excreted 36% of the chromium(VI) dose in urine and 13.9% in the feces within 7 days; 8 and 24.2% of the chromium(III) was excreted in the urine and feces within the same time period, respectively (Yamaguchi et al. 1983). Within 4 days after an intravenous dose of <sup>51</sup>chromium as chromium(III) chloride at 3 mg/kg chromium, rats excreted 5.23% of the dose in the feces and 16.3% in the urine (Gregus and Klaassen 1986).

In rats treated by intravenous injection with <sup>51</sup>chromium-labeled sodium chromate (chromium(VI)) or chromium(III) trichloride at 0.0003 or 0.345 mg chromium/kg, the bile contained 2–2.5% of the dose following chromium(VI) exposure; however, after chromium(III) exposure the concentration in the bile was  $\approx$ 50 times lower (Manzo et al. 1983). Similarly, 3.5–8.4% of chromium(VI) compounds was excreted in the bile as chromium(III), compared to 0.1–0.5% of chromium(III) compounds, after intravenous injection in rats (Cikrt and Bencko 1979; Norseth et al. 1982). Administration of

## 3. HEALTH EFFECTS

diethylmaleate, which depletes glutathione, resulted in only chromium(VI) in the bile after injection of sodium chromate.

Two hours after dosing rats intravenously with potassium dichromate at 0.45–4.5 mg chromium(VI)/kg, 1.4–2.2% of the chromium was recovered in the bile. Less than 1% of the total measurable chromium in the bile was identified as chromium(VI) compounds (Cavalleri et al. 1985).

Male Swiss mice exposed to 52 mg chromium(III)/kg as chromium chloride by single intraperitoneal injection or subcutaneous injection had plasma clearance half-times of 41.2 and 30.6 hours, respectively. In each case, blood levels reached control levels by 6–10 days (Sipowicz et al. 1997).

#### **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



## 3. HEALTH EFFECTS

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 3-5 shows a conceptualized representation of a PBPK model.

PBPK models for chromium are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations. Two PBPK models for chromium have been reported that simulated developed by O'Flaherty absorption, distribution, metabolism, elimination, and excretion of chromium(III) and chromium(VI) compounds in the rat (O'Flaherty 1993c, 1996) and human (O'Flaherty et al. 2001).

#### **3.4.5.1 O'Flaherty Model (1993a, 1996, 2001)**

The structure of the O'Flaherty model is depicted in Figure 3-6. Values for chromium parameters in the rat and human model are presented in Table 3-10. The model includes compartments representing bone, kidney, liver, gastrointestinal tract, plasma, poorly-perfused tissues (e.g., muscle, skin), red blood cells, respiratory tract, and well-perfused tissues (e.g., brain, heart, lung, viscera). Chromium(VI) is assumed to











## 3. HEALTH EFFECTS

**Validation of the model.** Optimization of parameter values and evaluation of the rat model are described in O'Flaherty (1996). Initial values for the rat model were established based on data reported in various intravenous, oral, or intratracheal rat studies (Bragt and van Dura 1983; Cavalleri et al. 1985; Cikrt and Bencko 1979; Edel and Sabbioni 1985; MacKenzie et al. 1959; Mertz et al. 1969; Thompson and Hollis 1958; Weber 1983). Parameter values were optimized against data on kinetics of tissue levels and chromium excretion measured in rats that received intratracheal doses of  $^{51}\text{Cr(VI)}$  or  $^{51}\text{Cr(III)}$  (Bragt and van Dura 1983; Edel and Sabbioni 1985; Weber 1983). The optimized rat model was evaluated by comparing predictions of blood  $^{51}\text{Cr}$  kinetics to observations made in rats exposed 6 hours/day for 4 days to dusts of zinc [ $^{51}\text{Cr}$ ]chromate (76% respirable, Langård et al. 1978). Predicted blood concentrations during exposure and postexposure kinetics agreed with observations. The model was also evaluated against data from a drinking water study in which rats were exposed to drinking water concentrations of  $\text{K}_2\text{Cr(VI)O}_4$  ranging from 0.45 to 25 mg/L, or to  $\text{Cr(III)Cl}_3$  at a concentration of 25 mg/L for a period of 1 year (MacKenzie et al. 1958). This was not a completely independent evaluation of the model since data from this study were used to set parameters for fractional uptake of chromium into bone. Ranges for predicted:observed ratios for terminal tissue levels in rats exposed to 0.45–25 mg chromium(VI)/L were 1.2–5 for liver, 0.3–1.2 for kidney, and 0.2–1.5 for bone (femur). The ratio for rats exposed to 25 mg chromium(III)/L were 15 for liver, 0.9 for kidney, and 2 for bone.

Optimization and evaluation of the human model is described in O'Flaherty et al. (2001). The model was optimized with data on plasma and red blood cell chromium concentrations, and urinary chromium excretion in adult subjects who ingested a single dose of chromium(III) as  $\text{CrCl}_3$  or chromium(VI) as  $\text{K}_2\text{Cr}_2\text{O}_7$  (Finley et al. 1997; Kerger et al. 1996a, see Section 3.4.1.2 for description of these studies). The model was evaluated against data on plasma chromium concentration kinetics and urinary excretion of chromium in a single adult subject who ingested 4 mg chromium(VI)/day as  $\text{K}_2\text{Cr}_2\text{O}_7$  for 17 days (Paustenbach et al. 1996; see Section 3.4.1.2), with the only adjusted parameter being the absorption rate constant. Although the model was optimized based on data from single dose studies, it reproduced the observed steady-state plasma chromium concentration, time to steady state, and elimination kinetics following cessation of the 17-day exposure.

**Risk assessment.** The model accounts for most of the major features of chromium(VI) and chromium(III) absorption and kinetics, and reduction chromium(VI) to chromium(III), uptake into and retention in red blood cells, and uptake and retention in bone. The human model associated bone chromium kinetics with bone formation and resorption and provides a structure for simulating age-dependent kinetics attributable to changes in bone turnover (e.g., growth, pregnancy, senescence).

### 3. HEALTH EFFECTS

Bioavailability of chromium from environmental sources is mostly unknown, except for a few chemically defined salts.

**Target tissues.** The rat and human models include parameters for predicting levels of chromium(III) and chromium(VI) in plasma, red blood cells, kidney, liver, bone, gastrointestinal tract, and respiratory tract. However, the rat model was calibrated against data on the above tissues, only for single dose intratracheal or intravenous exposures. Evaluations of predictions for repeated-dose exposures have been limited to blood concentration kinetics in an acute repeated dose inhalation exposure; and for terminal bone, kidney, and liver chromium levels in a 1-year drinking water study. The human model has been calibrated against data on plasma and red blood cell chromium concentrations and urinary chromium excretion following single oral doses administered to humans. Evaluation of predictions of repeated-dose outcomes have been limited to plasma and urine chromium kinetics, based on a study of a single subject exposure to chromium(VI) in drinking water for 17 days.

**Species extrapolation.** Evaluation of the robustness of extrapolation of the rat or human models to other species has not been reported.

**Interroute extrapolation.** The rat and human models include parameters for simulating inhalation and ingestion of chromium. The rat model was calibrated against data from single-dose intratracheal or intravenous exposures, and was evaluated against repeated-dose studies of inhaled and ingested chromium. The human model was calibrated and evaluated with data from ingestion studies; evaluation of the robustness of the model for predicting chromium kinetics following exposures to other routes has not been reported.

## 3.5 MECHANISMS OF ACTION

### 3.5.1 Pharmacokinetic Mechanisms

The absorption of inhaled chromium compounds depends on a number of factors, including physical and chemical properties of the particles (oxidation state, size, solubility) and the activity of alveolar macrophages. Chromium has been identified in the tissues of occupationally-exposed humans, suggesting that chromium can be absorbed from the lungs (Cavalleri and Minoia 1985; Gylseth et al. 1977; Kiilunen et al. 1983; Mancuso 1997b; Minoia and Cavalleri 1988; Randall and Gibson 1987; Tossavainen et al. 1980). Animal studies have also demonstrated increased amounts of chromium in the blood following inhalation or intratracheal instillation exposures (Baetjer et al. 1959b; Bragt and van



## 3. HEALTH EFFECTS

Dura 1983; Langård et al. 1978; Visek et al. 1953; Wiegand et al. 1984, 1987). Chromium(VI) is more rapidly absorbed into the bloodstream than is chromium(III) (Gao et al. 1993; Suzuki et al. 1984). Chromium that is not absorbed in the lungs may be cleared via mucociliary clearance and enter the gastrointestinal tract.

Chromium is poorly absorbed from the gastrointestinal tract; the primary site of chromium absorption appears to be the jejunum (Donaldson and Barreras 1966). The bioavailability of chromium compounds seems to be most dependent on the oxidation state of the chromium atom. However, other factors, including formulation of the chromium, can influence the extent of absorption. Inorganic chromium(III) is very poorly absorbed, with only 0.5–2.8% of dietary chromium absorbed via the gastrointestinal tract of humans (Anderson 1986; Anderson et al. 1983; Donaldson and Barreras 1966; Gargas et al. 1994; Kerger et al. 1996a; Kuykendall et al. 1996). Human studies demonstrate that chromium(VI) is effectively reduced to chromium(III) by gastric juices (De Flora et al. 1987a) and in general, chromium(VI) is better absorbed than chromium(III) following oral exposure in humans (Donaldson and Barreras 1966; Finley et al. 1996b; Kerger et al. 1996a; Kuykendall et al. 1996). Absorption efficiencies ranging from 1.7 to 6.9% have been estimated in humans (Finley et al. 1996a; Kerger et al. 1996a, 1997; Kuykendall et al. 1996). Ingestion of chromium with a meal appears to increase the absorption efficiency (Chen et al. 1973).

Both chromium(III) and chromium(VI) can penetrate human skin to some extent, especially if the skin is damaged. Following dermal exposure, chromium has been detected in the blood, feces, and urine of exposed humans (Brieger 1920), though in this study, the skin was damaged, which likely facilitated absorption. An average rate of systemic uptake of chromium(VI) in humans submersed in chlorinated water containing potassium dichromate(VI) for 3 hours was  $1.5 \times 10^{-4}$   $\mu\text{g}/\text{cm}^2\text{-hour}$  (Corbett et al. 1997). Chromium(VI) appears to penetrate the skin faster than chromium(III) (Mali et al. 1963; Spruit and van Neer 1966; Wahlberg 1970), though many other factors may be involved, including solvent (Liden and Lundberg 1979) and concentration (Baranowska-Dutkiewicz 1981).

Absorbed chromium is carried throughout the body in the blood, eventually being distributed to all tissues. Greatest concentrations of chromium are found in the blood, liver, lung, spleen, kidney, and heart (Kaufman et al. 1970; Schroeder et al. 1962; Teraoka 1981). Because insoluble chromium is not completely cleared or absorbed following inhalation exposure, greater levels of chromium are often found in lung tissues following inhalation of chromium compounds than following other methods of exposure. Tissue levels appeared to be higher after exposure to chromium(VI) than to chromium(III). This may be due to the greater ability of chromium(VI) to cross cell membranes and may also be a function of

## 3. HEALTH EFFECTS

administration of doses high enough to overwhelm the chromium(VI) reduction mechanisms. De Flora et al. (1997) have demonstrated that liver, erythrocytes, whole blood, lung epithelial fluid, alveolar macrophages, and peripheral parenchyma cells all have the ability to reduce chromium(VI) to chromium(III). Chromium has been detected in breast milk (Casey and Hambidge 1984; Shmitova 1980), but the relationship between chromium exposure, dietary or otherwise, and breast milk chromium levels is inconclusive (Anderson et al. 1993; Engelhardt et al. 1990; Mohamedshah et al. 1998).

Systemic chromium(III) does not appear to be stored for extended periods of time within the tissues of the body. However, the prolonged half-life of chromium(VI) compared to chromium(III) in humans (Kerger et al. 1997) and animals indicate that a portion of the absorbed chromium(VI) dose that is not converted to chromium(III) is being sequestered inside cells. Single- and multiple-exposure studies in humans have shown a one-compartment clearance half-time in humans on the order of 36 hours (Kerger et al. 1997; Paustenbach et al. 1996) following oral exposure. This half-time is sufficiently long to allow for accumulation of chromium following regular repeated exposure. Following inhalation exposure, insoluble chromium that is not cleared from the lungs may remain for a considerable time. In the blood, chromium(VI) is taken up by erythrocytes and reduced to chromium(III) which forms complexes with hemoglobin and other intracellular macromolecules; these complexes are retained within the erythrocyte for the life-span of the cell (Paustenbach et al. 2003).

Inhaled chromium can be eliminated from the lungs by absorption into the bloodstream, by mucociliary clearance, and by lymphatic system clearance (Bragt and van Dura 1983; Perrault et al. 1995; Visek et al. 1953; Wiegand et al. 1984, 1987). The primary routes of elimination of absorbed chromium is urine and feces. It can also be eliminated in hair and fingernails (Randall and Gibson 1989; Stearns et al. 1995a; Takagi et al. 1986). Chromium, once reduced to chromium(III) in the liver, is then conjugated with glutathione and enters bile where it is excreted in the feces (Norseth et al. 1982). Because chromium is poorly absorbed following oral exposure, a large percentage of the amount ingested is excreted in the feces. The half-time of urinary excretion of chromium is short, 4–10 hours for inhalation exposure (Kiilunen et al. 1983), 10 hours for oral exposure to chromium(III) (Kerger et al. 1996a), and 40 hours for oral exposure to chromium(VI) (Kerger et al. 1996a, 1997). Following dermal exposure, chromium that is not absorbed into the bloodstream will remain on the skin until it is eliminated, usually by washing or other physical processes. Absorbed chromium is primarily eliminated in the urine.

## 3. HEALTH EFFECTS

**3.5.2 Mechanisms of Toxicity**

The toxic potency of chromium is dependent on the oxidation state of the chromium atom, with chromium(VI) more potent than chromium(III). The mechanisms of chromium toxicity and carcinogenicity are very complex. They are mediated partly through reactive intermediates during intracellular reduction of chromium(VI) to chromium(III) and oxidative reactions, and partly mediated by chromium(III) which is the final product of intracellular chromium(VI) reduction and forms deleterious complexes with critical target macromolecules (Chen and Shi 2002; Costa 2003; Costa and Klein 2006a; Ding and Shi 2002; Jeejeebhoy 1999; Levina and Lay 2005; Liu and Shi 2001; O'Brien et al. 2003; Paustenbach et al. 2003; Shrivastava et al. 2002; Zhitkovich 2005). Chromium(III) may form complexes with peptides, proteins, and DNA, resulting in DNA-protein crosslinks, DNA strand breaks, and alterations in cellular signaling pathways, which may contribute to toxicity and carcinogenicity of chromium compounds.

The greater toxic potency of chromium(VI) relative to chromium(III) most likely is related to two factors: (1) the higher redox potential of chromium(VI) (Levina and Lay 2005; Reddy and Chinthamreddy 1999); and (2) the greater ability of chromium(VI) to enter cells (Costa 2003). Differences in molecular structure contribute the greater cellular uptake of chromium(VI) compared to chromium(III) (Costa 2003; Costa and Klein 2006a). At physiological pH, chromium(VI) exists as the tetrahedral chromate anion, resembling the forms of other natural anions (e.g., sulfate and phosphate) which are permeable across nonselective membrane channels. Chromium(III), however, forms octahedral complexes and cannot easily enter through these channels. Therefore, the lower toxicity to chromium(III) may be due in part to lack of penetration through cell membranes. It follows that extracellular reduction of chromium(VI) to chromium(III) may result in a decreased penetration of chromium into cells, and therefore, a decreased toxicity.

The higher redox potential of chromium(VI) contributes to the higher toxic potency of chromium(VI) relative to chromium(III) (Levina and Lay 2005), because once it is taken into cells, chromium(VI) is rapidly reduced to chromium(III), with chromium(V) and chromium(IV) as intermediates. These reactions commonly involve intracellular species, such as ascorbate, glutathione, or amino acids (Aiyar et al. 1991; Blankenship et al. 1997; Capellmann et al. 1995; Hojo and Satomi 1991; Kim and Yurkow 1996; Lin et al. 1992; Liu et al. 1997b; Mao et al. 1995; Wiegand et al. 1984; Zhitkovich et al. 1996). Chromium(VI), chromium(V), and chromium(IV) have all been shown to be involved in Fenton-like oxidative cycling, generating oxygen radical species (Aiyar et al. 1991; Chen et al. 1997; Liu et al. 1997b;

## 3. HEALTH EFFECTS

Luo et al. 1996; Mao et al. 1995; Molyneux and Davies 1995; Tsou et al. 1996). It is believed that the formation of these radicals may be responsible for many of the deleterious effects of chromium on cells, including lipid peroxidation (Bagchi et al. 2002a; Hojo et al. 1999, 2000) and alterations in cellular communication, signaling pathways and cytoskeleton (Chen et al. 1997; Gao et al. 2002; Gunaratnam and Grant 2002, 2004; Kim and Yurkow 1996; Mikalsen 1990; O'Hara et al. 2007; Shumilla et al. 1998; Wang et al. 1996a; Xu et al. 1996; Ye et al. 1995). Cellular damage from exposure to many chromium compounds can be blocked by radical scavengers, further strengthening the hypothesis that oxygen radicals play a key role in chromium toxicity (Hojo et al. 2000; Luo et al. 1996; Tsou et al. 1996; Ueno et al. 1995a).

The products of metabolic reduction of chromium(VI) (free radicals and chromium(IV) and (V)) and the newly generated chromium(III) are thought to be in part responsible for the carcinogenic effects seen in human and animal studies. The interaction of free radicals, chromium(V), chromium(IV), and chromium(III) with DNA can result in structural DNA damage, functional damage, and other cellular effects (Levina and Lay 2005; Singh et al. 1998a). The types of chromium-induced structural damage include DNA strand breaks (Aiyar et al. 1991; Bagchi et al. 2002a; Bryant et al. 2006; Casadevall et al. 1999; Ha et al. 2004; Kuykendall et al. 1996; Manning et al. 1992; Messer et al. 2006; Pattison et al. 2001; Ueno et al. 1995a), DNA-protein crosslinks (Aiyar et al. 1991; Blankenship et al. 1997; Capellmann et al. 1995; Costa et al. 1996, 1997; Kuykendall et al. 1996; Lin et al. 1992; Manning et al. 1992; Mattagajasingh and Misra 1996; Miller et al. 1991; O'Brien et al. 2005; Quievryn et al. 2001; Zhitkovich et al. 1996), DNA-DNA interstrand crosslinks (Xu et al. 1996), chromium-DNA adducts, and chromosomal aberrations (Blankenship et al. 1997; Sugiyama et al. 1986a; Umeda and Nishimura 1979; Wise et al. 1993). Functional damage includes DNA polymerase arrest (Bridgewater et al. 1994a, 1994b, 1998), RNA polymerase arrest, mutagenesis, and altered gene expression. However, DNA double strand breaks may not be due to free radical formation, but due to the formation of chromium-DNA ternary adducts, which lead to repair errors and collapsed replication forks (Ha et al. 2004). Double strand breaks can also lead to alterations in cellular communication and effects on signaling pathways and cytoskeleton. In addition, results of recent studies in human lung cells suggest that chromosome instability is an important mechanism in the development of lung cancers; specifically, chromium-induced chromosome instability appears to be mediated through centrosome and spindle assembly checkpoint bypass (Holmes et al. 2006; Wise et al. 2006a).

Location of particle deposition in the lung and extracellular dissolution of chromium(VI) compounds (e.g., solubility) are also important considerations regarding the mechanism of chromium(VI)-induced

## 3. HEALTH EFFECTS

carcinogenesis. In chromate workers, analysis of bronchial tissues shows higher chromium concentrations in areas of bronchial bifurcation compared to other areas in the bronchi (Ishikawa et al. 1994a). Also, autopsy results show that some precancerous bronchial lesions originated at bronchial bifurcations (Ishikawa et al. 1994b). Solubility of chromium(VI) compounds may also play a role in carcinogenic potency, with extracellular dissolution of the chromium compound critical to activity (Wise et al. 2004). This hypothesis is supported by *in vitro* data suggesting that extracellular chromium ions are the proximate clastogen in Chinese hamster ovary cells (Wise et al. 2004).

Chromium(III) can also interact with DNA to form adducts/complexes and DNA-protein crosslinks that interfere with DNA replication and transcription, and can promote the expression of regulatory genes such as nuclear factor- $\kappa$ B, or may inhibit regulatory genes such as GRP78 (Chen et al. 1997; Kim and Yurkow 1996; Manning et al. 1992; Mikalsen 1990; O'Hara et al. 2003; Shumilla et al. 1998; Wang et al. 1996a; Xu et al. 1996; Ye et al. 1995). Disruption of these pathways by other compounds has been implicated in carcinogenesis. The structural and functional damage can lead to growth arrest (Xu et al. 1996) and apoptosis (Carlisle et al. 2000; Singh et al. 1999). Numerous studies show that chromium can induce apoptosis (Asatiani et al. 2004; Bagchi et al. 2001; Carlisle et al. 2000; Flores and Perez 1999; Gambelunghe et al. 2006; Gunaratnam and Grant 2002, 2004; He et al. 2007; Manyoats et al. 2002; Petit et al. 2004; Russo et al. 2005; Vasant et al. 2003); although the mechanism by which chromium induces apoptosis is not fully understood, it is believed to involve oxidative stress and activation of the p-53 protein (Pulido and Parrish 2003; Singh et al. 1998a).

### 3.5.3 Animal-to-Human Extrapolations

Species-related differences in chromium pharmacokinetics have been demonstrated, both between rodent species and between rodents and humans. However, studies directly examining species differences have been limited. Human microsomal chromium(VI) reduction is different from the P450-mediated microsomal reduction in rodents; specifically, the human system is much less oxygen-sensitive, has a much greater affinity for chromate, and is apparently mediated by flavoproteins (Myers and Myers 1998; Pratt and Myers 1993). Tissue distributions of chromium were found to be different between rats and mice after administration of bolus amounts of chromium(VI). Rat erythrocytes had a greater capacity to sequester chromium(VI) and reduce it to chromium(III) than mouse erythrocytes (Coogan et al. 1991b; Kargacin et al. 1993), thus demonstrating that both physiologic and metabolic differences can exist among species.

## 3. HEALTH EFFECTS

**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 isoflavonoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Based on results of *in vivo* and *in vitro* studies, chromium(VI) may alter function of the hypothalamic-pituitary axis function. Serum prolactin levels were decreased by 59% in male Wistar rats exposed to 74 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 30 days. Incubation of cultured rats anterior pituitary cells with 0.1–10  $\mu$ M chromium(VI) as potassium dichromate decreased prolactin secretion and cell viability (Quinteros et al. 2007). No additional assessments of hypothalamic-

## 3. HEALTH EFFECTS

pituitary axis function were conducted in this study. Serum testosterone levels were decreased by 20.8% in male New Zealand rabbits administered 3.6 mg chromium(VI)/kg/day as potassium dichromate for 10 weeks by gavage (Yousef et al. 2006); however, since function of the hypothalamic-pituitary-gonadal axis was not assessed, it is unclear if this effect reflects endocrine disruption.

**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

## 3. HEALTH EFFECTS

sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990b; 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).

Chromium(III) is an essential nutrient required for maintaining normal glucose metabolism. The IOM of the NAS determined an adequate intake of 0.2 µg chromium/day for infants aged 0–6 months; 5.5 µg chromium/day for infants aged 7–12 months; 11 µg chromium/day for children aged 1–3 years; 15 µg chromium/day for children aged 4–8 years; 25 µg chromium/day for boys aged 9–13 years; 21 µg chromium/day for girls aged 9–13 years; 35 µg chromium/day for boys aged 14–18 years; and 24 µg chromium/day for girls aged 14–18 years (IOM 2001).

There is a limited amount of information available on the toxicity of chromium in children. Most of the available data come from several case reports of children ingesting lethal concentrations of chromium(VI). A variety of systemic effects were observed in a 22-month-old who accidentally ingested an unknown amount of sodium dichromate (Ellis et al. 1982), a 1-year-old who ingested an unknown amount of ammonium dichromate (Reichelderfer 1968), a 17-year-old who intentionally ingested 29 mg chromium(VI)/kg as potassium dichromate (Clochesy 1984; Iserson et al. 1983), and a 14-year-old who ingested 7.5 mg chromium(VI)/kg as potassium dichromate (Kaufman et al. 1970). The effects included pleural effusion, bronchopneumonia, hypoxic changes in the myocardium, decreased blood pressure and cardiac output, abdominal pain and vomiting, gastrointestinal burns and hemorrhage, and liver and kidney necrosis. An enlarged brain and cerebral edema were also observed in the 14-year-old (Kaufman et al.



## 3. HEALTH EFFECTS

1970). These effects are similar to effects observed in adults who have ingested lethal doses and are part of the sequelae leading to death.

A number of additional health effects have been observed in adults exposed to chromium (primarily chromium(VI)) at work. The primary targets appear to be the respiratory tract, gastrointestinal tract, hematological system, liver, and kidneys; an increased cancer risk has also been observed. Dermal contact in chromium sensitized individuals can lead to an allergic type dermatitis. In the absence of data to the contrary, it is likely that these organs/systems will also be sensitive targets in children. There is insufficient information to determine whether the susceptibility of children would differ from that of adults.

Although there are no human studies that examined developmental end points, animal studies have consistently shown that chromium, particularly chromium(VI), is a developmental toxicant. A number of developmental effects have been reported in oral studies involving maternal exposure to  $\geq 46$  mg chromium(VI)/kg/day as potassium dichromate (Al-Hamood et al. 1998; Junaid et al. 1996b; Trivedi et al. 1989). The observed effects included increases in postimplantation losses, gross abnormalities (e.g., subdermal hemorrhage, decreased ossification, kinky tail), and impaired development of the reproductive system (e.g., impaired fertility in female offspring). Similar developmental effects (e.g., post implantation losses, subdermal hemorrhage, decreased ossification) have also been observed in the offspring of rats and mice exposed to  $\geq 37$  mg chromium(VI)/kg/day for 20 or 90 days prior to mating (Junaid et al. 1996a; Kanojia et al. 1996, 1998). Conflicting results have been found for chromium(III). No developmental effects were reported in the offspring of rats fed 1,806 mg chromium(III)/kg/day as chromium oxide for 60 days before mating and throughout gestation (Ivankovic and Preussmann 1975). However, impaired development of the reproductive system (decreased reproductive tissue weight and impaired fertility) were observed in the offspring of mice exposed to 74 mg chromium(III)/kg/day as chromium chloride (Al-Hamood et al. 1998). Developmental effects have also been observed following intraperitoneal administration of chromium(III) chloride (Iijima et al. 1983; Matsumoto et al. 1976).

Chromium may be transferred to fetuses through the placenta and to infants via breast milk. Elevated levels of chromium have been reported in umbilical cord blood, placentae, and breast milk of women working in a dichromate(VI) manufacturing facility (Shmitova 1980). As noted elsewhere in the profile, the reliability of this study is suspect because the levels of chromium in the blood and urine of the control women were much higher than background levels. Measurement of the chromium content in 255 samples from 45 lactating American women revealed that most samples contained  $<0.4$   $\mu\text{g/L}$ , and the mean value

### 3. HEALTH EFFECTS

was 0.3 µg/L (Casey and Hambidge 1984). While these probably represent background levels in women whose main exposure to chromium is via the diet, the findings indicate that chromium may be transferred to infants via breast milk. These findings in humans are supported by animal data. Studies in rats and mice have shown that chromium(VI) and chromium(III) crosses the placenta and enters into fetal tissue. Elevated levels of chromium have been observed in the placenta and fetal tissue of rats and mice exposed to potassium dichromate(VI) in drinking water during pregnancy (Saxena et al. 1990a). The levels of chromium in the placenta were 3- and 3.2-fold higher in the exposed rats and mice, respectively, than in controls and fetal tissue chromium levels were 3.1- and 9.6-fold higher, respectively; the difference over control was only statistically significant in the mice. Another study (Danielsson et al. 1982) also found elevated fetal tissue levels of chromium. The chromium levels in the fetal tissues were 12–19% of maternal blood levels following maternal intravenous injections of sodium dichromate(VI) on gestational days 12–15 or 16–18 and 0.4–0.8% following maternal intravenous injections of chromium(III) trichloride on gestational days 12–15 or 16–18. A study of transplacental transfer of chromium(III) in different forms indicated that placental transport varies with the chemical form (Mertz et al. 1969). Higher levels of chromium were found in the neonates of rats fed chromium in a commercial diet as compared to neonates of rats fed a chromium-deficient diet and given drinking water containing chromium acetate monohydrate. Similarly chromium levels were significantly elevated in the offspring of rats administered chromium in the form of chromodulin from Brewer's yeast by gavage than in the offspring of rats administered chromium trichloride intravenously or by gavage.

There is very little information available in which to assess whether the pharmacokinetic properties of chromium would be different in children. Sullivan et al. (1984) found that gastrointestinal absorption of radiolabeled chromium chloride, administered by gavage, was 10 times higher in 2-day-old rats as compared to levels absorbed in adult rats. A similar pattern of distribution in the body was found in the immature and mature rats.

#### 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).

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

### 3. HEALTH EFFECTS

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 chromium 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 chromium 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 Chromium**

As an essential nutrient, chromium is normally present in blood and urine. Chromium in body fluids (e.g., blood and urine) is the exposure biomarker of choice. Mean dietary chromium intake in the general U.S. population was estimated as 0.505  $\mu\text{g}/\text{kg}/\text{day}$  (equivalent to 35.35  $\mu\text{g}/\text{day}$ , assuming a body weight of 70 kg), with a range of 0.293–0.867  $\mu\text{g}/\text{kg}/\text{day}$  (Moschandreas et al. 2002); however, only a small amount of dietary chromium is absorbed ( $\leq 3\%$ ). The IOM of the NAS (IOM 2001) determined an

## 3. HEALTH EFFECTS

adequate intake (e.g., a level typically consumed by healthy individuals) of 20–45 µg chromium(III)/day for adolescents and adults. Daily dietary intake levels have been shown to correlate with total excretion of chromium in the urine and feces (Bunker et al. 1984). The IOM (2001) reported average plasma chromium concentrations of 2–3 nmol/L (equivalent to 0.10–16 µg/L) and an average urinary chromium excretion of 0.22 µg/L or 0.2 µg/day; endogenous chromium concentrations also have been reported as 0.01–0.17 µg/L (median 0.06 µg/L) in serum (Sunderman et al. 1989), 0.24–1.8 µg/L (median 0.4 µg/L) in urine (Iyengar and Woittiez 1988), and 0.234 mg/kg in hair (Takagi et al. 1986). However, normal chromium levels in human fluid and tissues should be interpreted with caution. The low sensitivity of the most commonly used detection methods and the ubiquitous presence of chromium in laboratories make detection of low levels of chromium in blood and urine difficult.

Exposure to chromium may result in increased chromium concentrations in blood (whole blood, serum, and erythrocytes), urine, expired air, hair, and nails; of these, elevations of chromium in blood and urine are considered the most reliable indicators of exposure (Barceloux 1999; Caglieri et al. 2006). Urinary elimination half-times for absorbed chromium(III) range from 10–40 hours (Kerger et al. 1996a). Assuming an elimination half-time of 40 hours, steady state, plasma concentration, and urinary excretion rate of chromium would reach 95% of steady state levels in approximately 7 days (Paustenbach et al. 1996). Once steady state is achieved, the daily amount of chromium excreted in urine will reflect the daily amount absorbed. With cessation of exposure levels of chromium in plasma and urine will reach 5% of steady state within 7 days. The relatively rapid elimination kinetics of absorbed chromium(III) has implications for the use of plasma and urine as biomarkers of exposure to chromium. Plasma and urinary chromium concentrations will largely reflect relatively recent exposure (i.e., exposures that occurred several weeks prior to the sample may not be detected from plasma or urinary chromium measurements). During relatively constant or repetitive exposures that achieve a steady state in plasma, daily urinary chromium excretion measured on a single day can be expected to be highly correlated with chromium intake. This correlation will weaken with greater intermittency in the exposure, with greater dependence on the time of sampling with respect to the most recent exposure. The above general principles apply to exposures to absorbed chromium(III) compounds; however, absorbed chromium(VI) has a longer retention time in blood. Chromium(VI) that enters blood is taken up by red blood cells, reduced to chromium(III), and, in the process, form adducts with red blood cell hemoglobin and other proteins. These complexes are sufficiently stable to remain in the red blood cells for a substantial fraction of the lifespan of the red blood cell. Therefore, following absorption of chromium(VI) into blood, the elimination half-time of chromium in blood will be substantially longer than that in plasma. The elimination half-time of injected chromium(VI) (e.g., sodium chromate-51, used in the clinical assessment

## 3. HEALTH EFFECTS

of red blood cell volume) is approximately 25–35 days (Dever et al. 1989). Based on a half-time of 30 days in red blood cells, with cessation of exposure to and absorption of chromium(IV), levels of chromium in red blood cells will reach 5% of a previous steady state level within 130 days.

Although chromium also accumulates in white blood cells, erythrocyte chromium has been shown to be a more sensitive measure of chromium exposure (Coogan et al. 1991b; Lukanova et al. 1996). An increase in plasma levels of chromium may reflect both recent exposure and exposure that occurred during the past few months (e.g., chromium that is sequestered within erythrocytes for the lifespan of the cell), whereas elevated urine chromium primarily reflects exposure over the past 1–2 days (Barceloux 1999). Distinct measurements of chromium in plasma and whole blood (reflecting intracellular distribution to erythrocytes) also be useful in distinguishing exposures to chromium(VI) compounds versus chromium(III) compounds; increased plasma levels of chromium may indicate exposure to both chromium(VI) and chromium(III), whereas increased chromium in erythrocytes indicates exposure to chromium(VI), since chromium(III) is not taken up by erythrocytes. For example, evaluation of postshift whole blood, serum, erythrocytes, and urine in groups of dichromate production workers exposed mainly to chromium(VI) or chromium(III) showed relationships between exposure type (e.g., chromium(VI) or chromium(III)) and chromium in blood and urine (Minoia and Cavalleri 1988). In 22 workers exposed primarily to chromium(VI) (0.008–0.212 mg chromium(VI)/m<sup>3</sup>, 0.010–0.10 mg chromium(III)/m<sup>3</sup>), the mean postwork-shift urinary chromium level was 31.5 µg total chromium/L; chromium(VI) was not detected in the urine samples (detection limit=0.05 µg chromium(VI)/L) due to *in vivo* reduction of chromium(VI) to chromium(III). Concentrations of total chromium in serum, erythrocytes, and whole blood were 2.2, 8.9 and 6.9 µg/L, respectively; compared with control levels of 1.1, 1.0, and 1.4 µg/L, respectively. In 15 workers exposed primarily to chromium(III) (0.046–1.689 mg chromium(III)/m<sup>3</sup>, 0.002–0.023 mg chromium(VI)/m<sup>3</sup>), the mean postwork-shift urinary chromium level was 24.7 µg total chromium/L and concentrations of total chromium in serum, erythrocytes, and whole blood were 3.1 µg/L, 1.4, and 1.8, respectively. The level of chromium in serum of the workers exposed mainly to chromium(III) was significantly ( $p<0.001$ ) higher than that measured in workers exposed mainly to chromium(VI) or in controls. The level of chromium in erythrocytes of the workers exposed mainly to chromium(III) was significantly ( $p<0.001$ ) less than that in workers exposed mainly to chromium(VI). The finding of higher levels of chromium in serum and lower levels of chromium in erythrocytes of workers exposed mainly to chromium(III) than in workers exposed mainly to chromium(VI) reflects the relative inability of chromium(III) to enter erythrocytes.

## 3. HEALTH EFFECTS

Although exposure to chromium may produce increases in chromium levels in both blood and urine chromium levels, the relationship between blood and urinary chromium levels may vary. Entry of chromium(VI) into the red blood cells probably reflects a competition between plasma reduction to chromium(III) and red blood cells uptake of chromium(VI) and not the result or consequence of the exhaustion of plasma reducing ability. When hexavalent chromium is incubated with washed isolated erythrocytes, almost all of the entire dose is taken up by the cells. Chromium(VI) is then reduced inside the cells to trivalent chromium, essentially trapping it inside the erythrocyte. In contrast, little chromium(III) appears to be taken up by erythrocytes *in vitro* incubations (Aaseth et al. 1982; Bentley 1977; Donaldson and Barreras 1966; Gray and Sterling, 1950). When chromium(VI) is incubated with whole blood or erythrocytes plus plasma, only a fraction (depending on conditions) of the chromium(VI) is taken up by the erythrocytes (Coogan et al. 1991b; Corbett et al. 1998; Lewalter et al. 1985; Wiegand et al. 1985), most likely due to the reduction of a portion of chromium(VI) to chromium(III) outside of the erythrocyte (Capellmann and Bolt 1992; Korallus et al. 1984; Richelmi et al. 1984). Thus, chromium(III) is then largely excluded from the erythrocyte. However, Korallus (1986a, 1986b) has proposed that the relationship between blood and urinary chromium levels may vary, possibly due to variability in plasma reduction capacity. *In vitro* experiments indicate that when chromium(VI) plasma levels exceed the plasma reduction capacity (PRC), chromium(VI) enters erythrocytes, is reduced, and binds to hemoglobin. The bond persists for the lifetime of the erythrocytes (120 days); therefore, a single determination of chromium in erythrocytes allows a longitudinal evaluation of exposure for an extended period in the past. Low chromium concentrations in erythrocytes indicate that the amount of chromium(VI) uptake did not exceed the PRC. Limited evidence suggests that the capacity of human plasma to reduce chromium(VI) compounds to chromium(III) compounds varies, with slow and fast reducers recognized (Korallus 1986a, 1986b). It is not clear what is responsible for individual differences in the PRC, although difference in magnitude of PRC appears to correlate with the levels of ascorbic acid in plasma.

The relationship between serum and urine chromium levels to occupational exposure levels has been investigated in numerous studies, with results showing correlations between exposure levels and chromium levels in blood and urine (Gylseth et al. 1977; Iarmarcovai et al. 2005; Kilburn et al. 1990; Lewalter et al. 1985; Lindberg and Vesterberg 1983a; McAughey et al. 1988; Medeiros et al. 2003a; Minoia and Cavalleri 1988; Muttamara and Leong 2004; Mutti et al. 1985b; Randall and Gibson 1987, 1989; Saner et al. 1984; Sathwara et al. 2007; Simpson and Gibson 1992; Sjogren et al. 1983; Stridsklev et al. 2004; Takagi et al. 1986; Tola et al. 1977; Wiegand et al. 1988). In workers exposed to chromium(VI) as chromium trioxide in the chrome plating industry, a significant correlation ( $r=0.71$ ) was

## 3. HEALTH EFFECTS

observed found between exposure levels and postshift urinary chromium; for a TWA exposure of  $0.002 \text{ mg chromium(VI)/m}^3$ , the mean urinary chromium level was  $5.2 \text{ } \mu\text{g/L}$  (excluding workers with obvious skin contamination) (Lindberg and Vesterberg 1983a). Significant correlations were observed between chromium concentrations in air (measured by personal sampling devices; 8-hour TWA) and levels of chromium in blood ( $r=0.99$ ) and urine ( $r=0.89$ ) in workers at a chromium alloy facility (Muttamara and Leong 2004). In areas of low exposure, the air concentration of chromium (type not specified) was  $5.75 \text{ } \mu\text{g/m}^3$ ; in workers in this area, mean chromium concentrations in blood and urine (duration of sample collection was not reported) were  $0.925$  and  $0.095 \text{ } \mu\text{g/dL}$ , respectively. In areas of high exposure, the air concentration of chromium was  $7.25 \text{ } \mu\text{g/m}^3$ , in workers in this area, mean chromium concentrations in blood and urine were  $3.64$  and  $0.34 \text{ } \mu\text{g/dL}$ , respectively. An increase in urinary chromium of  $12.2 \text{ } \mu\text{g/g creatinine}$  above preexposure values or a total concentration of  $29.8 \text{ } \mu\text{g/g creatinine}$  (end-of-shift values) corresponded to an air concentration of  $50 \text{ } \mu\text{g chromium(VI)/m}^3$  from welding fumes (Mutti et al. 1985b). Examination of end-of-shift chromium levels indicated a correlation between urinary chromium levels and exposure to soluble chromium(VI) compounds, but not to insoluble chromates or chromium(III) compounds (Minoia and Cavalleri 1988; Mutti et al. 1985b). The relationship between workroom air concentrations of water soluble chromium(VI) compounds and daily increases in urinary chromium (preexposure values subtracted from end-of-shift values) are shown in Figure 3-7. Serum and urine concentrations of chromium were significantly elevated in a group of 73 tannery workers, with exposure primarily to chromium(III) compounds, compared to a group of 52 control subjects, at the end of the workweek on Friday and before exposure began on Monday (Randall and Gibson 1987). Serum and urine chromium levels correlated with work area of the tannery, with the highest concentrations in workers handling wet hides in the chrome tanning and wringing departments. The time-weighted average level of total chromium in tannery air was  $1.7 \text{ } \mu\text{g/m}^3$  and did not vary significantly among the various tanneries involved in the study or among the various work areas of each tannery, with chromium(VI) levels in tannery air were below the detection limit of ( $0.1 \text{ } \mu\text{g/m}^3$ ).

Urinary and blood chromium have also been used as a biomarker for environmental exposure (Bukowski et al. 1991; Chang et al. 2006; Fagliano et al. 1997). However, interpretation of results may be limited by several factors, including that exposure must be sufficient such that urinary and blood concentrations are higher than the range of background concentrations and analytical limit of detection, high inter- and intrapersonal variability, and that different chemical forms have different bioavailabilities (Paustenbach et al. 1997; Finley et al. 1996b; Gargas et al. 1994; Kerger et al. 1997). Furthermore, the short half-life of chromium (e.g., at least 90% of absorbed chromium is eliminated within 24 hours) make it difficult to assess exposure incidents. Low-level, intermittent exposure, such as would occur with environmental





## 3. HEALTH EFFECTS

exposures to soil, dust, and residential drinking water, may not be detected with urinary monitoring; however, it is more likely that urinary monitoring would detect higher-level continuous exposure or daily inhalation exposure to chromium(VI). Paustenbach et al. (1997) note that chromium intakes would have to exceed 2 µg/day in order to distinguish the exposure from background. Large interpersonal variability (as high as a factor of 10) and intrapersonal variability (as high as a factor of 3) can result in highly variable erroneous conclusions regarding significant differences among populations.

### 3.8.2 Biomarkers Used to Characterize Effects Caused by Chromium

Chromium has been shown to produce effects to several systems, including the respiratory, gastrointestinal, hematological, and immunological systems (see Section 3.2); however, many of these effects are not specific for chromium. Although effects to these physiological systems can be assessed with blood and respiratory function tests and by physical examination, these assessments would not serve as biomarkers specific for effects of chromium as impairment of these systems can result from a variety of other causes, including chemical toxicity, nutritional insufficiencies, and disease.

Occupational exposure to chromium and its compounds has caused respiratory effects, such as pneumonitis, impaired pulmonary function, nasal septum perforations, irritation of the mucosa, inflammation, and cancer. In addition, chromium can be irritating and corrosive to the skin. Chromium exposure may cause asthma attacks and dermatitis in sensitive individuals. Workers with urinary levels of chromium >15 µg/g creatinine had increased retinol binding protein and tubular antigens in the urine. The workroom levels ranged from 0.05 to 1.0 mg chromium(VI)/m<sup>3</sup> as chromium trioxide (Franchini and Mutti 1988). The urine of chromium(VI) exposed workers in a chromate production plant contained higher levels of a brush border protein and of retinol-binding protein in the urine than did nonexposed controls (Mutti et al. 1985a). In a study of currently exposed chrome platers, ex-chrome platers, and referent groups of nonexposed workers, the urinary levels of β<sub>2</sub>-microglobulin were significantly higher (p=0.045), and elevated levels occurred more often in the presently exposed groups compared with its age-matched control group. The levels of β<sub>2</sub>-microglobulin in the urine of the ex-chrome platers, however, were not different than those of its age-matched control group (Lindberg and Vesterberg 1983b). Another study of hard chrome electroplaters found a higher prevalence of workers with elevated N-acetyl-β-glucosaminidase levels (Liu et al. 1998). Although this study also found higher levels of β<sub>2</sub>-microglobulins in the chrome plater, the prevalence of elevated values was not significantly increased. The presence of low molecular weight proteins, such as retinol binding protein, antigens, or

## 3. HEALTH EFFECTS

$\beta_2$ -microglobulin in the urine is believed to be an early indication of kidney dysfunction. The lack of a significant difference in the ex-chrome platers compared with the control group suggests that the chromium-induced kidney damage may be reversible. Cell culture and cell free studies discussed in Section 3.5.2 demonstrated that chromium forms protein-DNA crosslinks and adducts with DNA, and that these end points may be potentially useful biological markers, indicating the possibility of genotoxic effects or cancer in humans exposed to chromium. However, no increases in protein-DNA crosslinks were observed in white cells from volunteers who were exposed to chromium(VI) in drinking water (Kuykendall et al. 1996).

The possibility of using an immune-function assay as a potential biomarker for humans exposed to chromium has been examined (Snyder et al. 1996). Isolated mononuclear cells from 46 individuals who lived and/or worked in areas in northern New Jersey at sites contaminated by chromium processing were stimulated by pokeweed mitogen. Rates of stimulated cell growth and production of interleukin 6 (IL-6) were measured and compared to a control population of people who lived/worked in uncontaminated areas. There was no significant increase in mitogen stimulation between people from contaminated areas and controls, but there was a significant (36%) decrease in the levels of IL-6 in monocytes in the chromium exposed group. IL-6 is an important cytokine that is involved in the T-cell helper pathway of antibody production. The significance of the lower levels may lead to decreased levels of antibody production.

The effects of chromium(III) chloride, sodium chromate(VI), and potassium chromate(VI) on proliferation of mononuclear leukocytes obtained from chromium sensitive individuals (confirmed with positive patch tests) was compared to nonsensitive controls (confirmed by negative patch tests) (Räsänen et al. 1991). Isolated cells were exposed to 25–50  $\mu\text{g/mL}$  culture medium of chromium(III) chloride and to 0.025 to 0.1  $\mu\text{g/mL}$  culture medium chromium(VI) salts, which gave optimum responses and cell growth ratios of treated/nontreated cells from eight sensitive individuals ranging from 1.56 to 13.22, average=5.8 (chromium(III)), from 2.24 to 11.43, average 5.4 sodium chromate, and from 1.82 to 9.48, average 5.4potassium dichromate. The nonsensitive individuals' ratios were consistently lower with ranges from 0.90 to 2.28 and average ratios of 1.14, 1.30, and 1.56, respectively. The authors felt that this *in vitro* methodology could be used diagnostically to assess chromium-sensitive individuals.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (Agency for Toxic Substances and Disease Registry 1990c) and for information on biomarkers for neurological effects see OTA (1990).

## 3. HEALTH EFFECTS

**3.9 INTERACTIONS WITH OTHER CHEMICALS**

Potassium dichromate (10 mg/kg) administered by subcutaneous injection potentiated the effects of the nephrotoxins, mercuric chloride, citrinin, and hexachloro-1,3-butadiene, in rats. Effects on renal function included changes in urine volume, osmolality, electrolyte and glucose excretion, and a reduction in renal cortical slice organic ion transport. Chromium(VI) compounds potentiated the effect of mercuric chloride on organic acid uptake but not organic base uptake by renal cortical slices (Baggett 1986; Haberman et al. 1987). A similar experiment with another nephrotoxin, maleic acid, demonstrated the potentiating effect of potassium dichromate (10 mg/kg administered subcutaneously) (Christenson et al. 1989). Christenson et al. (1989) suggested that the combination of potassium dichromate with maleic acid might enhance damage to the brush border of the renal proximal tubules or that damage to the luminal cells by potassium dichromate might allow maleic acid to more easily enter the cells.

Concomitant exposure of female Sprague-Dawley rats to chromium(VI) potassium dichromate and ethanol in drinking water for 22 weeks indicates that ethanol may enhance the hepatic effects of chromium(VI) (Acharya et al. 2001). Serum enzyme activity of ALT in rats treated with 10% ethanol and 25 mg chromium(VI)/L (3.8 mg chromium(VI)/kg/day) was significantly increased compared to treatment of rats with ethanol or chromium(VI) alone. However, the toxicological significance of this finding is uncertain, since serum ALT activities of rats treated with ethanol and chromium(VI) were increased by only 18% compared to treatment of rats with chromium(VI) alone.

Interactions between selenium in the diet and ammonium dichromate in the drinking water were investigated in a study using rats. During the experiment, one rat died and the other rats had atrophy of the central liver lobe when given selenium alone. Dietary selenium and ammonium chromate in combination caused hepatic necrosis, resulting in the death of four rats (Moxon and DuBois 1939). Although the rats were not fed chromium alone, other studies indicate that the liver is a target for chromium exposure (see Section 3.2). The mechanism for the interaction was not discussed.

Exposure of female hairless mice to ultraviolet light in combination with chromium(VI) as potassium chromate in drinking water at concentrations of 2.5 or 5.0 mg potassium chromate(VI)/L (approximately 0.18 or 0.35 mg chromium(VI)/kg/day) for 182 days, or in the diet at concentrations of 0, 2.5, or 5.0 mg potassium chromate(VI)/kg food (approximately 0.13 or 0.26 mg chromium(VI)/kg/day) for 26 weeks, produced an increased incidence of skin tumors compared to animals exposed to UV light alone or

## 3. HEALTH EFFECTS

chromium(VI) alone (Davidson et al. 2004; Uddin et al. 2007). Exposure to chromium(VI) alone did not result in neoplasms. The chromium-induced enhancement of UV light-induced skin tumors did not appear to be mediated through oxidative damage, since concomitant treatment with vitamin E or selenomethionine did not decrease the chromium effect.

Concomitant inhalation exposure to ozone and chromium(VI) may alter pulmonary clearance mechanisms in the deep lung (Cohen et al. 2003). Compared to rats treated with insoluble chromium(VI) as calcium chromate (0.34–0.36 mg chromium(VI)/m<sup>3</sup>) alone for up to 48 weeks, concomitant exposure to ozone (0.59 mg/m<sup>3</sup>) resulted in decreased particle uptake and altered postphagocytic/endocytic processing of chromium particles by alveolar macrophages. However, since toxicity was not assessed in this study, it is not known if ozone-induced alteration in alveolar macrophage function would result in increased toxicity of chromium(VI).

A number of studies indicate an increase in the mutagenic effects of chromium(VI) compounds in combination with other chemicals. Synergism has been observed between chromium(VI) and 9-aminoacridine, nitrilotriacetic acid, and azide (Bronzetti and Galli 1989; Gava et al. 1989a; LaVelle 1986a, 1986b; Montaldi et al. 1987), but the mechanisms are not clearly understood. Potassium dichromate potentiated mutations produced by sodium azide in *S. typhimurium* or by 9-aminoacridine in *S. typhimurium* and *E. coli*. Although the data were insufficient for speculation on the specific biochemical mechanism, it was suggested that the potentiation involved a specific effect of potassium dichromate on the interaction of 9-aminoacridine or sodium azide with DNA or on subsequent DNA replication and/or repair (LaVelle 1986a, 1986b). Nitrilotriacetic acid, which appears to have no genotoxic potential itself, increased the frequencies of sister chromatid exchanges in Chinese hamster ovary cells and of micronuclei and chromosomal aberrations in cultured human lymphocytes that were seen with lead chromate alone. However, nitrilotriacetic acid had no effect on the dose-related induction of sister chromatid exchanges in Chinese hamster ovary cells that was seen with potassium chromate alone. It was suggested that nitrilotriacetic acid increased the solubility of the originally insoluble lead chromate, leading to increased uptake of the metal cation by the cells and subsequent increased genotoxicity (Montaldi et al. 1987). Nitrilotriacetic acid increased the frequency of point mutations in *S. cerevisiae* observed with a low concentration of sodium chromate, but decreased the frequency with a 5-fold higher concentration of sodium chromate. It was suggested that at the low concentration of sodium chromate, nitrilotriacetic acid affected the uptake of chromium(VI), favoring reduction to chromium(III) ions, which formed a complex with nitrilotriacetic acid that can cross the membrane and interact with DNA. At the high dose of sodium chromate, nitrilotriacetic acid may have affected the mechanism of

## 3. HEALTH EFFECTS

recombination repair of DNA breaks induced by chromate oxidizing activity (Bronzetti and Galli 1989). Nitritotriacetic acid also increased the mutagenicity of potassium dichromate in *S. typhimurium* and *D. melanogaster*, presumably by favoring the reduction of chromium(VI) to chromium(III) (Gava et al. 1989a). Thus, it is possible that other hazardous substances at hazardous waste sites may be more dangerous due to the presence of chromium(VI).

Ascorbic acid has been shown to have a protective effect in rats administered lethal dermal doses of potassium dichromate (25 mg chromium(VI)/rat), and in preventing ulcerations of the skin (Samitz 1970). The nephrotoxicity due to subcutaneous injections of potassium chromate in rats was prevented by intramuscular administration of ascorbic acid (Powers et al. 1986). This occurred mainly through the reduction of chromium(VI) to the less toxic chromium(III) state. In cultured human bronchial cells, co-exposure to ascorbic acid and sodium chromate blocked chromate-induced clastogenicity by preventing uptake of chromium(VI) ions by cells (Wise et al. 2004). Vitamin E protected against, while vitamin B<sub>2</sub> enhanced, the cytotoxicity and DNA strand breaks induced by sodium chromate in Chinese hamster cells *in vitro*. Vitamin E may exert its protective effect by scavenging radicals and/or chromium(V) during the reduction of chromium(VI) (Sugiyama 1991) (see Section 3.11.3). N-Acetylcysteine, the glutathione precursor, was reported to be effective in increasing the urinary excretion of chromium in rats (Nadig 1994).

Studies have examined the effects of interactions between chromium and arsenic on blood cholesterol and glucose levels and changes in organ weight in rats (Aguilar et al. 1997). Groups of five male Wistar rats were given food containing 5 µg/g of either arsenic(V) oxide, chromium(III) chloride, or a combination of both chemicals for 10 weeks. Organ weight to body weight ratios of liver, spleen, lung, kidney, and heart were similar to control values for the three exposed groups. Arsenic alone increased the cholesterol blood level from 47.27(±6.85 SD) mg/dL in the control group to 96.83(±6.11 SD). The combination of arsenic and chromium reduced the blood cholesterol level to 46.69(±6.11 SD) mg/dL. Neither chemical alone or in combination affected blood glucose levels. In most tissues, the combination of chemicals reduced the chromium level appreciably below control values. Supplemental chromium increased arsenic levels in liver, kidney, spleen, heart, and red blood cells, and reduced levels of arsenic in lung and hair tissues. Chromium did not appear to alter concentrations of arsenic in the liver.

A study examining the chromium(VI) reduction in microsomes noted that the level of iron in the test system markedly influenced the V<sub>max</sub> of chromium(VI) reduction, suggesting that coexposure to

### 3. HEALTH EFFECTS

chromium(VI) and agents that increase intracellular iron might lead to increased risk for chromium(VI) toxicity (Myers and Myers 1998).

The effects of chromium(III) chloride and sodium chromate(VI) on the hepatotoxicity of carbon tetrachloride exposure to mouse hepatocytes were examined by Tezuka et al. (1995). Primary cultures of mouse hepatocytes were pretreated with 10 or 100  $\mu$ M chromium for 24 hours followed by exposure to 1–5 mM carbon tetrachloride for up to 1 hour. Chromium(VI) pretreatment significantly reduced the cell toxicity as well as lipid peroxidation caused by carbon tetrachloride. Chromium(III) pretreatment did not have any effect on cell toxicity. About 50% of chromium(VI) was taken up and reduced in the cells by 90% to chromium(III) within 10 minutes. The initial uptake rate of chromium(III) into cells was greater than 500-fold less than chromium(VI), and only about 5% was absorbed. The protection against carbon tetrachloride damage by chromium(VI) was attributed to its rapid uptake and conversion to chromium(III), and it was determined that chromium(III) acts as a radical scavenger for the free radicals generated by carbon tetrachloride within the cell. Furthermore, chromium(VI) pretreatment reduced the activity of NADPH cytochrome c reductase, which metabolizes carbon tetrachloride to reactive species. In a previous study (Tezuka et al. 1991), the same group found that pretreating mice and rats with chromium(III) also protected against hepatic toxicity.

In order to examine the speciation of chromium in lemonade, Kool Aid, tea, dripped coffee, percolated coffee, and orange juice, potassium chromate(VI) was added to each of the beverages at a chromium concentration of 10 mg/L (Kerger et al. 1996b). After 15 minutes, the concentrations of chromium(VI) were determined to be <0.4 mg/L for orange juice, <0.3 mg/L for coffee and tea, 2 mg/L for Kool Aid, and 0.3 mg/L for lemonade. After 3–5 hours, essentially no residual chromium(VI) remained. At higher concentrations (50 mg/L chromium(VI)), >99, 40, and 84% of the chromium(VI) was reduced after 3–5 hours in orange juice, lemonade, and coffee, respectively (not tested at the higher concentration in Kool Aid and tea). The reducing capacities were not correlated with total organic carbon or pH. The reducing capacities of the beverages were attributed in part to ascorbic acid in lemonade and orange juice and to tannins in tea and coffee.

#### **3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE**

A susceptible population will exhibit a different or enhanced response to chromium than will most persons exposed to the same level of chromium in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke).

### 3. HEALTH EFFECTS

These parameters result in reduced detoxification or excretion of chromium, or compromised function of organs affected by chromium. Populations who are at greater risk due to their unusually high exposure to chromium are discussed in Section 6.7, Populations with Potentially High Exposures.

Acute inhalation LC<sub>50</sub> and oral and dermal LD<sub>50</sub> studies suggest that female animals are more sensitive to the lethal effects of chromium(VI) compounds (see Sections 3.2.1.1, 3.2.2.1, and 3.2.3.1). Whether human females are more sensitive than males to toxic effects of chromium or its compounds is not known. Other information identifying possible susceptible populations was not located. The primary and most sensitive effects of exposure to chromium compounds to the respiratory, gastrointestinal, hematological, and immunological systems; thus, individuals with preexisting conditions of these systems may be at increased risk of exposure to chromium compounds. Due to the sensitizing effects of chromium, some individuals who are sensitive to chromium may develop asthma as an anaphylactic response to inhaled chromium. Also, there is limited evidence in some individuals have less ability than others to reduce chromium(VI) in the bloodstream and are more likely to be affected by the adverse effects of chromium exposure (Korallus 1986a, 1986b). The ability to reduce chromium(VI) in the bloodstream may be related to the ascorbic levels in the plasma. However, the metabolic reduction of chromium(VI) may result in bioactivation and/or detoxification.

Since chronic inhalation of cigarette smoke may result in squamous metaplasia in the respiratory mucosa, the risk of lung cancer due to inhalation of carcinogenic chromium compounds may be exacerbated in individuals who smoke cigarettes or are excessively exposed to passive smoke (Albert 1991).

#### **3.11 METHODS FOR REDUCING TOXIC EFFECTS**

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

Haddad LM, Shannon MW, Winchester JF, eds. 1998. Chromium. In: Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia, PA: W.B. Sanders Company, 794-795.

Leikin JB, Paloucek FP, eds. 2002. In: Leikin and Paloucek's poisoning and toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp, Inc., 372-379.

## 3. HEALTH EFFECTS

Schonwald S. 2004. Chromium. In: Dart RC, ed. Medical toxicology. 3rd ed. Philadelphia, PA: Lippicott Williams & Wilkins, 1415-1417.

### 3.11.1 Reducing Peak Absorption Following Exposure

General recommendations for reducing absorption of chromium following acute inhalation exposure have included moving the patient to fresh air, monitoring for respiratory distress, and administering humidified supplemental oxygen with assisted ventilation if required (Haddad et al. 1998; Schonwald 2004). If pulmonary effects such as bronchoconstriction are present, treatment with oxygen and bronchodilator drugs may be administered (Haddad et al. 1998). The absorption of inhaled chromium compounds depends on such factors as oxidation state, particle size, and solubility. Chromium(VI) passes through the alveolar lining of the lungs to the bloodstream more readily than does chromium(III) (see Section 3.4.1.1), and more soluble compounds are absorbed more readily than those that are less soluble (Bragt and van Dura 1983). Although chromium(VI) is more readily absorbed from the lungs than chromium(III), various components of the respiratory system can reduce chromium(VI) to chromium(III), which is far less capable of crossing cell membranes than chromium(VI), thereby reducing the bioavailability of chromium to target cells other than the lung (De Flora and Wetterhahn 1989). Epithelial lining fluid (ELF) is capable of reducing chromium(VI) (Petrilli et al. 1986b) and may represent the first line of defense against inhaled chromium(VI). Ascorbic acid (vitamin C) and glutathione, both of which were found to reduce chromium(VI) to chromium(III) in cell-free bronchoalveolar lavage fluid or soluble fractions of rat lungs *in vitro*, appear to be involved in this activity of ELF (Suzuki and Fukuda 1990). Uptake and reduction of chromium(VI) by pulmonary alveolar macrophages, catalyzed by NADH- or NADPH-dependent cytosolic enzyme activities, may lead to virtually irreversible sequestration and efficient removal by mucociliary action (De Flora and Wetterhahn 1989; De Flora et al. 1984, 1987b). Reduction of chromium(VI) within pulmonary alveolar macrophage homogenates was stimulated in rats by the administration of the glutathione precursor, N-acetylcysteine (De Flora and Wetterhahn 1989). As mentioned above, the reduction of chromium(VI) to chromium(III) by these various processes within the lungs serves as a natural defense mechanism by decreasing the amount of chromium absorbed and enhancing mucociliary clearance of chromium(III). However, reduction of chromium(VI) to chromium(III) generates reactive intermediates, which may produce adverse effects. Theoretically, further clearance from the lungs might be achieved by the administration of expectorants, but the efficacy of such a procedure has not been tested.



## 3. HEALTH EFFECTS

Chromium(III) is also poorly absorbed by the gastrointestinal tract, and chromium(VI) is reduced to chromium(III) in the gastric environment, limiting the bioavailability of chromium(VI) (De Flora et al. 1987a; Donaldson and Barreras 1966). Thus, the oral toxicity of chromium metal is low. However, chromium(VI) compounds are highly corrosive to the gastrointestinal tract and can lead to hepatic, renal, hematological, and neurological effects (Clochesy 1984; Coogan et al. 1991a; Diaz-Mayans et al. 1986; Iserson et al. 1983; Kaufman et al. 1970; Kumar and Rana 1982, 1984; Samitz 1970; Saryan and Reedy 1988). The reduction of chromium(VI) to chromium(III) in the stomach is greatly enhanced at low pH and shortly after meals due to increased gastric juice secretion (De Flora et al. 1987a). Therefore, administration of food might help decrease the gastrointestinal absorption of chromium. The enhanced reduction of chromium(VI) at low pH suggests that, theoretically, oral administration of bicarbonates and antacids should be avoided. Oral administration of ascorbic acid to further reduce chromium(VI) to chromium(III) might further decrease bioavailability (Haddad et al. 1998; Schonwald 2004), although this has not been proven (Leikin and Paloucek 2002; Schonwald 2004). Other recommendations for reducing gastrointestinal absorption of chromium include diluting with water or saline followed by gastric lavage (Schonwald 2004). Inducing emesis with syrup of ipecac is not recommended because of the possibility of irritation or burns to the esophagus (Nadig 1994; Schonwald 2004).

In cases of dermal exposure, the skin should be thoroughly washed to prevent chromium absorption by the skin (Haddad et al. 1998; Leikin and Paloucek 2002; Schonwald 2004). As chromium(VI), but not chromium(III), is readily absorbed by the skin, ascorbic acid in the washing solution could reduce chromium(VI) to chromium(III), thus decreasing absorption. Application of the calcium disodium salt of ethylenediamine tetraacetic acid (EDTA), which acts as a chelating agent, has also been recommended after washing with water and application of ascorbic acid (Nadig 1994), especially in cases where the skin has been cut or abraded (Burrows 1983). Ascorbic acid was found to protect chromium-sensitive workers who handled chromates in the lithographing and printing industries from dermatitis. The ascorbic acid (10% solution) was kept near the work areas, and the workers soaked their hands and forearms as soon as possible after handling the chromate mixtures. In addition, ascorbic acid prevented ulcerations of the skin in rats treated with potassium dichromate dermally (Samitz 1970). An antichrome powder consisting of a mixture of 40% sodium metabisulfite, 20% ammonium chloride, 20% tartaric acid, and 20% sucrose as a 10% aqueous solution was effective in reducing the healing time of chrome sores on the skin of guinea pigs to which potassium dichromate had been applied (Samitz and Epstein 1962). Thorough irrigation with water has been recommended if the eyes have been exposed (Haddad et al. 1998; Schonwald 2004).

### 3. HEALTH EFFECTS

Both the cytotoxic effects of chromium(III) chloride, chromium(III) nitrate, sodium chromate(VI), sodium dichromate(VI), potassium dichromate(VI), and chromium(V) potassium sulfate dodecahydrate and the ability of ascorbic acid, glutathione 4-acetamido-4'-isothiocyanato-2,2-stibenedisulphonic acid (SITS) to prevent chromium toxicity in transformed human keratinocytes were examined (Little et al. 1996). This cell line was used because histopathological studies have shown that dichromate compounds have caused keratinocyte necrosis. Cells were exposed to the chromium salts for 24 hours, and the viability of the cultures was examined for their ability to take up neutral red dye and release lactate dehydrogenase into the media. None of the chromium(III) or chromium(V) salts seemed toxic to the cells at concentrations up to about 100  $\mu$ M. The chromium(VI) salts showed toxicity at about 8  $\mu$ M, and there was little cell survival at 100  $\mu$ M. The dose-response curves were similar for all chromium(VI) salts tested. Similar experiments were conducted with normal human keratinocytes obtained from abdominoplasties or breast reductions from six donors and treated with sodium dichromate. The toxicity to normal cells overall seemed to be less than in the transformed line. Ascorbic acid at 500  $\mu$ M completely inhibited the cell toxicity caused by chromium(VI), whereas glutathione and SITS were less effective. Ascorbate probably protected cells by reducing chromium(VI) and chelation of the reduced complex. Glutathione may have formed complexes with the chromium(VI), which eventually led to chromium(III), whereas SITS may have inhibited the cellular uptake of the chromate by altering the non-specific membrane anion carrier. The authors conclude that these available drugs provide protection against cytotoxicity to keratinocytes involved in dermatitis and may be useful to prevent toxic reactions to metals contacting the skin.

The effect of decreasing the concentration of water-soluble chromium in cement from about 10 to 2 ppm on the incidences of chromium-induced dermatitis was examined among construction workers in Finland (Roto et al. 1996). After 1987, when the decrease occurred, allergic dermatitis caused by chromium in the industry was reduced by 33% from previous levels, whereas irritant contact dermatitis remained unchanged.

#### **3.11.2 Reducing Body Burden**

Once chromium has been absorbed, it can be widely distributed throughout the body (see Section 3.4.2). Forced diuresis with careful monitoring of fluid and electrolyte status has been suggested, but not proven, to increase the elimination of chromates (Haddad et al. 1998). In a case report of a fatality after ingestion of potassium chromate, hemodialysis and charcoal hemoperfusion did not significantly remove chromium from whole blood and had little effect on the management of chromium toxicity (Iserson et al. 1983).

## 3. HEALTH EFFECTS

However, hemodialysis was effective in saving the life of an electroplater who accidentally swallowed plating fluid containing chromium trioxide (Fristedt et al. 1965). Because chromium may be sequestered in erythrocytes, exchange transfusion has been used as a way to decrease the body burden in serious acute poisoning (Kelly et al. 1982).

Both chromium(VI) and chromium(III) can be transported in the blood. Chromium(III) tends to bind to plasma proteins and is excreted in the urine. Chromium(VI) may be poorly reduced to chromium(III) in plasma, but this reduction can be enhanced by the intravenous administration of ascorbic acid (Korallus et al. 1984). However, reactions of chromium(VI) with sulfhydryl compounds or ascorbate may have mixed effects on toxicity, since such reactions yield reactive chromium intermediates, reactive oxygen species, and free cysteinyl and carbon radical species, which may be more damaging than chromium(VI) itself (Reynolds and Zhitkovich 2007; Shi et al. 1994; Stearns et al. 1994). Generally, treatments for reducing body burden of chromium are chelation therapies similar to those used to reduce body burdens of other metals, although the use of ascorbic acid is specific for chromium. Use of hemodialysis and N-acetylcysteine has been suggested to enhance elimination (Haddad et al. 1998; Leikin and Paloucek 2002; Schonwald 2004), however, this has not been proven. N-acetylcysteine, the glutathione precursor, was reported to be more effective than EDTA or dimercaptosuccinic acid in increasing the urinary excretion of chromium in rats (Banner et al. 1986; Nadig 1994); however, chelation with agents available in human clinical medicine, such as British Anti Lewisite (dimercaprol) and EDTA, has been shown to be generally ineffective in increasing the elimination of chromium (Ellis et al. 1982). However, calcium EDTA, administered intravenously, resulted in a rapid increase in the urinary excretion of chromium in metal workers (Sata et al. 1998). Other polyaminocarboxylic acid chelating agents may be effective in removing chromium from organs. In rats injected with potassium chromate, subsequent treatment with various polyaminocarboxylic acid chelating agents resulted in significant removal of chromium from the liver, kidney, heart, or brain, depending on the agent. Ethylenediamine N,N'-diacetic acid (EDDA) removed significant amounts of chromium from the liver and heart. Ethylenediamine N,N'-di(O-hydroxyphenyl acetic acid (EDDHA) removed significant amounts of chromium from the kidney, heart, and brain. N-(2-hydroxyethyl)ethylenediamine triacetic acid (HEDTA) removed significant amounts of chromium from the liver and kidney. Hexamethylene 1,6-diamino N,N,N',N'-tetraacetic acid (HDTA) removed significant amounts of chromium from the liver, kidney, and brain. Triethylene tetramine N,N,N',N',N'',N''-hexaacetic acid (TTHA) removed significant amounts of chromium from the liver. Ethyleneglycol-bis-(2-aminoethyl) tetraacetic acid (EGATA) did not remove significant amounts of chromium from any of the organs. The relative ability of the polyaminocarboxylic acids to remove chromium from organs may be related to the number of amino or carboxyl groups as complexing centers

## 3. HEALTH EFFECTS

or by the presence of hydroxyl groups (Behari and Tandon 1980). The use of these agents in humans has not been tested. Chromium(VI), but not chromium(III), can readily cross cell membranes.

Chromium(VI) readily enters erythrocytes, where it is reduced to chromium(III) by glutathione, and chromium(III) is essentially trapped within erythrocytes, where it binds to proteins, primarily hemoglobin. This may explain the fact that chromium shows little toxicity at sites distant from administration sites (De Flora and Wetterhahn 1989). The chromium(III) trapped within the erythrocytes would be released upon natural destruction of the erythrocyte and excreted in the urine.

### 3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The reduction of chromium(VI) to chromium(III) inside of cells may be an important mechanism for the toxicity of chromium, whereas reduction of chromium(VI) outside of cells may be a major mechanism of protection. After entering target cells, chromium(VI) itself and/or the metabolically reduced valence states exert toxic effects, as discussed in detail below (De Flora and Wetterhahn 1989). Administration of a reducing agent (such as ascorbate) early enough after exposure to reduce chromium(VI) to chromium(III) in extracellular fluids before chromium(VI) penetrates cells may reduce toxicity; however, increased intracellular ascorbate may enhance toxicity. For example, in animal studies, ascorbic acid has been shown to protect against lethality of dermal potassium dichromate (Samitz 1970) and prevent nephrotoxicity of subcutaneously administered potassium chromate (Powers et al. 1986). However, increased intracellular ascorbate concentrations has been shown to enhance chromium(VI) toxicity in cultured human fibroblasts (Reynolds and Zhitkovich 2007). Therefore, agents that enhance reduction of chromium(VI) to chromium(III) may have mixed effects on toxicity. The effect of ascorbate or other reducing agents on chromium toxicity in humans has not been established.

Once chromium enters the cell, ligand displacement and/or redox reactions of chromium(VI) with enzymes, proteins, and other molecules leads to reduction to chromium(V), chromium(IV), and chromium(III), with the generation of active oxygen species and radicals. The resulting toxicity depends on the nature of the cellular component that reacts with chromium(VI) and on the nature of the reactive species formed from the reaction. Chromium(VI) can be reduced metabolically by a number of cellular components under physiological conditions. Reduction by glutathione or cysteine can lead to generation of all valence states (particularly chromium(V)) and radicals. For example, *in vitro* reaction of chromium(VI) with glutathione led to the formation of glutathione thiyl radicals and chromium(V) complexes (Aiyar et al. 1991). Chromium(V)-glutathione complexes have been shown to form DNA adducts. Reduction by ascorbate leads to chromium(III), but chromium(V) has been generated by the

## 3. HEALTH EFFECTS

reaction of chromium(VI) with riboflavin (vitamin B<sub>2</sub>) and ribose derivatives (De Flora and Wetterhahn 1989). Reaction of chromium(VI) with hydrogen peroxide has led to the formation of chromium(V) complexes and hydroxyl radicals (Aiyar et al. 1991). Other important intracellular reduction reactions of chromium(VI) involve enzyme-catalyzed and NADPH-dependent mechanisms. Microsomal reduction of chromium(VI) by cytochrome P450 to chromium(III) may involve the transient formation of chromium(V) (De Flora and Wetterhahn 1989). Chromium(III), the final stable product of chromium(VI) reduction, can form chromium-DNA adducts and mediate crosslinking of DNA strands and DNA protein (De Flora and Wetterhahn 1989; Manning et al. 1992; Xu et al. 1996). Thus, the metabolic reduction of chromium(VI) may represent bioactivation and/or detoxification. If a bioactivation process, intracellular reduction of chromium(VI) would lead to the ultimate toxic species. Conversely, if chromium(VI) is the toxic agent, then effects would be elicited only if the amount of chromium(VI) entering target cells saturates the reducing mechanisms.

Differences in the intracellular metabolic pathways that result in the reduction of chromium(VI) will affect the nature of the reactive intermediates. For example, chelating ligands, such as glutathione and sugars, stabilize chromium(V) as an oxidation state, increasing its lifetime in the cell and ability to reach DNA in the nucleus. Cytochrome P450-dependent reduction of chromium(VI) to chromium(V) and chromium(IV), with generation of reactive radicals, which takes place in the endoplasmic reticulum, could occur in close enough proximity to the nuclear membrane and nonenzymatic reduction within the nucleus could occur in close enough proximity to chromatin for the transient intermediates to exert their effects, such as DNA strand breaks and radical-DNA adducts. As noted above, chromium(III) can form chromium-DNA adducts and mediate crosslinking of DNA strands and DNA protein (De Flora and Wetterhahn 1989).

The role of glutathione in chromium-induced renal toxicity was investigated by Hojo and Satomi (1991). Male ddY mice (6 animals per dose group) were administered potassium dichromate(VI) (0.6 mmol chromium/kg), potassium tetraperoxo-chromate(V) (1.0 mmol/kg), green chromium(V)-glutathione complex (1.0 mmol/kg), and chromium nitrate (III) (0.6 mmol/kg); animals were sacrificed 24 hours after chromium injection and changes in kidney weight and function were assessed. Chromium(VI) resulted in a 10.7%±2.7 decrease in body weight, a 2-fold increase in serum urea nitrogen, a decrease in kidney nonprotein sulfhydryl contents (3.3±0.1 versus control values of 3.7±0.1) and a decrease of kidney-glutathione reductase activity from a control value of 17.4±1.5 to 14.1±1.3 U/g. Potassium tetraperoxo-chromate(V) treatment resulted in 50% of the animals dying. Body weights and kidney-glutathione reductase activity were much lower than for animals treated with chromium(VI), and serum

## 3. HEALTH EFFECTS

urea levels were  $102.9 \pm 17.7$  mg/dL, which is about twice that observed in animals treated with chromium(VI). The chromium(V) glutathione complex was much less toxic and showed values that were similar or close to control values. Pretreatment with 10 mmol/kg glutathione methyl ester in the chromium(VI)-treated animals appeared to reduce the body weight loss and caused the serum urea levels to be normal. Butathione sulfoximine (an inhibitor of glutathione synthesis) greatly enhanced the levels of serum urea, loss of glutathione reductase activity and decrease in kidney nonprotein sulfhydryl groups. Butathione sulfoximine pretreatment resulted in one of the six animals dying. Animals treated with chromium(III) experienced weight loss, but other parameters were not markedly changed from control values. Pretreatment with butathione sulfoximine in animals treated with chromium(III) only caused a decrease in kidney nonprotein sulfhydryl groups. The authors indicated that with excess levels of glutathione, chromium(VI) is more readily reduced to chromium(III), whereas at lower levels of glutathione the reduction process is slower, resulting in slower reduction of the more toxic intermediate chromium(V). Also, at higher concentrations of glutathione, chromium(V)-glutathione complexes may form which may prevent chromium(V) from reacting at target sites that elicit toxic responses.

As discussed above, reactive intermediates formed during intracellular reduction of chromium(VI) to chromium(III) may interact with hydrogen peroxide, generating hydroxyl radicals, which can induce cell damage. Several animal and *in vitro* studies have assessed the effects of anti-oxidant agents on chromium-induced oxidative cell injury. Administration of folic acid, a free radical scavenger, to rabbits reduced potassium dichromate-induced increases in the concentration of free radical in liver, testes, brain, kidney, and lung and in serum liver enzyme activities of AST and ALT (El-Demerdash et al. 2006). Vitamin E, an antioxidant, has been shown to reduce potassium dichromate-induced renal toxicity and hepatotoxicity in rats (Appenroth et al. 2001; Arreola-Mendoza et al. 2006; Rao et al. 2006). Vitamin B<sub>6</sub>, which may have anti-oxidant potential due to its role as a co-factor in the synthesis of cysteine, reduced oxidative stress in the liver of rats exposed to potassium dichromate (Anand 2005). *In vitro* studies indicated that vitamin E protected against, while vitamin B<sub>2</sub> enhanced, the cytotoxicity and DNA single-strand breaks induced by sodium chromate in Chinese hamster cells. Formation of DNA-protein crosslinks by chromium(VI) in cell culture was prevented by addition of ascorbic acid (Capellmann et al. 1995), and ascorbic acid protected cells against chromosomal breakage and apoptosis. Vitamin E also protected cells against chromosomal breaks (Blankenship et al. 1997) and decreased chromium(III)-induced oxidative damage to calf thymus DNA *in vitro*, as indicated by decreased formation of 8-hydroxydeoxyguanosine (Qi et al. 2000). Vitamin E may exert its protective effect by scavenging radicals and/or chromium(V) during the reduction of chromium(VI) (Sugiyama 1991). Selenium (as sodium selenate), an essential trace element, has been shown to reduce the genotoxicity of chromium

### 3. HEALTH EFFECTS

dichromate in human lymphocytes *in vitro* as assessed by the Comet assay, although sodium selenite and selenous acid enhanced chromium-induced DNA damage; sodium selenate also decreased chromium-induced genotoxicity in *S. typhimurium* (strain TA102), as assessed by the Ames assay (Cemeli et al. 2003). Other vitamins or essential elements might also be effective in mitigating the effects of chromium by modulating the metabolic processes. The use of vitamins and essential elements for reducing the toxicity of chromium has not been studied in humans.

Thyroxine was found to ameliorate acute renal failure induced in rats by potassium dichromate, possibly by stimulating gluconeogenesis and Na-K ATPase activity in the renal cortex, influencing protein synthesis, and promoting glucose and amino acid uptake by epithelial cells. These events would be expected to aid in the repair and regeneration of the damaged tubular epithelial cells (Siegel et al. 1984). The use of thyroxine has not been tested in humans.

Todralazine, an antihypertensive drug, was found to markedly reduce the mutagenic activity of potassium dichromate (VI) in the bacterial tester strain TA100 and in the *B. subtilis* rec assay (Gasiorowski et al. 1997). Spectroanalysis indicated that chromium(VI) was reduced to chromium(III) by todralazine and that todralazine formed a complex with the chromium(III) ions. The reduction and complexing of chromium may have prevented chromium from crossing the membrane and may have prevented harmful interactions with DNA. Another study by this group found that complexing copper(II) chromate(VI) to organic ligands (e.g., 2-(2'-pyridyl)imidazole, 2,2'-bipyridyl, 1,10-phenanthroline) resulted in a decrease in the mutagenicity of chromium(VI) as assessed by the Ames and *B. subtilis* rec assays (Gasiorowski et al. 1998).

#### 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 chromium 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 chromium.

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

## 3. HEALTH EFFECTS

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 Chromium**

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to chromium are summarized in Figures 3-8 and 3-9. The purpose of these figures is to illustrate the existing information concerning the health effects of chromium. Each dot in the figures 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.

A major source of oral exposure of humans to chromium is via the diet including chromium-rich diet supplements. Chromium(III) at low levels is essential to nutrition, and studies of chromium deficiency have been conducted. Information regarding health effects of exposure to chromium(VI) or chromium(III) in humans comes mainly from case reports of acute accidental or intentional ingestion, acute accidental dermal exposure, and from occupational case reports and epidemiology studies, which primarily involve inhalation and dermal exposure. In occupational studies, it is often difficult to separate exposure to chromium(VI) from chromium(III). Case reports have shown that ingestion and dermal contact with chromium(VI) can cause death. These reports have also described the serious systemic and neurological sequelae of exposure leading to death. Occupational exposures to chromium(VI) and/or chromium(III) are associated with respiratory and nasal, cardiovascular, gastrointestinal, hematological, hepatic, renal, and dermal effects. Immunological effects in humans exposed by inhalation and dermal contact consist of sensitization resulting in asthma and contact dermatitis, which can be exacerbated by oral exposure. Limited information was available regarding reproductive effects of occupational exposure to chromium(VI). Limited information was found on neurological behavioral effects. Information is also available regarding genotoxic effects in workers exposed to chromium(VI) and cancer in workers exposed to chromium(VI) and/or chromium(III).

































## 3. HEALTH EFFECTS

2004; Randall and Gibson 1987; Stridsklev et al. 2004; Sathwara et al. 2007), hair (Randall and Gibson 1989; Saner et al. 1984; Takagi et al. 1986), and erythrocytes (Lukanova et al. 1996; Minoia and Cavalleri 1988) to occupational exposure levels. All current methods of biological monitoring are useful primarily for occupational exposure scenarios. Since chromium is an essential element, levels of chromium compounds have to be relatively high in humans before they signify an increase due to exposure. Hair has been useful in determining chronic occupational exposure to chromium in high concentrations (Randall and Gibson 1989); the usefulness of this method for detecting prior exposures is limited to a timespan of months (Simpson and Gibson 1992). Erythrocytes (with a half-life of 120 days) can be used to monitor intermediate exposures, and blood or urine can be used to determine acute exposures (Korallus 1986a, 1986b). Occupational exposure to chromium can cause chromosomal aberrations (Koshi et al. 1984; Sarto et al. 1982; Stella et al. 1982). Therefore, chromosomal abnormalities may be useful for monitoring chromium exposure; however, other chemicals are capable of causing these effects. Chromium(VI) compounds are able to bind to macromolecules in the body and can form DNA-protein crosslinks (Coogan et al. 1991b). However, no increase in these crosslinks was observed in leukocytes from volunteers over a 240-minute time period after ingestion of chromium(VI) as potassium chromate (Kuykendall et al. 1996). The identification of chromium-protein/peptide complexes specific for chromium(VI) exposure and small enough to be excreted in the urine may be useful for biomonitoring in detecting low level exposure to populations near hazardous waste sites. As discussed in Section 3.8.1, there are a number of limitations to using urinary monitoring to assess environmental exposure to chromium (Paustenbach et al. 1997). However, urinary monitoring has the advantage of easy sample collection and is noninvasive. Mathematical models have been used to identify “excess” urinary chromium in a population exposed to low levels of chromium (Fagliano et al. 1997). Further refinement of these models as more data are collected from unexposed and exposed populations will also be useful in detecting low level exposures.

**Effect.** Chromosomal aberrations have been observed in workers exposed by inhalation to chromium compounds (Koshi et al. 1984; Sarto et al. 1982; Stella et al. 1982). Moreover, chromium(VI) compounds can bind to macromolecules that are excreted in the urine (Coogan et al. 1991b). The use of these techniques to detect chromosomal aberrations and chromium-macromolecular complexes would be useful in identifying populations near hazardous waste sites that would be at higher risk. In addition, the finding of increased retinol binding protein,  $\beta_2$ -microglobulin, and brush border proteins in the urine of workers exposed to chromium may serve as an early indication of kidney damage (Franchini and Mutti 1988; Lindberg and Vesterberg 1983b; Liu et al. 1998; Mutti et al. 1985b). Additional screening for low molecular weight proteins in occupationally exposed individuals will help to determine if these proteins





## 3. HEALTH EFFECTS

been found in animals after oral exposure (Kargacin et al. 1993; Witmer et al. 1989, 1991). The distribution of chromium in animals after intratracheal, parenteral, or dermal exposure is greatest in the lungs, liver, kidneys, blood, spleen, testes, and brain (Baetjer et al. 1959a; Behari and Tandon 1980; Bryson and Goodall 1983; Coogan et al. 1991b; Lim et al. 1983; Mutti et al. 1979; Tandon et al. 1979; Visek et al. 1953; Wahlberg and Skog 1965; Weber 1983). Oral exposure studies indicate that higher levels of chromium(VI) compounds are absorbed than are levels of chromium(III) compounds. Studies in humans occupationally and environmentally exposed to chromium(VI) (Casey and Hambidge 1984; Shmitova 1980) and in animals exposed to chromium(VI) or chromium(III) demonstrate the ability for chromium to cross the placenta (Mertz et al. 1969; Saxena et al. 1990a). Chromium(VI) crosses more readily than chromium(III).

There are no data to indicate that the route of exposure influences the metabolism of chromium. Regardless of the route of exposure, chromium(VI) inside the body is reduced to chromium(III) by ascorbic acid, glutathione, or by the NADPH-dependent cytochrome P450 system (Aaseth et al. 1982; Chen and Shi 2002; Costa 2003; Costa and Klein 2006a; De Flora et al. 1984, 1997; Ding and Shi 2002; Garcia and Jennette 1981; Gruber and Jennette 1978; Jeejeebhoy 1999; Levina and Lay 2005; Liu and Shi 2001; Liu et al. 1995; Mikalsen et al. 1989; O'Brien et al. 2003; Paustenbach et al. 2003; Petrilli et al. 1985, 1986a; Samitz 1970; Shrivastava et al. 2002; Suzuki and Fukuda 1990; Wiegand et al. 1984; Zhitkovich 2005).

Analysis of the urine of workers occupationally exposed to chromium(VI) indicates that chromium is excreted in the trivalent form, which is consistent with *in vivo* reduction of chromium(VI) to chromium(III) (Cavalleri and Minoia 1985; Minoia and Cavalleri 1988). Oral studies in humans and animals indicate that most of the chromium(VI) or chromium(III) ingested is excreted in the feces (Bunker et al. 1984; Donaldson and Barreras 1966; Donaldson et al. 1984; Henderson et al. 1979; Sayato et al. 1980), consistent with the poor gastrointestinal absorption of chromium. After dermal exposure of humans and animals, chromium can be found in the urine and feces (Brieger 1920; Wahlberg and Skog 1965). Chromium has been detected in hair and fingernails of the general population of several countries (Takagi et al. 1986, 1988) and in the breast milk of nursing mothers (Casey and Hambidge 1984), indicating these media as routes of excretion. Data regarding excretion after exposure of animals to chromium(VI) or chromium(III) by other routes indicated that excretion occurs rapidly, and primarily via the kidneys, once chromium(VI) is reduced (Gregus and Klaassen 1986; Yamaguchi et al. 1983). Thus, absorption, distribution, and excretion of chromium have been studied extensively. Additional studies









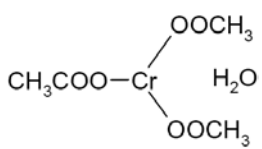
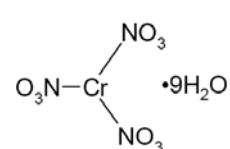
3. HEALTH EFFECTS

This page is intentionally blank.



## 4. CHEMICAL AND PHYSICAL INFORMATION

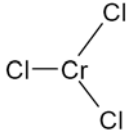
**Table 4-1. Chemical Identity of Chromium and Compounds**

Characteristic	Information		
Chemical name	Chromium(0)	Chromium(III) acetate, monohydrate	Chromium(III) nitrate, nonahydrate
Synonym(s)	Chrome; Chrom (German); Chrome (French)	Acetic acid, chromium salt, hydrate; chromic acetate, hydrate	Nitric acid, chromium (III) salt, nonahydrate; chromium nitrate, nonahydrate
Registered trade name(s)	Chrome	No data	No data
Chemical formula	Cr	$\text{Cr}(\text{CH}_3\text{COO})_3 \cdot \text{H}_2\text{O}$	$\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$
Chemical structure	Cr		
Identification numbers:			
CAS registry	7440-47-3	25013-82-5	7789-02-8
NIOSH RTECS	GB420000	AG3053333	GB6300000
EPA hazardous waste	D007	No data	No data
OHM/TADS	7216647	No data	No data
DOT/UN/NA/IMDG shipping	Not assigned	No data	No data
HSDB	910	No data	No data
NCI	Not assigned	No data	No data



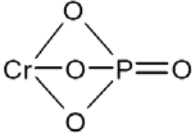
## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-1. Chemical Identity of Chromium and Compounds**

Characteristic	Information		
Chemical name	Chromium(III) chloride	Chromium(III) chloride, hexahydrate	Ferrochromite (Chromium[III])
Synonym(s)	Chromium trichloride	Hexaaquachromium (III) chloride	Chromite
Registered trade name(s)	C177295	No data	No data
Chemical formula	CrCl <sub>3</sub>	Cr(Cl) <sub>3</sub> •6H <sub>2</sub> O	FeCr <sub>2</sub> O <sub>4</sub>
Chemical structure		Cr[Cl <sub>2</sub> (H <sub>2</sub> O) <sub>4</sub> ]Cl•2H <sub>2</sub> O	FeOCr <sub>2</sub> O <sub>3</sub>
Identification numbers:			
CAS registry	10025-73-7	10060-12-5	1308-31-2
NIOSH RTECS	GB5425000	GB5450000	GB4000000
EPA hazardous waste	No data	No data	D007
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data
HSDB	No data	No data	2963
NCI	No data	No data	No data

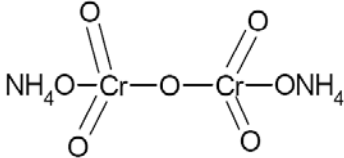
## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-1. Chemical Identity of Chromium and Compounds**

Characteristic	Information		
Chemical name	Chromium(III) oxide	Chromium(III) phosphate	Chromium(III) sulfate
Synonym(s)	Chromium sesquioxide; dichromium trioxide	Chromumorthophosphate; phosphoric acid, chromium (III) salt	Sulfuric acid, chromium (III) salt
Registered trade name(s)	No data	Amaudon's Green	Chromitan B
Chemical formula	Cr <sub>2</sub> O <sub>3</sub>	CrPO <sub>4</sub>	Cr <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>
Chemical structure	O=Cr—O—Cr=O		SO <sub>4</sub> =Cr—SO <sub>4</sub> —Cr=SO <sub>4</sub>
Identification numbers:			
CAS registry	1308-38-9	7789-04-0	10101-53-8
NIOSH RTECS	GB6475000	GB6840000	GB7200000
EPA hazardous waste	D007	No data	D0007
OHM/TADS	Not assigned	No data	7800052
DOT/UN/NA/IMDG shipping	Not assigned	No data	Not assigned
HSDB	1619	No data	2543
NCI	Not assigned	No data	Not assigned

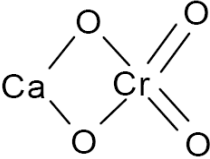
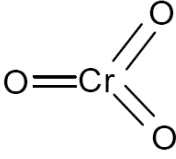
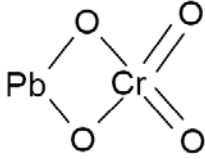
## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-1. Chemical Identity of Chromium and Compounds**

Characteristic	Information		
Chemical name	Sodium chromite (Chromium[III])	Chromium(IV) oxide	Ammonium dichromate (Chromium[VI])
Synonym(s)	No data	Chromium dioxide	Chromic acid, diamonium salt
Registered trade name(s)	No data	No data	No data
Chemical formula	NaCrO <sub>2</sub>	CrO <sub>2</sub>	(NH <sub>4</sub> ) <sub>2</sub> Cr <sub>2</sub> O <sub>7</sub>
Chemical structure	NaO-Cr=O	O=Cr=O	
Identification numbers:			
CAS registry	12314-42-0	12018-01-8	7789-09-5
NIOSH RTECS	No data	GB6400000	HX7650000
EPA hazardous waste	No data	D007	Not assigned
OHM/TADS	No data	No data	7217321
DOT/UN/NA/IMDG shipping	No data	No data	UN1439; IM05.1
HSDB	No data	1620	481
NCI	No data	No data	No data

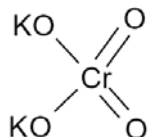
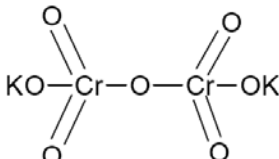
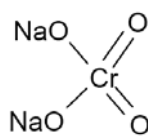
## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-1. Chemical Identity of Chromium and Compounds**

Characteristic	Information		
Chemical name	Calcium chromate (Chromium[VI])	Chromium(VI) trioxide	Lead chromate (Chromium[VI])
Synonym(s)	Chromic acid, calcium salt	Chromic acid, chromium anhydride	Chromic acid, lead salt
Registered trade name(s)	Calcium Chrome Yellow	No data	Chrome Yellow G
Chemical formula	CaCrO <sub>4</sub>	CrO <sub>3</sub>	PbCrO <sub>4</sub>
Chemical structure			
Identification numbers:			
CAS registry	13765-19-0	1333-82-0	7758-97-6
NIOSH RTECS	GB2750000	GB6650000	GB2975000
EPA hazardous waste	U032; D007	D007	D007; D008
OHM/TADS	7800051	Not assigned	Not assigned
DOT/UN/NA/IMDG shipping	NA9096	YB1463/UN15.1; IM05.1	Not assigned
HSDB	248	518; NA1463	1650
NCI	Not assigned	UN1463	Not assigned

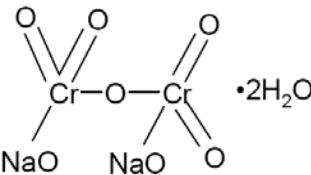
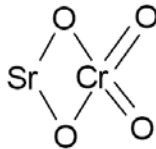
## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-1. Chemical Identity of Chromium and Compounds**

Characteristic	Information		
Chemical name	Potassium chromate (Chromium[VI])	Potassium dichromate (Chromium[VI])	Sodium chromate (Chromium[VI])
Synonym(s)	Chromic acid, dipotassium salt	Chromic acid, dipotassium salt	Chromic acid, disodium salt
Registered trade name(s)	No data	No data	Caswell No. 757
Chemical formula	$K_2CrO_4$	$K_2Cr_2O_7$	$Na_2CrO_4$
Chemical structure			
Identification numbers:			
CAS registry	7789-00-6	7778-50-9	7775-11-3
NIOSH RTECS	GB2940000	HX7680000	GB2955000
EPA hazardous waste	No data	No data	D007
OHM/TADS	7217277	7217278	7216891
DOT/UN/NA/IMDG shipping	NA9142	NA1479; IM09.0	No data
HSDB	1249	1238	2962
NCI	Not assigned	Not assigned	Not assigned

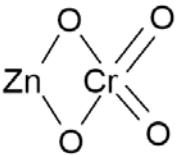
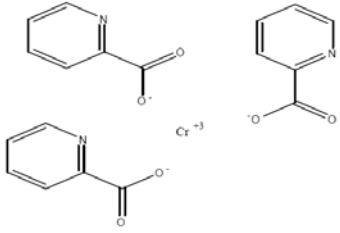
## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-1. Chemical Identity of Chromium and Compounds**

Characteristic	Information	
Chemical name	Sodium dichromate, dihydrate (Chromium[VI])	Strontium chromate (Chromium[VI])
Synonym(s)	Chromic acid, disodium salt; dihydrate	Chromic acid, strontium salt
Registered trade name(s)	No data	No data
Chemical formula	$\text{NaCr}_2\text{O}_7 \cdot 2\text{H}_2\text{O}$	$\text{SrCrO}_4$
Chemical structure		
Identification numbers:		
CAS registry	7789-12-0	7789-06-2
NIOSH RTECS	HX7750000	GB3240000
EPA hazardous waste	No data	D007
OHM/TADS	No data	780058
DOT/UN/NA/IMDG shipping	No data	NA9149
HSDB	No data	2546
NCI	No data	Not assigned

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-1. Chemical Identity of Chromium and Compounds**

Characteristic	Information	
Chemical name	Zinc chromate (Chromium[VI])	Chromium(III) picolinate
Synonym(s)	Chromic acid, zinc salt	CrPic; Chromium 2-pyridinecarboxylate; Chromium; tris(picolinato)-; Picolinic acid; chromium salt
Registered trade name(s)	CI Pigment Yellow	No data
Chemical formula	ZnCrO <sub>4</sub>	C <sub>18</sub> H <sub>12</sub> CrN <sub>3</sub> O <sub>6</sub>
Chemical structure		
Identification numbers:		
CAS registry	13530-65-9	14639-25-9
NIOSH RTECS	GB3290000	No data
EPA hazardous waste	D007	No data
OHM/TADS	7217401	No data
DOT/UN/NA/IMDG shipping	Not assigned	No data
HSDB	6188	No data
NCI	Not assigned	No data

Sources: HSDB 2008; NIOSH 2005

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; 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

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-2. Physical and Chemical Properties of Chromium and Compounds**

Property	Chromium	Chromium(III) acetate, monohydrate	Chromium(III) nitrate, nonahydrate	Chromium(III) chloride
Molecular weight	51.996	229.13	400.15	158.35
Color	Steel-gray	Gray-green or bluish-green	Purple or violet	Violet or purple
Physical state	Solid	Solid	Solid	Solid
Melting point	1,90±10 °C	No data	60 °C	≈1,150 °C
Boiling point	2,642 °C	No data	Decomposes at 100 °C	Decomposes at 1,300 °C
Density at 20 °C	7.14 (28 °C) <sup>a</sup>	No data	No data	2.87 (25 °C) <sup>a</sup>
Odor	odorless	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 20 °C	Insoluble	Soluble	Soluble	Slightly soluble in hot water
Organic solvents	Insoluble in common organic solvents	45.4 g/L in methanol (15 °C); 2 g/L in acetone (15 °C)	Soluble in ethanol and acetone	Insoluble in cold water, acetone, methanol, and ether
Partition coefficients:				
Log K <sub>ow</sub>	Not applicable	Not applicable	Not applicable	Not applicable
Log K <sub>oc</sub>	Not applicable	Not applicable	Not applicable	Not applicable
Vapor pressure at 20 °C	1 mmHg (1,616 °C)	No data	No data	No data
Henry's law constant at 25 °C	Not applicable	Not applicable	Not applicable	Not applicable
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data



## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-2. Physical and Chemical Properties of Chromium and Compounds**

Property	Chromium(III) chloride, hexahydrate	Ferrocromite (Chromium[III])	Chromium(III) oxide	Chromium(III) phosphate
Molecular weight	266.45	223.84	151.99	146.97
Color	Violet	Brown-black	Green	Gray-brown to black <sup>d</sup>
Physical state	Solid	Solid	Solid	Solid
Melting point	83 °C	No data	2,435 °C	>1,800 °C
Boiling point	No data	No data	3,000 °C	No data
Density at 20 °C	1.76 <sup>b</sup>	4.97 (20 °C)	5.22 (25 °C) <sup>b</sup>	2.94 (32.5 °C) <sup>a,c</sup>
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 20 °C	58.5 g/100 cc at 25 °C	Insoluble	Insoluble	Insoluble <sup>c</sup>
Organic solvents	Soluble in ethanol	No data	Insoluble in ethanol	Insoluble in alcohol, acetone
Partition coefficients:				
Log K <sub>ow</sub>	No data	Not applicable	Not applicable	Not applicable
Log K <sub>oc</sub>	No data	Not applicable	Not applicable	Not applicable
Vapor pressure at 20 °C	No data	No data	No data	No data
Henry's law constant at 25 °C	No data	Not applicable	Not applicable	Not applicable
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-2. Physical and Chemical Properties of Chromium and Compounds**

Property	Chromium(III) sulfate	Sodium chromite (Chromium[III])	Chromium(IV) oxide	Ammonium dichromate (Chromium[IV])
Molecular weight	392.18	106.98	83.99	252.07
Color	Violet, red, peach	No data	Brown-black	Orange
Physical state	Solid	No data	Solid	Solid
Melting point	No data	No data	Decomposes at 300 °C	Decomposes at 180 °C
Boiling point	No data	No data	Not applicable	Not applicable
Density at 20 °C	3.012	No data	No data	2.15 (25 °C) <sup>a</sup>
Odor	No data	No data	No data	odorless
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 20 °C	Insoluble	No data	Insoluble	In water (wt/wt): 15.5% (0 °C); 26.67% (20 °C); 36.99% (40 °C); 46.14% (60 °C); 54.20% (80 °C)
Organic solvents	soluble in alcohols	No data	No data	Soluble in alcohols, insoluble in acetone
Partition coefficients:				
Log K <sub>ow</sub>	Not applicable	Not applicable	Not applicable	Not applicable
Log K <sub>oc</sub>	Not applicable	Not applicable	Not applicable	Not applicable
Vapor pressure at 20 °C	No data	No data	No data	No data
Henry's law constant at 25 °C	Not applicable	Not applicable	Not applicable	Not applicable
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-2. Physical and Chemical Properties of Chromium and Compounds**

Property	Calcium chromate (Chromium[VI])	Chromium(VI) trioxide	Lead chromate (Chromium[VI])	Potassium chromate (Chromium[VI])
Molecular weight	156.07	99.99	323.19	194.19
Color	Yellow	Red	Yellow	Yellow
Physical state	Solid	Solid	Solid	Solid
Melting point	No data	197 °C	844 °C	975 °C
Boiling point	No data	Decomposes	Decomposes	No data
Density at 20 °C	2.89 <sup>b</sup>	2.70 (25 °C)	6.12 (15 °C)	2.732 (18 °C)
Odor	No data	Odorless	No data	Odorless
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 20 °C	2.23 g/100 mL	61.7 g/100 cc at 0 °C	5.8 µg/100 mL	62.9 g/100 at 20 °C
Organic solvents	No data	Soluble in ethanol, ethyl ether, sulfuric and nitric acids	Soluble 0.2 mg/l water	62.9 G/100 cc water (20 °C)
		Soluble 61.7 g/100 cc water (0 °C)	Insoluble in acetic acid; soluble in dilute nitric acid and in solution of fixed alkali hydroxides	79.2 g/100 cc water (100 °C)
		67.45 g/100 cc water (100 °C)	Soluble in acid, insoluble in ammonia	Insoluble in alcohol
		167.299 lb/100 lb water (70 °F)		
		Soluble in acetic acid and acetone		
Partition coefficients:				
Log K <sub>ow</sub>	Not applicable	Not applicable	Not applicable	Not applicable
Log K <sub>oc</sub>	Not applicable	Not applicable	Not applicable	Not applicable
Vapor pressure at 20 °C	No data	No data	No data	0
Henry's law constant at 25 °C	Not applicable	Not applicable	Not applicable	Not applicable
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-2. Physical and Chemical Properties of Chromium and Compounds**

Property	Potassium dichromate (Chromium[VI])	Sodium chromate (Chromium[VI])	Sodium dichromate, dihydrate (Chromium[VI])
Molecular weight	294.18	161.97	298.00
Color	Red	Yellow	Red
Physical state	Solid	Solid	Solid
Melting point	398 °C	792 °C	356.7 °C
Boiling point	Decomposes at 500 °C	No data	Decomposes at 400 °C
Density at 20 °C	2.676 (25 °C)	2.710–2.736 <sup>b</sup>	2.52 (13 °C)
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 at 20 °C	4.9 g/100 cc at 0 °C	87.3 g/100 cc at 30 °C	230 g/100 cc at 0 °C
Organic solvents	Insoluble in ethanol and acetone	Soluble in methanol	Insoluble in ethanol
Partition coefficients:			
Log K <sub>ow</sub>	Not applicable	Not applicable	Not applicable
Log K <sub>oc</sub>	Not applicable	Not applicable	Not applicable
Vapor pressure at 20 °C	No data	No data	No data
Henry's law constant at 25 °C	Not applicable	Not applicable	Not applicable
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

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-2. Physical and Chemical Properties of Chromium and Compounds**

Property	Strontium chromate (Chromium[VI])	Zinc chromate (Chromium[VI])	Chromium(III) picolinate
Molecular weight	203.61	181.97	418.3 <sup>c</sup>
Color	Yellow	Lemon-yellow	Ruby red <sup>d</sup>
Physical state	Solid	Solid	Crystal <sup>d</sup>
Melting point	No data	No data	No data
Boiling point	No data	No data	No data
Density at 20 °C	3.895 (15 °C)	3.40 <sup>b</sup>	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 at 20 °C	0.12 g/100 cc at 15 °C	Insoluble	1 ppm at 25 °C <sup>d</sup>
Organic solvents	Soluble in acetyl acetone	Insoluble in acetone	>6 g/L (DMSO) <sup>d</sup>
Partition coefficients:			
Log K <sub>ow</sub>	Not applicable	Not applicable	1.753 <sup>e</sup>
Log K <sub>oc</sub>	Not applicable	Not applicable	No data
Vapor pressure at 20 °C	No data	No data	No data
Henry's law constant at 25 °C	Not applicable	Not applicable	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

<sup>a</sup>Temperature at which the densities were measured has been given only when such data are available

<sup>b</sup>Temperature at which density was measured was not specified.

<sup>c</sup>O'Neil et al. 2006

<sup>d</sup>Broadhurst et al. 1997

<sup>e</sup>Chakov et al. 1999

DMSO=dimethylsulfoxide

## 4. CHEMICAL AND PHYSICAL INFORMATION

In humans, chromium(III) is an essential nutrient that may play a role in glucose, fat, and protein metabolism possibly by potentiating the action of insulin. However, there is some emerging controversy whether chromium(III) is essential and more work has been suggested to elucidate its mechanism of action. Chromium picolinate, a trivalent form of chromium complexed with picolinic acid, is used as a dietary supplement, because it is claimed to speed metabolism and may have anti-diabetic effects (Broadhurst et al. 1997). However, there still remains controversy over the use of chromium(III) in diabetes, and several researchers claim no demonstrated effects of chromium(III) on diabetes or insulin resistance (Althuis et al. 2002). Currently, the mechanism of transport and absorption of chromium picolinate has not been determined, although spectroscopic analysis has shown that chromium picolinate is a very stable complex in the body and its absorption properties may be due to its ability to cross membranes (Chakov et al. 1999).

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

### 5.1 PRODUCTION

Tables 5-1 and 5-2 list the facilities in each state that manufacture or process chromium, the intended use, and the range of maximum amounts of chromium that are stored on site. There are currently 3,567 facilities that produce or process chromium in the United States. The data listed in Tables 5-1 and 5-2 are derived from the Toxics Release Inventory (TRI) (TRI06 2008). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list.

Chromium metal is commercially produced in the United States by the reduction of chromite ore with carbon, aluminum, or silicon, and subsequent purification. Sodium chromate and dichromate are produced by roasting chromite ore with soda ash. Most other chromium compounds are produced from sodium chromate and dichromate (Hartford 1979; Papp and Lipin 2001; Westbrook 1979). For example, basic chromic sulfate ( $\text{Cr}(\text{OH})\text{SO}_4$ ), commonly used in tanning, is commercially produced by the reduction of sodium dichromate with organic compounds (e.g., molasses) in the presence of sulfuric acid or by the reduction of dichromate with sulfur dioxide. Lead chromate, commonly used as a pigment, is produced by the reaction of sodium chromate with lead nitrate or by reaction of lead monoxide with chromic acid solution (IARC 1990).

The major manufacturers of chromium compounds in 2007 are summarized in Table 5-3 (SRI 2007). Tables 5-1 and 5-2 report the number of facilities in each state that manufacture and process chromium, the intended use of the products, and the range of maximum amounts of chromium products that are stored on site. The data reported in Tables 5-1 and 5-2 are derived from TRI of EPA (TRI06 2008). The TRI data should be used with caution since only certain types of facilities were required to report. Hence, this is not an exhaustive list.

### 5.2 IMPORT/EXPORT

Chromite ore and foundry sand; chromium chemicals, ferroalloys, and metal; and stainless steel represent the bulk of the market for chromium. In 2006, the United States produced chromium ferroalloys, metal, chemicals, and stainless steel. The United States is a major producer of the end products of chromium,

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

**Table 5-1. Facilities that Produce, Process, or Use Chromium**

State <sup>a</sup>	Number of facilities	Minimum amount on site in pounds <sup>b</sup>	Maximum amount on site in pounds <sup>b</sup>	Activities and uses <sup>c</sup>
AK	2	10,000	999,999	12
AL	94	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	52	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AZ	56	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CA	174	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	48	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
CT	72	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
DE	12	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12
FL	45	0	499,999,999	1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 13, 14
GA	88	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
HI	1	10,000	99,999	8
IA	82	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
ID	14	0	999,999	1, 3, 5, 8, 9, 10, 12, 13
IL	138	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	157	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	47	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KY	98	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	70	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
MA	66	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MD	48	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ME	16	0	9,999,999	1, 2, 3, 8, 12
MI	162	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	74	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	67	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MS	34	0	499,999,999	1, 2, 3, 5, 7, 8, 10, 11, 12
MT	12	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 14
NC	79	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	14	1,000	999,999	1, 2, 3, 5, 7, 8, 9, 12, 13
NE	35	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
NH	21	0	49,999,999	3, 6, 7, 8, 9, 11, 12
NJ	99	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NM	17	100	999,999	2, 3, 6, 7, 8, 9, 10, 11, 12
NV	41	100	999,999	1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NY	118	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OH	229	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	83	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OR	68	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PA	238	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14



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

**Table 5-1. Facilities that Produce, Process, or Use Chromium**

State <sup>a</sup>	Number of facilities	Minimum amount on site in pounds <sup>b</sup>	Maximum amount on site in pounds <sup>b</sup>	Activities and uses <sup>c</sup>
PR	11	0	99,999,999	1, 2, 3, 5, 8, 9, 11, 12
RI	18	0	999,999	1, 2, 3, 6, 7, 8, 9, 11, 12
SC	97	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SD	15	100	999,999	1, 5, 7, 8, 9, 11, 12, 13, 14
TN	101	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	189	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	54	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	61	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VT	14	100	999,999	2, 3, 4, 6, 8, 9, 11
WA	64	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WI	123	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	40	100	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
WY	9	0	99,999	1, 8, 9, 11, 12, 13

aPost office state abbreviations used

bAmounts on site reported by facilities in each state

cActivities/Uses:

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

Source: TRI06 2008 (Data are from 2006)

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

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

State <sup>a</sup>	Number of facilities	Minimum amount on site in pounds <sup>b</sup>	Maximum amount on site in pounds <sup>b</sup>	Activities and uses <sup>c</sup>
AK	12	10,000	9,999,999	1, 2, 3, 5, 7, 8, 10, 11, 12, 13, 14
AL	125	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	73	0	99,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
AZ	79	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CA	185	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	31	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
CT	58	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
DE	29	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
FL	71	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	119	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
HI	9	1,000	999,999	7, 8, 10, 11
IA	62	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ID	23	0	49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IL	219	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	191	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	64	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KY	107	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	75	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MA	67	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MD	70	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ME	27	100	499,999,999	1, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MI	196	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	71	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	91	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MS	69	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MT	17	100	999,999	1, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
NC	119	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	14	1,000	999,999	1, 3, 5, 7, 8, 9, 10, 11, 12, 13, 14
NE	37	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
NH	16	0	99,999	1, 4, 5, 7, 8, 9, 10, 11
NJ	121	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NM	32	100	10,000,000,000	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
NV	40	100	499,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NY	140	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OH	303	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	59	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OR	59	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
PA	272	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

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

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

State <sup>a</sup>	Number of facilities	Minimum amount on site in pounds <sup>b</sup>	Maximum amount on site in pounds <sup>b</sup>	Activities and uses <sup>c</sup>
PR	22	0	9,999,999	1, 2, 3, 5, 7, 8, 10, 11, 12, 13, 14
RI	20	0	999,999	2, 3, 4, 7, 8, 9, 12
SC	103	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SD	11	100	99,999	1, 2, 3, 5, 6, 7, 8, 9, 11, 13
TN	118	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	279	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	62	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	73	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VT	8	100	99,999	2, 3, 7, 8, 10, 11
WA	72	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
WI	127	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	74	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
WY	20	0	9,999,999	1, 2, 3, 4, 5, 7, 9, 11, 12, 13, 14

<sup>a</sup>Post office state abbreviations used

<sup>b</sup>Amounts on site reported by facilities in each state

<sup>c</sup>Activities/Uses:

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

Source: TRI06 2008 (Data are from 2006)

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

**Table 5-3. Major Manufacturers of Chromium Compounds in 2007**

Chemical	Manufacturer	Location
Chromic anhydride	Johnson Matthey, Inc.; Alfa Aesar	Ward Hill, Massachusetts
Chromic hydrate	Elementis Chromium LP	Corpus Christi, Texas
Chromic sulfate	Blue Grass Chemical Specialties, LLC Elementis LTP L.P.	New Albany, Indiana Amarillo, Texas Dakota City, Nebraska Milwaukee, Wisconsin
Chromium(III) acetate	Johnson Matthey, Inc.; Alfa Aesar	Ward Hill, Massachusetts
	Blue Grass Chemical Specialties, LLC	New Albany, Indiana
	McGean-Rohco, Inc.; McGean Specialty Chemical Division	Cleveland, Ohio
Chromium(III) acetylacetonate	The Shepherd Chemical Company	Cincinnati, Ohio
	MacKenzie Company The Shepherd Chemical Company	Bush, Louisiana Cincinnati, Ohio
Chromium boride	CERAC, Inc. Johnson Matthey, Inc.; Alfa Aesar	Milwaukee, Wisconsin Ward Hill, Massachusetts
Chromium carbonyl	Strem Chemicals Incorporated	Newburyport, Massachusetts
	McGean-Rohco, Inc.; McGean Specialty Chemicals Division	Cleveland, Ohio
Chromium(III) chloride	Blue Grass Chemical Specialties, LLC	New Albany, Indiana
	McGean-Rohco, Inc.; McGean Specialty Chemicals Division	Cleveland, Ohio
Chromium diboride	Johnson Matthey, Inc.; Alfa Aesar	Ward Hill, Massachusetts
Chromium difluoride	Atotech USA, Inc.	Rock Hill, South Carolina
Chromium 2-ethylhexanoate	OM Group, Inc.	Franklin, Pennsylvania
	The Shepherd Chemical Company	Cincinnati, Ohio
Chromium fluoride	Atotech USA	Rock Hill, South Carolina
Chromium hexacarbonyl	Strem Chemicals Incorporated	Newburyport, Massachusetts
Chromium hydroxide	Elementis Chromium LP	Corpus Christi, Texas
Chromium(III) hydroxide	Elementis Chromium LP	Corpus Christi, Texas
Chromium hydroxyl diacetate	McGean-Rohco, Inc.; McGean Specialty Chemicals Division	Cleveland, Ohio
Chromium hydroxyl dichloride	McGean-Rohco, Inc.; McGean Specialty Chemicals Division	Cleveland, Ohio
Chromium naphthenate	OM Group, Inc.	Franklin, Pennsylvania
Chromium nitrate	Blue Grass Chemical Specialties, LLC	New Albany, Indiana
	McGean-Rohco Inc.; McGean Specialty Chemicals Division	Cleveland, Ohio
	The Shepherd Chemical Company	Cincinnati, Ohio
Chromium octenoate	OM Group, Inc.	Franklin, Pennsylvania
	The Shepherd Chemical Company	Cincinnati, Ohio
Chromium octoate	OM Group, Inc.	Franklin, Pennsylvania
	The Shepherd Chemical Company	Cincinnati, Ohio
Chromium oxide	Elementis Chromium LP	Corpus Christi, Texas

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

**Table 5-3. Major Manufacturers of Chromium Compounds in 2007**

Chemical	Manufacturer	Location
Chromium potassium sulfate	McGean-Rohco, Inc.; McGean Specialty Chemicals Division	Cleveland, Ohio
Chromium-silicon monoxide	CERAC, Inc.	Milwaukee, Wisconsin
Chromium(III) sulfate	Blue Grass Chemical Specialties, LLC Elementis LTP L.P.	New Albany, Indiana Amarillo, Texas Dakota City, Nebraska Milwaukee, Wisconsin
	Johnson Mathey, Inc.; Alfa Aesar	Ward Hill, Massachusetts
Chromotropic acid, disodium salt	Johnson-Mathhey, Inc.; Alfa Aesar	Ward Hill, Massachusetts

Source: SRI 2007

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

which include chromium chemicals, metal, and stainless steel, but until recently, the United States had not mined chromium (Stokinger 1981; USGS 2008b). Oregon Resources Corporation (ORC), a subsidiary of Industrial Minerals Corporation (Australia), extracted bulk samples of chromite ore at its surface mine in Coos County, Oregon. ORC developed its material beneficiation process to recover chromite, garnet, and zircon minerals with production expected to start in 2008 (IMC 2007). Although chromium is currently mined in Oregon, the United States receives the majority of chromium ores from other countries. From 2003 to 2006, chromium contained in chromite ore and chromium ferroalloys and metal were imported from South Africa (34%), Kazakhstan (18%), Russia (7%), Zimbabwe (6%), and other (35%) (USGS 2008b).

U.S. imports and exports are summarized in Table 5-4 (USGS 2008a).

### 5.3 USE

The metallurgical, refractory, and chemical industries are the fundamental users of chromium. In the metallurgical industry, chromium is used to produce stainless steels, alloy cast irons, nonferrous alloys, and other miscellaneous materials. In 1988, the U.S. chemical and metallurgical industries accounted for 83.9% and the refractory industry for 16.1% of the total domestic consumption of chromite (USDI 1988a). The stainless steel industry is the leading consumer of chromium materials. A significant amount of chromium is imported and exported in stainless steel mill products and scrap, with ferrochromiums as the main components used by the metallurgical industry. Typical weight percent of chromium in stainless steel and chromium alloys ranges from 11.5 to 30%. In the refractory industry, chromium is a component in chrome and chrome-magnesite, magnesite-chrome bricks, and granular chrome-bearing and granular chromite, which are used as linings for high temperature industrial furnaces. In the chemical industry, both chromium(III) and chromium(VI) are used primarily in pigments. Other uses include chromium(VI) in metal finishing, chromium(III) in leather tanning, and chromium(VI) in wood preservatives. Table 5-5 lists the approximate distribution of use for chromium chemicals in the major applications in the United States and Western world in 1996 with a comparison to use in the United States for 1951 (Barnhart 1997). Smaller amounts of chromium are used as catalysts and in miscellaneous applications, such as drilling muds, chemical manufacturing, textiles, toners for copying machines, magnetic tapes, and dietary supplements (Carlton 2003; CMR 1988a, 1988b; Davis and Vincent 1997; EPA 1984a; IARC 1990; Papp and Lipin 2001; Radivojevic and Cooper 2008; USDI 1988a). Chromium alloys are also used in metal joint prostheses (Sunderman et al. 1989). Chromium picolinate, a trivalent form of chromium complexed with picolinic acid, is used as a dietary supplement,

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

**Table 5-4. U.S. Chromium Imports and Exports**

Year	Imports (thousands of metric tons gross weight)	Exports (in thousands of metric tons gross weight)
2003	441	188
2004	489	171
2005	503	220
2006	520	212
2007	510	210

Source: USGS 2008a

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

**Table 5-5. Historical Use of Chromium in the United States and Western World**

Use	1996 Western world	1996 United States	1951 United States
Wood preservation	15%	52%	2%
Leather tanning	40%	13%	20%
Metals finishing	17%	13%	25%
Pigments	15%	12%	35%
Refractory	3%	3%	1%
Other	10%	7%	17%

Source: Barnhart 1997



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

with the claim that it reduces symptoms of type II diabetes and hypoglycemia (Broadhurst et al. 1997), although a recent meta-review concludes that the results are still inconclusive (Althuis et al. 2002).

#### 5.4 DISPOSAL

Information regarding the disposal of finished products and wastes produced during the manufacturing of consumable items that contain chromium is limited. In 1987, 25% of the chromium demand in the United States was supplied by recycled stainless steel scrap. Although a large portion of the chromium wastes from plating operations is also recovered, large amounts of chromium-containing waste waters from plating, finishing, and textile industries are discharged into surface waters. A substantial amount of chromium enters sewage treatment plants from industrial and residential sources (Klein et al. 1974; TRI06 2008). Presently, slag from roasting/leaching of chromite ore is one of the materials excluded from regulation under the Resource Conservation and Recovery Act by the 1980 Bevill Amendment. However, emission control dust or sludge from ferrochromium and ferrochromium-silicon production is listed as hazardous waste by EPA (1988b). Land filling appears to be the most important method for the disposal of chromium wastes generated by chemical industries. Of the total chromium released in the environment by chemical industries, approximately 82.3% is released on land. An equally large amount of chromium waste is transferred off-site (see Section 5.2). It is anticipated that most of this off-site waste will be disposed of in landfills after proper treatment. It is important to convert chromium wastes into forms of chromium that have low mobilities in soils and low availabilities to plants and animals before land disposal. Chromium(III) oxide is one such form. Chromium in chemical industry wastes occurs predominantly in the hexavalent form. The treatment of chromium(VI) waste often involves reduction to chromium(III) and precipitation as the hydrous oxide with lime or caustic soda. Chromium(III) waste can also be converted into hydrous oxide or may be incinerated to form the oxide before land disposal. There is not much known about the disposal method of waste refractory materials used as lining for metallurgical furnaces or the disposal practices for the finished products containing chromium, such as chromium-containing pigments (Fishbein 1981; Komori et al. 1990a; NRCC 1976; Polprasert and Charnpratheep 1989; Westbrook 1979).

Chromium is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1995). Disposal of wastes containing chromium is controlled by a number of federal regulations (see Chapter 8).

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

This page is intentionally blank.

## 6. POTENTIAL FOR HUMAN EXPOSURE

### 6.1 OVERVIEW

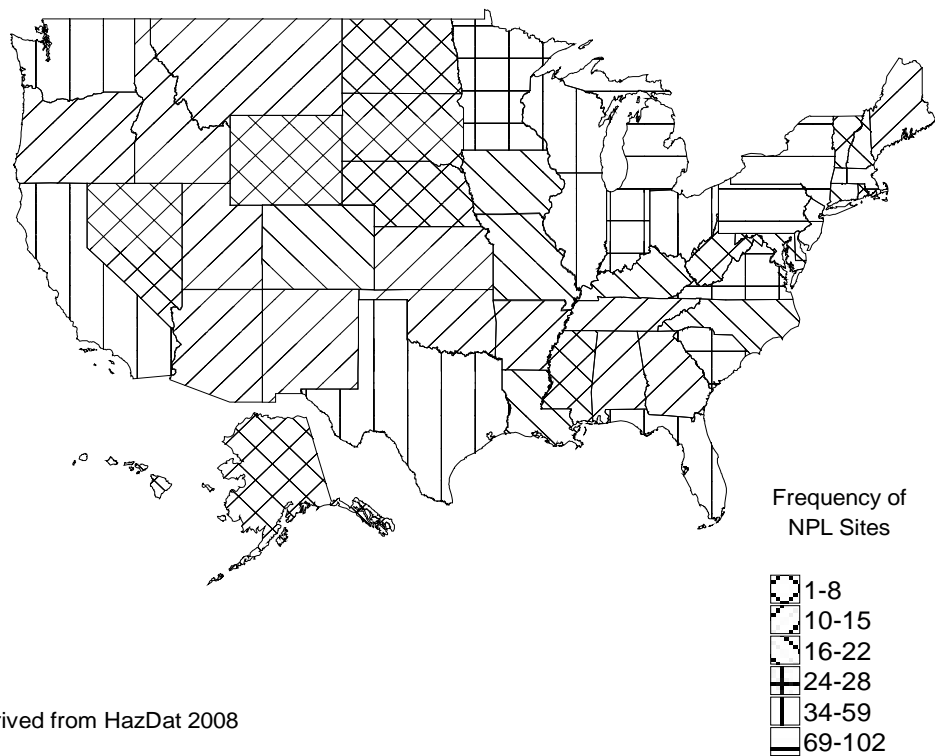
Chromium has been identified in at least 1,127 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2008). However, the number of sites evaluated for chromium is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 1,117 are located within the United States and 10 are located in the Commonwealth of Puerto Rico (not shown).

Human exposure to chromium occurs from both natural and anthropogenic sources. Chromium is present in the Earth's crust, with the main natural source of exposure being continental dust present in the environment (Barnhart 1997; Fishbein 1981; Pellerin and Booker 2000). Chromium is released into the environment in larger amounts as a result of human activities, which account for 60–70% of the total emissions of atmospheric chromium (Alimonti et al. 2000; Barceloux 1999; Seigneur and Constantinous 1995). This is indicated by the value of the enrichment factor (the enrichment factor relates the amount of chromium relative to an aluminum standard) of 3.5–8.1 (Dasch and Wolff 1989; Milford and Davidson 1985). Elements with enrichment factors >1 are assumed to have originated from anthropogenic sources (Schroeder et al. 1987). Of the estimated 2,700–2,900 tons of chromium emitted to the atmosphere annually from anthropogenic sources in the United States, approximately one-third is in the hexavalent form (EPA 1990b; Johnson et al. 2006). Industrial releases to the air, water, and soil are also potential sources of chromium exposure, and account for the majority of the anthropogenic releases (Johnson et al. 2006). The electroplating, leather tanning, and textile industries release large amounts of chromium to surface waters (Avudainayagam et al. 2003; Fishbein 1981; Johnson et al. 2006). Disposal of chromium-containing commercial products and coal ash from electric utilities and other industries are major sources of chromium releases into the soil (Barceloux 1999; Nriagu and Pacyna 1988). Solid waste and slag produced during chromate manufacturing processes when disposed of improperly in landfills can be potential sources of chromium exposure as well (Barceloux 1999; Kimbrough et al. 1999).

Chromium is primarily removed from the atmosphere by fallout and precipitation. The residence time of chromium in the atmosphere has not been directly measured, but by using copper as a model, it is expected to be <10 days (Nriagu 1979). The arithmetic mean concentrations of total chromium in the ambient air in United States, urban, suburban, and rural areas monitored during 1977–1984 ranged from

6. POTENTIAL FOR HUMAN EXPOSURE

**Figure 6-1. Frequency of NPL Sites with Chromium Contamination**



Derived from HazDat 2008

## 6. POTENTIAL FOR HUMAN EXPOSURE

5 to 525 ng/m<sup>3</sup>, with the vast majority of samples <100 ng/m<sup>3</sup> (EPA 1984a, 1990b). Ambient air in the United States usually contains very little chromium; at most measuring stations, the concentration was <300 ng/m<sup>3</sup> and median levels were <20 ng/m<sup>3</sup>. As a result of smoking, indoor air contaminated with chromium can be 10–400 times greater than outdoor air concentrations (WHO 2003).

Chromium in the aquatic phase occurs in the soluble state or as suspended solids adsorbed onto clayish materials, organics, or iron oxides. Most of the soluble chromium is present as chromium(VI) or as soluble chromium(III) complexes and generally accounts for a small percentage of the total. Soluble chromium(VI) may persist in some bodies of water, but will eventually be reduced to chromium(III) by organic matter or other reducing agents in water (Cary 1982; EPA 1984a; Lide 1998). The residence times of chromium (total) in lake water range from 4.6 to 18 years, with the majority of the chromium in lakes and rivers ultimately deposited in the sediments (Schmidt and Andren 1984). In the United States, chromium concentrations are up to 84 µg/L in surface water and 0.2–1 µg/L in rainwater (WHO 2003). Most drinking water supplies in the United States contain <5µg/L of chromium (WHO 2003). In ocean water, the mean chromium concentration is 0.3 µg/L (Cary 1982). In the United States, the groundwater concentration of chromium is generally low, with measurements in the range of 2–10 µg/L in shallow groundwater; levels as high as 50 µg/L have been reported in some supplies (WHO 2003).

Total chromium concentrations in U.S. soils range from 1 to 2,000 mg/kg, with a mean of 37.0 mg/kg (USGS 1984). Chromium(III) in soil is mostly present as insoluble carbonate and oxide of chromium(III); therefore, it will not be mobile in soil. The solubility of chromium(III) in soil and its mobility may increase due to the formation of soluble complexes with organic matter in soil, with a lower soil pH potentially facilitating complexation (Avudainayagam et al. 2003). Chromium has a low mobility for translocation from roots to the aboveground parts of plants (Calder 1988; Cary 1982; EPA 1984a, 1985a; King 1988; Stackhouse and Benson 1989).

A common area for exposure to chromium is from food sources. The typical chromium levels in most foods range from <10 to 1300 µg/kg, with the highest concentrations being found in meat, fish, fruits, and vegetables (WHO 2003). The general population is exposed to chromium by inhaling air, drinking water, or eating food or food supplements that contain chromium. However, the primary source of exposure for non-occupational workers to chromium comes from food sources, although drinking water can be a source of exposure when the levels are >25 µg/L (WHO 2003).

## 6. POTENTIAL FOR HUMAN EXPOSURE

Dermal exposure to chromium may also occur during the use of consumer products that contain chromium, such as wood treated with copper dichromate or chromated copper arsenate and leather tanned with chromic sulfate. In addition, people who reside in the vicinity of chromium waste disposal sites and chromium manufacturing and processing plants have a greater probability of elevated chromium exposure (Pellerin and Booker 2000).

Exposure to chromium for occupational groups can be two orders of magnitude higher than the exposure to the general population (Hemminki and Vainio 1984). Occupational exposure to chromium occurs mainly from chromate production, stainless steel production and welding, chrome plating, production of ferrochrome alloys, chrome pigment production and user industries, and from working in tanning industries (Pellerin and Booker 2000; Stern 1982)

## 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 2005). 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  $\geq 25,000$  pounds of any TRI chemical or otherwise uses  $>10,000$  pounds of a TRI chemical in a calendar year (EPA 2005).

### 6.2.1 Air

Estimated releases of 337,330 pounds of chromium to the atmosphere from 938 domestic manufacturing and processing facilities in 2006, accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). Estimated releases of 490,546 pounds of chromium compounds to the atmosphere from 1,521 domestic manufacturing and processing facilities in

## 6. POTENTIAL FOR HUMAN EXPOSURE

2006, accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). These releases are summarized in Tables 6-1 and 6-2.

Total chromium has been identified in air samples at 48 of 1,699 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2008).

Continental dust flux is the main natural source of chromium in the atmosphere; volcanic dust and gas flux are minor natural sources of chromium in the atmosphere (Fishbein 1981). Chromium is released into the atmosphere mainly by anthropogenic stationary point sources, including industrial, commercial, and residential fuel combustion, *via* the combustion of natural gas, oil, and coal (Kimbrough et al. 1999; Pacyn and Pacyn 2001; Seigneur and Constantinou 1995). Other important anthropogenic stationary point sources of chromium emission to the atmosphere are metal industries, such as chrome plating and steel production (EPA 1990b; Johnson et al. 2006; Pacyn and Pacyn 2001). Approximately one-third of the atmospheric releases of chromium are believed to be in the hexavalent form, chromium(VI) (Johnson et al. 2006). Other potentially small sources of atmospheric chromium emission are cement-producing plants (cement contains chromium), the wearing down of asbestos brake linings that contain chromium, incineration of municipal refuse and sewage sludge, and emission from chromium-based automotive catalytic converters. Emissions from cooling towers that previously used chromate chemicals as rust inhibitors are also atmospheric sources of chromium (EPA 1984b, 1990b; Fishbein 1981).

### 6.2.2 Water

Estimated releases of 114,852 pounds of chromium to surface water from 938 domestic manufacturing and processing facilities in 2006, accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). Estimated releases of 574,728 pounds of chromium compounds to surface water from 1,521 domestic manufacturing and processing facilities in 2006, accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008).

Total chromium has been identified in surface water and groundwater samples at 427 of 1,699 and 813 of 1,699 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2008).

## 6. POTENTIAL FOR HUMAN EXPOSURE

**Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Chromium<sup>a</sup>**

State <sup>c</sup>	RF <sup>d</sup>	Reported amounts released in pounds per year <sup>b</sup>							Total release	
		Air <sup>e</sup>	Water <sup>f</sup>	UI <sup>g</sup>	Land <sup>h</sup>	Other <sup>i</sup>	On-site <sup>j</sup>	Off-site <sup>k</sup>	On- and off-site	
AK	1	0	0	21,000	22,000	0	43,000	0	43,000	
AL	20	4,558	298	0	52,862	185,896	7,667	235,947	243,614	
AR	12	5,637	269	0	13,686	0	5,644	13,948	19,592	
AZ	12	163,323	32	0	532,831	11,705	688,637	19,253	707,891	
CA	39	1,430	493	0	79,064	6,434	46,152	41,270	87,422	
CO	6	21	27	0	32,156	27,070	32,039	27,235	59,274	
CT	13	139	1,617	0	47,929	14,315	194	63,806	64,000	
DE	2	5	0	0	364	0	5	364	369	
FL	15	1,955	59	0	134,519	722	48,148	89,107	137,255	
GA	20	1,765	372	0	57,841	2,012	7,127	54,863	61,990	
IA	23	4,049	709	0	38,226	92,627	4,476	131,135	135,611	
ID	2	56	0	0	334,455	0	334,511	0	334,511	
IL	48	5,578	21,374	0	77,246	16,042	5,964	114,277	120,241	
IN	57	15,780	5,443	0	2,043,519	85,506	17,947	2,132,301	2,150,248	
KS	11	1,895	1,013	0	3,173	4,800	2,370	8,511	10,881	
KY	30	8,287	1,255	0	141,687	15,575	9,129	157,674	166,803	
LA	19	2,455	115	0	17,611	5	4,985	15,200	20,185	
MA	21	1,765	413	0	11,206	21,137	4,000	30,522	34,522	
MD	1	258	15	0	0	250	258	265	523	
ME	5	144	1,123	0	102	405	154	1,620	1,774	
MI	37	12,336	1,149	0	90,611	10,492	13,929	100,658	114,587	
MN	8	1,758	54	0	5,866	1	1,758	5,921	7,679	
MO	24	7,789	5,731	0	9,668	559	8,312	15,435	23,747	
MS	12	7,045	527	0	20,851	250	7,067	21,607	28,673	
MT	2	32	0	0	687,248	0	687,280	0	687,280	
NC	22	1,199	123	0	19,368	68,337	1,306	87,722	89,028	
ND	2	22	6	0	4,953	0	24	4,957	4,981	
NE	7	1,072	517	0	74,072	2,450	1,072	77,039	78,111	
NH	3	90	8	0	253	18,567	90	18,829	18,919	
NJ	8	790	20	0	14,411	0	793	14,428	15,221	
NM	2	15	0	0	218,200	0	218,215	0	218,215	
NV	9	985	241	0	333,614	930	332,702	3,067	335,769	
NY	30	3,591	3,831	0	126,761	22,484	3,782	152,884	156,667	
OH	90	12,810	11,949	69	663,116	215,357	398,183	505,118	903,301	
OK	16	3,742	920	0	24,379	255	4,006	25,290	29,296	
OR	8	1,811	69	0	138,906	4	134,460	6,330	140,790	



## 6. POTENTIAL FOR HUMAN EXPOSURE

**Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Chromium<sup>a</sup>**

State <sup>c</sup>	RF <sup>d</sup>	Reported amounts released in pounds per year <sup>b</sup>							Total release	
		Air <sup>e</sup>	Water <sup>f</sup>	UI <sup>g</sup>	Land <sup>h</sup>	Other <sup>i</sup>	On-site <sup>j</sup>	Off-site <sup>k</sup>	On- and off-site	
PA	87	17,076	3,949	0	1,021,579	76,723	69,470	1,049,856	1,119,326	
PR	2	11,148	0	0	5	0	11,148	5	11,153	
RI	2	6	250	0	0	32	6	282	287	
SC	22	4,725	524	0	251,022	3,488	6,185	253,573	259,759	
SD	5	79	0	0	16,948	0	16,579	448	17,027	
TN	21	3,305	1,433	0	122,693	7,882	106,296	29,017	135,313	
TX	50	8,436	25,278	467,512	446,753	1,922	900,179	49,722	949,901	
UT	6	583	14	0	67,972	1,189	21,198	48,560	69,757	
VA	11	553	983	0	67,637	2,706	1,054	70,825	71,878	
VT	2	23	15	0	0	3,229	23	3,244	3,267	
WA	12	6,355	18,695	0	32,792	14,277	7,647	64,472	72,119	
WI	74	10,761	3,927	0	896,104	28,906	12,125	927,573	939,698	
WV	5	25	5	0	26,059	251	19,025	7,315	26,340	
WY	2	69	8	0	28,658	250	28,477	508	28,985	
<b>Total</b>	<b>938</b>	<b>337,330</b>	<b>114,852</b>	<b>488,581</b>	<b>9,050,976</b>	<b>965,042</b>	<b>4,274,796</b>	<b>6,681,985</b>	<b>10,956,781</b>	

<sup>a</sup>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.

<sup>b</sup>Data in TRI are maximum amounts released by each facility.

<sup>c</sup>Post office state abbreviations are used.

<sup>d</sup>Number of reporting facilities.

<sup>e</sup>The sum of fugitive and point source releases are included in releases to air by a given facility.

<sup>f</sup>Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

<sup>g</sup>Class I wells, Class II-V wells, and underground injection.

<sup>h</sup>Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.

<sup>i</sup>Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

<sup>j</sup>The sum of all releases of the chemical to air, land, water, and underground injection wells.

<sup>k</sup>Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI06 2008 (Data are from 2006)

## 6. POTENTIAL FOR HUMAN EXPOSURE

**Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Chromium Compounds<sup>a</sup>**

State <sup>c</sup>	RF <sup>d</sup>	Reported amounts released in pounds per year <sup>b</sup>							Total release	
		Air <sup>e</sup>	Water <sup>f</sup>	UI <sup>g</sup>	Land <sup>h</sup>	Other <sup>i</sup>	On-site <sup>j</sup>	Off-site <sup>k</sup>	On- and off-site	
AK	3	5	2	0	1,319,096	0	1,319,103	0	1,319,103	
AL	47	13,993	3,753	0	1,286,925	130,962	1,209,640	225,993	1,435,633	
AR	26	2,962	1,237	0	52,072	196,825	43,413	209,683	253,096	
AZ	19	3,337	1,848	0	2,744,366	11,427	2,742,448	18,530	2,760,978	
CA	59	1,521	43,301	1,467	368,099	109,292	269,108	254,573	523,681	
CO	12	550	3	0	68,120	309	45,180	23,802	68,982	
CT	13	886	1,309	0	14,000	52,417	949	67,664	68,613	
DE	9	2,273	825	0	228,879	31,033	75,776	187,234	263,010	
DL	37	4,736	537	0	579,255	16,676	515,478	85,726	601,204	
GA	47	8,471	3,549	0	779,139	9,673	752,026	48,806	800,832	
HI	1	0	0	0	0	0	0	0	0	
IA	15	5,283	1,841	0	183,140	20,675	46,619	164,320	210,938	
ID	1	3,330	5	0	435,548	0	438,883	0	438,883	
IL	93	8,438	37,556	1,458	2,105,214	267,923	667,536	1,753,052	2,420,589	
IN	92	60,518	169,387	1,900	2,947,399	362,957	1,521,315	2,020,847	3,542,162	
KS	23	52,599	2,923	250	312,827	201,641	138,199	432,041	570,240	
KY	48	37,387	7,866	0	842,740	106,458	737,981	256,469	994,451	
LA	19	1,862	1,192	0	225,541	25,554	153,523	100,626	254,149	
MA	13	802	34	0	123,335	18,418	30,059	112,530	142,589	
MD	23	3,519	1,247	5	117,989	175,703	75,846	222,617	298,463	
ME	6	26	45,771	0	39,978	20,486	486	105,775	106,261	
MI	83	12,043	19,271	14,202	550,023	105,809	269,032	432,316	701,349	
MN	24	1,680	32,504	0	120,801	75,465	81,013	149,438	230,451	
MO	30	4,152	774	0	384,845	20,519	114,340	295,950	410,290	
MS	25	2,349	1,146	844,400	960,595	284,408	1,797,876	295,022	2,092,898	
MT	7	3,172	0	0	307,563	660	200,490	110,904	311,394	
NC	47	13,844	2,000	0	1,478,427	198,532	1,434,308	258,495	1,692,803	
ND	7	4,833	243	0	328,820	1,587	151,221	184,262	335,483	
NE	12	4,333	3,817	0	106,858	6,997	87,413	34,592	122,005	
NH	3	56	0	0	2,200	2	1,856	402	2,258	
NJ	21	2,543	3,178	0	70,282	51,995	12,637	115,360	127,998	
NM	4	987	140	0	193,622	0	194,369	380	194,749	
NV	9	406	350	0	3,139,144	0	3,139,886	14	3,139,900	
NY	31	3,873	1,160	0	92,555	132,591	72,200	157,979	230,179	
OH	115	36,176	48,506	1,395,849	3,242,604	2,760,101	2,877,140	4,606,096	7,483,236	
OK	18	19,020	714	11,502	463,558	10,538	439,890	65,442	505,332	
OR	20	713	154	0	233,263	2,733	198,714	38,149	236,863	

## 6. POTENTIAL FOR HUMAN EXPOSURE

**Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Chromium Compounds<sup>a</sup>**

State <sup>c</sup>	RF <sup>d</sup>	Air <sup>e</sup>	Water <sup>f</sup>	UI <sup>g</sup>	Land <sup>h</sup>	Other <sup>i</sup>	Reported amounts released in pounds per year <sup>b</sup>			On- and off-site
							On-site <sup>j</sup>	Off-site <sup>k</sup>	Total release	
PA	119	81,454	81,764	0	2,869,224	613,481	1,267,287	2,378,635	3,645,922	
PR	5	560	0	0	179	0	560	179	739	
RI	4	82	5	0	375	0	87	375	462	
SC	33	7,058	13,395	0	767,121	27,752	190,802	624,524	815,326	
SD	2	0	0	0	0	0	0	0	0	
TN	47	6,027	17,121	0	2,499,080	4,200	2,039,524	486,903	2,526,428	
TX	107	30,761	5,206	24,558	1,448,331	109,977	741,400	877,432	1,618,832	
UT	16	2,954	567	0	2,137,746	32,207	1,911,981	261,493	2,173,474	
VA	25	2,393	2,801	0	282,803	4,409	253,251	39,155	292,406	
VT	1	0	0	0	250	0	0	250	250	
WA	15	521	791	0	183,135	29,607	165,742	48,312	214,053	
WI	52	5,014	5,557	0	402,601	104,162	8,132	509,202	517,334	
WV	27	27,051	9,245	0	1,303,237	57,066	864,358	532,241	1,396,599	
WY	6	3,994	135	0	117,102	0	121,231	0	121,231	
Total	1521	490,546	574,728	2,295,591	38,460,006	6,393,229	29,420,309	18,793,790	48,214,098	

<sup>a</sup>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.

<sup>b</sup>Data in TRI are maximum amounts released by each facility.

<sup>c</sup>Post office state abbreviations are used.

<sup>d</sup>Number of reporting facilities.

<sup>e</sup>The sum of fugitive and point source releases are included in releases to air by a given facility.

<sup>f</sup>Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

<sup>g</sup>Class I wells, Class II-V wells, and underground injection.

<sup>h</sup>Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.

<sup>i</sup>Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

<sup>j</sup>The sum of all releases of the chemical to air, land, water, and underground injection wells.

<sup>k</sup>Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI06 2008 (Data are from 2006)

## 6. POTENTIAL FOR HUMAN EXPOSURE

On a worldwide basis, the major chromium source in aquatic ecosystems is domestic waste water effluents (32.2% of the total) (Barceloux 1999). The other major sources are metal manufacturing (25.6%), ocean dumping of sewage (13.2%), chemical manufacturing (9.3%), smelting and refining of nonferrous metals (8.1%), and atmospheric fallout (6.4%) (Nriagu and Pacyna 1988). Annual anthropogenic input of chromium into water has been estimated to exceed anthropogenic input into the atmosphere (Nriagu and Pacyna 1988). However, land erosion, a natural source of chromium in water, was not included in the Nriagu and Pacyna (1988) estimation of chromium contributions to the aquatic environment.

### 6.2.3 Soil

Estimated releases of 9,050,976 pounds of chromium to soils from 938 domestic manufacturing and processing facilities in 2006, accounted for about 82% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). An additional 965,042 pounds of chromium were transferred to waste broker for disposal. Estimated releases of 38,460,006 pounds of chromium compounds to soils from 1,521 domestic manufacturing and processing facilities in 2006, accounted for about 80% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). An additional 1,131,559 million pounds, constituting about 3.4% of the total environmental emissions, were released *via* underground injection (TRI06 2008). An additional 6,393,229 pounds were transferred to waste broker for disposal. These releases are summarized in Tables 6-1 and 6-2.

Total chromium has been identified in soil and sediment samples at 696 of 1,699 and 471 of 1,699 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2008).

On a worldwide basis, the disposal of commercial products that contain chromium may be the largest contributor, accounting for 51% of the total chromium released to soil (Nriagu and Pacyna 1988). Other significant sources of chromium release into soil include the disposal of coal fly ash and bottom fly ash from electric utilities and other industries (33.1%), agricultural and food wastes (5.3%), animal wastes (3.9%), and atmospheric fallout (2.4%) (Nriagu and Pacyna 1988). Solid wastes from metal manufacturing constituted <0.2% to the overall chromium release in soil. However, the amount of chromium in sludge or residue that is disposed of in landfills by manufacturing and user industries that

## 6. POTENTIAL FOR HUMAN EXPOSURE

treat chromate wastes in ponds and lagoons is not included in the estimation by Nriagu and Pacyna (1988).

### 6.3 ENVIRONMENTAL FATE

#### 6.3.1 Transport and Partitioning

Chromium is present in the atmosphere primarily in particulate form; naturally occurring gaseous forms of chromium are rare (Cary 1982; Kimbrough et al. 1999; Seigneur and Constantinou 1995). The transport and partitioning of particulate matter in the atmosphere depends largely on particle size and density. Atmospheric particulate matter is deposited on land and water via wet and dry deposition. Wet, dry, and total deposition rates of chromium and several other trace metals in remote, rural and urban areas were summarized by Schroeder et al. (1987). Deposition rates tended to be highest in urban areas that had greater atmospheric levels of chromium as compared to rural and remote locations. The rates of wet and dry deposition are dependent upon several factors, including particle and aerosol size distribution (Kimbrough et al. 1999). The mass mean aerodynamic diameter (MMAD) of chromium aerosols or particulates emitted from several industrial sources are  $\leq 10 \mu\text{m}$  and it has been estimated that chromium-containing particulates emitted from these industrial sources can remain airborne for 7–10 days and are subject to long-range transport (Kimbrough et al. 1999). Based on a troposphere to stratosphere turnover time of 30 years (EPA 1979), atmospheric particles with a residence time of  $< 10$  days are not expected to transport from the troposphere to the stratosphere and there are no data in the reviewed literature indicating that chromium particles are transported from the troposphere to the stratosphere (Pacyna and Ottar 1985).

Since chromium compounds cannot volatilize from water, transport of chromium from water to the atmosphere is not likely, except by transport in windblown sea sprays. Most of the chromium released into water will ultimately be deposited in the sediment. A very small percentage of chromium in the water column is present in both soluble and insoluble forms. In the aquatic phase, chromium(III) occurs mostly as suspended solids adsorbed onto clayish materials, organics, or iron oxide ( $\text{Fe}_2\text{O}_3$ ) present in water. Approximately 10.5–12.6% of chromium in the aquatic phase of the Amazon and Yukon Rivers was in solution, the rest being present in the suspended solid phase (Cary 1982; King 1988). The ratio of chromium in suspended solids to dissolved form in an organic-rich river in Brazil was 2.1 (Malm et al. 1988).

## 6. POTENTIAL FOR HUMAN EXPOSURE

The bioconcentration factor (BCF) for chromium(VI) in rainbow trout (*Salmo gairdneri*) is 1. In bottom-feeder bivalves, such as the oyster (*Crassostrea virginica*), blue mussel (*Mytilus edulis*), and soft shell clam (*Mya arenaria*), the BCF values for chromium(III) and chromium(VI) range from 86 to 192 (EPA 1980, 1984a; Fishbein 1981; Schmidt and Andren 1984). The bioavailability of chromium(III) to freshwater invertebrates (*Daphnia pulex*) decreased with the addition of humic acid (Ramelow et al. 1989). This decrease in bioavailability was attributed to lower availability of the free form of the metal due to its complexation with humic acid. Based on this information, chromium is not expected to biomagnify in the aquatic food chain. Although higher concentrations of chromium have been reported in plants growing in high chromium-containing soils (e.g., soil near ore deposits or chromium-emitting industries and soil fertilized by sewage sludge) compared with plants growing in normal soils, most of the increased uptake in plants is retained in roots, and only a small fraction is translocated in the aboveground part of edible plants (Cary 1982; WHO 1988). Therefore, bioaccumulation of chromium from soil to aboveground parts of plants is unlikely (Petruzzelli et al. 1987). There is no indication of biomagnification of chromium along the terrestrial food chain (soil-plant-animal) (Cary 1982).

The mobility of chromium in soil is dependent upon the speciation of chromium, which is a function of redox potential and the pH of the soil. In most soils, chromium will be present predominantly in the chromium(III) oxidation state. This form has very low solubility and low reactivity, resulting in low mobility in the environment (Barnhart 1997; Jardine et al. 1999; Robson 2003). Under oxidizing conditions, chromium(VI) may be present in soil as  $\text{CrO}_4^{2-}$  and  $\text{HCrO}_4^-$  (James et al. 1997). In this form, chromium is relatively soluble and mobile. A leachability study comparing the mobility of several metals, including chromium, in soil demonstrated that chromium had the least mobility of all of the metals studied (Sahuquillo et al. 2003). These results support previous data finding that chromium is not very mobile in soil, especially in the trivalent oxidation state (Balasoio et al. 2001; Jardine et al. 1999; Lin et al. 1996; Robson 2003). These results are further supported by a leachability investigation in which chromium mobility was studied for a period of 4 years in a sandy loam (Sheppard and Thibault 1991). The vertical migration pattern of chromium in this soil indicated that after an initial period of mobility, chromium forms insoluble complexes and little leaching is observed. Chromium present as insoluble oxide,  $\text{Cr}_2\text{O}_3 \cdot n\text{H}_2\text{O}$ , exhibited limited mobility in soil (Rifkin et al. 2004). Flooding of soils and the subsequent anaerobic decomposition of plant detritus matters may increase the mobilization of chromium(III) in soils due to formation of soluble complexes (Stackhouse and Benson 1989). This complexation may be facilitated by a lower soil pH.

## 6. POTENTIAL FOR HUMAN EXPOSURE

A smaller percentage of total chromium in soil exists as soluble chromium(VI) and chromium(III) complexes, which are more mobile in soil. Chromium that is irreversibly sorbed onto soil (e.g., in the interstitial lattice of goethite, FeOOH) will not be bioavailable to plants and animals under any condition. Organic matter in soil is expected to convert soluble chromate, chromium(VI), to insoluble chromium(III) oxide, Cr<sub>2</sub>O<sub>3</sub> (Calder 1988). Surface runoff from soil can transport both soluble and bulk precipitate of chromium to surface water. Soluble and unadsorbed chromium(VI) and chromium(III) complexes in soil may leach into groundwater. The leachability of chromium(VI) in the soil increases as the pH of the soil increases. On the other hand, lower pH present in acid rain may facilitate leaching of acid-soluble chromium(III) complexes and chromium(VI) compounds in soil. Chromium has a low mobility for translocation from roots to aboveground parts of plants (Cary 1982). However, depending on the geographical areas where the plants are grown, the concentration of chromium in aerial parts of certain plants may differ by a factor of 2–3 (Cary 1982).

**6.3.2 Transformation and Degradation****6.3.2.1 Air**

In the atmosphere, chromium(VI) may be reduced to chromium(III) at a significant rate by vanadium (V<sup>2+</sup>, V<sup>3+</sup>, and VO<sup>2+</sup>), Fe<sup>2+</sup>, HSO<sup>3-</sup>, and As<sup>3+</sup> (EPA 1987b; Kimbrough et al. 1999). Conversely, chromium(III), if present as a salt other than Cr<sub>2</sub>O<sub>3</sub>, may be oxidized to chromium(VI) in the atmosphere in the presence of at least 1% manganese oxide (EPA 1990b). The estimated atmospheric half-life for chromium(VI) reduction to chromium(III) was reported in the range of 16 hours to about 5 days (Kimbrough et al. 1999).

**6.3.2.2 Water**

The reduction of chromium(VI) to chromium(III) and the oxidation of chromium(III) to chromium(VI) in water has been investigated extensively. Reduction of chromium(VI) to chromium(III) can occur under suitable conditions in the aqueous environment, if an appropriate reducing agent is available. The most significant reducing agents present in aqueous systems include (in order of decreasing reduction ability) organic matter, hydrogen sulfide, sulfur, iron sulfide, ammonium, and nitrate (Kimbrough et al. 1999). The reduction of chromium(VI) by S<sup>-2</sup> or Fe<sup>+2</sup> ions under anaerobic conditions occurs rapidly, with the reduction half-life ranging from instantaneous to a few days (Seigneur and Constantinos 1995). However, the reduction of chromium(VI) by organic sediments and soils was much slower and depended on the type and amount of organic material and on the redox condition of the water. The reduction half-

## 6. POTENTIAL FOR HUMAN EXPOSURE

life of chromium(VI) in water with soil and sediment ranged from 4 to 140 days, with the reaction typically occurring faster under anaerobic rather than aerobic conditions (Saleh et al. 1989). Generally, the reduction of chromium(VI) to chromium(III) is also favored under acidic conditions (Kimbrough et al. 1999).

Oxidation of chromium(III) to chromium(VI) can also occur in the aqueous environment, depending on several factors. Although oxygen is known to oxidize chromium(III) to chromium(VI), dissolved oxygen by itself in natural waters did not cause any measurable oxidation of chromium(III) to chromium(VI) over a period of 128 days (Saleh et al. 1989). When chromium(III) was added to lake water, a slow oxidation of chromium(III) to chromium(VI) occurred, corresponding to an oxidation half-life of nine years. Addition of 50 mg/L manganese oxide accelerated the process, decreasing the oxidation half-life to approximately 2 years (Saleh et al. 1989). The oxidation of chromium(III) to chromium(VI) during chlorination of water was highest in the pH range of 5.5–6.0 (Saleh et al. 1989). However, the process would rarely occur during chlorination of drinking water because of the low concentrations of chromium(III) in these waters, and the presence of naturally occurring organics that may protect chromium(III) from oxidation, either by forming strong complexes with chromium(III) or by acting as a reducing agent to free available chlorine (EPA 1988c). In chromium(III)-contaminated waste waters having pH ranges of 5–7, chlorination may convert chromium(III) to chromium(VI) in the absence of chromium(III)-complexing and free chlorine reducing agents (EPA 1988c).

Chromium speciation in groundwater also depends on the redox potential and pH conditions in the aquifer. Chromium(VI) predominates under highly oxidizing conditions; whereas chromium(III) predominates under reducing conditions. Oxidizing conditions are generally found in shallow, oxygenated aquifers, and reducing conditions generally exist in deeper, anaerobic groundwaters. In natural groundwater, the pH is typically 6–8, and  $\text{CrO}_4^{2-}$  is the predominant species of chromium in the hexavalent oxidation state, while  $\text{Cr}(\text{OH})_2^{+1}$  will be the dominant species in the trivalent oxidation state. This species and other chromium(III) species will predominate in more acidic pH;  $\text{Cr}(\text{OH})_3$  and  $\text{Cr}(\text{OH})_4^{-1}$  predominate in more alkaline waters (Calder 1988).

### 6.3.2.3 Sediment and Soil

The fate of chromium in soil is greatly dependent upon the speciation of chromium, which is a function of redox potential and the pH of the soil. In most soils, chromium will be present predominantly in the chromium(III) state. This form has very low solubility and low reactivity resulting in low mobility in the



## 6. POTENTIAL FOR HUMAN EXPOSURE

environment and low toxicity in living organisms (Ashley et al. 2003; Barnhart 1997; EPA 1994b). Under oxidizing conditions, chromium(VI) may be present in soil as  $\text{CrO}_4^{-2}$  and  $\text{HCrO}_4^-$  (James et al. 1997). In this form, chromium is relatively soluble, mobile, and toxic to living organisms. In deeper soil where anaerobic conditions exist, chromium(VI) will be reduced to chromium(III) by  $\text{S}^{-2}$  and  $\text{Fe}^{+2}$  present in soil. The reduction of chromium(VI) to chromium(III) is possible in aerobic soils that contain appropriate organic energy sources to carry out the redox reaction, with the reduction of chromium(VI) to chromium(III) facilitated by low pH (Cary 1982; EPA 1990b; Saleh et al. 1989).

The oxidation of chromium(III) to chromium(VI) in soil is facilitated by the presence of organic substances, oxygen, manganese dioxide, moisture, and the elevated temperatures in surface soil that result from brush fires (Calder 1988; Cary 1982). Organic forms of chromium(III) (e.g., humic acid complexes) are more easily oxidized than insoluble oxides. However, oxidation of chromium(III) to chromium(VI) was not observed in soil under conditions of maximum aeration and a maximum pH of 7.3 (Bartlett and Kimble 1976). It was later reported that soluble chromium(III) in soil can be partly oxidized to chromium(VI) by manganese dioxide in soil, and the process is enhanced at pH values  $>6$  (Bartlett 1991). Because most chromium(III) in soil is immobilized due to adsorption and complexation with soil materials, the barrier to this oxidation process is the lack of availability of mobile chromium(III) to immobile manganese dioxide in soil surfaces. Due to this lack of availability of mobile chromium(III) to manganese dioxide surfaces, a large portion of chromium in soil will not be oxidized to chromium(VI), even in the presence of manganese dioxide and favorable pH conditions (Bartlett 1991; James et al. 1997).

The microbial reduction of chromium(VI) to chromium(III) has been discussed as a possible remediation technique in heavily contaminated environmental media or wastes (Chen and Hao 1998; EPA 1994b). Factors affecting the microbial reduction of chromium(VI) to chromium(III) include biomass concentration, initial chromium(VI) concentration, temperature, pH, carbon source, oxidation-reduction potential, and the presence of both oxyanions and metal cations. Although high levels of chromium(VI) are toxic to most microbes, several resistant bacterial species have been identified that could ultimately be employed in remediation strategies (Chen and Hao 1998; EPA 1994b). Elemental iron, sodium sulfite, sodium hydrosulfite, sodium bisulfite, sodium metabisulfite sulfur dioxide, and certain organic compounds such as hydroquinone have also been shown to reduce chromium(VI) to chromium(III) and have been discussed as possible remediation techniques in heavily contaminated soils (Higgins et al. 1997; James et al. 1997). The limitations and efficacy of these and all remediation techniques are dependent upon the ease in which the reducing agents are incorporated into the contaminated soils.

## 6. POTENTIAL FOR HUMAN EXPOSURE

**6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT**

Reliable evaluation of the potential for human exposure to chromium depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of chromium 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 chromium 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 chromium in a variety of environmental media are detailed in Chapter 7.

**6.4.1 Air**

Levels of total chromium in the ambient air in U.S. urban and nonurban areas during 1977–1984 are reported in EPA's National Aerometric Data Bank (EPA 1984a, 1990b). According to this databank, the arithmetic mean total chromium concentrations from a total of 2,106 monitoring stations ranged from 5 to 525 ng/m<sup>3</sup>. The two locations that showed the highest total arithmetic mean chromium concentrations were in Steubenville, Ohio, in 1977 (525 ng/m<sup>3</sup>) and in Baltimore, Maryland, in 1980 (226 ng/m<sup>3</sup>) (EPA 1990b). Arithmetic mean total chromium concentrations in only 8 of 173 sites monitored in 1984 were >100 ng/m<sup>3</sup> (EPA 1990b).

An indoor/outdoor air study was conducted in southwestern Ontario to measure levels of chromium(VI) and the size fraction of chromium(VI). Indoor and outdoor samples were taken from 57 homes during the summer months of 1993. The concentrations were 0.1–0.6 ng/m<sup>3</sup> indoors (geometric mean 0.2 ng/m<sup>3</sup>) and were 0.10–1.6 ng/m<sup>3</sup> outdoors (geometric mean 0.55 ng/m<sup>3</sup>). The indoor concentrations were less than half of the outdoor concentrations. Analysis of airborne chromium(VI) particles showed that they were inhalable in size (Bell and Hipfner 1997). A study measured the levels of chromium(VI) and total chromium in the ambient air in Hudson County, New Jersey. The concentrations of chromium(VI) in the indoor air of residences in Hudson County in 1990 ranged from 0.38 to 3,000 ng/m<sup>3</sup>, with a mean of 1.2 ng/m<sup>3</sup> (Falerios et al. 1992).

Another study analyzed the relationship between soil levels of chromium and chromium content of the atmosphere. An indoor/outdoor study was conducted at 25 industrial sites in Hudson County, New Jersey to analyze soils containing chromite ore processing residues. The industrial sites include industrial, manufacturing, trucking, and warehouse facilities. The study found industrial indoor chromium(VI) and

## 6. POTENTIAL FOR HUMAN EXPOSURE

total chromium concentrations to be 0.23–11 and 4.1–130 ng/m<sup>3</sup> and industrial outdoor chromium(VI) and total chromium concentrations to be 0.013–15.3 and 1.9–84.5 ng/m<sup>3</sup>. The results of this study found that higher levels of chromium(VI) in soil do not necessarily result in higher levels of chromium(VI) in air (Finley et al. 1993). The mean concentration of total chromium at the same sites was 7.1 ng/m<sup>3</sup>, with a concentration range of 3.7–12 ng/m<sup>3</sup>. Monitoring data in Hudson County, New Jersey has shown a background chromium(VI) concentration of 0.2–3.8 ng/m<sup>3</sup> with a mean concentration of 1.2 ng/m<sup>3</sup> (Scott et al. 1997a). The airborne total chromium concentration range was 1.5–10 ng/m<sup>3</sup> with a mean concentration of 4.5 ng/m<sup>3</sup> (Scott et al. 1997a). The mean airborne chromium(VI) and total chromium concentrations in the indoor air of industrial sites in Hudson County, New Jersey, contaminated by chromite ore-processing residue were 3 ng/m<sup>3</sup> (range, 0.23–11 ng/m<sup>3</sup>) and 23 ng/m<sup>3</sup> (range, 4.11–130 ng/m<sup>3</sup>), respectively. The mean airborne chromium(VI) and total chromium concentrations in outdoor air for the same sites were 9.9 ng/m<sup>3</sup> (range, 0.13–110 ng/m<sup>3</sup>) and 37 ng/m<sup>3</sup> (range, 1.9–250 ng/m<sup>3</sup>), respectively (Falerios et al. 1992).

An air dispersion model was developed which accurately estimated chromium(VI) concentrations at two of these industrial sites in Hudson County, New Jersey (Scott et al. 1997b). The background corrected airborne concentrations in ng/m<sup>3</sup> for seven sampling dates are reported as measured (modeled values in parentheses): 0.0 (0.41); 6.2 (7.7); 0.9 (1.7); 2.8 (2.7); 0.0 (0.08); 0.3 (0.1); and 1.2 (0.12). The estimated percent levels of chromium(III) and chromium(VI) in the U.S. atmosphere from anthropogenic sources are given in Table 6-3 (EPA 1990b). Fly ash from a coal-fired power plant contained 1.4–6.1 mg/kg chromium(VI) (Stern et al. 1984). In a field study to assess inhalation exposure to chromium during showering and bathing activities, the average chromium(VI) concentration in airborne aerosols ranged from 87 to 324 ng/m<sup>3</sup> when water concentrations of 0.89–11.5 mg/L of chromium(VI) were used in a standard house shower (Finley et al. 1996a).

The concentrations of atmospheric chromium in remote areas range from 0.005 to 2.6 ng/m<sup>3</sup> (Barrie and Hoff 1985; Cary 1982; Schroeder et al. 1987; Sheridan and Zoller 1989). Saltzman et al. (1985) compared the levels of atmospheric chromium at 59 sites in U.S. cities during 1968–1971 with data from EPA's National Aerometric Data Bank file for 1975–1983. They concluded that atmospheric chromium levels may have declined in the early 1980s from the levels detected in the 1960s and 1970s.

## 6. POTENTIAL FOR HUMAN EXPOSURE

**Table 6-3. Estimates of U.S. Atmospheric Chromium Emissions from Anthropogenic Sources**

Source category	Estimated number of sources	Chromium emissions (metric tons/year)	Estimated hexavalent chromium (percent)
Combustion of coal and oil	Many	1,723	0.2
Chromium chemical manufacturing	2	18	67
Chemical manufacturing cooling towers	2,039	43	100
Petroleum refining cooling towers	475	32	100
Specialty/steel production	18	103	2.2
Primary metal cooling towers	224	8	100
Chrome plating	4,000	700	~100
Comfort cooling towers	38,000	7.2–206	100
Textile manufacturing cooling towers	51	0.1	100
Refractory production	10	24	1.3
Ferrochromium production	2	16	5.4
Sewage sludge incineration	133	13	<0.1
Tobacco cooling towers	16	0.2	100
Utility industry cooling towers	6	1.0	100
Chrome ore refining	6	4.8	<0.1
Tire and rubber cooling towers	40	0.2	100
Glass manufacturing cooling towers	3	0.01	100
Cement production	145	3	0.2
Municipal refuse incineration	95	2.5	0.3
National total			2,700–2,900

Source: EPA 1990b

## 6. POTENTIAL FOR HUMAN EXPOSURE

**6.4.2 Water**

Chromium concentrations in U.S. river water usually range from <1 to 30 µg/L (EPA 1984a; Malm et al. 1988; Ramelow et al. 1987), with a median value of 10 µg/L (Eckel and Jacob 1988; Smith et al. 1987). Chromium concentrations in lake water generally do not exceed 5 µg/L (Borg 1987; Cary 1982), with higher levels of chromium related to anthropogenic pollution sources. Dissolved chromium concentrations of 0.57–1.30 µg/L were reported in the Delaware River near Marcus Hook and Fieldsboro, Pennsylvania in January 1992, with chromium(III) composing 67% of the total (Riedel and Sanders 1998). In March 1992, these concentrations decreased to 0.03–0.23 µg/L. In general, the concentration of chromium in ocean water is much lower than that in lakes and rivers. The mean chromium concentration in ocean water is 0.3 µg/L, with a range of 0.2–50 µg/L (Cary 1982). The mean concentration of chromium in rainwater is 0.14–0.9 µg/L (Barrie et al. 1987; Dasch and Wolff 1989).

The concentrations of total chromium in groundwater at the Idaho National Engineering Laboratory, where chromate is used as a corrosion inhibitor, ranged from <1 to 280 µg/L (USGS 1989). The water from a village well situated near a waste pond receiving chromate waste in Douglas, Michigan, contained 10,800 µg/L chromium(VI). Similarly, water from a private well adjacent to an aircraft plant in Nassau County, New York, contained 25,000 µg/L chromium(VI), while water from a public well adjacent to another aircraft plant in Bethpage, New York, contained 1,400 µg/L chromium(VI) (Davids and Lieber 1951). In a later study, water from an uncontaminated well in Nassau County, New York, contained an undetectable level of chromium(VI), whereas a contaminated well in the vicinity of a plating plant contained 6,000 µg/L chromium(VI) (Lieber et al. 1964). A high chromium concentration (120 µg/L) was detected in private drinking water wells adjacent to an NPL site in Galena, Kansas (Agency for Toxic Substances and Disease Registry 1990a).

The chromium levels detected in drinking water in an earlier study (1962–1967 survey) may be erroneous due to questionable sampling and analytical methods (see Section 7.1) (EPA 1984a). Total chromium levels in drinking water were reported to range from 0.2 to 35 µg/L (EPA 1984a). Most drinking water supplies in the United States contain <5 µg/L of total chromium (WHO 2003). The concentration of chromium in household tap water may be higher than supply water due to corrosion of chromium-containing pipes. At a point of maximum contribution from corrosion of the plumbing system, the peak chromium in tap water in Boston, Massachusetts was 15 µg/L (Ohanian 1986). A survey that targeted drinking waters from 115 Canadian municipalities during 1976–1977 reported the median and the range of chromium concentrations to be <2.0 µg/L (detection limit) and <2.0–8.0 µg/L, respectively (Meranger

## 6. POTENTIAL FOR HUMAN EXPOSURE

et al. 1979). A recent monitoring survey of drinking water by the California Department of Public Health found that levels of chromium(VI) were  $<10 \mu\text{g/L}$  in 86% (2,003 out of 2,317 sources) of the drinking water sources sampled; however, levels above  $50 \mu\text{g/L}$  were noted in six sources (CDPH 2007). In this survey, a source was defined as those reporting more than a single detection of chromium(VI) and may include both raw and treated sources, distribution systems, blending reservoirs, and other sampled entities. These data did not include agricultural wells, monitoring wells, or more than one representation of the same source (e.g., a source with both raw and treated entries is counted a single source).

### 6.4.3 Sediment and Soil

The chromium level in soils varies greatly and depends on the composition of the parent rock from which the soils were formed. Basalt and serpentine soils, ultramafic rocks, and phosphorites may contain chromium as high as a few thousand mg/kg (Merian 1984) whereas soils derived from granite or sandstone will have lower concentrations of chromium (Swaine and Mitchell 1960). The concentration range of chromium in 1,319 samples of soils and other surficial materials collected in the conterminous United States was 1–2,000 mg/kg, with a geometric mean of 37 mg/kg (USGS 1984). Chromium concentrations in Canadian soils ranged from 5 to 1,500 mg/kg, with a mean of 43 mg/kg (Cary 1982). In a study with different kinds of soils from 20 diverse sites including old chromite mining sites in Maryland, Pennsylvania, and Virginia, the chromium concentration ranged from 4.9 to 71 mg/kg (Beyer and Cromartie 1987). A polynuclear aromatic hydrocarbon (PAH) soil study was conducted to determine the metal levels in soil at the edge of a busy road that runs through the Aplerbecker Forest in West Germany. Chromium(VI) concentrations of 64 mg/kg were measured, and these concentrations were 2- to 4-fold higher along the road than in the natural forest (Munch 1993). The soil beneath decks treated with chrominated copper arsenate (CCA), a wood preservative, had an average chromium content of 43 mg/kg (Stilwell and Gorny 1997).

Chromium has been detected at a high concentration (43,000 mg/kg) in soil at the Butterworth Landfill site in Grand Rapid City, Michigan, which was a site listed on the NPL (Agency for Toxic Substances and Disease Registry 1990b).

Chromium was detected in sediment obtained from the coastal waters of the eastern U.S. seashore at concentrations of 3.8–130.9  $\mu\text{g/g}$  in 1994 and 0.8–98.1  $\mu\text{g/g}$  in 1995 (Hyland et al. 1998).

## 6. POTENTIAL FOR HUMAN EXPOSURE

**6.4.4 Other Environmental Media**

The concentration of chromium in the particulate portion of melted snow collected from two urban areas (Toronto and Montreal) of Canada ranged from 100 to 3,500 mg/kg (Landsberger et al. 1983). In the suspended materials and sediment of water bodies, chromium levels ranged from 1 to 500 mg/kg (Byrne and DeLeon 1986; EPA 1984a; Mudroch et al. 1988; Ramelow et al. 1987). The chromium concentration in incinerated sewage sludge ash may be as high as 5,280 mg/kg (EPA 1984a).

Total chromium levels in most fresh foods are extremely low (vegetables [20–50 µg/kg], fruits [20 µg/kg], and grains and cereals [40 µg/kg]) (Fishbein 1984). The chromium levels of various foods are reported in Table 6-4. In a study to find the concentrations of chromium in edible vegetables in Tarragon Province, Spain, the highest levels of chromium were found in radish root and spinach, with a nonsignificant difference between the samples collected in two areas (northern industrial and southern agricultural). The samples ranged in concentration from 0.01 to 0.21 µg/g (industrial) and from 0.01 to 0.22 µg/g (agricultural) (Schuhmacker et al. 1993). Acidic foods that come into contact with stainless steel surfaces during harvesting, processing, or preparation for market are sometimes higher in chromium content because of leaching conditions. Processing, however, removes a large percentage of chromium from foods (e.g., whole-grain bread contains 1,750 µg/kg chromium, but processed white bread contains only 140 µg/kg; and molasses contains 260 µg/kg chromium, but refined sugar contains only 20 µg/kg chromium) (Anderson 1981; EPA 1984a).

Chromium levels in oysters, mussels, clams, and mollusks vary from <0.1 to 6.8 mg/kg (dry weight) (Byrne and DeLeon 1986; Ramelow et al. 1989). Fish and shellfish collected from ocean dump sites off New York City, Delaware Bay, and New Haven, Connecticut, contained <0.3–2.7 mg/kg chromium (wet weight) (Greig and Jones 1976). The chromium concentration in fish sampled from 167 lakes in the northeastern United States was 0.03–1.46 µg/g with a mean concentration of 0.19 µg/g (Yeardley et al. 1998). Higher levels of chromium in forage of meat animals have been reported for plants grown in soils with a high concentration of chromium (see Section 6.3.1). Cigarette tobacco reportedly contains 0.24–14.6 mg/kg chromium, but no estimates were available regarding the chromium levels in inhaled cigarette smoke (Langård and Norseth 1986). Cigarette tobacco grown in the United States contains ≤6.3 mg/kg chromium (IARC 1980).

Cement-producing plants are a potential source of atmospheric chromium. Portland cement contains 41.2 mg/kg chromium (range 27.5–60 mg/kg). Soluble chromium accounts for 4.1 mg/kg (range 1.6–

## 6. POTENTIAL FOR HUMAN EXPOSURE

**Table 6-4. Chromium Content in Various U.S. Foods**

Sample	Mean concentration (µg/kg)	Reference
Fresh vegetables	30–140	EPA 1984a
Frozen vegetables	230	EPA 1984a
Canned vegetables	230	EPA 1984a
Fresh fruits	90–190	EPA 1984a
Fruits	20	EPA 1984a
Canned fruits	510	EPA 1984a
Dairy products	100	EPA 1984a
Chicken eggs	160–520	Kirpatrick and Coffin 1975
Chicken eggs	60	Kirpatrick and Coffin 1975
Whole fish	50–80	EPA 1984a
Edible portion of fresh fin fish	<100–160	Eisenberg and Topping 1986
Meat and fish	110–230	EPA 1984a
Seafoods	120–470	EPA 1984a
Grains and cereals	40–220	EPA 1984a
Sugar, refined <sup>a</sup>	<20	WHO 1988

<sup>a</sup>Value in Finnish sugar



## 6. POTENTIAL FOR HUMAN EXPOSURE

8.8 mg/kg) of which 2.9 mg/kg (range 0.03–7.8 mg/kg) is chromium(VI) (Fishbein 1981). The wearing down of vehicular brake linings that contain asbestos represents another source of atmospheric chromium. Asbestos may contain  $\approx 1,500$  mg/kg of chromium. The introduction of catalytic converters on U.S. automobiles in 1975 in the United States represented an additional source of atmospheric chromium. Catalysts, such as copper chromite, emit  $<10^6$  metal-containing condensation nuclei per cubic centimeter in vehicular exhaust, under various operating conditions (Fishbein 1981).

**6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE**

The general population is exposed to chromium by inhaling ambient air, ingesting food, and drinking water containing chromium. Home-based exposures can occur to the families of occupational workers in what is known as worker-to-family exposures. Home exposures can also occur through proximity to hazardous waste sites (Pellerin and Booker 2000). A study measured the relationships between chromium in household dust and chromium in the urine of Hudson County, New Jersey residents (Pellerin and Booker 2000). Three major producers of chromium (VI) in the form of chromate were active in the area for over 70 years, and produced over 2 million tons of chromium containing slag waste (Pellerin and Booker 2000). Chromium (VI) levels as high as several hundred parts per million were measured in some of the soil samples extracted from the area (Pellerin and Booker 2000).

Dermal exposure of the general public to chromium can occur from skin contact with consumer products that contain chromium. Some of the consumer products known to contain chromium are certain wood preservatives, cement, cleaning materials, textiles, and leather tanned with chromium (WHO 1988). Both chromium(III) and chromium(VI) are known to penetrate the skin, although chromium(VI) penetrates to a higher degree (Robson 2003). However, no quantitative data for dermal exposure to chromium-containing consumer products were located. Levels of chromium in ambient air ( $<0.01$ – $0.03$   $\mu\text{g}/\text{m}^3$ ) (Fishbein 1984; Pellerin and Booker 2000) and tap water ( $<1$   $\mu\text{g}/\text{L}$ ) (Pellerin and Booker 2000) have been used to estimate the daily intake of chromium via inhalation ( $<0.2$ – $0.6$   $\mu\text{g}$ ) and tap water ( $<4$   $\mu\text{g}$ ). These estimates are based on an air inhalation rate of  $20$   $\text{m}^3/\text{day}$  and a drinking water consumption rate of  $2$   $\text{L}/\text{day}$ . The daily chromium intake for the U.S. population from consumption of selected diets (diets with 25 and 43% fat) has been estimated to range from 25 to 224  $\mu\text{g}$  with an average of 76  $\mu\text{g}$  (Kumpulainen et al. 1979). The chromium concentrations in tissues and body fluids of the general population are given in Table 6-5.

## 6. POTENTIAL FOR HUMAN EXPOSURE

**Table 6-5. Chromium Content in Tissues and Body Fluids of the General Population**

Sample	Median or mean	Range	Reference
Serum	0.006 µg/L	0.01–0.17 µg/L	Sunderman et al. 1987
Urine	0.4 µg/L	0.24–1.8 µg/L	Iyengar and Woittiez 1988
Lung	201 µg/kg (wet weight)	28–898 µg/kg (wet weight)	Raithel et al. 1987
Breast milk	0.30 µg/L	0.06–1.56 µg/L	Casey and Hambidge 1984
Hair	0.234 mg/kg	Not available	Takagi et al. 1986
Nail	0.52 mg/kg	No applicable	Takagi et al. 1988

## 6. POTENTIAL FOR HUMAN EXPOSURE

Workers in industries that use chromium can be exposed to concentrations of chromium two orders of magnitude higher than exposure to the general population, and that workers in some 80 different professions may be exposed to chromium (VI) (Hemminki and Vainio 1984; Pellerin and Booker 2000). Occupational exposure to chromium occurs mainly from chromate production, stainless steel production and welding, chromium plating, ferrochrome alloys and chrome pigment production, and working in tanning industries (Ashley et al. 2003). A list of industries that may be sources of chromium exposure is given in Table 6-6. For most occupations, exposure is due to both chromium(III) and chromium(VI) present as soluble and insoluble fractions. However, exceptions include the tanning industry, where exposure is mostly from soluble chromium(III), and the plating industry, where exposure is due to soluble chromium(VI). The typical concentration ranges of airborne chromium(VI) to which workers in these industries were exposed during an average of 5–20 years of employment were: chromate production, 100–500  $\mu\text{g}/\text{m}^3$ ; stainless steel welding, 50–400  $\mu\text{g}/\text{m}^3$ ; chromium plating, 5–25  $\mu\text{g}/\text{m}^3$ ; ferrochrome alloys, 10–140  $\mu\text{g}/\text{m}^3$ ; and chrome pigment, 60–600  $\mu\text{g}/\text{m}^3$  (Stern 1982). In the tanning industry, except for two bath processes, the typical exposure range due to chromium(III) was 10–50  $\mu\text{g}/\text{m}^3$ . A study of chromium (VI) levels of in the air of a chrome plating shop measured concentrations of chromium (VI) in the range of 10–30  $\mu\text{g}/\text{m}^3$  for chrome plating shops with local exhaust (Pellerin and Booker 2000). In plating shops without local exhaust, the levels were much higher, up to 120  $\mu\text{g}/\text{m}^3$  (Pellerin and Booker 2000). In an occupational exposure study of chromium in an aircraft construction factory, airborne samples were collected over a 4-hour period; urinary samples were collected at the beginning (Monday), end (Friday), and after the work shift in order to analyze the absorption of chromium during working hours (Gianello et al. 1998). The air sampling results were 0.02–1.5  $\text{mg}/\text{m}^3$ , and the urine sampling results were 0.16–7.74  $\mu\text{g}/\text{g}$  creatinine. Compared to the ACGIH and BEI-ACGIH Hygiene Standard of 50  $\mu\text{g}/\text{m}^3$ , both sets of results indicated a very low risk of exposure. The National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimated that 304,829 workers in the United States were potentially exposed to chromium(VI) (NIOSH 1989). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey only estimates the number of workers potentially exposed to chemicals in the workplace.

In a survey of workers in pigment factories in England that produced strontium and lead chromate, the concentrations of chromium in the whole blood in exposed workers ranged from 3 to 216  $\mu\text{g}/\text{L}$ , compared to a level of <1  $\mu\text{g}/\text{L}$  for the nonoccupationally exposed population (McAughey et al. 1988). The corresponding concentrations in the urine of exposed workers and the unexposed population were 1.8–575  $\mu\text{g}$  chromium/g creatinine and <0.5  $\mu\text{g}$  chromium/g creatinine, respectively (McAughey et al. 1988).

## 6. POTENTIAL FOR HUMAN EXPOSURE

**Table 6-6. Industries that May be Sources of Chromium Exposure**


---

Abrasives manufacturers	Laboratory workers
Acetylene purifiers	Leather finishers
Adhesives workers	Linoleum workers
Aircraft sprayers	Lithographers
Alizarin manufacturers	Magnesium treaters
Alloy manufactures	Match manufacturers
Aluminum anodizers	Metal cleaners
Anodizers	Metal workers
Battery manufacturers	Milk preservers
Biologists	Oil drillers
Blueprint manufacturers	Oil purifiers
Boiler scalers	Painters
Candle manufacturers	Palm-oil bleachers
Cement workers	Paper water proofers
Ceramic workers	Pencil manufacturers
Chemical workers	Perfume manufacturers
Chromate workers	Photoengravers
Chromium-alloy workers	Photographers
Chromium-alum workers	Platinum polishers
Chromium platers	Porcelain decorators
Copper etchers	Pottery frosters
Copper-plate strippers	Pottery glazers
Corrosion-inhibitor workers	Printers
Crayon manufacturers	Railroad engineers
Diesel locomotive repairmen	Refractory-brick manufacturers
Drug manufacturers	Rubber manufacturers
Dye manufacturers	Shingle manufacturers
Dyers	Silk-screen manufacturers
Electroplaters	Smokeless-powder manufacturers
Enamel workers	Soap manufacturers
Explosive manufacturers	Sponge bleachers
Fat purifiers	Steel workers
Fireworks manufacturers	Tanners
Flypaper manufacturers	Textile workers
Furniture polishers	Wallpaper printers
Fur processors	Wax workers
Glass-fibre manufacturers	Welders
Glue manufacturers	Wood-preservative workers
Histology technicians	Wood stainers
Jewelers	

---

Source: IARC 1990

## 6. POTENTIAL FOR HUMAN EXPOSURE

Other investigators have found a higher lung burden for chromium in occupational groups than in unexposed groups. The median concentration of chromium in the lungs of deceased smelter workers in Sweden was 450  $\mu\text{g}/\text{kg}$  (wet weight), compared to a value of 110  $\mu\text{g}/\text{kg}$  (wet weight) for rural controls and 199  $\mu\text{g}/\text{kg}$  (wet weight) for urban controls (Gerhardsson et al. 1988).

**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 ingest inappropriate materials (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).

Children living in vicinities where there are chromium waste sites nearby may be exposed to chromium to a greater extent than adults through inhalation of chromium particulates and through contact with contaminated soils. One study has shown that the average concentration of chromium in the urine of children at ages five and younger was significantly higher than in adults residing near sites where chromium waste slag was used as fill material (Fagliano et al. 1997), and the soil levels of a hazardous waste disposal site in New Jersey were measured at levels up to 120  $\mu\text{g}/\text{m}^3$  (Pellerin and Booker 2000). The tendency of young children to ingest soil, either intentionally through pica or unintentionally through hand-to-mouth activity, is well documented and can result in ingestion of chromium present in soil and dust. Soil may affect the bioavailability of contaminants in several ways, most likely by acting as a competitive sink for the contaminants. In the presence of soil, the contaminants will partition between absorption by the gut and sorption onto the soil particles. If a soil has a longer residence time in the gut than food particles, then sorption may enhance the overall absorption of the contaminant (Sheppard et al. 1995). If the contaminant is irreversibly bound to soil particles, then the contaminant is unlikely to be absorbed in the gastrointestinal tract. Hexavalent chromium exists in soils as a relatively soluble anion

## 6. POTENTIAL FOR HUMAN EXPOSURE

and may be present in bioavailable form, possibly with enhanced absorption due to the presence of the soil itself. In contrast, chromium(III) present in soil is generally not very soluble or mobile under most environmental conditions and is not readily bioavailable (James et al. 1997). Studies discussing the oral absorption of chromium in rats from a soil surface in which 30% of the chromium was in hexavalent form and 70% was in trivalent form suggested that while absorption in animals is quite low, chromium appeared to be better absorbed from soil than from soluble chromate salts (Witmer et al. 1989, 1991). However, less than half of the administered dose of chromium could be accounted for in this study, and in separate experiments with low dosages administered to the rats, the control animals actually had higher concentrations of chromium than the animals that were administered the oral dose. Children may accidentally ingest chromium picolinate in households whose members use this product as a dietary supplement unless it is well stored and kept away from children. Small amounts of chromium are used in certain consumer products such as toners in copying machines and printers, but childhood exposure from these sources are expected to be low. Children may also be exposed to chromium from parents' clothing or items removed from the workplace if the parents are employed in a setting where occupational exposure is significant (see Section 6.5). Chromium has been detected in breast milk at concentrations of 0.06–1.56 µg/L (Casey and Hambidge 1984), suggesting that children could be exposed to chromium from breast-feeding mothers. Studies on mice have shown that chromium crosses the placenta and can concentrate in fetal tissue (Danielsson et al. 1982; Saxena et al. 1990a).

A study done on the potential exposure of teenagers to airborne chromium from steel dust in the New York City subway system found significantly higher concentrations of chromium than in home and ambient samples. The conclusion from the study was that the increased concentration was most likely due to steel dust present in the subway system as the source of chromium (Chillrud et al. 2004). Chromium levels in the New York City subway system are greater than ambient levels by approximately two orders of magnitude. Levels observed in the study of chromium  $\approx 84$  ng/m<sup>3</sup> are similar to chronic reference guidelines in both Canada and the United States and were 40–100 times the adult range in the estimated  $10^{-5}$  lifetime cancer risk (Chillrud et al. 2004). The reference values for exposure to chromium range from 2 to 100 ng/m<sup>3</sup> (Wu et al. 2001). The study measured total chromium levels, without separating the species of chromium into chromium (III) and chromium (VI). Previous studies have suggested that airborne chromium generated from steel welding have a significant amount of chromium(VI) present, extending the possibility that there is a possibility for chromium(VI) to be present in the steel dust in the New York City subway system as well (Chillrud et al. 2004; Edme et al. 1997).

## 6. POTENTIAL FOR HUMAN EXPOSURE

Another study done on the bones of deceased neonatal humans in Poland found that statistically significant differences in chromium concentrations were observed. In addition, a positive correlation between pairs of metals was observed, specifically between the pairing of chromium and lead. (Baranowski et al. 2002). Bones were chosen to examine, since they are a useful reference in regards to heavy metal exposure and accumulation, and are therefore an accurate measure of chronic exposure.

**6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES**

In addition to individuals who are occupationally exposed to chromium (see Section 6.5), there are several groups within the general population that have potentially high exposures (higher-than-background levels) to chromium. Persons using chromium picolinate as a dietary supplement will also be exposed to higher levels of chromium than those not ingesting this product (Anderson 1998b). Like many other products used to promote weight loss or speed metabolism, there is also the potential for overuse of this product by some members of the population in order to achieve more dramatic results (Wasser et al. 1997). People may also be exposed to higher levels of chromium if they use tobacco products, since tobacco contains chromium (IARC 1980).

Workers in industries that use chromium are one segment of the population that is especially at high risk to chromium exposure. Many industrial workers are exposed to chromium(VI) levels in air that exceed the accepted occupational exposure limits (Blade et al. 2007). Occupational exposure from chromate production, stainless steel welding, chromium plating, and ferrochrome and chrome pigment production is especially significant since the exposure from these industries is to chromium(VI). Occupational exposure to chromium(III) compounds may not be as great a concern as exposure to chromium(VI) compounds. Among the general population, residents living near chromate production sites may be exposed to higher levels of chromium(VI) in air. Ambient concentrations as high as  $2.5 \mu\text{g}/\text{m}^3$  chromium in air were detected in a 1977 sample from Baltimore, Maryland (EPA 1984a). People who live near chromium waste disposal sites and chromium manufacturing and processing plants may be exposed to elevated levels of chromium. The airborne concentrations of chromium(VI) and total chromium in a contaminated site in Hudson County, New Jersey were studied (Falerios et al. 1992). The mean concentrations of both chromium(VI) and total chromium in indoor air of the contaminated site were about three times higher than the mean indoor air concentrations of uncontaminated residential sites in Hudson County. Although the mean concentration of chromium(VI) in outdoor air was much lower than the current occupational exposure limit of  $50 \mu\text{g}/\text{m}^3$ , levels in 10 of 21 samples at the contaminated site exceeded the background urban outdoor chromium(VI) concentration of  $4 \text{ ng}/\text{m}^3$ . Similarly, the total

## 6. POTENTIAL FOR HUMAN EXPOSURE

chromium concentration in 11 of 21 outdoor air samples from the contaminated site exceeded the outdoor mean concentration of 15 ng/m<sup>3</sup> for urban New Jersey. However, recent sampling data from Hudson County, New Jersey have shown that more than two-thirds of previously sampled sites contaminated with chromite ore processing residue did not have statistically significant mean concentrations greater than the background levels (Scott et al. 1997a). These data, as well as the results of a soil dispersion model (Scott et al. 1997b), suggest that heavy vehicular traffic over unpaved soil surfaces containing chromium(VI) are required for high levels of atmospheric chromium(VI) at these sites. Persons using contaminated water for showering and bathing activities may also be exposed via inhalation to potentially high levels of chromium(VI) in airborne aerosols (Finley et al. 1996a). In a field study to simulate daily bathing activity, airborne chromium(VI) concentrations were about 2 orders of magnitude greater than ambient outdoor air concentrations when water concentrations of 5.4 and 11.5 mg/L were used in the shower.

A study was conducted from September to November 1989 to determine the levels of chromium in urine and red blood cells of state employees who worked at a park (with only indirect exposure potential) adjacent to chromium-contaminated sites in Hudson County, New Jersey (Bukowski et al. 1991). The chromium levels in red blood cells and urine of 17 of these employees showed no differences compared to 36 employees who worked at state parks outside Hudson County. The authors concluded that urinary and blood levels of chromium are poor biological markers in gauging low-level environmental exposure to chromium. This study also concluded that chromium levels in blood and urine depended on other confounding variables, such as exercise, past employment in a chromium-exposed occupation, beer drinking, and diabetic status. Other lifestyle (e.g., smoking), dietary, or demographic factors had no measurable effect on blood and urinary chromium. These conclusions are consistent with the results of a study that measured the urinary excretion of chromium following oral ingestion of chromite ore processing residue material for three days (Finley and Paustenbach 1997). These results indicate no statistical difference in mean urinary chromium concentrations in groups of individuals exposed to chromite ore processing residue material versus the control group. High levels of chromium were detected in the urine and hair of individuals living near a chromite ore-processing plant in Mexico (Rosas et al. 1989), which suggests the possibility of using these media as biological markers in gauging long term, high-level environmental exposure to chromium.

Elevated levels of chromium in blood, serum, urine, and other tissues and organs have been observed in patients with cobalt-chromium knee and hip arthroplasts (Coleman et al. 1973; Michel et al. 1987; Sunderman et al. 1989).



## 6. POTENTIAL FOR HUMAN EXPOSURE

The chromium content in cigarette tobacco from the United States has been reported to be 0.24–6.3 mg/kg (IARC 1980), but neither the chemical form nor the amount of chromium in tobacco smoke is known. People who use tobacco products may be exposed to higher-than-normal levels of chromium.

## 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 chromium 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 chromium.

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.** As seen in Section 4.2, the relevant physical and chemical properties of chromium and its compounds are known (Hartford 1979; NIOSH 2008; Weast 1985) and prediction of environmental fate and transport of chromium in environmental media is possible. However, the physical or chemical forms and the mode by which chromium(III) compounds are incorporated into biological systems are not well characterized. The determination of the solubilities of hexavalent chromium compounds in relevant body fluids (e.g., the solubility of chromates in lung fluid) may also be helpful.

**Production, Import/Export, Use, Release, and Disposal.** Knowledge of a chemical's production volume is important because it may indicate environmental contamination and human exposure. If a chemical's production volume is high, there is an increased probability of general population exposure via consumer products and environmental sources, such as air, drinking water, and food. Data concerning the production (Hartford 1979; Papp and Lipin 2001; SRI 1997; USGS 2008b), import (USGS 2008b), and use (CMR 1988a, 1988b; EPA 1984a; IARC 1990; Papp and Lipin 2001;

## 6. POTENTIAL FOR HUMAN EXPOSURE

USDI 1988a; USGS 2008b) of commercially significant chromium compounds are available. Chromium is not generally used to process foods for human consumption or added to foods other than diet supplements. Thus, consumer exposure to chromium occurs mostly from natural food sources (Bennett 1986; EPA 1984a; Kumpulainen et al. 1979), but this exposure will increase particularly for people who consume acidic food cooked in stainless steel utensils (Anderson 1981; EPA 1984a). Exposure to chromium occurs to a much lesser extent from products such as toners of photocopying machines, some wood treatment chemicals, and through other chromium-containing consumer products (CMR 1988a, 1988b; EPA 1984a; IARC 1990; USDI 1988a).

As seen in Tables 6-1 and 6-2, the largest amount of chromium from production and user facilities is disposed of on land or transferred to an off-site location. More detailed site-and medium-specific (e.g., air, water, or soil) release data for chromium that is disposed of off-site are necessary to assess the exposure potential to these compounds from different environmental media and sources. There are EPA guidelines regarding the disposal of chromium wastes and OSHA regulations regarding the levels of chromium in workplaces (EPA 1988a; OSHA 1998a).

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 2006, became available in May of 2008. This database is updated yearly and should provide a list of industrial production facilities and emissions.

**Environmental Fate.** Information is available to permit assessment of the environmental fate and transport of chromium in air (Pacyna and Pacyna 2001; Schroeder et al. 1987; Scott et al. 1997a, 1997b), water (Cary 1982; Comber and Gardner 2003; EPA 1980, 1984a; Fishbein 1981; Schmidt and Andren 1984; WHO 2003) and soil (Ashley et al. 2003; Avudainayagam et al. 2003; Balasoju et al. 2001; Bartlett 1991; Calder 1988; Cary 1982; Jardine et al. 1999; Rifkin et al. 2004). Chromium is primarily removed from the atmosphere by fallout and precipitation. By analogy with copper, the residence time of chromium in the atmosphere is expected to be <10 days (Nriagu 1979). Most of the chromium in lakes and rivers will ultimately be deposited in the sediments. Chromium in the aquatic phase occurs in the soluble state or as suspended solids adsorbed onto clayish materials, organics, or iron oxides (Cary 1982). Most of the soluble chromium is present as chromium(VI) or as soluble chromium(III) complexes and generally accounts for a small percentage of the total (Cary 1982). Additional data, particularly regarding chromium's nature of speciation, would be useful to fully assess chromium's fate in air. For example, if chromium(III) oxide forms some soluble salt in the air due to speciation, its removal by wet deposition

## 6. POTENTIAL FOR HUMAN EXPOSURE

will be faster. No data regarding the half-life of chromium in the atmosphere or a measure of its persistence are available. In aquatic media, sediment will be the ultimate sink for chromium, although soluble chromates may persist in water for years (Cary 1982; EPA 1984a). Additional data elucidating the nature of speciation of chromium in water and soil would also be desirable and a direct measurement of the chromium residence time in the atmosphere would be useful.

**Bioavailability from Environmental Media.** The bioavailability of chromium compounds from contaminated air, water, soil, or plant material in the environment has not been adequately studied. Absorption studies of chromium in humans and animals provide information regarding the extent and rate of inhalation (Cavalleri and Minoia 1985; Kiilunen et al. 1983; Langård et al. 1978) and oral exposure (Anderson 1981, 1986; Anderson et al. 1983; Donaldson and Barreras 1966; Randall and Gibson 1987; Suzuki et al. 1984). A sorption study has measured the amount of chromium(VI) when iron particles are present in the water samples; the conclusion was that soluble chromium(VI) present in the water could sorb on to iron particles present in the acidic environment of the stomach, and thus, be less bioavailable (Parks et al. 2004). These available absorption studies indicate that chromium(VI) compounds are generally more readily absorbed from all routes of exposure than are chromium(III) compounds. This is consistent, in part, with the water solubilities of these compounds (Bragt and van Dura 1983). The bioavailability of both forms is greater from inhalation exposure than from ingestion or dermal exposure. The bioavailability of chromium from soil depends upon several factors (Witmer et al. 1989). Factors that may increase the mobility of chromium in soils include the speculated conversion of chromium(III) to chromium(VI), increases in pH, and the complexation of chromium(III) with organic matter from water-soluble complexes. Data on the bioavailability of chromium compounds from actual environmental media and the difference in bioavailability for different media need further development.

**Food Chain Bioaccumulation.** It is generally believed that chromium does not bioconcentrate in fish (EPA 1980, 1984a; Fishbein 1981; Schmidt and Andren 1984) and there is no indication of biomagnification of chromium along the aquatic food chain (Cary 1982). However, recent skin biopsy data indicate that North Atlantic right whales are exposed to hexavalent chromium and accumulate a range of 4.9–10 µg chromium/g tissue with a mean of 7.1 µg chromium/g tissue (Wise et al. 2008). Some data indicate that chromium has a low mobility for translocation from roots to aboveground parts of plants (Cary 1982; WHO 1988). However, more data regarding the transfer ratio of chromium from soil to plants and biomagnification in terrestrial food chains would be desirable.

## 6. POTENTIAL FOR HUMAN EXPOSURE

**Exposure Levels in Environmental Media.** The atmospheric total chromium concentration in the United States is typically  $<10 \text{ ng/m}^3$  in rural areas and  $10\text{--}30 \text{ ng/m}^3$  in urban areas (Fishbein 1984; WHO 2003). Most drinking water supplies in the United States contain  $<5 \text{ }\mu\text{g/L}$  of chromium (WHO 2003). The chromium level in soils varies greatly and depends on the composition of the parent rock from which the soils were formed. Basalt and serpentine soils, ultramafic rocks, and phosphorites may contain chromium as high as a few thousand  $\text{mg/kg}$  (Merian 1984), whereas soils derived from granite or sandstone will have lower concentrations of chromium (Swaine and Mitchell 1960). The concentration range of chromium in 1,319 samples of soils and other surficial materials collected in the conterminous United States was  $1\text{--}2,000 \text{ mg/kg}$ , with a geometric mean of  $37 \text{ mg/kg}$  (USGS 1984). There is a large variation in the available data regarding the levels of chromium in foods (EPA 1984a). Concentrations ranges are  $30\text{--}230 \text{ }\mu\text{g/kg}$  in vegetables,  $20\text{--}510 \text{ }\mu\text{g/kg}$  in fruits,  $40\text{--}220 \text{ }\mu\text{g/kg}$  in grains and cereals, and  $110\text{--}230 \text{ }\mu\text{g/kg}$  in meats and fish (EPA 1984a). It would be useful to develop nationwide monitoring data on the levels of chromium in U.S. ambient air and drinking water, and these data should quantitate levels of both chromium(III) and chromium(VI) and not just total chromium.

**Exposure Levels in Humans.** The general population is exposed to chromium by inhaling ambient air and ingesting food and drinking water containing chromium. Dermal exposure of the general public to chromium can occur from skin contact with certain consumer products that contain chromium or from contact with chromium contaminated soils. Some of the consumer products known to contain chromium are certain wood preservatives, cement, cleaning materials, textiles, and leather tanned with chromium (WHO 1988). However, no quantitative data for dermal exposure to chromium-containing consumer products were located. Levels of chromium in ambient air ( $<0.01\text{--}0.03 \text{ }\mu\text{g/m}^3$ ) (Fishbein 1984; WHO 2003) and tap water ( $<2 \text{ }\mu\text{g/L}$ ) (WHO 2003) have been used to estimate the daily intake of chromium via inhalation ( $<0.2\text{--}0.6 \text{ }\mu\text{g}$ ) and tap water ( $<4 \text{ }\mu\text{g}$ ). These estimates are based on an air inhalation rate of  $20 \text{ m}^3/\text{day}$  and a drinking water consumption rate of  $2 \text{ L/day}$ . The daily chromium intake for the U.S. population from consumption of selected diets (diets with 25 and 43% fat) has been estimated to range from 25 to 224  $\mu\text{g}$ , with an average of 76  $\mu\text{g}$  (Kumpulainen et al. 1979). This value is within the range established by the World Health Organization (WHO) as a mean chromium intake from food and water of  $52\text{--}943 \text{ }\mu\text{g/day}$  (WHO 2003). However, few data on the levels of chromium in body tissues or fluids for populations living near hazardous waste sites are available. Such data could be a useful tool as an early warning system against harmful exposures. In addition, there is a need for data on the background levels of chromium in body fluids of children. Such data would be important in assessing the exposure levels of this group of people.

## 6. POTENTIAL FOR HUMAN EXPOSURE

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

**Exposures of Children.** Limited data exist regarding exposure and body burdens of chromium in children. Chromium has been detected in breast milk at concentrations of 0.06–1.56 µg/L (Casey and Hambidge 1984), suggesting that children could be exposed to chromium from breast-feeding mothers. Studies in mice have shown that chromium crosses the placenta and can concentrate in fetal tissue (Danielsson et al. 1982; Saxena et al. 1990a). Because children living near areas contaminated with chromium have been shown to have elevated chromium levels in urine as compared to adults (Fagliano et al. 1997), additional body burden studies are required to evaluate the exposures and the potential consequences that this might have upon children. This is particularly important around heavily contaminated soils where children may be exposed dermally or through inhalation of soil particulates during play activities. These studies may determine if children may be more susceptible than adults to the toxic effects of chromium including immunosensitivity. Studies are necessary that examine children's weight-adjusted intake of chromium and determine how it compares to that of adults. Since chromium is often detected in soil surfaces and children ingest soil either intentionally through pica or unintentionally through hand-to-mouth activity, pica is a unique exposure pathway for children. Studies have shown that although absorption of chromium is low, it may be enhanced slightly from contaminated soil surfaces (Witmer et al. 1989, 1991).

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 chromium 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

The Federal Research in Progress (FEDRIP 2008) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1 (see Table 6-7).

## 6. POTENTIAL FOR HUMAN EXPOSURE

**Table 6-7. Ongoing Studies on Chromium**

Principal investigator	Affiliation	Research description
David Brautigam	University of Virginia	Define the biochemical basis of chromium enhancement of insulin action
William Cefalu	Pennington Biomedical Research Center	Study the changes in insulin uptake on chromium supplementation
Mitchell Cohen	New York University School of Medicine	Study biological interactions of metals and improve design of metallopharmaceuticals
Jeffrey Elmendorf	Indiana University: Purdue University at Indianapolis	Chromium action and role in the glucose transport system
Emily Horvath	Indiana University: Purdue University at Indianapolis	Cellular insulin resistance mechanisms
Joshua Jacobs	Rush University Medical Center	Metal release and effects in people with metal-on-hip replacements
Sushil Jain	Louisiana State University	Cytokine production; role of chromium in preventing oxidative stress
Umesh Masharani	University of California, San Francisco	The effects of chromium on insulin action
Mahmood Mozaffari	Medical College of Georgia	Effect of chromium on glucose metabolism
Charles Myers	Medical College of Wisconsin	Study the mechanisms of chromium(VI) in the human lung system
Patricia Opresko	University of Pittsburgh at Pittsburgh	Understand the mechanisms of genomic instability associated with aging
Viresh Rawal	University of Chicago	Investigation of metal-salen complexes for use in C-C bond forming reactions; Diels-Alder catalyst development
James Rigby	Wayne State University	Study metal mediated cyclo-addition reactions to synthesize natural products
Diane Stearns	Northern Arizona University	Study the difference in mutations caused by soluble chromium vs. insoluble chromium; discover mechanism of cellular entry by soluble chromium compounds
Kent Sugden	University of Montana	Study the role of chromium in DNA mutations and cancer
Bo Xu	Southern Research Institute	The effect of chromium exposure on DNA damage
Ziling Xue	University of Tennessee, Knoxville	Development of an analytical method to determine chromium levels in biological fluids
Anatoly Zhitkovich	Brown University	Study the role of chromium in genetic alteration of cells after exposure

Source: FEDRIP 2008

## 7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring chromium compounds, their metabolites, and other biomarkers of exposure to chromium compounds. The intent is not to provide an exhaustive list of analytical methods, but to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are 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 lower detection limits and/or to improve accuracy and precision in detection.

### 7.1 BIOLOGICAL MATERIALS

Several methods are available for the analysis of chromium in different biological media, with some recent methods of chromium determination reported in Table 7-1. Multiple reviews on the subject provide more detailed descriptions of the available analytical methods (EPA 1984a; Fishbein 1984; IARC 1986a, 1990; Torgriksen 1982; WHO 1988). Frequently used methods for determining low levels of chromium in biological samples include neutron activation analysis (NAA); mass spectrometry (MS); graphite spark atomic emission spectrometry (AES); and graphite furnace atomic absorption spectrometry (GFAAS) (Greenberg and Zeisler 1988; Plantz et al. 1989; Urasa and Nam 1989; Veillon 1989). A newly added technique includes the use of total reflection X-ray fluorescence (TXRF) for analysis of total chromium in the air (Adekola and Eletta 2007).

There are numerous issues and considerations in collecting and analyzing the chromium content in presented samples. Some of these issues include problems with collection, contamination, and determining accurate concentration levels of the chromium content in the samples. The determination of trace quantities of chromium in biological materials requires special precautionary measures, from the initial sample collection process to the final analytical manipulations of the samples.

Contaminates including dust contamination or losses of the samples during collection, transportation, and storage should be avoided (EPA 1984a). Chromium-containing grinding and homogenizing equipment should not be used for preparation of biological samples. Reagents of the highest purity should be used to

## 7. ANALYTICAL METHODS

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Plasma	Wet ashing with HNO <sub>3</sub> /HClO <sub>4</sub> /H <sub>2</sub> SO <sub>4</sub> ; residue complexed with APDC and extracted with MIBK; evaporated residue dissolved deposited in HNO <sub>3</sub> /HCE, and solution on a polycarbonate foil	PIXE	0.3 µg/L	87% at 4.5 µg/g	Simonoff et al. 1984
Blood, serum	Sample after wet digestion converted to a volatile chelate usually with fluorinated acetylacetone	GC/ECD	0.03 pg 0.5 pg 1.0 ng	No data	Fishbein 1984
Serum	Mg(NO <sub>3</sub> ) <sub>3</sub> added to serum, dried by Lyophilization, ashed, and dissolved in 0.1 N HCl	GFAAS	0.005 µg/L	103% at 0.30 µg/L	Randall and Gibson 1987
Blood	Diluted with 0.1% EDTA and 5% isopropanol	GFAAS-Zeeman-effect background correction	0.09 µg/L	No data	Dube 1988
Blood or tissue	Wet ashing with HNO <sub>3</sub> /HClO <sub>4</sub> /H <sub>2</sub> SO <sub>4</sub>	ICP-AES	1 µg/100 g blood 0.2 µg/g tissue	114% recovery at 10 µg/sample	NIOSH 1994a (Method No. 8005)
Erythrocytes	Dilution with Triton X100	GFAAS	No data	No data	Lewalter et al. 1985
Serum and urine	HNO <sub>3</sub> de-proteinization	GFAAS with pyrolytic graphite tube and Zeeman background correction	0.02 µg/L (serum) 0.1 µg/L (urine)	No data	Sunderman et al. 1989
Body fluids (milk, urine, etc.)	Dried sample ashed by oxygen plasma, H <sub>2</sub> O <sub>2</sub> addition, drying, dilution in 1N HCl	GFAAS with tungsten iodide or deuterium arc or CEWM background correction	<0.25 µg/L	91% at 0.55 µg/L	Kumpulainen 1984
Urine	None	GFAAS	0.05 µg/L	91% at 0.22 µg/L	Randall and Gibson 1987



## 7. ANALYTICAL METHODS

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	None	GFAAS with CEWM background correction and WM-AES	0.09 µg/L (CEWM-AAS) 0.02 µg/L (WM-AES)	No data	Harnly et al. 1983
Urine	No sample preparation other than addition of yttrium internal standard	ICP-AES	12 µg/L	77% at 13 µg/L	Kimberly and Paschal 1985
Urine	Sorption onto polydithiocarbonate resin, ash sorbate in low temperature oxygen plasma and dissolve in HNO <sub>3</sub> /HClO <sub>4</sub>	ICP-AES	0.1 µg/sample	100% recovery at 1 µg/50mL urine	NIOSH 1994b (Method 8310)
Urine	None	GFAAS	0.0052 µg/L	No data	Kiilunen et al. 1987
Urine	Sample spiked with standard chromium (standard addition)	GFAAS	0.03–0.04 µg/L	No data	Veillon et al. 1982
Urine	Diluted with water	GFAAS-Zeeman-effect-background correction	0.09 µg/kg	No data	Dube 1988
Milk powder	Mixed with water	GFAAS	5 µg/kg	134–141% at 17.7 µg/kg	Wagley et al. 1989
Tissue(Chromium(V))	Injection of sodium dichromate	EPR	0.1 mmol/kg	No data	Liu et al. 1994

AAS = atomic absorption spectrophotometry; APDC = ammonium pyrrolidine dithiocarbonate; CEWM = continuum source echelle monochromator wavelength-modulated; ECD = electron capture detector; EDTA = ethylenediaminetetraacetic acid; EPR = electron paramagnetic resonance spectroscopy; GC = gas chromatography; GFAS = graphite furnace AAS; H<sub>2</sub>O<sub>2</sub> = hydrogen peroxide; H<sub>2</sub>SO<sub>4</sub> = sulfuric acid; HCl = hydrochloric acid; HClO<sub>4</sub> = perchloric acid; HNO<sub>3</sub> = nitric acid; ICP-AES = inductively coupled plasma-atomic emission spectrometry; Mg(NO<sub>3</sub>)<sub>3</sub> = magnesium nitrate; MIBK = methylisobutyl ketone; MS = mass spectrometry; PIXE = proton-induced X-ray emission spectrometry; XRF = X-ray fluorescence analysis; WM-AES = wavelength-modulated atomic emission spectrometry

## 7. ANALYTICAL METHODS

avoid contamination, and the potential loss of chromium due to volatilization during wet and dry ashing should be minimized (EPA 1984a).

The determination of chromium in most biological samples is difficult because of the matrix interference and the very low concentrations present in these samples. Prior to 1978, numerous erroneous results were reported for the chromium level in urine using electrothermal atomic absorption spectrometry (EAAS) because of the inability of conventional atomic absorption spectrometry systems to correct for the high nonspecific background absorption. Similarly, the reported serum and plasma chromium concentrations of normal subjects have varied more than 5,000-fold since the early 1950s. The chromium levels in human serum or plasma as reported in the mid-1980s ranged from 0.01 to 0.3  $\mu\text{g/L}$ , and the daily urinary excretion rate of chromium in healthy and nonoccupationally exposed humans is  $<1 \mu\text{g/day}$  (Anderson 1987; Harnly et al. 1983; Sunderman et al. 1989; Veillon 1989).

The problem of generating accurate data for chromium in biological samples is further complicated by the lack of Standard Reference Materials (SRM). Standards in chromium certified materials, such as brewer's yeast (DOC 1976c), bovine liver (DOC 1977b, 1982), human serum (DOC 1985, 1993b, 2003), urine (DOC 1993c), orchard leaves (DOC 1977a), spinach leaves (DOC 1976b, 1996), pine needles (DOC 1993a), oyster tissue (DOC 1983, 1989), and tomato leaves (DOC 1976a), have been issued by the National Institute of Standards and Technology (formerly the National Bureau of Standards). However, due to the previous lack of SRMs, older data should be interpreted with caution (EPA 1984a), unless the data are verified by interlaboratory studies (WHO 1988).

In addition to the consideration of contamination and potential loss of sample, it should be noted that chromium may exist as several different oxidation states in biological media. Two of the most common oxidation states are chromium (III) and chromium (VI). Each of these oxidation states displays very different physical and biological properties. In biological samples where chromium is generally present as chromium(III), the choice of a particular method is dictated by several factors, including the type of sample, its chromium level, and the scope of the analysis (Kumpulainen 1984).

The preceding factors, in combination with the desired precision and accuracy and the cost of analysis, should be considered in selecting a particular analytical method. Although the methods reported in Table 7-1 represent some of the more recent methods, they are not necessarily the ones most commonly used. A comparison of the various standard methods and approaches for maintaining sample purity and integrity during sampling, handling, and analysis are provided by Kumpulainen (1984).

## 7. ANALYTICAL METHODS

**7.2 ENVIRONMENTAL SAMPLES**

Analytical methods for determining chromium in environmental samples are reported in Table 7-2. The three commonly used methods that have the greatest sensitivity for chromium detection in air are GFAAS, instrumental neutron activation analysis (INAA), and graphite spark atomic emission spectrometry (Schroeder et al. 1987). Measurements of low levels of chromium concentrations in water have been made by specialized methods, such as inductively coupled plasma mass spectrometry (ICP-MS), capillary column gas chromatography (HRGC) of chelated chromium with electron capture detection (ECD), and electrothermal vaporization inductively coupled plasma mass spectrometry (Gonzalez et al. 2005; Henshaw et al. 1989; Malinski et al. 1988; Parks et al. 2004; Schaller and Neeb 1987). A method using high performance liquid chromatography (HPLC) interfaced with direct current plasma emission spectrometer has been used for the determination of chromium(III) and chromium(VI) in water samples (Krull et al. 1983). An acid digestion procedure followed by AAS has been developed that can quantify chromium(VI) in soil, sediment, and sludge (Ayyamperumal 2006; Oygard et al. 2004). The preferred methods for digestion of environmental samples have been discussed by Griepink and Tolg (1989).

Many of the same issues with the biological samples are also present in environmental analysis, including issues of collection, contamination, and detection. Chromium may be present in both the trivalent and hexavalent oxidation states in most ambient environmental and occupational samples, and the distinction between soluble and insoluble forms of chromium(VI) is sometimes necessary. The quantification of soluble and insoluble chromium is done by determining chromium concentrations in aqueous filtered and unfiltered samples. However, soluble chromium(VI) may be reduced to chromium(III) on filtering media, particularly at low concentrations, and under acidic conditions. Teflon® filter and alkaline solution are most suitable to prevent this reduction (Sawatari 1986). Routine analytical methods are not available that can quantify the concentration of both chromium(VI) and chromium(III) in air samples when present at a total concentration of  $<1 \mu\text{g}/\text{m}^3$  (EPA 1990a), although two methods described in Table 7-2 can determine chromium(VI) concentrations alone in air at a minimum detection limit of  $0.1 \text{ ng}/\text{m}^3$  for a  $20\text{-m}^3$  sample (CARB 1990).

As in the case of biological samples, contamination and chromium loss in environmental samples during sample collection, storage, and pretreatment should be avoided. Chromium loss from aqueous samples

## 7. ANALYTICAL METHODS

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (total chromium)	Air particulate matter collected on filter is cut out and irradiated with X-ray photons	XRF	0.017 µg/m <sup>3</sup>	No data	Wiersema et al. 1984
Air (total chromium)	The collected particulates in filter dissolved in HNO <sub>3</sub> , dried and redissolved in acidified water	ICP-AES	0.05–0.2 ng/m <sup>3</sup>	No data	Barrie and Hoff 1985
Air (total chromium)	Particulate matter collected on cellulose ester filter, digested with aqua regia	ICP-AES	1 µg/m <sup>3</sup>	87–102% at 0.5–100 µg	Lo and Arai 1988
Air (total chromium)	Air particulate collected on cellulose ester filter, wet wash with HCl/HNO <sub>3</sub>	Flame atomic absorption	0.06 µg/sample	98% at 45–90 µg/sample	NIOSH 1994c (Method 7024)
Air (total chromium)	Sample collected on cellulose ester membrane filter dissolved in acid mixtures	ICP-AES	1 µg/sample	98% at 2.5 µg/filter	NIOSH 1994d (Method 7300)
Air (chromium(VI))	Sample collected on sodium carbonate-impregnated cellulose filter leached with sodium bicarbonate	Ion chromatography/coulometric	0.1 ng/m <sup>3</sup> for 20 m <sup>3</sup> sample	89–99% at 100 ng	CARB 1990
Air (chromium(VI))	Sample collected in filters containing sodium bicarbonate buffer at 15 L/minute	Ion chromatography/coulometric	0.01 ng/m <sup>3</sup> for 20 m <sup>3</sup> sample	94%	Sheehan et al. 1992
Occupational air (welding fumes)	The particular matter on filter wet ashed with H <sub>2</sub> SO <sub>4</sub> and chromium(III) oxidized to chromium(VI) by addition of Na <sub>2</sub> O <sub>2</sub> ; the centrifuged solution was acidified with HCl and reduced to chromium(III) by SO <sub>2</sub> ; the solution was complexed with β-isopropyl tropolone in CHCl <sub>3</sub>	HPLC-UV	10 pg	No data	Maiti and Desai 1986

## 7. ANALYTICAL METHODS

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Occupational air (chromium (VI))	Extract with 0.05 M $(\text{NH}_4)_2\text{SO}_4$ -0.5 M $(\text{NH}_4)_2\text{SO}_4$ .1 M $\text{NH}_3$ .	FIA-UV/VIS	0.11 ng	>90%	Wang et al. 1997a
Welding fumes (total chromium(VI))	Air particulate collected on PVC filter is extracted with hot 3% $\text{Na}_2\text{CO}_3$ and 2% $\text{NaOH}$ , acidified with $\text{H}_2\text{SO}_4$ and complexed with diphenyl carbazide	Spectrophotometry at 540 nm	0.05 $\mu\text{g}/\text{sample}$	No data	NIOSH 1994e (Method 7600); Zarka 1985
Welding fumes (total chromium(VI))	Air particulate collected on PVC filter, extracted with $\text{H}_2\text{SO}_4$ and complexed with diphenylcarbazine	Chromatography at 540 nm Spectrophotometry at 540 nm	3.5 $\mu\text{g}/\text{sample}$	No data	NIOSH 1994f (Method 7604)
Simultaneous determination of chromium(III) and chromium(VI) in water extract from metal fumes	Sample solution at pH 5 reacted with disodium ethylenediamine tetraacetic acid at 50 °C for 1 hour	HPLC on anion exchange column with $\text{Na}_2\text{CO}_3$ eluting solution and simultaneous UV and AAS detection	0.2 ng by UV for chromium(VI) 2.0 ng by UV 5.0 ng by AAS for chromium (IV) 5 ng by AAS for chromium (III)	95–105% at 0.002–2.0 $\mu\text{g}$	Suzuki and Serita 1985
Atmospheric deposition (snow); determination in soluble (chromium(VI)) and particulate (chromium(III)) part	The melted snow filtered through Nucleopore filter; the filtrate acidified with $\text{HNO}_3$ ; and dried by freeze-drier; residue dissolved in $\text{HNO}_3$ ; this preconcentrated solution placed in plastic tubes; both plastic tube and Nucleopore filter irradiated with protons	PIXE	2 $\mu\text{g}/\text{L}$ (soluble portion) 26 $\mu\text{g}/\text{L}$ (snow particle)	No data	Jervis et al. 1983; Landsberger et al. 1983
	Either the above Nucleopore filter or the preconcentrated liquid placed in plastic vial is irradiated by thermal neutron	INAA	5 $\mu\text{g}/\text{L}$ (soluble portion) 115 $\mu\text{g}/\text{g}$ (snow particle)	No data	Jervis et al. 1983; Landsberger et al. 1983

## 7. ANALYTICAL METHODS

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Drinking water, surface water, and certain domestic and industrial effluents (dissolved chromium(VI))	Complex chromium(VI) in water with APDC at pH 2.4 and extracted with MIBK	Furnace AAS	2.3 µg/L	No data	EPA 1983c (Method 218.5)
Drinking water, groundwater and water effluents (chromium(VI))	Buffer solution introduced into ion chromatograph. Derivatized with dipenylcarbazide	Ion chromatography spectrophotometry at 530 nm	0.3 µg/L	100% at 100 µg/L	EPA 1996a (Method 7199)
Waste water and industrial effluent for chromium(VI) only	Buffered sample mixed with AlCl <sub>3</sub> and the precipitate separated by centrifugation or filtration	DPPA at pH 10–12	30 µg/L	90% at 0.2 mg/L	Harzdorf and Janser 1984
Waste water 1986 (chromium(VI))	Sample mixed with a masking agent and cetyltrimethylammonium bromide solution at pH 4.7–6.6, heated in water bath at 50 °C for 10 minutes	Spectrophotometry at 583 nm	Lower than diphenylcarbazone method	No data	Qi and Zhu 1986
Water (total chromium)	Calcium nitrate added to water and chromium is converted to chromium(III) by acidified H <sub>2</sub> O <sub>2</sub>	GFAAS or ICP/AES	1.0 µg/L (GFAAS) 7.0 µg/L	97–101% at 19–77 µg/L	EPA 1983a, 1986a (Method 218.2 and 7191)
Industrial wastes, soils, sludges, sediments, and other solid wastes (total chromium)	Digest with nitric acid/hydrogen peroxide	ICP-AES	4.7 µg/L	101% at 3.75 mg/L	EPA 1996b (Method 6010b)
Oil wastes, oils, greases, waxes, crude oil (soluble chromium)	Dissolve in xylene or methyl isobutyl ketone	AAS or GFAAS	0.05 mg/L	107% at 15 µg/L	EPA 1986b (Method 7190)

## 7. ANALYTICAL METHODS

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Groundwater, domestic and industrial waste (chromium[VI])	Chromium(VI) is coprecipitated with lead sulfate, reduced, and resolubilized in nitric acid	AAS or GFAAS	0.05 mg/L (AAS) 2.3 µg/L (GFAAS)	93–96% at 40 µg/L	EPA 1986c (Method 7195)
Groundwater-EP extract, domestic, and industrial waste (chromium[VI])	Chelation with ammonium pyrrolidine dithiocarbonate and extraction with methyl isobutyl ketone	AAS	No data	96% at 50 µg/L	EPA 1983b, 1986d (Method 218.4 and 7197)
Water, waste water, and EP extracts (chromium(VI))	Direct	DPPA	10 µg/L	93% at 5 mg/L	EPA 1986e (Method 7198)
Soil, sediment and sludges (chromium(VI))	Acid digestion extraction using HNO <sub>3</sub>	AAS	No data	85–115%	Ayyamperumal 2006; Oygard et al. 2004

AAS=atomic absorption spectrophotometry; AlCl<sub>3</sub>=aluminum chloride; APDC=ammonium pyrrolidine dithiocarbonate; CHCl<sub>3</sub>=chloroform; DPPA=differential pulse polarographic analysis; EAAS=electrothermal atomic absorption spectrometry; EP=extraction procedure (for toxicity testing); FIA/uv/vis=flow injection analysis-ultraviolet/visible spectroscopy; GFAAS=graphite furnace atomic absorption spectrometry; H<sub>2</sub>SO<sub>4</sub>=sulfuric acid; HCl=hydrochloric acid; HNO<sub>3</sub>=nitric acid; HPLC=high pressure liquid chromatography; ICP-AES=inductively coupled plasma-atomic emission spectrometry; INAA=instrumental neutron activation analysis; MIBK=methylisobutyl ketone; Na<sub>2</sub>O<sub>2</sub>=sodium peroxide; NaOH=sodium hydroxide; Na<sub>2</sub>CO<sub>3</sub>=sodium carbonate; (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>=ammonium sulfate; NH<sub>3</sub>=ammonia; PIXE=proton-induced X-ray emission spectrometry; SO<sub>2</sub>=sulfur dioxide; UV=ultraviolet; XRF=X-ray fluorescence analysis

## 7. ANALYTICAL METHODS

due to adsorption on storage containers should be avoided by using polyethylene or similar containers and acidifying the solution to the proper pH.

### 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 chromium compounds 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 chromium compounds.

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

#### 7.3.1 Identification of Data Needs

**Methods for Determining Biomarkers of Exposure and Effect.** There are studies correlating chromium in urine (Cocker et al. 2007; Gylseth et al. 1977; Kilburn et al. 1990; Lindberg and Vesterberg 1983a; McAughey et al. 1988; Minoia and Cavalleri 1988; Mutti et al. 1985b; Sjogren et al. 1983; Tola et al. 1977), blood (Kilburn et al. 1990; Lewalter et al. 1985; McAughey et al. 1988; Wiegand et al. 1988), hair (Randall and Gibson 1987, 1989; Takagi et al. 1986), hair in children (Chiba et al. 2004), nails (Takagi et al. 1988), and erythrocytes (Lukanova et al. 1996) to occupational exposure levels. Since chromium is an essential element, levels of chromium compounds have to be relatively high in humans before they signify an increase due to exposure. Hair has been useful in determining chronic occupational exposure to chromium in high concentrations (Randall and Gibson 1989), although the utility of this method for detecting prior exposures has a limited timespan of months (Simpson and Gibson 1992). Analytical methods to detect chromium concentrations in urine (Randall and Gibson 1987), whole blood (Case et al. 2001; Dube 1988; Fahrni 2007), serum/plasma (Simonoff et al. 1984), and tissue (Fahrni 2007; Liu et al. 1994) have been reported. Generally, the detection limits are in the sub ppb to ppb range, and recoveries are good (>70%).



## 7. ANALYTICAL METHODS

Chromium induced DNA-protein complexes were prepared as a biomarker of exposure, as discussed in Section 3.12.2. These complexes can be detected by potassium chloride-sodium dodecyl sulfate mediated precipitation. These methods have a number of inherent limitations including tedious methodology and being subject to considerable interindividual and interlaboratory variations (Singh et al. 1998b). Only one study has attempted to utilize this biomarker, and it was found that volunteers exposed to chromium in drinking water showed no increase in protein-DNA crosslinking in blood cells (Kuykendall et al. 1996). This suggests that this procedure may not be sensitive enough for use in environmental monitoring unless an individual has received a potentially toxic level of exposure. In addition, chromium forms chromium-DNA complexes inside of cells, and these complexes constitute a potential biomarker for the assessment of environmental or occupational exposure. A novel method has been described for the sensitive detection of chromium-DNA adducts using inductively coupled plasma mass spectrometry (Singh et al. 1998b). The detection limits of this method are in the parts per trillion range and allow for the detection of as few as 2 chromium adducts per 10,000 bases, which coupled with the low DNA sample requirements, make this method sensitive enough to measure background levels in the population. There are no data to determine whether there are age-specific biomarkers of exposure or effects or any interactions with other chemicals that would be specific for children.

**Methods for Determining Parent Compounds and Degradation Products in Environmental**

**Media.** Methods are available and in use for detecting chromium in air, water, and soil environments. Air contaminated with chromium(VI), particularly in occupational settings, is of great concern. Methods have been developed that can determine low levels of total chromium and chromium(VI) in the air, with detection limits in the ng/m<sup>3</sup> range and excellent recoveries (90% or better) (Ashley et al. 2003; Barrie and Hoff 1985; CARB 1990; NIOSH 1994c, 1994d; Sheehan et al. 1992). These methods are sufficient to determine background chromium levels in the environment and levels at which health effects may occur. Chromium can be detected in water at concentrations in the ppb range (Abu-Saba and Flegal 1997; EPA 1983a, 1996a; Harzdorf and Janser 1984 Parks et al. 2004) and household and bottled drinking water (Al-Saleh and Al-Doush 1998), with recoveries of  $\geq 90\%$  being reported in some studies. In addition, there are also methods that can differentiate chromium(VI) from chromium(III) in water samples (EPA 1986c). A reliable analytical method for extracting and quantifying chromium, including chromium(VI), from soil surfaces has also been reported (Ayyamperumal et al. 2006; Oygard et al. 2004). Analytical methods exist that are sufficient for measuring background levels of chromium in soil (Ayyamperumal et al. 2006; EPA 1996b; Finley and Paustenbach 1997; Oygard et al. 2004) and water (EPA 1983a, 1983b, 1983c, 1986a, 1996a; Finley and Paustenbach 1997) and also water samples collected from various geological sites of interest (Gonzalez et al. 2005; Parks et al. 2004).

## 7. ANALYTICAL METHODS

**7.3.2 Ongoing Studies**

Analytical methods for the detection of chromium compounds at increasingly lower concentrations are currently under development. Targeted areas of interest include air, water, and soil monitoring, with special emphasis being placed on populations considered vulnerable or potentially at risk, such as children and occupational workers. Additionally, more reliable methods to separate chromium(III) analysis from chromium(VI) analysis in collected samples is a source of interest and active research.

## 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.

An MRL of  $5 \times 10^{-6}$  mg chromium(VI)/m<sup>3</sup> has been derived for intermediate- and chronic-duration inhalation exposure to chromium(VI) as chromium trioxide mist and other dissolved hexavalent chromium aerosols and mists. The MRL is based on a LOAEL of 0.002 mg chromium(VI)/m<sup>3</sup> for upper respiratory effects in humans in the occupational exposure study by Lindberg and Hedenstierna (1983), which spanned both intermediate and chronic durations.

An MRL of 0.0003 mg chromium(VI)/m<sup>3</sup> has been derived for intermediate-duration inhalation exposure to chromium(VI) as particulate hexavalent chromium compounds. The MRL is based on a benchmark concentration of 0.016 mg chromium(VI)/m<sup>3</sup> for increases in lactate dehydrogenase activity in bronchiolavage fluid from rats in the study by Glaser et al. (1990).

An MRL of 0.005 mg chromium(VI)/kg/day has been derived for intermediate-duration oral exposure to hexavalent chromium compounds for hematological effects (e.g., microcytic, hypochromic anemia) in rats using data from a study by NTP (2008a). Because several hematological parameters are used to define the clinical picture of anemia, the MRL is based on the average BMDL<sub>2sd</sub> values for hemoglobin, MCV, and MCH of 0.52 mg chromium(VI)/kg/day.

An MRL of 0.001 mg chromium(VI)/kg/day has been derived for chronic-duration oral exposure to hexavalent chromium compounds. The MRL is based on a benchmark dose of 0.09 mg chromium(VI)/kg/day for diffuse epithelial hyperplasia of the duodenum in mice in a study by NTP (2008a).

An MRL of 0.005 mg chromium(III)/m<sup>3</sup> has been derived for intermediate-duration inhalation exposure to insoluble trivalent chromium particulate compounds. The MRL is based on a minimal LOAEL of 3 mg chromium(III)/m<sup>3</sup> for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in rats in the study by Derelanko et al. (1999).

## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

An MRL of 0.0001 mg chromium(III)/m<sup>3</sup> has been derived for intermediate-duration inhalation exposure to soluble trivalent chromium particulate compounds. The MRL is based on a LOAEL of 3 mg chromium(III)/m<sup>3</sup> for nasal and larynx lesions in rats in the study by Derelanko et al. (1999).

A chronic oral reference dose (RfD) of 0.003 mg chromium(VI)/kg/day has been derived and verified by EPA for soluble salts of chromium(VI) (e.g., potassium chromate, sodium chromate, potassium dichromate, and sodium dichromate) (IRIS 2008). The RfD is based on a NOAEL for systemic effects in rats exposed to 2.5 mg chromium(VI)/kg/day as potassium chromate in the drinking water for 1 year in the study by MacKenzie et al. (1958).

A chronic inhalation RfC of 0.008 µg chromium(VI)/m<sup>3</sup> has been derived and verified by EPA for chromic acid mists and dissolved chromium(VI) aerosols (IRIS 2008). The RfC is based on a LOAEL for nasal septum atrophy in workers exposed to 0.002 mg chromium(VI)/m<sup>3</sup> (Lindberg and Hedenstierna 1983).

A chronic inhalation RfC of 0.0001 mg chromium(VI)/m<sup>3</sup> has been derived and verified by EPA for chromium(VI) particulates (IRIS 2008). The RfC is based on a benchmark concentration of 0.016 mg chromium(VI)/m<sup>3</sup> derived from data for lactate dehydrogenase activity in bronchoalveolar lavage fluid in rats exposed to sodium dichromate (Glaser et al. 1990).

A chronic oral RfD of 1.5 mg chromium(III)/kg/day has been derived and verified by EPA for insoluble salts of chromium(III) (e.g., chromium oxide and chromium sulfate) (IRIS 2008). The RfD is based on a NOAEL for systemic effects in rats fed 1,800 mg chromium(III)/kg/day for 5 days/week for 600 feedings (840 total days) in the study by Ivankovic and Preussmann (1975). EPA has determined that the data are inadequate for the development of an RfC for chromium(III) due to the lack of relevant toxicity study addressing the respiratory effects of chromium(III) (IRIS 2008).

The Institute of Medicine (IOM) of the National Academy of Sciences (NAS) determined an adequate intake (e.g., a level typically consumed by healthy individuals) of 20–45 µg chromium(III)/day for adolescents and adults (IOM 2001)

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

## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

**Table 8-1. Regulations and Guidelines Applicable to Chromium**

Agency	Description	Information	Reference
<u>INTERNATIONAL</u>			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2008
	Chromium, metallic	Group 3 <sup>a</sup>	
	Chromium (III) compounds	Group 3 <sup>a</sup>	
	Chromium (VI)	Group 1 <sup>b</sup>	
WHO	Air quality guidelines		WHO 2000
	Chromium (VI)	1 µg/m <sup>3</sup> for a lifetime risk of 4x10 <sup>-2</sup>	
	Drinking water quality guidelines		WHO 2004
	Chromium (for total chromium)	0.05 mg/L <sup>c</sup>	
<u>NATIONAL</u>			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)		ACGIH 2007
	Calcium chromate (as Cr)	0.001 mg/m <sup>3</sup>	
	Chromium and inorganic compounds (as Cr)		
	Metal and chromium (III) compounds	0.5 mg/m <sup>3</sup>	
	Water-soluble chromium (VI) compounds	0.05 mg/m <sup>3</sup>	
	Insoluble chromium (VI) compounds	0.01 mg/m <sup>3</sup>	
	Lead chromate		
	As Pb	0.05 mg/m <sup>3</sup>	
	As Cr	0.012 mg/m <sup>3</sup>	
	Strontium chromate (as Cr)	0.0005 mg/m <sup>3</sup>	
	Zinc chromates (as Cr)	0.01 mg/m <sup>3</sup>	
	TLV basis (critical effects)		
	Calcium chromate (as Cr)	Lung cancer	
	Chromium		
	Metal and chromium (III) compounds	Upper respiratory tract and skin irritation	
	Water-soluble chromium (VI) compounds	Upper respiratory tract irritation and cancer	
	Insoluble chromium (VI) compounds	Lung cancer	

## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

**Table 8-1. Regulations and Guidelines Applicable to Chromium**

Agency	Description	Information	Reference
<b>NATIONAL (cont.)</b>			
ACGIH	TLV basis (critical effects)		ACGIH 2007
	Lead chromate	Male reproductive damage, teratogenic effects, and vasoconstriction	
	As Pb		
	As Cr		
	Strontium chromate (as Cr)	Cancer	
	Zinc chromates (as Cr)	Nasal cancer	
EPA	AEGL-1, -2, and -3	No data	EPA 2007a
	Second list of AEGL priority chemicals for guideline development		EPA 2008a
	Chromium (III) chloride	Yes	
	Hazardous air pollutant		EPA 2007b
	Chromium compounds	Yes	42 USC 7412
NIOSH	REL (8-hour TWA)		NIOSH 2005
	Chromium, metal, chromium (II), and chromium (III) compounds	0.5 mg/m <sup>3</sup>	
	REL (10-hour TWA)		
	Chromium (VI) trioxide (as Cr) <sup>d,e</sup>	0.001 mg/m <sup>3</sup>	
	IDLH		
	Chromium, metal (as Cr)	250 mg/m <sup>3</sup>	
	Chromium (VI) trioxide (as chromium [VI]) <sup>e</sup>	15 mg/m <sup>3</sup>	
	Target organs		
	Chromium, metal	Eyes, skin, and respiratory system	
	Chromium (VI) trioxide	Blood, respiratory system, liver, kidneys, eyes, and skin	
	Category of pesticides		NIOSH 1992
	Potassium chromate	Group 1 pesticide	
	Potassium dichromate	Group 1 pesticide	
	Sodium chromate	Group 1 pesticide	
OSHA	PEL (8-hour TWA) for general industry (ceiling limit)		OSHA 2007a 29 CFR 1910.1000, Table Z-2
	Chromium (II) compounds (as Cr)	0.5 mg/m <sup>3</sup>	
	Chromium (III) compounds (as Cr)	0.5 mg/m <sup>3</sup>	
	Chromium metal and insoluble salt (as Cr)	1.0 mg/m <sup>3</sup>	
	Chromium (VI) compounds	5 µg/m <sup>3</sup>	OSHA 2007d 29 CFR 1910.1026

## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

**Table 8-1. Regulations and Guidelines Applicable to Chromium**

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
	PEL (8-hour TWA) for shipyard industry (ceiling limit)		OSHA 2007c 29 CFR 1915.1000
	Chromium (II) compounds (as Cr)	0.5 mg/m <sup>3</sup>	
	Chromium (III) compounds (as Cr)	0.5 mg/m <sup>3</sup>	
	Chromium metal and insoluble salt (as Cr)	1.0 mg/m <sup>3</sup>	
	Chromium (VI) compounds	0.5 µg/m <sup>3</sup>	OSHA 2007e 29 CFR 1915.1026
OSHA	PEL (8-hour TWA) for construction industry (ceiling limit)		OSHA 2007b 29 CFR 1926.55, Appendix A
	Chromium (II) compounds (as Cr)	0.5 mg/m <sup>3</sup>	
	Chromium (III) compounds (as Cr)	0.5 mg/m <sup>3</sup>	
	Chromium metal and insoluble salt (as Cr)	1.0 mg/m <sup>3</sup>	
	Chromium (VI) compounds	0.5 µg/m <sup>3</sup>	OSHA 2007f 29 CFR 1926.1126
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act		EPA 2008b 40 CFR 116.4
	Ammonium dichromate	Yes	
	Calcium chromate	Yes	
	Chromium (III) sulfate	Yes	
	Potassium chromate	Yes	
	Strontium chromate	Yes	
	Drinking water standards and health advisories		EPA 2006a
	Chromium (total)		
	1-day health advisory for a 10-kg child	1 mg/L	
	10-day health advisory for a 10-kg child	1 mg/L	
	DWEL	0.1 mg/L	
	Lifetime	No data	
	National secondary drinking water standards		EPA 2003
	Chromium (total)		
	MCL	0.1 mg/L	
	Public health goal	0.1 mg/L	

## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

**Table 8-1. Regulations and Guidelines Applicable to Chromium**

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
	National recommended water quality criteria <sup>g</sup>	No data	EPA 2006b
	Chromium (III)		
	Freshwater CMC	570 µg/L	
	Freshwater CCC	74 µg/L	
	Chromium (VI)		
	Freshwater CMC	16 µg/L	
	Freshwater CCC	11 µg/L	
	Saltwater CMC	1,100 µg/L	
	Saltwater CCC	50 µg/L	
EPA	Toxic pollutants designated pursuant to Section 307(a)(1) of the Clean Water Act		EPA 2008i 40 CFR 401.15
	Chromium and compounds	Yes	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act		EPA 2008c 40 CFR 117.3
	Chromium (III) sulfate	100 pounds	
	Potassium chromate	10 pounds	
	Strontium chromate	10 pounds	
c. Food			
EPA	Inert ingredients permitted for use in nonfood use pesticide products		EPA 2008e
	Chromium (III) oxide	Yes	
	Sodium chromate	Yes	
FDA	Bottled drinking water		FDA 2007a 21 CFR 165.110
	Chromium	0.1 mg/L	
	EAFUS <sup>h</sup>	No data	FDA 2008
	Indirect food additives: adhesives and components of coatings		FDA 2007b 21 CFR 175.105
	Sodium chromate	Yes	
	Recommended daily intake		FDA 2007c 21 CFR 101.9
	Chromium	120 µg	



## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

**Table 8-1. Regulations and Guidelines Applicable to Chromium**

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2007
	Calcium chromate (as Cr)	A2 <sup>i</sup>	
	Chromium		
	Metal and chromium (III) compounds	A4 <sup>j</sup>	
	Water-soluble chromium (VI) compounds	A1 <sup>k</sup>	
	Insoluble chromium (VI) compounds	A1 <sup>k</sup>	
	Lead chromate		
	As Pb	A2 <sup>i</sup>	
	As Cr	A2 <sup>i</sup>	
	Strontium chromate (as Cr)	A2 <sup>i</sup>	
Zinc chromates (as Cr)	A1 <sup>k</sup>		
ACGIH	Biological exposure indices		ACGIH 2007
	Chromium		
	Water-soluble chromium (VI) fume		
	Total chromium in urine at end of shift at end of workweek	25 µg/L	
	Total chromium in urine increase during shift	10 µg/L	
EPA	Carcinogenicity classification		IRIS 2008
	Chromium(III), insoluble salts	Group D <sup>l</sup>	
	Chromium (VI)		
	Inhalation route of exposure	Group A <sup>m</sup>	
	Oral route of exposure	Group D <sup>l</sup>	
	RfC		
	Chromium(III), insoluble salts	Not available	
	Chromium (VI)		
	Chromic acid mists and dissolved Cr (VI) aerosols	8x10 <sup>-6</sup> mg/m <sup>3</sup>	
	Cr(VI) particulates	1x10 <sup>-4</sup> mg/m <sup>3</sup>	
RfD			
Chromium(III), insoluble salts	1.5 mg/kg/day		
Chromium (VI)	3x10 <sup>-3</sup> mg/kg/day		
Master Testing List	Yes <sup>n</sup>	EPA 2008f	
RCRA waste minimization PBT priority chemical list		EPA 1998c 63 FR 60332	
Chromium	Yes		

## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

**Table 8-1. Regulations and Guidelines Applicable to Chromium**

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list		EPA 2008d 40 CFR 264, Appendix IX
	Chromium (total)	Yes	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance		EPA 2008j 40 CFR 302.4
	Ammonium dichromate	Yes <sup>o</sup>	
	Calcium chromate	Yes <sup>o,p</sup>	
	Chromium	Yes <sup>q</sup>	
	Chromium and compounds	Yes <sup>r</sup>	
	Chromium (III) sulfate	Yes <sup>o</sup>	
	Potassium chromate	Yes <sup>o</sup>	
	Strontium chromate	Yes <sup>o</sup>	
EPA	Superfund, emergency planning, and community right-to-know		
	Reportable quantity		EPA 2008j 40 CFR 302.4
	Ammonium dichromate	10 pounds	
	Chromium	5,000 pounds	
	Calcium chromate	10 pounds	
	Chromium and compounds	None <sup>s</sup>	
	Chromium (III) sulfate	1,000 pounds	
	Potassium chromate	10 pounds	
	Strontium chromate	10 pounds	
	Effective date of toxic chemical release reporting		EPA 2008h 40 CFR 372.65
	Chromium	01/01/1987	
	Extremely Hazardous Substances		EPA 2008g 40 CFR 355, Appendix A
	Chromium (III) chloride		
	Reportable quantity	1 pound	
	Threshold planning quantity	1,000 pounds	

## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

**Table 8-1. Regulations and Guidelines Applicable to Chromium**

Agency	Description	Information	Reference
<b>NATIONAL (cont.)</b>			
NTP	Carcinogenicity classification		NTP 2005
	Chromium (VI) compounds	Known to be human carcinogens	
	Calcium chromate		
	Chromium (VI) trioxide		
	Ferrocchromite		
	Lead chromate		
	Strontium chromate		
	Zinc chromate		

<sup>a</sup>Group 3: The agent is not classifiable as to its carcinogenicity to humans.

<sup>b</sup>Group 1: The agent is carcinogenic to humans.

<sup>c</sup>Provisional guideline value, as there is evidence of a hazard, but the available information on health effects is limited.

<sup>d</sup>The NIOSH REL (10-hour TWA) is 0.001 mg Cr(VI)/m<sup>3</sup> for all hexavalent chromium (Cr[VI]) compounds. NIOSH considers all chromium (VI) compounds (including chromic acid, tert-butyl chromate, zinc chromate, and chromyl chloride) to be potential occupational carcinogens.

<sup>e</sup>NIOSH potential occupational carcinogen.

<sup>f</sup>Group 1 pesticides: contains the pesticides that pose a significant risk of adverse acute health effects at low concentrations.

<sup>g</sup>The CMC is an estimate of the highest concentration of a material in surface water to which an aquatic community can be exposed briefly without resulting in an unacceptable effect. The CCC is an estimate of the highest concentration of a material in surface water to which an aquatic community can be exposed indefinitely without resulting in an unacceptable effect.

<sup>h</sup>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.

<sup>i</sup>A2: Suspected human carcinogen.

<sup>j</sup>A4: Not classifiable as a human carcinogen.

<sup>k</sup>A1: Confirmed human carcinogen.

<sup>l</sup>Group D: not classified as to its human carcinogenicity.

<sup>m</sup>Group A: known human carcinogen by the inhalation route of exposure.

<sup>n</sup>Chromium was recommended to the MTL by ATSDR in 1994 and the testing needs development is currently underway. The testing needs include acute toxicity, neurotoxicity, reproductive, and immunotoxicity health effects.

<sup>o</sup>Designated CERCLA hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act.

<sup>p</sup>Designated CERCLA hazardous substance pursuant to Section 3001 of the Resource Conservation and Recovery Act.

<sup>q</sup>Designated CERCLA hazardous substance pursuant to Section 307(a) of the Clean Water Act.

<sup>r</sup>Designated CERCLA hazardous substance pursuant to Section 307(a) of the Clean Water Act and Section 112 of the Clean Air Act.

<sup>s</sup>Indicates that no reportable quantity is being assigned to the generic or broad class.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; CCC = Criterion Continuous Concentration; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; CMC = Criteria Maximum Concentration; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; 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; MTL = Master Testing List; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PBT = persistent, bioaccumulative, and toxic; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TSD = transport, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

8. REGULATIONS, ADVISORIES, AND GUIDELINES

This page is intentionally blank.

## 9. REFERENCES

- \*Aaseth J, Alexander J, Norseth T. 1982. Uptake of  $^{51}\text{Cr}$ -chromate by human erythrocytes - A role of glutathione. *Acta Pharmacol Toxicol* 50:310-315.
- Abdel-Wahhab MA, Ahmed HH. 2004. Protective effect of Korean Panax ginseng against chromium VI toxicity and free radicals generation in rats. *J Ginseng Res* 28(1):11-17.
- \*Abu-Saba K, Flegal AR. 1997. Temporally variable freshwater sources of dissolved chromium to the San Francisco Bay estuary. *Environ Sci Technol* 31:3455-3460.
- ACGIH. 1998. TLVs and BEIs for chemical substances and physical agents. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 26, 99.
- \*ACGIH. 2007. Chromium. Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 20.
- +\*Acharya S, Mehta K, Krishnan S, et al. 2001. A subtoxic interactive toxicity study of ethanol and chromium in male Wistar rats. *Alcohol* 23(2):99-108.
- Acharya UR, Mishra M, Tripathy RR, et al. 2006. Testicular dysfunction and antioxidative defense system of Swiss mice after chromic acid exposure. *Reprod Toxicol* 22:87-91.
- +\*Adachi S. 1987. Effect of chromium compounds on the respiratory system: Part 5. Long term inhalation of chromic acid mist in electroplating by C57BL female mice and recapitulation on our experimental studies. *Jpn J Ind Health* 29:17-33.
- +\*Adachi S, Yoshimura H, Katayama H, et al. 1986. Effects of chromium compounds on the respiratory system: Part 4. Long term inhalation of chromic acid mist in electroplating to ICR female mice. *Jpn J Ind Health* 28:283-287.
- +\*Adachi S, Yoshimura H, Miyayama R, et al. 1981. Effects of chromium compounds on the respiratory system: Part 1. An experimental study of inhalation of chromic acid mist in electroplating. *Jpn J Ind Health* 23:294-299.
- \*Adekola FA, Eletta OAA. 2007. A study of heavy metal pollution of Asa River, Ilorin. Nigeria; trace metal modeling and geochemistry. *Environ Monit Assess* 125:157-163.
- \*Adinolfi M. 1985. The development of the human blood-CSF-brain barrier. *Dev Med Child Neurol* 27:532-537.
- \*Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. *Environ Health Perspect Suppl* 103(7):103-112.

---

+ Cited in Supplemental Document

\* Cited in text

## 9. REFERENCES

- \*Agency for Toxic Substances and Disease Registry. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles. Atlanta, GA: Agency for Toxic Substances and Disease Registry, Division of Toxicology.
- \*Agency for Toxic Substances and Disease Registry. 1990a. Health assessment for Cherokee County-Galena subsite National Priorities List (NPL) site, Galena, Cherokee County, Kansas, Region 7. Atlanta, GA: Agency for Toxic Substances and Disease Registry, CERCLIS No. KSD980741862. PB90112053.
- \*Agency for Toxic Substances and Disease Registry. 1990b. Health assessment for Butterworth Landfill, Kent County, Michigan, Region 5. Agency for Toxic Substances and Disease Registry, CERCLIS No. MIDO62222997. Atlanta, GA. PB90106899.
- \*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.
- Aghdassi E, Salit IE, Fung L, et al. 2006. Is chromium an important element in HIV-positive patients with metabolic abnormalities? An hypothesis generating pilot study. *J Am Coll Health* 25(1):56-63.
- +\*Aguilar MV, Martinez-Para C, Gonzalez J. 1997. Effects of arsenic(V)-chromium(III) interaction on plasma glucose and cholesterol levels in growing rats. *Ann Nutr Metab* 41:189-195.
- Ahmad I, Maria VL, Oliveira M, et al. 2006. Oxidative stress and genotoxic effects in gill and kidney of *Anguilla anguilla* L. exposed to chromium with or without pre-exposure to beta-naphthoflavone. *Mutat Res* 608(1):16-28.
- \*Aitio A, Jarvisalo J, Kiilunen M, et al. 1984. Urinary excretion of chromium as an indicator of exposure to trivalent chromium sulphate in leather tanning. *Int Arch Occup Environ Health* 54:241-249.
- Aitio A, Jarvisalo J, Kiilunen M, et al. 1988. Chromium. In: Clarkson TW, Friberg L, Norberg CF, et al., eds. *Biological monitoring of toxic metals*. New York, NY: Plenum Press, 369-382.
- \*Aiyar J, Berkovits HJ, Floyd RA, et al. 1991. Reaction of chromium(VI) with glutathione or with hydrogen peroxide: Identification of reactive intermediates and their role in chromium(VI)-induced DNA damage. *Environ Health Perspect* 92:53-62.
- \*Aiyar J, Borges K, Floyd RA, et al. 1989. Role of chromium(V), glutathione thiyl radical and hydroxyl radical intermediates in chromium(VI)-induced DNA damage. *Toxicol Environ Chem* 22:135-148.
- +Akatsuka K, Fairhall LT. 1934. The toxicology of chromium. *J Ind Hyg* 16:1-24.
- \*Albert RE. 1991. Issues in the risk assessment of chromium. *Environ Health Perspect* 92:91-92.
- Alcedo JA, Misra M, Hamilton JW, et al. 1994. The genotoxic carcinogen chromium(VI) alters the metal-inducible expression but not the basal expression of the metallothionein gene in vivo. *Carcinogenesis* 15(5):1089-1092.
- Alexander J, Aaseth J, Norseth T. 1982. Uptake of chromium by rat liver mitochondria. *Toxicology* 24:115-122.

## 9. REFERENCES

- +\*Alderson M, Rattan N, Bidstrup L. 1981. Health of workmen in the chromate-producing industry in Britain. *Br J Ind Med* 38:117-124.
- Aldrich MV, Gardea-Torresdey JL, Peralta-Videa JR, et al. 2003. Uptake and reduction of Cr(VI) to Cr(III) by mesquite (*Prosopis* spp.): Chromate-plant interaction and hydroponics and solid media studied using XAS. *Environ Sci Technol* 37:1859-1864.
- +\*Al-Hamood MH, Elbetieha A, Bataineh H. 1998. Sexual maturation and fertility of male and female mice exposed prenatally and postnatally to trivalent and hexavalent chromium compounds. *Reprod Fertil Dev* 10:179-183.
- Ali I, Aboul-Enain HY. 2002. Speciation of arsenic and chromium metal ions by reversed phase high performance liquid chromatography. *Chemosphere* 48(3):275-278.
- \*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 MJ, Myer BJ, Millett PJ, et al. 1997. The effects of particulate cobalt, chromium and cobalt-chromium alloy on human osteoblast-like cells in vitro. *J Bone Jt Surg Am* 79-B(3):475-482.
- Al-Sabti K, Franko M, Andrijanič S, et al. 1994. Chromium-induced micronuclei in fish. *J Appl Toxicol* 14(5):333-336.
- \*Al-Saleh I, Al-Doush I. 1998. Survey of trace elements in household and bottled drinking water samples collected in Riyadh, Saudi Arabia. *Sci Total Environ* 216:181-192.
- \*Althuis MD, Jordan NE, Ludington EA, et al. 2002. Glucose and insulin responses to dietary chromium supplements: A meta-analysis. *Am J Clin Nutr* 76:148-155.
- \*Altman PK, Dittmer DS. 1974. *Biological handbooks: Biology data book, Vol. III, 2nd ed.* Bethesda, MD: Federation of American Societies for Experimental Biology, 1987-2008, 2041.
- +\*American Chrome and Chemicals. 1989. Chromic acid. Material safety data sheets. Corpus Christi, TX: American Chrome and Chemicals, Inc.
- \*Amrani S, Rizki M, Creus A, et al. 1999. Genotoxic activity of different chromium compounds in larval cells of *Drosophila melanogaster*, as measured in the wing spot test. *Environ Mol Mutagen* 34:47-51.
- Amstad P, Hussain SP, Cerutti P. 1994. Ultraviolet B light-induced mutagenesis of p53 hotspot codons 248 and 249 in human skin fibroblasts. *Mol Carcinog* 10:181-188.
- \*Anand SS. 2005. Protective effects of vitamin B6 in chromium-induced oxidative stress in liver. *J Appl Toxicol* 25:440-443.
- Anderlini VC. 1992. The effect of sewage on trace metal concentrations and scope for growth in *Mytilus edulis aoteanus* and *Perna canaliculus* from Wellington Harbour, New Zealand. *Sci Total Environ* 125:263-288.

## 9. REFERENCES

- \*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*. Aberdeen Proving Ground, MD. U.S. Army Chemical Research Development and Engineering Center.
- \*Andersen ME, Clewell HJ, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. *Toxicol Appl Pharmacol* 87:185-205.
- Anderson LM, Sipowicz MA, Yu W, et al. 1999. Chromium(III) as a male pre-conception carcinogen in mice. In: Sarkar B, ed. *Metals and genetics*. Plenum Press, 171-182.
- \*Anderson RA. 1981. Nutritional role of chromium. *Sci Total Environ* 17:13-29.
- \*Anderson RA. 1986. Chromium metabolism and its role in disease processes in man. *Clin Physiol Biochem* 4:31-41.
- \*Anderson RA. 1987. Chromium. In: Mertz W ed. *Trace elements in human and animal nutrition*. 5th ed. Vol. 1. San Diego, CA: Academic Press, Inc., 225-244.
- \*Anderson RA. 1998a. Chromium, glucose intolerance and diabetes. *J Am Coll Nutr* 17(6):548-555.
- \*Anderson RA. 1998b. Effects of chromium on body composition and weight loss. *Nutr Rev* 56(9):266-270.
- \*Anderson RA. 2003. Chromium and insulin resistance. *Nutr Res Rev* 16(2):267-275.
- +\*Anderson RA, Bryden NA, Polansky MM. 1997b. Lack of toxicity of chromium chloride and chromium picolinate in rats. *J Am Coll Nutr* 16(3):273-279.
- Anderson RA, Bryden NA, Evock-Clover CM, et al. 1997a. Beneficial effects of chromium on glucose and lipid variables in control and somatotropin-treated pigs are associated with increased tissue chromium and altered tissue copper, iron, and zinc. *J Anim Sci* 75:657-661.
- +\*Anderson RA, Bryden NA, Patterson KY, et al. 1993. Breast milk chromium and its association with chromium intake, chromium excretion, and serum chromium. *Clin Nutr* 57:519-523.
- \*Anderson RA, Bryden NA, Polansky MM, et al. 1996. Dietary chromium effects on tissue chromium concentrations and chromium absorption in rats. *J Trace Elem Exp Med* 9:11-25.
- \*Anderson RA, Cheng N, Bryden NA, et al. 1997c. Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes. *Diabetes* 46:1786-1791.
- +\*Anderson RA, Polansky MM, Bryden NA, et al. 1983. Effects of chromium supplementation on urinary Cr excretion of human subjects and correlation of Cr excretion with selected clinical parameters. *J Nutr* 113:276-281.
- Andrew AS, Warren AJ, Barchowsky A, et al. 2003. Genomic and proteomic profiling of responses to toxic metals in human lung cells. *Environ Health Perspect* 111(6):825-838.
- Angerer J, Amin W, Heinrich-Ramm R, et al. 1987. Occupational chronic exposure to metals: I. Chromium exposure of stainless steel welders biological monitoring. *Int Arch Occup Environ Health* 59:503-512.



## 9. REFERENCES

- Anguilar MV, Mateos CJ, Para MCM. 2002. Determination of chromium in cerebrospinal fluid using electrothermal atomisation atomic absorption spectrometry. *J Trace Elem Med Biol* 16(4):221-225.
- Anjum F, Shakoori AR. 1997. Sublethal effects of hexavalent chromium on the body growth rate and liver function enzymes of phenobarbitone-pretreated and promethazine-pretreated rabbits. *J Environ Pathol Toxicol Oncol* 16(1):51-59.
- Anonymous. 2006. Chromium supplementation. *Med Lett Drugs Ther* 48:7-8.
- Anton A, Serrano T, Angulo E, et al. 2000. The use of two species of crayfish as environmental quality sentinels: The relationship between heavy metal content, cell and tissue biomarkers and physico-chemical characteristics of the environment. *Sci Total Environ* 247:239-251.
- Antonini J, Roberts J. 2007. Chromium in stainless steel welding fume suppresses lung defense responses against bacterial infection in rats. *J Immunotoxicol* 4(2):117-127.
- +Anwar RA, Langham RF, Hoppert CA, et al. 1961. Chronic toxicity studies: III. Chronic toxicity of cadmium and chromium in dogs. *Arch Environ Health* 3:456-460.
- Aoyama K, Baohui X. 2007. Contact sensitizer potassium dichromate alters lymphocyte populations in draining lymph nodes and blood in mice. *Toxicol Mech Methods* 17(8):475-481.
- Apostoli P, Maranelli G, Duca PG, et al. 1997. Reference values of urinary chromium in Italy. *Int Arch Occup Environ Health* 70:173-179.
- +Appenroth D, Braunlich H. 1988. Age dependent differences in sodium dichromate nephrotoxicity in rats. *Exp Pathol* 33:179-185.
- \*Appenroth D, Karge E, Kiessling G, et al. 2001. LLU-alpha, an endogenous metabolite of gamma-tocopherol, is more effective against metal nephrotoxicity in rats than gamma tocopherol. *Toxicol Lett* 122:255-265.
- Apte AD, Tare V, Bose P. 2006. Extent of oxidation of Cr(III) to Cr(VI) under various conditions pertaining to natural environment. *J Hazard Mater* 128(2-3):164-174.
- Arakawa H, Watanabe N, Tajmir-Riahi HA. 2001. Calf-thymus DNA interaction with Cr(III)-gallate and Cr(III)-ethyle gallate studied by FTIR spectroscopy and capillary electrophoresis. *Bull Chem Soc Jpn* 74:1075-1082.
- Arakawa H, Wu F, Costa M, et al. 2006. Sequence specificity of Cr(III)-DNA adduct formation in the p53 gene: NGG sequences are preferential adduct-forming sites. *Carcinogenesis* 27(3):639-645.
- Armbruster DA, Rudolph FB. 1976. Rat liver pyruvate carboxylase: Inhibition by chromium nucleotide complexes. *J Biol Chem* 251:320-323.
- Armitage P, Doll R. 1954. The age distribution of cancer and a multi-stage theory of carcinogenesis. *Br J Cancer* 8:1-12.
- \*Arreola-Mendoza L, Reyes JL, Melendez E, et al. 2006. Apha-tocopherol protects against the renal damage caused by potassium dichromate. *Toxicology* 218:237-246.

## 9. REFERENCES

- +\*Aruldhas MM, Subramanian S, Sekhar P, et al. 2004. Microcanalization in the epididymis to overcome ductal obstruction caused by chronic exposure to chromium -- a study in the mature bonnet monkey (*Macaca radiata* Geoffroy). *128*:127-137.
- +\*Aruldhas MM, Subramanian S, Sekhar P, et al. 2005. Chronic chromium exposure-induced changes in testicular histoarchitecture are associated with oxidative stress: Study in a non-human primate (*Macaca radiata* Geoffroy). *Hum Reprod* 20(10):2801-2813.
- +\*Aruldhas MM, Subramanian S, Sekhar P, et al. 2006. In vivo spermatotoxic effect of chromium as reflected in the epididymal epithelial principal cells, basal cells, and intraepithelial macrophages of a nonhuman primate (*Macaca radiata* Geoffroy). *Fertil Steril* 86(Suppl 3):1097-1105.
- Arunkumar RI, Rajasekaran P, Michael RD. 2000. Differential effect of chromium compounds on the immune response of the African mouth breeder *Oreochromis mossambicus* (Peters). *Fish Shellfish Immunol* 10(8):667-676.
- \*Asatiani N, Sapojnikova N, Abuladze M, et al. 2004. Effects of Cr(VI) long-term and low-dose action on mammalian antioxidant enzymes (an in vitro study). *J Inorg Biochem* 98:490-496.
- \*Ashley K, Howe AM, Demange M, et al. 2003. Sampling and analysis considerations for the determination of hexavalent chromium in workplace air. *J Environ Monit* 5(5):707-716.
- Asmatullah, Noreen MA. 1999. Effect of oral administration of hexavalent chromium on total body weight, chromium uptake and histological structure of mouse liver. *Punjab Univ J Zool* 14:53-63.
- Asmatullah SNQ, Shakoori AR. 1998. Hexavalent chromium-induced congenital abnormalities in chick embryos. *J Appl Toxicol* 18:167-171.
- Athavale P, Shum KW, Chen Y, et al. 2007. Occupational dermatitis related to chromium and cobalt: Experience of dermatologists (EPIDERM) and occupational physicians (OPRA) in the U.K. over an 11-year period (1993–2004). *Br J Dermatol* 157(3):518-522.
- Atiq ur Rahman M, Sakano T. 2001. Health impact assessment of chrome-based leather tanning: Short report of an ongoing case study of Pakistan. *Promot Educ* 8(1):21-22.
- Atli G, Alptekin O, Tukul S, et al. 2006. Response of catalase activity to Ag<sup>+</sup>, Cd<sup>2+</sup>, Cr<sup>6+</sup>, Cu<sup>2+</sup> and Zn<sup>2+</sup> in five tissues of freshwater fish *Oreochromis niloticus*. *Comp Biochem Physiol* 143(2):218-224.
- \*Avudainayagam S, Megharaj M, Owens G, et al. 2003. Chemistry of chromium in soils with emphasis on tannery waste sites. *Rev Environ Contam Toxicol* 178:53-91.
- +\*Axelsson G, Rylander R. 1980. Environmental chromium dust and lung cancer mortality. *Environ Res* 23:469-476.
- +\*Axelsson G, Rylander R, Schmidt A. 1980. Mortality and incidence of tumours among ferrochromium workers. *Br J Ind Med* 37:121-127.
- Ay AN, Zumreoglu-Kara B, Oner R, et al. 2003. Effects of neutral, cationic, and anionic chromium ascorbate complexes on isolated human mitochondrial and genomic DNA. *J Biochem Mol Biol* 36(4):403-408.

## 9. REFERENCES

- \*Ayyamperumal T, Jonathan MP, Srinivasalu S, et al. 2006. Assessment of acid leachable trace metals in sediment cores from River Uppanar, Cuddalor, southeast coast of India. *Environ Pollut* 143:34-45.
- Baetjer AM. 1950a. Pulmonary carcinoma in chromate workers: I. A review of the literature and report of cases. *Int Arch Ind Hyg Occup Med* 2(5):487-504.
- +\*Baetjer AM. 1950b. Pulmonary carcinoma in chromate workers: II. Incidence and basis of hospital records. *Int Arch Ind Hyg Occup Med* 2(5):505-516.
- +\*Baetjer AM, Damron C, Budacz V. 1959a. The distribution and retention of chromium in men and animals. *Arch Ind Health* 20:136-150.
- +\*Baetjer AM, Lowney JF, Steffee H, et al. 1959b. Effect of chromium on incidence of lung tumors in mice and rats. *Arch Ind Health* 20:124-135.
- \*Bagchi D, Bagchi M, Stohs SJ. 2001. Chromium (VI)-induced oxidative stress, apoptotic cell death and modulation of p53 tumor suppressor gene. *Mol Cell Biochem* 222:149-158.
- \*Bagchi D, Balmoori J, Bagchi M, et al. 2002a. Comparative effect of TCDD, endrin, naphthalene and chromium (VI) on oxidative stress and tissue damage in the liver and brain tissues of mice. *Toxicology* 175:73-82.
- Bagchi D, Joshi SS, Bagchi M. 2000. Cadmium-and chromium-induced oxidative stress, DNA damage, and apoptotic cell death in cultured human chronic myelogenous leukemic K562 cells, promyelocytic leukemic HL-60 cells, and normal human peripheral blood mononuclear cells. *J Biochem Mol Toxicol* 14(1):33-41.
- Bagchi D, Stohs SJ, Downs BW, et al. 2002b. Cytotoxicity and oxidative mechanisms of different forms of chromium. *Toxicology* 180:5-22.
- Bagdon RE, Hazen RE. 1991. Skin permeation and cutaneous hypersensitivity as a basis for making risk assessment of chromium as a soil contaminant. *Environ Health Perspect* 92:111-119.
- \*Baggett JM. 1986. Chromium and the potentiative interaction with some other nephrotoxins. In: Serrone D, ed. *Proceedings of chromium symposium 1986: An update*. Pittsburgh, PA: Industrial Health Foundation, 59-78.
- Baggett JM, Berndt WO. 1984. Interaction of potassium dichromate with the nephrotoxins, mercuric chloride and citrinin. *Toxicology* 33:157-169.
- Baggett JM, Berndt WO. 1985. The effect of potassium dichromate and mercuric chloride on urinary excretion and organ subcellular distribution of [<sup>203</sup>Hg]mercuric chloride in rats. *Toxicol Lett* 29:115-121.
- +Baines AD. 1965. Cell renewal following dichromate induced renal tubular necrosis. *Am J Pathol* 47:851-876.
- Bajza Z, Vrcek IV. 2001. Water quality analysis of mixtures obtained from tannery waste effluents. *Ecotoxicol Environ Saf* 50:15-18.

## 9. REFERENCES

- Baker TSU, Arlauskas A, Tandon RK, et al. 1986. Toxic and genotoxic action of electric-arc welding fumes on cultures mammalian cells. *J Appl Toxicol* 6:357-362.
- Balamurugan K, Rajaram R, Ramasami T, et al. 2002. Chromium(III)-induced apoptosis of lymphocytes: Death decision by Ros and Src-family tyrosine kinases. *Free Radic Biol Med* 33(12):1622-1640.
- \*Balasoiu CF, Zagury GJ, Deschenes L. 2001. Partitioning and speciation of chromium, copper, and arsenic in CCA-contaminated soils: Influence of soil composition. *Sci Total Environ* 280(1-3):239-255.
- Balasubramaniam P, Gawkrödger DJ. 2003. Chromate: Still and important occupational allergen for men in the UK. *Contact Dermatitis* 49(3):162-163.
- Bale JF, Zimmerman B, Dawson JD, et al. 1999. Cytomegalovirus transmission in child care homes. *Arch Pediatr Adolesc Med* 153(1):75-79.
- Banerjee ADK. 2003. Heavy metal levels and solid phase speciation in street dusts of Delhi, India. *Environ Pollut* 123(1):95-105.
- Banks RB, Cooke RT. 1986. Chromate reduction by rabbit liver aldehyde oxidase. *Biochem Biophys Res Commun* 137(1):8-14.
- +\*Banner W, Koch M, Capin M, et al. 1986. Experimental chelation therapy in chromium, lead, and boron intoxication with N-acetylcysteine and other compounds. *Toxicol Appl Pharmacol* 83:142-147.
- Baral A, Engelken R, Stephens W, et al. 2006. Evaluation of aquatic toxicities of chromium and chromium-containing effluents in reference to chromium electroplating industries. *Arch Environ Contam Toxicol* 50:496-502.
- \*Baranowski J, Norska-Borowka I, Baranowska I. 2002. Determination of heavy metals in the bones and livers of deceased neonatal humans. *Bull Environ Contam Toxicol* 69:1-7.
- +\*Baranowska-Dutkiewicz B. 1981. Absorption of hexavalent chromium by skin in man. *Arch Toxicol* 47:47-50.
- \*Barceloux DG. 1999. Chromium. *Clin Toxicol* 37(2):173-194.
- Barchowsky A, O'Hara KA. 2003. Metal-induced cell signaling and gene activation in lung diseases. *Free Radic Biol Med* 34(9):1130-1135.
- \*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessment. *Regul Toxicol Pharmacol* 8:471-486.
- \*Barnhart J. 1997. Chromium chemistry and implications for environmental fate and toxicity. *J Soil Contam* 6(6):561-568.
- \*Barrie LA, Hoff RM. 1985. Five years of air chemistry observations in the Canadian Arctic. *Atmos Environ* 19(12):1995-2010.
- \*Barrie LA, Lindberg SE, Chan WH, et al. 1987. On the concentration of trace metals in precipitation. *Atmos Environ* 21:1133-1135.

## 9. REFERENCES

- \*Bartlett R. 1991. Chromium cycling in soils and water: Links, gaps, and methods. *Environ Health Perspect* 92:17-24.
- \*Bartlett RJ, Kimble JM. 1976. Behavior of chromium in soils: Trivalent forms. *J Environ Qual* 5:379-386.
- Basiak J, Trzeciak A, Maecka-Panas E, et al. 1999. DNA damage and repair in human lymphocytes and gastric mucosa cells exposed to chromium and curcumin. *Teratog Carcinog Mutagen* 19:19-31.
- \*Basketter D, Horev L, Slodovnik D, et al. 2001. Investigation of the threshold for allergic reactivity to chromium. *Contact Dermatitis* 44:70-74.
- Basketter DA, Briatico-Vangosa G, Kaestner W, et al. 1993. Nickel, cobalt and chromium in consumer products: A role in allergic contact dermatitis? *Contact Dermatitis* 28:15-25.
- Basu TK, Donaldson D. 2003. Intestinal absorption in health and disease: Micronutrients. *Best Pract Res Clin Gastroenterol* 17(6):957-979.
- +\*Bataineh H, Al-Hamood MH, Elbetieha A, et al. 1997. Effect of long-term ingestion of chromium compounds on aggression, sex behavior and fertility in adult male rat. *Drug Chem Toxicol* 20(3):133-149.
- +\*Bataineh H, Bataineh Z, Daradka H. 2007. Short-term exposure of female rats to industrial metal salts: Effect on implantation and pregnancy. *Reprod Med Biol* 6(3):179-183.
- \*Beaumont JJ, Sedman RM, Reynolds SD, et al. 2008. Cancer mortality in a Chinese population exposed to hexavalent chromium in drinking water. (Comment in: *Epidemiology* 19(1):1-2, *Epidemiology* 19(1):24-26). *Epidemiology* 19(1):12-23.
- Beck JN, Sneddon J. 2000. Metal concentrations in soils and sediments in Southwest Louisiana. *Anal Lett* 33(10):1913-1959.
- +\*Becker N. 1999. Cancer mortality among arc welders exposed to fumes containing chromium and nickel: Results of a third follow-up: 1989-1995. *J Occup Environ Med* 41(4):294-303.
- +\*Becker N, Claude J, Frenzel-Beyme R. 1985. Cancer risk of arc welders exposed to fumes containing chromium and nickel. *Scand J Work Environ Health* 11:75-82.
- \*Bednar CM, Kies C. 1991. Inorganic contaminants in drinking water correlated with disease occurrence in Nebraska. *Water Resour Bull* 27(4):631-635.
- +Behari J, Chandra SV, Tandon SK. 1978. Comparative toxicity of trivalent and hexavalent chromium to rabbits: III. Biochemical and histological changes in testicular tissue. *Acta Biol Med Ger* 37:463-468.
- +\*Behari JR, Tandon SK. 1980. Chelation in metal intoxication: VIII. Removal of chromium from organs of potassium chromate administered rats. *Clin Toxicol* 16(1):33-40.
- \*Bell RW, Hipfner JC. 1997. Airborne hexavalent chromium in Southwestern Ontario. *J Air Waste Manage Assoc* 47:905-910.

## 9. REFERENCES

- \*Bennett BG. 1986. Exposure assessment for metals involved in carcinogenesis. *IARC Sci Publ* 71:115-128.
- \*Bennicelli C, Camoirano A, Petruzzelli S, et al. 1983. High sensitivity of Salmonella TA102 in detecting hexavalent chromium mutagenicity and its reversal by liver and lung preparations. *Mutat Res* 122:1-5.
- \*Benova D, Hadjidekova V, Hristova R, et al. 2002. Cytogenetic effects of hexavalent chromium in Bulgarian chromium platers. *Mutat Res* 514:29-38.
- \*Bentley SA. 1977. Red cell survival studies reinterpreted. *Clin Haematol* 6(3):601-623
- +Berg NO, Berlin M, Bohgard M, et al. 1987. Bronchocarcinogenic properties of welding and thermal spraying fumes containing chromium in the rat. *Am J Ind Med* 11:39-54.
- \*Berger GS. 1994. Epidemiology of endometriosis. In: Berger GS, ed. *Endometriosis: Advanced management and surgical techniques*. New York, NY: Springer-Verlag, 3-7.
- Berner TO, Murphy MM, Slesinski R. 2004. Determining the safety of chromium tripicolinate for addition to foods as a nutrient supplement. *Food Chem Toxicol* 42(6):1029-1042.
- +Berry JP, Hourdry J, Galle P, et al. 1978. Chromium concentration by proximal renal tubule cells: An ultrastructural microanalytical and cytochemical study. *J Histochem Cytochem* 26:651-657.
- Bervoets L, Solis D, Romero AM, et al. 1998. Trace metal levels in chironomid larvae and sediments from a Bolivian river: Impact of mining activities. *Ecotoxicol Environ Saf* 41:275-283.
- \*Beyer WN, Cromartie EJ. 1987. A survey of Pb, Cu, Zn, Cd, Cr, As and Se in earthworms and soil from diverse sites. *Environ Monit Assess* 8:27-36.
- Beyersmann D. 2001. Chromium(III) and DNA damage. (Comment on: *Environ Health Perspect* 108(5):399-402). *Environ Health Perspect* 109(6):A250.
- Beyersmann D. 2002. Effects of carcinogenic metals on gene expression. *Toxicol Lett* 127:63-68.
- \*Beyersmann D, Koster A. 1987. On the role of trivalent chromium in chromium genotoxicity. *Toxicol Environ Chem* 14:11-22.
- Beyersmann D, Koster A, Buttner B. 1985. Model reactions of chromium compounds with mammalian and bacterial cells. In: Merian E, Frei RW, Hardi W, et al., eds. *Carcinogenic and mutagenic metal compounds: Environmental and analytical chemistry and biological effects*. London, UK: Gordon and Breach Science Publishers, 303-310.
- Bhattacharyya P, Chakraborty A, Chakrabarti K, et al. 2005. Chromium uptake by rice and accumulation in soil amended with municipal solid waste compost. *Chemosphere* 60(10):1481-1486.
- Bianchi V, Levis AG. 1985. Mechanisms of chromium genotoxicity. In: Merian E, Frei RW, Hardi W et al., eds. *Carcinogenic and mutagenic metal compounds: Environmental and analytical chemistry and biological effects*. London: Gordon and Breach Science Publishers, 269-294.

## 9. REFERENCES

- Bianchi V, Levis AG. 1987. Recent advances in chromium genotoxicity. *Toxicol Environ Chem* 15:1-24.
- Bianchi V, Levis AG. 1988. Review of genetic effects and mechanisms of action of chromium compounds. *Sci Total Environ* 71:351-355.
- Bianchi V, Dal Toso R, Debetto P, et al. 1980. Mechanisms of chromium toxicity in mammalian cell cultures. *Toxicology* 17:219-224.
- Bianchi V, Levis AG, Saggioro D. 1979. Differential cytotoxic activity of potassium dichromate on nucleoside uptake in BHK fibroblasts. *Chem Biol Interact* 24:137-151.
- +Bick RL, Girardi TV, Lack WJ, et al. 1996. Hodgkin's disease in association with hexavalent chromium exposure. *Int J Hematol* 64(3-4):257-262.
- +\*Bidstrup P. 1951. Carcinoma of the lung in chromate workers. *Br J Ind Med* 8:302-305.
- +\*Bidstrup P, Case R. 1956. Carcinoma of the lung in workmen in the bichromates-producing industry in Great Britain. *Br J Ind Med* 13:260-264.
- Biedermann KA, Landolph JR. 1987. Induction of anchorage independence in human diploid foreskin fibroblasts by carcinogenic metal salts. *Cancer Res* 47:3815-3823.
- Bilos C, Colombo JC, Presa MJR. 1998. Trace metals in suspended particles, sediments, and asiatic clams (*Corbicula fluminea*) of the Rio de la Plata Estuary, Argentina. *Environ Pollut* 99:1-11.
- Black CB, Cowan JA. 1997. Inert chromium and cobalt complexes as probes of magnesium-dependent enzymes. Evaluation of the mechanistic role of the essential metal cofactor in *Escherichia coli* exonuclease III. *Eur J Biochem* 243:684-689.
- \*Blade LM, Yencken MS, Wallace ME, et al. 2007. Hexavalent chromium exposures and exposure-control technologies in American enterprise: Results of NIOSH field research study. *J Occup Environ Hyg* 4(8):596-618.
- +Blair J. 1928. Chrome ulcers. Report on twelve cases. *J Am Med Assoc* 90:1927-1928.
- \*Blankenship LJ, Carlisle DL, Wise JP, et al. 1997. Induction of apoptotic cell death by particulate lead chromate: Differential effects of vitamins C and E on genotoxicity and survival. *Toxicol Appl Pharmacol* 146:270-280.
- Blankenship LJ, Manning FCR, Orenstein JM, et al. 1994. Apoptosis is the mode of cell death caused by carcinogenic chromium. *Toxicol Appl Pharmacol* 126:75-83.
- \*Blasiak J, Kowalik J. 2000. A comparison of the vitro genotoxicity of tri- and hexavalent chromium. *Mutat Res* 469(1):135-145.
- Blasiak J, Trzeciak A, Malecka-Panas E, et al. 1999. DNA damage and repair in human lymphocytes and gastric mucosa cells exposed to chromium and curcumin. *Teratog Carcinog Mutagen* 19:19-31.
- \*Bock M, Schmidt A, Bruckner T, et al. 2003. Contact dermatitis and allergy: Occupational skin disease in the construction industry. *Br J Dermatol* 149(6):1165-1171.

## 9. REFERENCES

- Boiano JM, Wallace Me, Sieber WK, et al. 2000. Comparison of three sampling and analytical methods for the determination of airborne hexavalent chromium. *J Environ Monit* 2(4):329-333.
- Bollweg G, Balaban C, Cox HJ, et al. 1995. Potential efficacy and toxicity of GM1 ganglioside against trimethyltin-induced brain lesions in rats: Comparison with protracted food restriction. *Neurotoxicology* 16(2):239-255.
- Bolt L, Ellwood DC, Hill MJ, et al. 1994. The role of colonic sulphate-reducing bacteria in the pharmacology of heavy metals. *Eur J Cancer Prev* 3:357-359.
- Bonardi M, Groppi F, Mainardi HS. 2002. High specific activity radioactive tracers: A powerful tool for studying very low level and long term exposure to different chemical forms of both essential and toxic elements. *Microchem J* 73:153-166.
- \*Bonatti S, Meini M, Abbondandolo A. 1976. Genetic effects of potassium dichromate in *Schizosaccharomyces pombe*. *Mutat Res* 38:147-150.
- \*Bonde JPE, Olsen JH, Hansen KS. 1992. Adverse pregnancy outcome and childhood malignancy with reference to paternal welding exposure. *Scand J Work Environ Health* 18:169-177.
- \*Borg H. 1987. Trace metals and water chemistry of forest lakes in northern Sweden. 1987. *Water Research* 21(1):65-72.
- Borges KM, Wetterhahn KE. 1989. Chromium cross-links glutathione and cysteine to DNA. *Carcinogenesis* 10:2165-2168.
- +\*Borneff I, Engelhardt K, Griem W, et al. 1968. Carcinogenic substances in water and soil. XXII. Mouse drinking study with 3,4-benzopyrene and potassium chromate. *Arch Hyg* 152:45-53.
- +\*Boscolo P, Di Gioacchino M, Bavazzano P, et al. 1997. Effects of chromium on lymphocyte subsets and immunoglobulins from normal population and exposed workers. *Life Sci* 60(16):1319-1325.
- Boscolo P, Di Gioacchino M, Conti P, et al. 1998. Expression of lymphocyte subpopulations, cytokine serum levels and blood and urine trace elements in nickel sensitised women. *Life Sci* 63(16):1417-1422.
- Boscolo P, Di Gioacchino M, Sabbioni E, et al. 1999. Expression of lymphocyte subpopulations, cytokine serum levels, and blood and urinary trace elements in asymptomatic atopic men exposed to an urban environment. *Int Arch Occup Environ Health* 72:26-32.
- Boscolo P, Di Gioacchino M, Sabbioni E, et al. 2000. Lymphocyte subpopulations, cytokines and trace elements in asymptomatic atopic women exposed to an urban environment. *Life Sci* 67(10):1119-1126.
- Bose RN, Moghaddas S, Mazzer PA, et al. 1999. Oxidative damage of DNA by chromium(V) complexes: Relative importance of base versus sugar oxidation. *Nucleic Acids Res* 27(10):2219-2226.
- +\*Bovet P, Lob M, Grandjean M. 1977. Spirometric alterations in workers in the chromium electroplating industry. *Int Arch Occup Environ Health* 40:25-32.



## 9. REFERENCES

- Brabander DJ, Keon N, Stanley RHR, et al. 1999. Intra-ring variability of Cr, As, Cd, and Pb in red oak revealed by secondary ion mass spectrometry: Implications for environmental biomonitoring. *Proc Natl Acad Sci USA* 96(25):14635-14640.
- Bradberry SM, Vale JA. 1999. Therapeutic review: Is ascorbic acid of value in chromium poisoning and chromium dermatitis? *Clin Toxicol* 37(2):195-200.
- Bradshaw LM, Fishwick D, Slater T, et al. 1998. Chronic bronchitis, work related respiratory symptoms, and pulmonary function in welders in New Zealand. *Occup Environ Med* 55:150-154.
- +\*Bragt PC, van Dura EA. 1983. Toxicokinetics of hexavalent chromium in the rat after intratracheal administration of chromates of different solubilities. *Ann Occup Hyg* 27(3):315-322.
- Branca M, Dessi A, Kozlowski H, et al. 1989. In vitro interaction of mutagenic chromium(VI) with red blood cells. *FEBS Lett* 257:52-54.
- Brandt-Rauf P. 2006. Editorial retraction. Cancer mortality in a Chinese population exposed to hexavalent chromium in water. (Comment on: *J Occup Environ Med* 39(4):315-319). *J Occup Environ Med* 48(7):749.
- Brandt-Rauf PW, Luo J, Cheng T, et al. 2000. Mutant oncoprotein biomarkers of vinyl chloride exposure. Applications to risk assessment. Human monitoring after environmental and occupational exposure to chemical and physical agents. *NATO Adv Stud Inst Ser A Life Sci* 313:243-248.
- +\*Braver ER, Infante P, Chu K. 1985. An analysis of lung cancer risk from exposure to hexavalent chromium. *Teratog Carcinog Mutagen* 5:365-378.
- Brendt WO. 1976. Renal chromium accumulation and its relationship to chromium-induced nephrotoxicity. *J Toxicol Environ Health* 1:449-459.
- \*Bridgewater LC, Manning FCR, Patierno SR. 1994a. Base-specific arrest of *in vitro* DNA replication by carcinogenic chromium: Relationship to DNA interstrand crosslinking. *Carcinogenesis* 15(11):2421-2427.
- \*Bridgewater LC, Manning FCR, Patierno SR. 1998. Arrest of replication by mammalian DNA polymerase  $\alpha$  and  $\beta$  caused by chromium-DNA lesions. *Mol Carcinogen* 23:201-206.
- \*Bridgewater LC, Manning FCR, Woo ES, et al. 1994b. DNA polymerase arrest by adducted trivalent chromium. *Mol Carcinogen* 9:122-133.
- +\*Brieger H. 1920. [The symptoms of acute chromate poisoning.] *Z Exper Path Therap* 21:393-408. (German)
- \*Briggs JA, Briggs RC. 1988. Characterization of chromium effects on a rat liver epithelial cell line and their relevance to *in vitro* transformation. *Cancer Res* 48:6484-6490.
- Bright P, Burge PS, O'Hickey SP, et al. 1997. Occupational asthma due to chrome and nickel electroplating. *Thorax* 52:28-32.

## 9. REFERENCES

- \*Broadhurst CL, Schmidt WF, Reeves JB, et al. 1997. Characterization and structure by NMR and FTIR spectroscopy, and molecular modeling of chromium(III) picolinate and nicotinate complexes utilized for nutritional supplementation. *J Inorg Biochem* 66:119-130.
- \*Bronzetti GL, Galli A. 1989. Influence of NTA on the chromium genotoxicity. *Toxicol Environ Chem* 23:101-104.
- \*Bronzetti G, Galli A, Boccardo P, et al. 1986. Genotoxicity of chromium *in vitro* on yeast: Interaction with DNA. *Toxicol Environ Chem* 13:103-111.
- +\*Brune D, Nordberg G, Wester PO. 1980. Distribution of 23 elements in the kidney, liver, and lungs of workers from a smeltery and refinery in north Sweden exposed to a number of elements and of a control group. *Sci Total Environ* 16:13-35.
- \*Bryant HE, Ying S, Helleday T. 2006. Homologous recombination is involved in repair of chromium-induced DNA damage in mammalian cells. *Mutat Res* 599:116-123.
- +\*Bryson WG, Goodall CM. 1983. Differential toxicity and clearance kinetics of chromium(III) or (VI) in mice. *Carcinogenesis* 4(12):1535-1539.
- \*Buckell M, Harvey DG. 1951. An environmental study of the chromate industry. *Br J Ind Med* 8:298-301.
- Buehrlen M, Harreus UA, Gamarra F, et al. 2007. Cumulative genotoxic and apoptotic effects of xenobiotics in a mini organ culture model of human nasal mucosa as detected by the alkaline single cell microgel electrophoresis assay and the annexin V-affinity assay. *Toxicol Lett* 169:152-161.
- Buhl KJ. 1997. Relative sensitivity of three endangered fishes, Colorado squawfish, bonytail, and razorback sucker, to selected metal pollutants. *Ecotoxicol Environ Saf* 37:186-192.
- \*Bukowski JA, Goldstein MD, Korn LR, et al. 1991. Biological markers in chromium exposure assessment: Confounding variables. *Arch Environ Health* 46(4):230-236.
- Bulbulian R, Pringle DD, Liddy MS. 1996. Chromium picolinate supplementation in male and female swimmers. *Med Sci Sports Exercise* 28:S11.
- Bundy KJ, Berzins D. 1998. Differential pulse polarographic analysis of lead and chromium content in Louisiana waters. *Environ Geochem Health* 20:45-51.
- +\*Bunker VW, Lawson MS, Delves HT, et al. 1984. The uptake and excretion of chromium by the elderly. *Am J Clin Nutr* 39:797-802.
- Burke T, Fagliano J, Goldoft M, et al. 1991. Chromite ore processing residue in Hudson County, New Jersey. *Environ Health Perspect* 92:131-137.
- \*Burrows D, ed. 1983. Adverse chromate reactions on the skin. In: Burrows D, ed. *Chromium: Metabolism and toxicity*. Boca Raton, FL: CRC Press, Inc., 137-163.
- Burton JL, Nonnecke BJ, Dubeski PL, et al. 1996. Effects of supplemental chromium on production of cytokines by mitogen-stimulated bovine peripheral blood mononuclear cells. *J Dairy Sci* 79:2237-2246.

## 9. REFERENCES

- \*Byrne CJ, DeLeon IR. 1986. Trace metal residues in biota and sediments from Lake Pontchartrain, Louisiana. *Bull Environ Contam Toxicol* 37:151-158.
- \*Caglieri A, Goldoni M, Acampa O, et al. 2006. The effect of inhaled chromium on different exhaled breath condensate biomarkers among chrome-plating workers. *Environ Health Perspect* 114(4):542-546.
- \*Calder LM. 1988. Chromium contamination of groundwater. *Adv Env Sci Technol* 20:215-229.
- Calevro F, Campani S, Raghianti M, et al. 1998. Tests of toxicity and teratogenicity in biphasic vertebrates treated with heavy metals (Cr<sup>3+</sup>, Al<sup>3+</sup>, Cd<sup>2+</sup>). *Chemosphere* 37(14-15):3011-3017.
- Campbell WW, Beard JL, Joseph LJ, et al. 1997. Chromium picolinate supplementation and resistive training by older men: Effects on iron-status and hematologic indexes. *Am J Clin Nutr* 66:944-949.
- \*Campbell WW, Joseph LJ, Davey SL, et al. 1999. Effects of resistance training and chromium picolinate on body composition and skeletal muscle in older men. *J Appl Physiol* 86(1):29-39.
- \*Camyre E, Wise SS, Milligan P, et al. 2007. Ku80 deficiency does not affect particulate chromate-induced chromosome damage and cytotoxicity in Chinese hamster ovary cells. *Toxicol Sci* 97(2):348-354.
- \*Capellmann M, Bolt HM. 1992. Chromium (VI) reducing capacity of ascorbic acid and of human plasma in vitro. *Arch Toxicol* 66:45-50.
- \*Capellmann M, Mikalsen A, Hindrum M, et al. 1995. Influence of reducing compounds on the formation of DNA-protein cross-links in HL-60 cells induced by hexavalent chromium. *Carcinogenesis* 16(5):1135-1139.
- \*CARB. 1990. Procedure for the analysis of hexavalent chromium at ambient atmospheric levels by ion-chromatography. El Monte, CA: California Air Resources Board.
- \*Carlisle DL, Pritchard DE, Singh J, et al. 2000. Apoptosis and P53 induction in human lung fibroblasts exposed to chromium (VI): Effect of ascorbate and tocopherol. *Toxicol Sci* 55:60-68.
- \*Carlton GN. 2003. Hexavalent chromium exposures during full-aircraft corrosion control. *Am Ind Hyg Assoc J* 64:668-672.
- +Carter WW. 1929. The effect of chromium poisoning on the nose and throat: The report of a case. *Med J Rec* 130:125-127.
- \*Cary EE. 1982. Chromium in air, soil and natural waters. In: Lang S, ed. *Topics in environmental health 5: Biological and environmental aspects of chromium*. New York, NY: Elsevier Biomedical Press, 49-64.
- \*Casadevall M, da Cruz Fresco P, Kortenkamp A. 1999. Chromium(VI)-mediated DNA damage: Oxidative pathways resulting in the formation of DNA breaks and abasic sites. *Chem Biol Interact* 123(2):117-132.
- \*Case CP, Ellis L, Turner JC, et al. 2001. Development of a routine method for the determination of trace metals in whole blood by magnetic sector inductively coupled plasma mass spectrometry with particular relevance to patients with total hip and knee arthroplasty. *Clin Chem* 47(2):275-280.

## 9. REFERENCES

- +\*Casey CE, Hambidge KM. 1984. Chromium in human milk from American mothers. *Br J Nutr* 52:73-77.
- +\*Cason JS. 1959. Report on three extensive industrial chemical burns. *Br Med J* 1:827-829.
- Cass GR, McRae GJ. 1986. Emissions and air quality relationships for atmospheric trace metals. In: Nriagu JO, Davidson CI, eds. *Toxic metals in the atmosphere*. New York, NY: John Wiley and Sons, Inc., 145-171.
- Casto BC, Meyers J, DiPaolo JA. 1979. Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. *Cancer Res* 39:193-198.
- Catsimpoolas N, Griffith AL, Skrabut EM, et al. 1976. Differential Cr uptake of human peripheral lymphocytes separated by density gradient electrophoresis. *Cell Immunol* 25:317-321.
- +\*Cavalleri A, Minoia C. 1985. Distribution in serum and erythrocytes and urinary elimination in workers exposed to chromium(VI) and chromium(III). *G Ital Med Lav* 7:35-38.
- +\*Cavalleri A, Minoia C, Richelmi P, et al. 1985. Determination of total and hexavalent chromium in bile after intravenous administration of potassium dichromate in rats. *Environ Res* 37:490-496.
- \*CDPH. 2007. Chromium-6 in drinking water: Sampling results. California Department of Public Health. <http://ww2.cdph.ca.gov/certlic/drinkingwater/pages/chromium6sampling.aspx>. August 21, 2008.
- Cefalu WT, Hu FB. 2004. Role of chromium in human health and diabetes. *Diabetes Care* 27(11):2741-2751.
- \*Cemeli E, Carder J, Anderson D, et al. 2003. Antigenotoxic properties of selenium compounds on potassium dichromate and hydrogen peroxide. *Teratog Carcinog Mutagen* 23(Suppl. 2):53-67.
- Cerulli J, Grabe DW, Gauthier I, et al. 1998. Chromium picolinate toxicity. *Ann Pharmacother* 32:428-431.
- Cervantes M, Glassman AB. 1996. Breast cancer cytogenetics: A review and proposal for clinical application. *Ann Clin Lab Sci* 26(3):208-214.
- Chadwick JK, Wilson HK, White MA. 1997. An investigation of occupational metal exposure in thermal spraying processes. *Sci Total Environ* 199:115-124.
- \*Chakov NE, Collins RA, Vincent JB. 1999. A re-investigation the electron spectra of chromium(III) picolinate complexes and high yield synthesis and characterization of  $\text{Cr}_2(\mu\text{-OH})_2(\text{pic})_4\cdot 5\text{H}_2\text{O}$  (Hpic=picolinate acid). *Polyhedron* 18:2891-2897.
- Chandra AK, Chatterjee A, Ghosh R, et al. 2007a. Effect of curcumin on chromium-induced oxidative damage in male reproductive system. *Environ Toxicol Pharmacol* 24(2):160-166.
- Chandra AK, Chatterjee A, Ghosh R, et al. 2007b. Chromium induced testicular impairment in relation to adrenocortical activities in adult albino rats. *Reprod Toxicol* 24:388-396.

## 9. REFERENCES

- \*Chang F, Wang S, Huang Y, et al. 2006. Biomonitoring of chromium for residents of areas with a high density of electroplating factories. *J Expo Sci Environ Epidemiol* 16(2):138-146.
- Chang GX, Mallard BA, Mowat DN, et al. 1996. Effect of supplemental chromium on antibody responses of newly arrived feeder calves to vaccines and ovalbumin. *Can J Vet Res* 60:140-144.
- Chaudhary S, Van Horn JD. 2006. Biphasic kinetics in the reaction between amino acids or glutathione and the chromium acetate cluster,  $[\text{Cr}_3(\text{OAc})_6]^+$ . *Mutat Res* 610:56-65.
- \*Chen CJ, Shih TS, Chang HY, et al. 2008. The total body burden of chromium associated with skin disease and smoking among cement workers. *Sci Total Environ* 391:76-81.
- \*Chen F, Shi X. 2002. Intracellular signal transduction of cells in response to carcinogenic metals. *Crit Rev Oncol Hematol* 42(1):105-121.
- Chen F, Ding M, Lu Y, et al. 2000. Participation of MAP kinase p38 and I $\kappa$ B kinase in chromium(VI)-induced NF- $\kappa$ B and AP-1 activation. *J Environ Pathol Toxicol Oncol* 19(3):231-238.
- \*Chen F, Ye J, Zhang X, et al. 1997. One-electron reduction of chromium(VI) by  $\alpha$ -lipoic acid and related hydroxyl radical generation, dG hydroxylation and nuclear transcription factor- $\kappa$ B activation. *Arch Biochem Biophys* 338(2):165-172.
- Chen J, Wey M, Yan M. 1999. The effects of chloride additives on adsorption of heavy metals during incineration. *J Air Waste Manage Assoc* 49(9):1116-1120.
- Chen JC, Wey MY, Chiang BC, et al. 1998. The simulation of hexavalent chromium formation under various incineration conditions. *Chemosphere* 36(7):1553-1564.
- \*Chen JM, Hao OJ. 1998. Microbial chromium (VI) reduction. *Crit Rev Environ Sci* 28(3):219-251.
- +\*Chen NSC, Tsai A, Dyer I. 1973. Effect of chelating agents on chromium absorption in rats. *J Nutr* 103:1182-1186.
- Chen W, Zhong G, Zhou Z, et al. 2005. Automation of liquid-liquid extraction-spectrophotometry using prolonged pseudo-liquid drops and handheld CCD for speciation of Cr(VI) and Cr(III) in water samples. *Anal Sci* 21(10):1189-1193.
- Cheng L, Liu S, Dixon K. 1998. Analysis of repair and mutagenesis of chromium-induced DNA damage in yeast, mammalian cells, and transgenic mice. *Environ Health Perspect Suppl* 106(Suppl. 4):1027-1032.
- Cheng L, Sonntag DM, deBoer J, et al. 2000. Chromium(VI)-induced mutagenesis in the lungs of the big blue transgenic mice. *J Environ Pathol Toxicol Oncol* 19(3):239-249.
- Cheng RYS, Alvord WG, Powell D, et al. 2002. Microarray analysis of altered gene expression in the TM4 Sertoli-like cell line exposed to chromium(III) chloride. *Reprod Toxicol* 16:223-236.
- Cheng TYS, Hockman T, Crawford E, et al. 2004. Epigenetic and gene expression changes related to transgenerational carcinogenesis. *Mol Carcinog* 40:1-11.

## 9. REFERENCES

- \*Chiba M, Sera K, Hashizume M, et al. 2004. Element concentrations in hair of children living in environmentally degraded districts of the East Aral Sea region. *J Radioanal Nucl Chem* 259(1):149-152.
- \*Chillrud SN, Epstein D, Ross JM, et al. 2004. Elevated airborne exposures of teenagers to manganese, chromium, and iron from steel dust and New York City's subways. *Environ Sci Technol* 38(3):732-737.
- Chirenje T, Ma LQ, Clark C, et al. 2003. Cu, Cr and As distribution in soils adjacent to pressure-treated decks, fences and poles. *Environ Pollut* 124(3):407-417.
- Chiu A, Chiu N, Shi X, et al. 1998. Activation of a procarcinogen by reduction: Cr<sup>6+</sup> - Cr<sup>5+</sup> - Cr<sup>4+</sup> - Cr<sup>3+</sup>. A case study by electron spin resonance (ESR/PMR). *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* C16(2):135-148.
- Chiu A, Katz AJ, Beaubier J, et al. 2004. Genetic and cellular mechanisms in chromium and nickel carcinogenesis considering epidemiologic findings. *Mol Cell Biochem* 255(1-2):181-194.
- Choi YW, Moon SH. 2001. A study on hexachromic ion selective electrode based on supported liquid membranes. *Environ Monit Assess* 70:167-180.
- Choi YW, Moon SH. 2004. Determination of Cr(VI) using an ion selective electrode with SLMs containing Aliquat336. *Environ Monit Assess* 92:163-178.
- Chorvatovičová D, Ginter E. 1989. Effect of Cr(VI) and vitamin C in transplacental micronucleus test in mice. *Biologia* 44:1033-1038.
- \*Chorvatovičová D, Kováčiková Z, Šandula J, et al. 1993. Protective effect of sulfoethylglucan against hexavalent chromium. *Mutat Res* 302:207-211.
- Chowdhuri DK, Narayan R, Saxena DK. 2001. Effect of lead and chromium on nucleic acid and protein synthesis during sperm-zona binding in mice. *Toxicol In Vitro* 15:605-613.
- +\*Chowdhury AR, Mitra C. 1995. Spermatogenic and steroidogenic impairment after chromium treatment in rats. *Indian J Exp Biol* 33:480-484.
- \*Christenson WR, Davis ME, Berndt WO. 1989. The effect of combined treatment with potassium dichromate and maleic acid on renal function in the rat. *Toxicol Lett* 49:21-27.
- +\*Cikrt M, Bencko V. 1979. Biliary excretion and distribution of <sup>51</sup>Cr(III) and <sup>51</sup>Cr(VI) in rats. *J Hyg Epidemiol Microbiol Immunol* 23:241-246.
- Cinquetti R, Mazzotti F, Acquati F, et al. 2003. Influence of metal ions on gene expression of BALB 3T3 fibroblasts. *Gene* 318:83-89.
- \*Clancy SP, Clarkson PM, DeCheke ME, et al. 1994. Effects of chromium picolinate supplementation on body composition, strength, and urinary chromium loss in football players. *Int J Sports Nutr* 4:142-153.
- +\*Clapp TC, Umbreit TH, Meeker RJ, et al. 1991. Bioavailability of lead and chromium from encapsulated pigment materials. *Bull Environ Contam Toxicol* 46:271-275.

## 9. REFERENCES

- Clarkson PM. 1997. Effects of exercise on chromium levels: Is supplementation required? *Sports Med* 23(6):341-349.
- Clemente GF. 1976. Trace element pathways from environment to man. *J Radioanal Chem* 32:25-41.
- \*Clewell HJ III, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. *Toxicol Ind Health* 1:111-113.
- +\*Clochesy JM. 1984. Chromium ingestion: A case report. *J Emerg Nurs* 10:281-282.
- \*CMR. 1988a. Chemical profile: Chromic acid. *Chem Mark Rep* October 24, 1988:54.
- \*CMR. 1988b. Chemical profile: Sodium bichromate. *Chem Mark Rep* October 17, 1988.
- Cobo JM, Castineira M. 1997. Oxidative stress, mitochondrial respiration, and glycemic control: Clues from chronic supplementation with Cr<sup>3+</sup> or As<sup>3+</sup> to male Wistar rats. *Nutrition* 13(11-12):965-970.
- \*Cocker J, Jones K, Morton J, et al. 2007. Biomonitoring at the UK Health and Safety Laboratory. *Int J Hyg Environ Health* 210(3-4):383-386.
- Cocker J, Morton J, Warren N, et al. 2006. Biomonitoring for chromium and arsenic in timber treatment plant workers exposed to CCA treated wood preservatives. *Ann Occup Hyg* 50(5):517-525.
- Codd R, Dillon CT, Levina A, et al. 2001. Studies on the genotoxicity of chromium: From the test tube to the cell. *Coord Chem Rev* 216-217:537-582.
- +Cohen HA. 1966. Carrier specificity of tuberculin-type reaction to trivalent chromium. *Arch Dermatol* 93:34-40.
- Cohen M, Prophete C, Sisco M, et al. 2006. Pulmonary immunotoxic potentials of metals are governed by select physiochemical properties: Chromium agents. *J Immunotoxicol* 3(2):69-81.
- Cohen MD, Kargacin B, Klein CB, et al. 1993. Mechanisms of chromium carcinogenicity and toxicity. *Crit Rev Toxicol* 23(3):255-281.
- \*Cohen MD, Sisco M, Baker K, et al. 2003. Impact of coexposure to ozone on the carcinogenic potential of inhaled chromium. *J Toxicol Environ Health A* 66(1):39-55.
- +\*Cohen MD, Zelikoff JT, Chen LC, et al. 1998. Immunotoxicologic effects of inhaled chromium: Role of particle solubility and co-exposure to ozone. *Toxicol Appl Pharmacol* 152:30-40.
- +\*Cohen SR, David DM, Kramkowski RS. 1974. Clinical manifestations of chromic acid toxicity: Nasal lesions in electroplate workers. *Cutis* 13:558-568.
- Cohen T, Que Hee SS, Ambrose RF. 2001. Trace metals in fish and invertebrates of three California coastal wetlands. *Mar Pollut Bull* 42(3):224-232.
- Cole P, Merletti F. 1980. Chemical agents and occupational cancer. *J Environ Pathol Toxicol* 3:399-417.

## 9. REFERENCES

- \*Cole P, Rodu B. 2005. Epidemiologic studies of chrome and cancer mortality: A series of meta-analyses. *Regul Toxicol Pharmacol* 43:225-231.
- +\*Coleman RF, Herrington J, Scales JT. 1973. Concentration of wear products in hair, blood, and urine after total hip replacement. *Br Med J* 1:527-529.
- Colsky AS, Peacock JS. 1990. Sodium pyruvate inhibits the spontaneous release of <sup>51</sup>Cr from RBC in chromium release assays. *J Immunol Methods* 129:139-141.
- \*Comber S, Gardner M. 2003. Chromium redox speciation in natural waters. *J Environ Monit* 5:410-413.
- +\*Coogan T, Motz J, Snyder C, et al. 1991a. Differential DNA-protein crosslinking in lymphocytes and liver following chronic drinking water exposure of rats to potassium chromate. *Toxicol Appl Pharmacol* 109:60-72.
- \*Coogan TP, Squibb KS, Motz J, et al. 1991b. Distribution of chromium within cells of the blood. *Toxicol Appl Pharmacol* 108:157-166.
- \*Corbett GE, Dodge DG, O'Flaherty EO, et al. 1998. *In vitro* reduction kinetics of hexavalent chromium in human blood. *Environ Res* 78:7-11.
- +\*Corbett GE, Finley BL, Paustenbach DJ, et al. 1997. Systemic uptake of chromium in human volunteers following dermal contact with hexavalent chromium (22 mg/L). *J Expo Anal Environ Epidemiol* 7(2):179-189.
- Corradi MG, Gorbi G, Ricci A, et al. 1995. Chromium-induced sexual reproduction gives rise to a Cr-tolerant progeny in *Scenedesmus acutus*. *Ecotoxicol Environ Safety* 32:12-18.
- \*Coryell VH, Stearns DM. 2006. Molecular analysis of hprt mutations induced by chromium picolinate in CHO AA8 cells. *Mutat Res* 610:114-123.
- Costa M. 1991. DNA-protein complexes induced by chromate and other carcinogens. *Environ Health Perspect* 92:45-52.
- Costa M. 1997. Toxicity and carcinogenicity of Cr(VI) in animal models and humans. *Crit Rev Toxicol* 27(5):431-442.
- Costa M. 1998. Carcinogenic metals. *Science Progress* 81(4):329-339.
- \*Costa M. 2003. Potential hazards of hexavalent chromate in our drinking water. *Toxicol Appl Pharmacol* 188(1):1-5.
- \*Costa M, Klein C. 2006a. Response to comments by Post and Stern on article "Toxicity and carcinogenicity of chromium compounds in humans". (Comment on: 36(2):155-163). *Crit Rev Toxicol* 36(9):779.
- Costa M, Klein CB. 2006b. Toxicity and carcinogenicity of chromium compounds in humans. (Comment in: *Crit Rev Toxicol* 36(9):777-778, discussion 779). *Crit Rev Toxicol* 36(2):155-163.



## 9. REFERENCES

- \*Costa M, Zhitkovich A, Gargas M, et al. 1996. Interlaboratory validation of a new assay for DNA-protein crosslinks. *Mutat Res* 369:13-21.
- \*Costa M, Zhitkovich A, Harris M, et al. 1997. DNA-protein cross-links produced by various chemicals, in cultured human lymphoma cells. *J Toxicol Environ Health* 50(5):433-449.
- Cox XB, Linton RW, Butler FE. 1985. Determination of chromium speciation in environmental particles. Multitechnique study of ferrochrome smelter dust. *Environ Sci Technol* 19:345-352.
- Criqui M, Austin M, Barrett-Connor E. 1979. The effect of non-response on risk ratios in a cardiovascular disease study. *J Chron Dis* 32:633-638.
- Cross HJ, Faux SP, Levy LS. 1997. Establishing an occupational exposure limit for hexavalent chromium in the European Union. *Regul Toxicol Pharmacol* 26:S72-S76.
- +\*Crump C, Crump K, Hack E, et al. 2003. Dose-response and risk-assessment of airborne hexavalent chromium and lung cancer mortality. *Risk Anal* 23(6):1147-1163.
- \*Cruz MJ, Costa R, Marquilles E, et al. 2006. Occupational asthma caused by chromium and nickel. *Arch Bronconeumol* 42(6):302-306.
- \*Cupo DY, Wetterhahn KE. 1985. Binding of chromium to chromatin and DNA from liver and kidney of rats treated with sodium dichromate and chromium(III) chloride *in vivo*. *Cancer Res* 45:1146-1151.
- Curtis A, Morton J, Balafa C, et al. 2007. The effects of nickel and chromium on human keratinocytes: Differences in viability, cell associated metal and IL-1alpha release. *Toxicol In Vitro* 21:809-819.
- +\*Da Costa JC, Jones FX, Rosenberger RC. 1916. Tanner's ulcer: Chrome sores - chrome holes - acid bites. *Ann Surg* 63:155-166.
- +\*Dalager NA, Mason TJ, Fraumeni JF, et al. 1980. Cancer mortality among workers exposed to zinc chromate paints. *J Occup Med* 22(1):25-29.
- Danadevi K, Rozati R, Banu BS, et al. 2004. Genotoxic evaluation of welders occupationally exposed to chromium and nickel using the Comet and micronucleus assays. *Mutagenesis* 19(1):35-41.
- Danadevi K, Rozati R, Reddy PP, et al. 2003. Semen quality of Indian welders occupationally exposed to nickel and chromium. *Reprod Toxicol* 17:451-456.
- Danford DE, Anderson RA. 1985. Beltsville Human Nutrition Research Center, U.S. Department of Agriculture. *Nutr Support Serv* 5:64.
- +\*Danielsson BRG, Hassoun E, Dencker L. 1982. Embryotoxicity of chromium: Distribution in pregnant mice and effects on embryonic cells in vitro. *Arch Toxicol* 51:233-245.
- Danielsson DA, Pehrson B. 1998. Effects of chromium supplementation on the growth and carcass quality of bulls fed a grain-based diet during the finishing period. *Vet Med (Prague)* 45:219-224.
- Darbre PD. 2006. Metallogestrogens: An emerging class of inorganic xenoestrogens with potential to add to the oestrogenic burden of the human breast. *J Appl Toxicol* 26:191-197.

## 9. REFERENCES

- \*Dasch JM, Wolff GT. 1989. Trace inorganic species in precipitation and their potential use in source apportionment studies. *Water Air Soil Pollut* 43:401-412.
- das Neves RP, Santos TM, Pereira MD, et al. 2002. Comparative histological studies on liver of mice exposed to Cr(VI) and Cr(V) compounds. *Hum Exp Toxicol* 21:365-369.
- \*Davids HW, Lieber M. 1951. Underground waste contamination by chromium wastes. *Water Sewage Works* 98:528-534.
- \*Davidson T, Kluz T, Burns F, et al. 2004. Exposure to chromium (VI) in the drinking water increases susceptibility to UV-induced skin tumors in hairless mice. *Toxicol Appl Pharmacol* 196:431-437.
- +\*Davies J. 1979. Lung cancer mortality of workers in chromate pigment manufacture: An epidemiological survey. *J Oil Colour Chem Assoc* 62:157-163.
- +\*Davies J. 1984. Lung cancer mortality among workers making lead chromate and zinc chromate pigments at three English factories. *Br J Ind Med* 41:158-169.
- +\*Davies J, Easton D, Bidstrup P. 1991. Mortality from respiratory cancer and other causes in United Kingdom chromate production workers. *Br J Ind Med* 48:299-313.
- \*Davis CM, Vincent JB. 1997. Chromium oligopeptide activates insulin receptor tyrosine kinase activity. *Biochemistry* 36:4382-4385.
- Davis CM, Sumrall KH, Vincent JB. 1996. A biologically active form of chromium may activate a membrane phosphotyrosine phosphatase (PTP). *Biochemistry* 35:12963-12969.
- Davis JJ, Gulson BL. 2005. Ceiling (attic) dust: A "museum" of contamination and potential hazard. *Environ Res* 99:177-194.
- Debetto P, Luciani S. 1988. Toxic effect of chromium on cellular metabolism. *Sci Total Environ* 71:365-377.
- D'Elia CF, Sanders JG, Capone DG. 1989. Analytical chemistry for environmental sciences: A question of confidence. *Environ Sci Technol* 23(7):768-774.
- \*De Flora S. 1978. Metabolic deactivation of mutagens in the Salmonella-microsome test. *Nature* 271:455-456.
- \*De Flora S. 1981. Study of 106 organic and inorganic compounds in the Salmonella/microsome test. *Carcinogenesis* 2(4):283-298.
- \*De Flora S. 2000. Threshold mechanisms and site specificity in chromium(VI) carcinogenesis. *Carcinogenesis* 21(4):533-541.
- \*De Flora S, Wetterhahn KE. 1989. Mechanisms of chromium metabolism and genotoxicity. *Life Chemistry Reports* 7:169-244.
- \*De Flora S, Badolati GS, Serra D, et al. 1987a. Circadian reduction of chromium in the gastric environment. *Mutat Res* 192:169-174.

## 9. REFERENCES

- \*De Flora S, Bagnasco M, Serra D, et al. 1990. Genotoxicity of chromium compounds. A review. *Mutat Res* 238:99-172.
- \*De Flora S, Bennicelli C, Znacchi P, et al. 1984. Metabolic activation and deactivation of mutagens by preparations of human lung parenchyma and bronchial tree. *Mutat Res* 139:9-14.
- \*De Flora S, Camoirana A, Bagnasco M, et al. 1997. Estimates of the chromium(VI) reducing capacity in human body compartments as a mechanism for attenuating its potential toxicity and carcinogenicity. *Carcinogenesis* 18(3):531-537.
- +\*De Flora S, Iltcheva M, Balansky RM. 2006. Oral chromium(VI) does not affect the frequency of micronuclei in hematopoietic cells of adult mice and of transplacentally exposed fetuses. *Mutat Res* 610:38-47.
- \*De Flora S, Petruzelli S, Camoirano A, et al. 1987b. Pulmonary metabolism of mutagens and its relationship with lung cancer and smoking habits. *Cancer Res* 47:4740-4745.
- De Flora S, Serra D, Basso C, et al. 1989. Mechanistic aspects of chromium carcinogenicity: Biological monitoring of exposure and the response at the subcellular level to toxic substances. *Arch Toxicol Suppl* 13:28-39.
- De Miguel E, Iribarren I, Chacon E, et al. 2007. Risk-based evaluation of the exposure of children to trace elements in playgrounds in Madrid (Spain). *Chemosphere* 66:505-513.
- \*Deng C, Lee HH, Xian H, et al. 1988. Chromosomal aberrations and sister chromatid exchanges of peripheral blood lymphocytes in Chinese electroplating workers: Effect of nickel and chromium. *J Trace Elem Exper Med* 1:57-62.
- \*Depault F, Cojocar M, Fortin F, et al. 2006. Genotoxic effects of chromium(VI) and cadmium(II) in human blood lymphocytes using the electron microscopy in situ end-labeling (EM-ISEL) assay. *Toxicol In Vitro* 20:513-518.
- De Raeve H, Vandecasteele C, Demedts M, et al. 1998. Dermal and respiratory sensitization to chromate in a cement floorer. *Am J Ind Med* 34:169-176.
- +\*Derelanko NJ, Rinehart WE, Hilaski RJ, et al. 1999. Thirteen-week subchronic rat inhalation toxicity study with a recovery phase of trivalent chromium compounds, chronic oxide, and basic chromium sulfate. *Toxicol Sci* 52(2):278-288.
- Desoize B. 2002. Cancer and metals and metal compounds: Part I-carcinogenesis. *Crit Rev Oncol Hematol* 42(1):1-3.
- \*Dever M, Hausler DW, Smith JE. 1989. Comparison between radioactive isotope chromium-51 and stable isotope chromium-50 labels for the determination of red blood cell survival. *J Anal Atom Spectrom* 4:361-363.
- \*Devi KD, Rozati R, Saleha Banu B, et al. 2001. In vivo genotoxic effect of potassium dichromate in mice leukocytes using comet assay. *Food Chem Toxicol* 39(8):859-865.

## 9. REFERENCES

Devi KP, Sairam M, Sreepriya M, et al. 2004. Immunomodulatory effects of *Premna tomentosa* (L. verbenaceae) extract in J 779 macrophage cell cultures under chromate (VI)-induced immunosuppression. *J Altern Complement Med* 10(3):535-539.

+\*Diaz-Mayans J, Laborda R, Nunez A. 1986. Hexavalent chromium effects on motor activity and some metabolic aspects of Wistar albino rats. *Comp Biochem Physiol* 83C(1):191-195.

Dillon CT, Lay PA, Bonin AM, et al. 1993. *In vitro* DNA damage and mutations induced by a macrocyclic tetraamide chromium(V) complex: Implications for the role of Cr(V) peptide complexes in chromium-induced cancers. *Carcinogenesis* 14(9):1875-1880.

\*Ding M, Shi X. 2002. Molecular mechanisms of Cr(VI)-induced carcinogenesis. *Mol Cell Biochem* 234/235:293-300.

Ding M, Shi X, Castranova V, et al. 2000. Predisposing factors in occupational lung cancer: Inorganic minerals and chromium. *J Environ Pathol Toxicol Oncol* 19(1&2):129-138.

Ding WJ, Chai Z, Duan P, et al. 1998. Serum and urine chromium concentrations in elderly diabetics. *Biol Trace Elem Res* 63:231-237.

\*DiPaolo JA, Casto BC. 1979. Quantitative studies of *in vitro* morphological transformation of Syrian hamster cells by inorganic metal salts. *Cancer Res* 39:1008-1013.

\*DiSilvestro RA, Dy E. 2007. Comparison of acute absorption of commercially available chromium supplements. *J Trace Elem Med Biol* 21(2):120-124.

Dixon JR, Lowe DB, Richards DE, et al. 1970. The role of trace metals in chemical carcinogenesis: Asbestos cancers. *Cancer Res* 30:1068-1074.

\*DOC. 1976c. Standard reference material 1569. Brewers yeast. National Bureau of Standards Certificate of Analysis. U.S. Department of Commerce.  
[http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED\\_CERTIFICATES/1569.pdf](http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED_CERTIFICATES/1569.pdf).  
April 23, 2008.

\*DOC. 1976b. Standard reference material 1570. Trace elements in spinach. National Bureau of Standards Certificate of Analysis. U.S. Department of Commerce.  
[http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED\\_CERTIFICATES/1570.pdf](http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED_CERTIFICATES/1570.pdf).  
April 23, 2008.

\*DOC. 1976a. Standard reference material 1573. Tomato leaves. National Bureau of Standards Certificate of Analysis. U.S. Department of Commerce.  
[http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED\\_CERTIFICATES/1573.pdf](http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED_CERTIFICATES/1573.pdf).  
April 23, 2008.

\*DOC. 1977a. Standard reference material 1571. Orchard leaves. National Bureau of Standards Certificate of Analysis. U.S. Department of Commerce.  
[http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED\\_CERTIFICATES/1571.pdf](http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED_CERTIFICATES/1571.pdf).  
April 23, 2008.

## 9. REFERENCES

- \*DOC. 1977b. Standard reference material 1577. Bovine liver. National Bureau of Standards Certificate of Analysis. U.S. Department of Commerce.  
[http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED\\_CERTIFICATES/1577.pdf](http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED_CERTIFICATES/1577.pdf).  
April 23, 2008.
- \*DOC. 1982. Standard reference material 1577a. Bovine liver. National Bureau of Standards Certificate of Analysis. U.S. Department of Commerce.  
[http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED\\_CERTIFICATES/1577a.pdf](http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED_CERTIFICATES/1577a.pdf).  
May 22, 2008.
- \*DOC. 1983. Standard reference material 1566. Oyster tissue. National Bureau of Standards Certificate of Analysis. U.S. Department of Commerce.  
[http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED\\_CERTIFICATES/1566.pdf](http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED_CERTIFICATES/1566.pdf).  
April 23, 2008.
- \*DOC. 1985. Standard reference material 909. Human serum. National Bureau of Standards Certificate of Analysis. U.S. Department of Commerce.  
[http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED\\_CERTIFICATES/909.pdf](http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED_CERTIFICATES/909.pdf).  
April 23, 2008.
- \*DOC. 1989. Standard reference material 1566a. Oyster tissue. National Bureau of Standards Certificate of Analysis. U.S. Department of Commerce.  
[http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED\\_CERTIFICATES/1566a.pdf](http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED_CERTIFICATES/1566a.pdf).  
April 23, 2008.
- \*DOC. 1993a. Standard reference material 1575. Pine needles. National Bureau of Standards Certificate of Analysis. U.S. Department of Commerce.  
[http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED\\_CERTIFICATES/1575.pdf](http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED_CERTIFICATES/1575.pdf).  
April 23, 2008.
- \*DOC. 1993b. Standard reference material 909a. Human serum. National Bureau of Standards Certificate of Analysis. U.S. Department of Commerce.  
[http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED\\_CERTIFICATES/909a.pdf](http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED_CERTIFICATES/909a.pdf).  
April 23, 2008.
- \*DOC. 1993c. Standard reference material 2670. Toxic metals in freeze-dried urine. National Bureau of Standards Certificate of Analysis. U.S. Department of Commerce.  
[http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED\\_CERTIFICATES/2670.pdf](http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED_CERTIFICATES/2670.pdf).  
May 22, 2008.
- \*DOC. 1996. Standard reference material 1570a. Trace elements in spinach leaves. National Bureau of Standards Certificate of Analysis. U.S. Department of Commerce.  
[http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED\\_CERTIFICATES/1570a%20July%2015,%201996.pdf](http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED_CERTIFICATES/1570a%20July%2015,%201996.pdf).  
April 23, 2008.
- \*DOC. 2003. Standard reference material 909b. Human serum. National Bureau of Standards Certificate of Analysis. U.S. Department of Commerce.  
[http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED\\_CERTIFICATES/909b.Nov19.2003.pdf](http://ts.nist.gov/MeasurementServices/ReferenceMaterials/ARCHIVED_CERTIFICATES/909b.Nov19.2003.pdf).  
April 23, 2008.

## 9. REFERENCES

- +DOD. 1947. The oral toxicity of hexavalent chromium. Washington, DC: U.S. Department of Defense. AD722266.
- \*Doisy RJ, Streeten DPH, Souma ML, et al. 1971. Metabolism of <sup>51</sup>chromium in human subjects-normal, elderly, and diabetic subjects. In: Mertz W, Cornatzer WE, eds. Newer trace elements in nutrition. New York, NY: Marcel Dekker, Inc., 155-168.
- +\*Donaldson DL, Smith CC, Yunice AA. 1984. Renal excretion of chromium-51 chloride in the dog. *Am J Physiol* 246(6):F870-F878.
- +\*Donaldson RM, Barreras RF. 1966. Intestinal absorption of trace quantities of chromium. *J Lab Clin Med* 68:484-493.
- \*Douglas GR, Bell RDL, Grant CE, et al. 1980. Effect of lead chromate on chromosome aberration, sister-chromatid exchange and DNA damage in mammalian cells in vitro. *Mutat Res* 77:157-163.
- \*Dube P. 1988. Determination of chromium in human urine by graphite furnace atomic absorption spectrometry with Zeeman-effect background correction. *Analyst* 113:917-921.
- Dubrovskaya VA, Wetterhahn KE. 1998. Effects of Cr(VI) on the expression of the oxidative stress genes in human lung cells. *Carcinogenesis* 19(8):1401-1407.
- Dudek EJ, Dobson AW, LeDoux SP, et al. 1998. Chromium(VI) induces specific types of mitochondrial DNA damage in human lung A549 cells. *Proc Am Assoc Cancer Res* 39:240.
- Duffus JH. 1996. Epidemiology and the identification of metals as human carcinogens. *Sci Prog* 79(4):311-326.
- Duranceau SJ, Poole J, Foster JV. 1999. Wet-pipe fire sprinklers and water quality: Cross-section control in new wet-pipe fire sprinkler systems should be vigorously pursued, but retrofitting is not recommended. *J Am Water Works Assoc* 91(7):78-90.
- +Dvizhkov PP, Fedorova VI. 1967. [Blastomogenic properties of chromium oxide]. *Vopr Onkol* 13:57-62. (Russian)
- +Eaton D, Stacey N, Wong K, et al. 1980. Dose-response effects of various metal ions on the rat liver metallothionein, glutathione, heme oxygenase, and cytochrome P-450. *Toxicol Appl Pharmacol* 55:393-402.
- \*Eckel WP, Jacob TA. 1988. Ambient levels of 24 dissolved metals in U.S. surface and ground waters. *Prepr Pap Natl Meet Am Chem Soc Div Environ Chem* 28:371-372.
- \*Edel J, Sabbioni E. 1985. Pathways of Cr (III) and Cr (VI) in the rat after intratracheal administration. *Hum Toxicol* 4(4):409-416.
- \*Edme JL, Shirali P, Mereau M, et al. 1997. Assessment of biological chromium among stainless steel and mild steel workers in relation to welding processes. *Int Arch Occup Environ Health* 70:237-242.
- +\*Edmundson WF. 1951. Chrome ulcers of the skin and nasal septum and their relation to patch testing. *J Invest Dermatol* 17:17-19.

## 9. REFERENCES

- \*EEH. 1976. An epidemiological study of lead chromate plants: Final report. Berkeley, CA: Equitable Environmental Health, Inc.
- +\*EEH. 1983. Mortality in employees of three plants which produced chromate pigments. Berkeley, CA: Equitable Environmental Health, Inc.
- \*Eisenberg M, Topping JJ. 1986. Trace metal residues in finfish from Maryland waters, 1978-1979. *J Environ Sci Health* 21(1):87-102.
- Eizaguirre-Garcia D, Rodriguez-Andres C, Watt GC, et al. 1999. A study of leukaemia in Glasgow in connection with chromium-contaminated land. *J Public Health Med* 21(4):435-438.
- Eizaguirre-Garcia D, Rodriguez-Andres C, Watt GCM. 2000. Congenital anomalies in Glasgow between 1982 and 1989 and chromium waste. *J Public Health Med* 22(1):54-58.
- Elbekai RH, El-Kadi AOS. 2007. Transcriptional activation and posttranscriptional modification of Cyp1a1 by arsenite, cadmium, and chromium. *Toxicol Lett* 172:106-119.
- +\*Elbetieha A, Al-Hamood MH. 1997. Long-term exposure of male and female mice to trivalent and hexavalent chromium compounds: Effect on fertility. *Toxicology* 116:39-47.
- \*El-Demerdash FM, Yousef MI, Elswad FAM. 2006. Biochemical study on the protective role of folic acid in rabbits treated with chromium (VI). *J Environ Sci Health B* 41(5):731-746.
- \*Elias Z, Mur J-M, Pierre F, et al. 1989a. Chromosome aberrations in peripheral blood lymphocytes of welders and characterization of their exposure by biological samples analysis. *J Occup Med* 31(5):477-483.
- \*Elias Z, Poirot O, Pezerat H, et al. 1989b. Cytotoxic and neoplastic transforming effects of industrial hexavalent chromium pigments in Syrian hamster embryo cells. *Carcinogenesis* 10(11):2043-2052.
- Elis A, Fromm P, Ninio A, et al. 2001. Employee exposure to chromium and plasma lipid oxidation. *Int J Occup Environ Health* 7:206-208.
- Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. *Ellenhorn's medical toxicology. Diagnosis and treatment of human poisoning*. 2nd ed. Baltimore, MD: Williams & Wilkins, 1098-1100, 162t.
- +\*Ellis EN, Brouhard BH, Lynch RE, et al. 1982. Effects of haemodialysis and dimercaprol in acute dichromate poisoning. *J Toxicol Clin Toxicol* 19(3):249-258.
- Elrashidi MA, Baligar VC, Korcak RF, et al. 1999. Ground water quality: Chemical composition of leachate of dairy manure mixed with fluidized bed combustion residue. *J Environ Qual* 28(4):1243-1251.
- +\*Elsaieed EM, Nada SA. 2002. Teratogenicity of hexavalent chromium in rats and the beneficial role of ginseng. *Bull Environ Contam Toxicol* 68:361-368.
- El-Tawil OS, Morgan AM. 2000. Teratogenic effects of trivalent and hexavalent chromium in rabbits. *Toxicologist* 54(1):32.
- +\*Engebrigtsen JK. 1952. Some investigations on hypersensitiveness to bichromate in cement workers. *Acta Derm Venereol* 32:462-468.

## 9. REFERENCES

- +\*Engel H, Calnan C. 1963. Chromate dermatitis from paint. *Br J Ind Med* 20:192-198.
- \*Engelhardt S, Moser-Veillon PB, Mangels AR, et al. 1990. Appearance of an oral dose of chromium (53Cr) in breast milk? In: Atkinson SA, Hanson LA, Chandra RK, eds. *Breast feeding, nutrition, infection and infant growth in developed and emerging countries*. St. John's, Canada: ARTS Biomedical Publishers and Distributors, 485-487.
- \*Enterline PE. 1974. Respiratory cancer among chromate workers. *J Occup Med* 16(8):523-526.
- EPA. 1975. National interim primary drinking water regulations. U.S. Environmental Protection Agency Fed Reg 40:59566-59587.
- EPA. 1978. Reviews of the environmental effects of pollutants: III. Chromium. Cincinnati, OH: Office of Research and Development, U.S. Environmental Protection Agency. EPA600178023.
- \*EPA. 1979. Water-related environmental fate of 129 priority pollutants: Vol. I: Introduction and technical background, metals and inorganics, pesticides and PCBs. Washington, DC: U.S. Environmental Protection Agency, 10-1 to 10-10. EPA440579029a.
- \*EPA. 1980. Ambient water quality criteria for chromium. Washington, DC: Office of Water Regulations and Standards, Criteria and Standards Division, U.S. Environmental Protection Agency. EPA440580035.
- EPA. 1981. U.S. Environmental Protection Agency. Fed Regist 45:4617-4618 as amended in 46 FR 27476-27477, May 20, 1981.
- EPA. 1982. Errata for Ambient Water Quality Criteria Documents. February 23, 1982, update. Washington, DC: Office of Water Regulations and Standards, U.S. Environmental Protection Agency.
- \*EPA. 1983a. Chromium. Method 218.2 (atomic absorption, furnace technique). Methods for chemical analysis of water and wastes. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600479020.
- \*EPA. 1983b. Chromium. Method 218.4 (atomic absorption, chelation-extraction). Methods for chemical analysis of water and wastes. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600479020.
- \*EPA. 1983c. Chromium, dissolved hexavalent (atomic absorption, furnace technique). Method 218.5. Methods for chemical analysis of water and wastes. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600479020.
- \*EPA. 1984a. Health assessment document for chromium. Research Triangle Park, NC: Environmental Assessment and Criteria Office, U.S. Environmental Protection Agency. EPA600883014F.
- \*EPA. 1984b. Locating and estimating air emissions from sources of chromium. Research Triangle Park, NC: Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency. 85106474.
- EPA. 1984c. Health effects assessment for hexavalent chromium. Cincinnati, OH: Office of Emergency and Remedial Response, U.S. Environmental Protection Agency. U.S. Environmental Protection Agency, ECAOCINHO19.



## 9. REFERENCES

EPA. 1984d. Health effects assessment for trivalent chromium. Washington, DC: Report to Office of Solid Waste and Emergency Response, Office of Emergency and Remedial Response, EPA540186035.

\*EPA. 1985a. Environmental profiles and hazard indices for constituents of municipal sludge: Chromium. Washington, DC: Office of Health and Environmental Assessment, U.S. Environmental Protection Agency.

EPA. 1985b. National primary drinking water regulations; synthetic organic chemicals, inorganic chemicals and microorganism; proposed rule. U.S. Environmental Protection Agency: Fed Regist 50:46966.

EPA. 1985c. Notification requirements; reportable quantity adjustments; final rule and proposed rule. U.S. Environmental Protection Agency: Fed Regist 50:13482.

EPA. 1985d. Drinking water criteria document for chromium (Final draft). Washington, DC: Criteria and Standards Division, Office of Drinking Water, U.S. Environmental Protection Agency. PB86118072.

\*EPA. 1986a. Chromium (atomic absorption, furnace technique): Method: 7191. Test methods for evaluating solid waste. Vol. 1A: Laboratory manual physical/chemical methods 3rd ed. SW-846. Washington, DC: Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency.

\*EPA. 1986b. Chromium (atomic absorption, direct aspiration): Method: 7190. Test methods for evaluating solid waste. Vol. 1A: Laboratory manual physical/chemical methods 3rd ed. Washington, DC: Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency. SW-846.

\*EPA. 1986c. Chromium, hexavalent (coprecipitation): Method: 7195. Test methods for evaluating solid waste. Vol. 1A: Laboratory manual physical/chemical methods 3rd ed. Washington, DC: Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency. SW-846.

\*EPA. 1986d. Chromium, hexavalent (chelation/extraction): Method: 7197. Test methods for evaluating solid waste. Vol. 1A: Laboratory manual physical/chemical methods 3rd ed. Washington, DC: Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency, SW-846.

\*EPA. 1986e. Chromium, hexavalent (differential pulse polarography): Method: 7198. Test methods for evaluating solid waste. Vol. 1A: Laboratory manual physical/chemical methods 3rd ed. Washington, DC: Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency. SW-846.

EPA. 1987a. Extremely hazardous substances list and threshold planning quantities; emergency planning and release notification requirements. U.S. Environmental Protection Agency. Fed Regist 52:13378-13410.

\*EPA. 1987b. Quality criteria for water 1986. Washington, DC: Office of Water Regulations and Standards, U.S. Environmental Protection Agency, EPA440586001.

\*EPA. 1988a. Analysis of the Clean Water Act effluent guidelines pollutants. Summary of the chemical regulated by industrial points source categories 40 CFR Parts 400-475. Draft. U.S. Environmental Protection Agency.

## 9. REFERENCES

\*EPA. 1988b. Mining waste exclusion. U.S. Environmental Protection Agency. Fed Regist 53:41288-41300.

\*EPA. 1988c. Fate of chromium(III) in chlorinated water. Cincinnati, OH: Office of Research and Development, U.S. Environmental Protection Agency. PB88130992.

\*EPA. 1988d. Recommendations for and documentation of biological values for use in risk assessment. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH. PB8817874.

EPA. 1989a. Interim methods for development of inhalation reference doses. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA600888066F.

EPA. 1989b. National primary and secondary drinking water regulations: Proposed rule. U.S. Environmental Protection Agency. Fed Regist 54:22062-22160.

EPA. 1989c. Reportable quantity adjustments: Delisting of ammonium thiosulfate. U.S. Environmental Protection Agency. Fed Regist 54:33426-33484.

\*EPA. 1990a. 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, Environmental Criteria and Assessment Office. EPA600890066A.

\*EPA. 1990b. Noncarcinogenic effects of chromium: Update to health assessment document. Research Triangle Park, NC: Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, U.S. Environmental Protection Agency. EPA600887048F.

EPA. 1991. National primary drinking water regulations-synthetic organic chemicals and inorganic chemicals; monitoring for unregulated contaminants; national primary drinking water regulations implementation; national secondary drinking water regulations. Final rule. Fed Regist 56:3526-3597.

EPA. 1994a. Test methods for evaluating solid waste. Vol. 1A: Laboratory manual physical/chemical methods 3rd ed. Washington, DC: Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency, SW-846.

\*EPA. 1994b. EPA ground water issue. Natural attenuation of hexavalent chromium in groundwater and soils. Washington, DC: U.S. Environmental Protection Agency. EPA540594505.

\*EPA. 1994c. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Office of Research and Development, Environmental Criteria and Assessment Office. EPA600890066F

\*EPA. 1995. Emergency planning and community -right-to-know act. Title III (SARA). U.S. Environmental Protection Agency.

\*EPA. 1996a. Method 7199: Determination of hexavalent chromium in drinking water, groundwater, and industrial wastewater effluents by ion chromatography. In: Test methods for evaluating solid waste. 3rd ed. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response. SW-846.

## 9. REFERENCES

- \*EPA. 1996b. Method 6010B: Inductively coupled plasma-atomic emission spectrometry. In: Test methods for evaluating solid waste. 3rd ed. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response. SW-846
- EPA. 1996c. Drinking water regulations and health advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Water. EPA822B96002.
- \*EPA. 1997. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. EPA630R96012.
- EPA. 1998a. Designation of hazardous substances. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4
- EPA. 1998b. Clean water effluent guidelines. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 406.
- \*EPA. 1998c. Notice of availability of RCRA waste minimization PBT chemical list. U.S. Environmental Protection Agency. Fed Regist 63:60332. <http://www.gpoaccess.gov/fr/index.html>. May 05, 2008.
- \*EPA. 2000. Benchmark dose technical guidance document. Washington, DC: U.S. Environmental Protection Agency. EPA630R00001.
- \*EPA. 2003. National primary drinking water standards. Washington, DC: U.S. Environmental Protection Agency, Office of Ground Water and Drinking Water. EPA816F03016. <http://www.epa.gov/safewater/mcl.html>. March 07, 2006.
- \*EPA. 2005. 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. 2006 Edition of the drinking water standards and health advisories. Washington, DC: Office of Water, U.S. Environmental Protection Agency. EPA822R06013. <http://www.epa.gov/waterscience/criteria/drinking/dwstandards.pdf>. April 11, 2007.
- \*EPA. 2006b. National recommended water quality criteria. Washington, DC: U.S. Environmental Protection Agency, Office of Water, Office of Science and Technology. <http://www.epa.gov/waterscience/criteria/nrwqc-2006.pdf>. January 08, 2008.
- \*EPA. 2007a. Acute exposure guideline levels (AEGLs) Washington, DC: Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency. <http://www.epa.gov/oppt/aegl/pubs/compiled.pdf>. April 24, 2008.
- \*EPA. 2007b. The Clean Air Act amendments of 1990 list of 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>. April 24, 2008.
- \*EPA. 2008a. Acute exposure guideline levels (AEGLs). Second AEGL chemical priority list. U.S. Environmental Protection Agency. [http://www.epa.gov/oppt/aegl/pubs/priority\\_2.htm](http://www.epa.gov/oppt/aegl/pubs/priority_2.htm). April 24, 2008.

## 9. REFERENCES

- \*EPA. 2008b. Designation of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 116.4. <http://www.epa.gov/lawsregs/search/40cfr.html>. April 24, 2008.
- \*EPA. 2008c. Determination of reportable quantities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 117.3. <http://www.epa.gov/lawsregs/search/40cfr.html>. April 24, 2008.
- \*EPA. 2008d. Groundwater monitoring list. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 264, Appendix IX. <http://www.epa.gov/lawsregs/search/40cfr.html>. May 05, 2008.
- \*EPA. 2008e. Inert ingredients permitted for use in nonfood use pesticide products. U.S. Environmental Protection Agency. <http://www.epa.gov/opprd001/inerts/lists.html>. April 24, 2008.
- \*EPA. 2008f. Master testing list. Washington, DC: Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency. <http://www.epa.gov/opptintr/chemtest/pubs/mtl.htm>. April 24, 2008.
- \*EPA. 2008g. The list of 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>. April 24, 2008.
- \*EPA. 2008h. Toxic chemical release reporting. Chemicals and chemical categories to which this part applies. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65. <http://www.epa.gov/lawsregs/search/40cfr.html>. April 24, 2008.
- \*EPA. 2008i. Toxic pollutants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 401.15. <http://www.epa.gov/lawsregs/search/40cfr.html>. April 24, 2008.
- \*EPA. 2008j. Designation of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4. <http://www.epa.gov/lawsregs/search/40cfr.html>.
- Escobar P, Sicard DM, Alfonso E, et al. 1998. The comet assay and DNA damage in a human population exposed to chromium compounds. *Environ Mol Mutagen* 31(Suppl 29):72.
- +\*Eun HC, Marks R. 1990. Dose-response relationships for topically applied antigens. *Br J Dermatol* 122:491-499.
- +Evan AP, Dail WG. 1974. The effects of sodium chromate on the proximal tubules of the rat kidney: Fine structural damage and lysozymuria. *Lab Invest* 30(6):704-715.
- \*Evans GW. 1989. The effect of chromium picolinate on insulin controlled parameters in humans. *Int J Biosocial Med Res* 11(2):163-180.
- Evans GW, Pouchnik DJ. 1993. Composition and biological activity of chromium-pyridine carboxylate complexes. *J Inorg Biochem* 49:177-187.
- Evoek-Clover CM, Polansky MM, Anderson RA, et al. 1993. Dietary chromium supplementation with or without somatotropin treatment alters serum hormones and metabolites in growing pigs without affecting growth performance. *J Nutr* 123:1504-1512.
- Ewis AA, Kondo K, Dang F, et al. 2006. Surfactant protein B gene variations and susceptibility to lung cancer in chromate workers. *Am J Ind Med* 49(5):367-373.

## 9. REFERENCES

- Fadhel ZA, Al-Hamood MH. 2000. Chromium-induced lipid peroxidation in nursing mice and their offspring. *Res Commun Pharmacol Toxicol* 5:167-175.
- \*Fagliano JA, Savrin J, Udasin I, et al. 1997. Community exposure and medical screening near chromium waste sites in New Jersey. *Regul Toxicol Pharmacol* 26:S13-S22.
- Fahmi CJ. 2007. Biological applications of x-ray fluorescence microscopy: Exploring the subcellular topography and speciation of transition metals. *Curr Opin Chem Biol* 11(2):127-127.
- Fahmy MA, Shoman HM, Hassan EES. 2002. The protective role of thiola and soybean seeds against the genotoxicity induced by potassium dichromate in mice. *Mutat Res* 517:1-12.
- \*Fahmi C. 2007. Biological applications of x-ray fluorescence microscopy: Exploring the subcellular topography and speciation of transition metals. *Curr Opin Chem Biol* 11:121-127.
- Fairhurst S, Minty CA. 1989. The toxicity of chromium and inorganic chromium compounds. Health and safety executive review. *Toxicity Review* 21. London: Her Majesty's Stationery Office.
- \*Falerios M, Schild K, Sheehan P et al. 1992. Airborne concentrations of trivalent and hexavalent chromium from contaminated soils at unpaved and partially paved commercial/industrial sites. *J Air Waste Manage Assoc* 42:40-48.
- Fatima S, Mahmood R. 2007. Vitamin C attenuates potassium dichromate-induced nephrotoxicity and alterations in renal brush border membrane enzymes and phosphate transport in rats. *Clin Chim Acta* 386(1-2):94-99.
- \*FDA. 2007a. Beverages. Bottled water. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 165.110. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. April 24, 2008.
- \*FDA. 2007b. Indirect food additives: Adhesives and components of coatings. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 175.105. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. April 24, 2008.
- \*FDA. 2007c. Nutrition labeling of food. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 101.9. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. May 20, 2008.
- \*FDA. 2008. EAFUS: A food additive database. U.S. Food and Drug Administration. <http://vm.cfsan.fda.gov/~dms/eafus.html>. April 24, 2008.
- \*Febel H, Szegedi B, Huszar S. 2001. Absorption of inorganic, trivalent and hexavalent chromium following oral and intrajejunal doses in rats. *Acta Vet Hung* 49(2):203-209.
- \*FEDRIP. 2008. Chromium. Federal Research in Progress database. Springfield, VA: National Technical Information Service.
- Feltzer SP, Dourson ML. 1997. Hexavalent chromium-contaminated soils: Options for risk assessment and risk management. *Regul Toxicol Pharmacol* 25:43-59.

## 9. REFERENCES

- Feng Z, Hu W, Rom WN, et al. 2003. Chromium(VI) exposure enhances polycyclic aromatic hydrocarbon-DNA binding at the p53 gene in human lung cells. *Carcinogenesis* 24(4):771-778.
- Fernandes MAS, Geraldine CFGC, Oliverira CR, et al. 2000. Chromate-induced human erythrocytes haemoglobin oxidation and peroxidation: Influence of vitamin E, vitamin C, salicylate, deferoxamine, and N-ethylmaleimide. *Toxicol Lett* 114:237-243.
- Fernandes MAS, Mota IM, Silva MTL, et al. 1999. Human erythrocytes are protected against chromate-induced peroxidation. *Ecotoxicol Environ Saf* 43(1):38-46.
- \*Fernandez-Nieto M, Quirce S, Carnes J, et al. 2006. Occupational asthma due to chromium and nickel salts. *Int Arch Occup Environ Health* 79:483-486.
- Fernandez-Nieto M, Quirce S, Cuesta J, et al. 2003. Occupational asthma due to chrome and nickel salts: Description of four cases. *J Allergy Clin Immunol* 111(2):S94.
- \*Finley B, Fehling K, Falerios M, et al. 1993. Field validation for sampling and analysis of airborne hexavalent chromium. *Appl Occup Environ Hyg* 8(3):191-200.
- Finley BL, Mayhall DA. 1994. Airborne concentrations of chromium due to contaminated interior building surfaces. *Appl Occup Hyg* 9:433-441.
- \*Finley BL, Paustenbach DJ. 1997. Using applied research to reduce uncertainty in health risk assessment: Five case studies involving human exposure to chromium in soil and groundwater. *J Soil Contam* 6(6):650-705.
- \*Finley BL, Kerger BD, Dodge DG, et al. 1996a. Assessment of airborne hexavalent chromium in the home following use of contaminated tapwater. *J Expo Anal Environ Epidemiol* 6(2):229-245.
- +\*Finley BL, Kerger BD, Katona MW, et al. 1997. Human ingestion of chromium (VI) in drinking water: Pharmacokinetics of following repeated exposure. *Toxicol Appl Pharmacol* 142:151-159.
- +\*Finley BL, Scott PK, Norton RL, et al. 1996b. Urinary chromium concentrations in humans following ingestion of safe doses of hexavalent and trivalent chromium: Implications for biomonitoring. *J Toxicol Environ Health* 48:479-499.
- \*Fishbein L. 1981. Sources, transport and alterations of metal compounds: An overview. I. Arsenic, beryllium, cadmium, chromium and nickel. *Environ Health Perspect* 40:43-64.
- \*Fishbein L. 1984. Overview of analysis of carcinogenic and/or mutagenic metals in biological and environmental samples: I. Arsenic, beryllium, cadmium, chromium and selenium. *Int J Environ Anal Chem* 17:113-170.
- Fisher AA. 1998. Cement injuries: Part I. Cement hand dermatitis resulting in "chrome cripples". *Cutis* 61(2):64.
- Flint GN, Carter SV, Fairman B. 1998. Skin allergy from exposure to alloys of chromium. *Contact Dermatitis* 39:315-316.
- \*Flores A, Perez JM. 1999. Cytotoxicity, apoptosis, and *in vitro* DNA damage induced by potassium chromate. *Toxicol Appl Pharmacol* 161:75-81.

## 9. REFERENCES

- +\*Foa V, Riboldi L, Patroni M, et al. 1988. Effects derived from long-term low-level chromium exposure in ferro-alloy metallurgy. Study of absorption and renal function in workers. *Sci Total Environ* 71:389-400.
- \*Fomon SJ. 1966. Body composition of the infant. Part I: The male reference infant. In: Falkner 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* 35:1169-1175.
- Foo SC, Khoo NY, Heng A, et al. 1993. Metals in hair as biological indices for exposure. *Int Arch Occup Environ Health* 65:S83-S86.
- Forbes RM, Erdman JW. 1983. Bioavailability of trace mineral elements. *Annu Rev Nutr* 3:213-231.
- \*Fornace AJ, Seres DS, Lechner JF, et al. 1981. DNA-protein cross-linking by chromium salts. *Chem Biol Interact* 36:345-354.
- Fowler JF, Kauffman CL, Marks JG, et al. 1999. An environmental hazard assessment of low-level dermal exposure to hexavalent chromium in solution among chromium-sensitized volunteers. *J Occup Environ Med* 41(3):150-160.
- Fox GN, Sabovic Z. 1998. Chromium picolinate supplementation for diabetes mellitus. *J Fam Pract* 46(1):83-86.
- Fradkin A, Janoff A, Lane B, et al. 1975. *In vitro* transformation of BHK21 cells grown in the presence of calcium chromate. *Cancer Res* 35:1058-1063.
- +\*Franchini I, Mutti A. 1988. Selected toxicological aspects of chromium(VI) compounds. *Sci Total Environ* 71:379-387.
- +\*Franchini I, Magnani F, Mutti A. 1983. Mortality experience among chromeplating workers. *Scand J Work Environ Health* 9:247-252.
- +Franchini I, Mutti A, Cavatorta A, et al. 1978. Nephrotoxicity of chromium. *Contrib Nephrol* 10:98-110.
- Fraser DJ, Brandt TL, Kroll DJ. 1995. Topoisomerase II $\alpha$  promoter trans-activation early in monocytic differentiation of HL-60 human leukemia cells. *Mol Pharmacol* 47:696-706.
- Freeman NC, Stern AH, Liroy PJ. 1997. Exposure to chromium dust from homes in a chromium surveillance project. *Arch Environ Health* 52(3):213-219.
- +\*Fregert S. 1975. Occupational dermatitis in a 10-year material. *Contact Dermatitis* 1:96-107.
- +\*Fregert S, Rorsman H. 1964. Allergy to trivalent chromium. *Arch Dermatol* 90:4-6.
- +\*Fregert S, Rorsman H. 1966. Allergic reactions to trivalent chromium compounds. *Arch Dermatol* 93:711-713.

## 9. REFERENCES

- +Fregert S, Hjorth N, Magnusson B, et al. 1969. Epidemiology of contact dermatitis. *Trans St John's Hosp Dermatol Soc* 55:17-35.
- +\*Frentzel-Beyme R. 1983. Lung cancer mortality of workers employed in chromate pigment factories. *J Cancer Res Clin Oncol* 105:183-188.
- Fresco P, Shacker F, Kortenkamp A. 1995. The reductive conversion of chromium (VI) by ascorbate gives rise to apurinic/aprimidinic sites in isolated DNA. *Chem Res Toxicol* 8:884-890.
- +\*Fristedt B, Lindqvist B, Schutz A, et al. 1965. Survival in a case of acute oral chromic acid poisoning with acute renal failure treated by haemodialysis. *Acta Med Scand* 177:153-159.
- \*Fryzek JP, Mumma MT, McLaughlin JK, et al. 2001. Cancer mortality in relation to environmental chromium exposure. *J Occup Environ Med* 43(7):635-640.
- +\*Fujii T, Sakamoto Y, Fukumori N, et al. 1976. [Primary eye irritation tests using a chromium dross extract]. *Annual Report of the Tokyo Metropolitan Research Laboratory of Public Health* 27:124-128. (Japanese)
- Fukai R. 1967. Valency state of chromium in seawater. *Nature* 213:901.
- \*Fukunaga M, Kurachi Y, Mizuguchi Y. 1982. Action of some metal ions on yeast chromosomes. *Chem Pharm Bull* 30(8):3017-3019.
- Fullerton A, Gammelgaard B, Avnstorp C, et al. 1993. Chromium content in human skin after in vitro application of ordinary cement and ferrous-sulphate-reduced cement. *Contact Dermatitis* 29:133-137.
- Furst A, Haro RT. 1969. A survey of metal carcinogenesis. *Prog Exp Tumor Res* 12:102-133.
- +\*Furst A, Schlauder M, Sasmore DP. 1976. Tumorigenic activity of lead chromate. *Cancer Res* 36:1779-1783.
- Fusheng Y, Yaping M, Zhongcheng W. 1999. Content of metals in different diameter airborne particles and effect on micronuclei formation in human lymphocytes. *J Hyg Res* 28(1):21-22.
- Gad SC. 1989. Acute and chronic systemic chromium toxicity. *Sci Total Environ* 86:149-157.
- +\*Gad SC, Powers WJ, Dunn BJ, et al. 1986. Acute toxicity of four chromate salts. In: Serrone DM, ed. *Chromium symposium 1986: An update*. Pittsburgh, PA: Industrial Health Foundation Inc., 43-58.
- Gagné SM, Li MX, Sykes BD. 1997. Mechanism of direct coupling between binding and induced structural change in regulatory calcium binding proteins. *Biochemistry* 36:4386-4392.
- +Gale TF. 1978. Embryotoxic effects of chromium trioxide in hamsters. *Environ Res* 16:101-109.
- +Gale TF. 1982. The embryotoxic response to maternal chromium trioxide exposure in different strains of hamsters. *Environ Res* 29:196-203.
- +Gale TF, Bunch JD III. 1979. The effect of the time of administration of chromium trioxide on the embryotoxic response in hamsters. *Teratology* 19:81-86.



## 9. REFERENCES

- \*Gambelunghe A, Piccinini R, Abbritti G, et al. 2006. Chromium VI-induced apoptosis in a human bronchial epithelial cell line (BEAS-2B) and a lymphoblastic leukemia cell line (MOLT-4). *J Occup Environ Med* 48(3):319-325.
- \*Gambelunghe A, Piccinini R, Ambrogi M, et al. 2003. Primary DNA damage in chrome-plating workers. *Toxicology* 188:187-195.
- +\*Gao M, Levy LS, Braithwaite RA, et al. 1993. Monitoring of total chromium in rat fluids and lymphocytes following intratracheal administration of soluble trivalent or hexavalent chromium compounds. *Hum Exp Toxicol* 12:377-382.
- +\*Gao M, Levy LS, Faux SP, et al. 1994. Use of molecular epidemiological techniques in a pilot study on workers exposed to chromium. *Occup Environ Med* 51:663-668.
- \*Gao N, Jiang BH, Leonard SS, et al. 2002. p38 Signaling-mediated hypoxia-inducible factor 1alpha and vascular endothelial growth factor induction by Cr(VI) in DU145 human prostate carcinoma cells. *J Biol Chem* 277(47):45041-45048.
- \*Garcia E, Cabrera C, Lorenzo ML, et al. 2001. Estimation of chromium bioavailability from the diet by an in vitro method. *Food Addit Contam* 18(7):601-606.
- \*Garcia J, Jennette K. 1981. Electron-transport cytochrome P-450 system is involved in the microsomal metabolism of the carcinogen chromate. *J Inorganic Biochem* 14:281-295.
- +\*Gargas ML, Norton RL, Paustenbach DJ, et al. 1994. Urinary excretion of chromium by humans following ingestion of chromium picolinate: Implications for biomonitoring. *Drug Metab Dispos* 22(4):522-529.
- \*Gasiorowski K, Szyba K, Wozniak D, et al. 1997. Inhibition of potassium dichromate mutagenicity by todralazine. *Mutagenesis* 12(6):411-415.
- \*Gasiorowski K, Szyba K, Wozniak D, et al. 1998. Genotoxicity of Cr(VI) can be markedly lowered by complexation of the chromate anion. *BioMetals* 11:175-181.
- \*Gass JK, Todd PM. 2007. Multiple manifestations of chromate contact allergy. *Contact Dermatitis* 56(5):290-291.
- \*Gava C, Costa R, Zordan M, et al. 1989a. Induction of gene mutations in Salmonella and Drosophila by soluble Cr(VI) compounds: Synergistic effects of nitrilotriacetic acid. *Toxicol Environ Chem* 22:27-38.
- \*Gava C, Perazzolo M, Zentilin L, et al. 1989b. Genotoxic potentiality and DNA-binding properties of acetylacetone, maltol, and their aluminum(III) and chromium(III) neutral complexes. *Toxicol Environ Chem* 22:149-157.
- Gavin IM, Gillis B, Arbieva Z, et al. 2007. Identification of human cell responses to hexavalent chromium. *Environ Mol Mutagen* 48:650-657.
- Geetha S, Ram MS, Mongia SS, et al. 2003. Evaluation of antioxidant activity of leaf extract of Seabuckthorn (*Hippophae rhamnoides* L.) on chromium(VI) induced oxidative stress in albino rats. *J Ethnopharmacol* 87(2-3):247-251.

## 9. REFERENCES

- Geier A, Bar-Shalom I, Beery R, et al. 1996. Induction of apoptosis in MDA-231 cells by protein synthesis inhibitors is suppressed by multiple agents. *Cancer Invest* 14(5):435-444.
- \*Gerhardsson L, Brune D, Nordberg GF, et al. 1988. Multielemental assay of tissues of deceased smelter workers and controls. *Sci Total Environ* 74:97-110.
- \*Gianello G, Masci O, Carelli G, et al. 1998. Occupational exposure to chromium—An assessment of environmental pollution levels and biological monitoring of exposed workers. *Ind Health* 36:74-77.
- Gibb HJ, Chen CW, Hiremath CB. 1988. Carcinogen risk assessment of chromium compounds. Washington, DC: Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency. EPA600D880129.
- +\*Gibb HJ, Lees PSJ, Pinsky PF, et al. 2000a. Clinical findings of irritation among chromium chemical production workers. *Am J Ind Med* 38:127-131.
- +\*Gibb HJ, Lees PSJ, Pinsky PF, et al. 2000b. Lung cancer among workers in chromium chemical production. *Am J Ind Med* 38:115-126.
- \*Giwerzman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. *Environ Health Perspect Suppl* 101(2):65-71.
- +\*Glaser U, Hochrainer D, Kloppel H, et al. 1985. Low level chromium(VI) inhalation effects on alveolar macrophages and immune functions in Wistar rats. *Arch Toxicol* 57:250-256.
- +\*Glaser U, Hochrainer D, Kloppel H, et al. 1986. Carcinogenicity of sodium dichromate and chromium(VI/III) oxide aerosols inhaled by male Wistar rats. *Toxicology* 42:219-232.
- +\*Glaser U, Hochrainer D, Oldiges H. 1988. Investigations of the lung carcinogenic potentials of sodium dichromate and Cr VI/III oxide aerosols in Wistar rats. *Environ Hyg* 1:111-116.
- +\*Glaser U, Hochrainer D, Steinhoff D. 1990. Investigation of irritating properties of inhaled CrVI with possible influence on its carcinogenic action. *Environ Hyg* 2:235-245.
- Gochfeld M. 1991. Panel discussion: Analysis of chromium: Methodologies and detection levels and behavior of chromium in environmental media. *Environ Health Perspect* 92:42-43.
- Gochfeld M, Witmer C. 1991. A research agenda for environmental health aspects of chromium, *Environ Health Perspect* 92:141-144.
- Goicolea A, Barrio RJ, de Balugera ZG, et al. 1998. Study of the toxicity in industrial soils by the bioluminescence assay. *J Environ Sci Health Part A* 33(5):863-875.
- +\*Goitre M, Bedello PG, Cane D. 1982. Chromium dermatitis and oral administration of the metal. *Contact Dermatitis* 8:208-209.
- \*Goldbohm RA, Tielemans ELJP, Heederik D, et al. 2006. Risk estimation for carcinogens based on epidemiological data: A structured approach, illustrated by an example on chromium. *Regul Toxicol Pharmacol* 44:294-310.

## 9. REFERENCES

Goldfrank LR, Flomenbaum NE, Lewin NA, et al. 2002. In: Goldfrank LR, ed. Goldfrank's toxicologic emergencies. 7th ed. New York, NY: McGraw-Hill, 1282, 1289-1290, 1134.

+\*Goldman M, Karotkin RH. 1935. Acute potassium bichromate poisoning. *Am J Med Sci* 189:400-403.

\*Goldsby RA, Kindt TJ, Osborne BA, et al. 2003. Hypersensitive reactions. *Immunology*. 5th ed. New York, NY: W.H. Freeman and Company, 361-386.

+\*Gomes E. 1972. Incidence of chromium-induced lesions among electroplating workers in Brazil. *Ind Med* 41(12):21-25.

\*Gomez-Arroyo S, Altamirano M, Villalobos-Pietrini R. 1981. Sister chromatid exchanges induced by some chromium compounds in human lymphocytes in vitro. *Mutat Res* 90:425-431.

\*Gonzalez AR, Ndung'u K, Flegal AR. 2005. Natural occurrence of hexavalent chromium in the aromas red sands aquifer, California. *Environ Sci Technol* 39:5505-5511.

\*Gonzalez-Vergara E, De Gonzalez BC, Hegenauer J, et al. 1981. Chromium coordination compounds of pyridoxal and nicotinic acid: Synthesis, absorption and metabolism. *Isr J Chem* 21:18-22.

Goulart M, Batoreu MC, Rodrigues AS, et al. 2005. Lipoperoxidation products and thiol antioxidants in chromium exposed workers. *Mutagenesis* 20(5):311-315.

\*Grant KE, Chandler RM, Castle AL, et al. 1997. Chromium and exercise training: Effect on obese women. *Med Sci Sports Exer* 29:992-998.

Grawe KP, Teiling-Gardlund A, Jalkestén E, et al. 2004. Increased spontaneous motor activity in offspring after maternal cadmium exposure during lactation. *Environ Toxicol Pharmacol* 17(1):35-40.

\*Gray SJ, Sterling K. 1950. The tagging of red cells and plasma proteins with radioactive chromium. *J Clin Invest* 29:1604-1613.

\*Greenberg RR, Zeisler R. 1988. A radiochemical procedure for ultratrace determination of chromium in biological materials. *J Radioanal Nucl Chem* 124(1):5-20.

+\*Gregus Z, Klaassen CD. 1986. Disposition of metals in rats: A comparative study of fecal, urinary, and biliary excretion and tissue distribution of eighteen metals. *Toxicol Appl Pharmacol* 85:24-38.

\*Greig RA, Jones J. 1976. Nondestructive neutron activation analysis of marine organisms collected from ocean dump sites of the middle eastern United States. *Arch Environ Contam Toxicol* 4(4):420-434.

\*Griepink B, Tolg G. 1989. Sample digestion for the determination of elemental traces in matrices of environmental concern. *Pure Appl Chem* 61(6):1139-1146.

Grogan CH. 1957. Experimental studies in metal carcinogenesis VIII. On the etiological factor in chromate cancer. *Cancer* 10:625-638.

Grogan CH, Oppenheimer H. 1955. Experimental studies in metal carcinogenesis. V. Interaction of Cr(III) and Cr(VI) compounds with proteins. *Arch Biochem Biophys* 56:204-221.

## 9. REFERENCES

- Gromadzinska J, Wasowicz W, Sklodowska M, et al. 1996. The influence of atmospheric chromium on selenium content and glutathione peroxidase activity in blood of tannery workers. *Environ Health Perspect* 104(12):1312-1316.
- +\*Gross PR, Katz SA, Samitz MH. 1968. Sensitization of guinea pigs to chromium salts. *J Invest Dermatol* 50(5):424-427.
- \*Gruber JE, Jennette KW. 1978. Metabolism of the carcinogen chromate by rat liver microsomes. *Biochem Biophys Res Commun* 82(2):700-706.
- \*Guillemin MP, Berode M. 1978. A study of the difference in chromium exposure in workers in two types of electroplating process. *Ann Occup Hyg* 21:105-112.
- +Gumbleton M, Nicholls PJ. 1988. Dose-response and time-response biochemical and histological study of potassium dichromate-induced nephrotoxicity in the rat. *Food Chem Toxicol* 26(1):37-44.
- \*Gunaratnam M, Grant MH. 2002. Chromium(VI)-induced damage to the cytoskeleton and cell death in isolated hepatocytes. *Biochem Soc Trans* 30(4):748-750.
- \*Gunaratnam M, Grant MH. 2004. Damage to F-actin and cell death induced by chromium VI and nickel in primary monolayer cultures of rat hepatocytes. *Toxicol In Vitro* 18:245-253.
- Gurjar BR, Mohan M, Sidhu KS. 1996. Potential health risks related to carcinogens in the atmospheric environment in India. *Regul Toxicol Pharmacol* 24:141-148.
- Gurson CT. 1977. The metabolic significance of dietary chromium. *Adv Nutr Res* 1:23-53.
- Gustavsson P, Jakobsson R, Johansson H, et al. 1998. Occupational exposures and squamous cell carcinoma of the oral cavity, pharynx, larynx, and oesophagus: A case-control study in Sweden. *Occup Environ Med* 55:393-400.
- Guthrie BE. 1982. The nutritional role of chromium. In: Lang S, ed. *Biological and environmental aspects of chromium*. Amsterdam: Elsevier Biomedical Press, 117-148.
- \*Guzelian PS, Henry CJ, Olin SS. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences Institute Press.
- +\*Gylseth B, Gundersen N, Lang S. 1977. Evaluation of chromium exposure based on a simplified method for urinary chromium determination. *Scand J Work Environ Health* 3:28-31.
- \*Ha L, Ceryak S, Patierno SR. 2003. Chromium (VI) activates ataxia telangiectasia mutated (ATM) protein. Requirement of ATM for both apoptosis and recovery from terminal growth arrest. *J Biol Chem* 278(20):17885-17894.
- \*Ha L, Ceryak S, Patierno SR. 2004. Generation of S phase-dependent DNA double-strand breaks by Cr(VI) exposure: Involvement of ATM in Cr(VI) induction of gamma-H2AX. *Carcinogenesis* 25(11):2265-2274.
- \*Haberman PJ, Baggett JM, Berndt WO. 1987. The effect of chromate on citrinin-induced renal dysfunction in the rat. *Toxicol Lett* 38:83-90.

## 9. REFERENCES

\*Haddad LM, Shannon MW, Winchester JF, eds. 1998. Chromium. In: Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia, PA: W.B. Sanders Company, 794-795.

+\*Haguenoer JM, Dubois G, Frimat P, et al. 1981. [Mortality due to bronch-pulmonary cancer in a factory producing pigments based on lead and zinc chromates]. In: Prevention of occupational cancer - International Symposium, Occupational Safety and Health Series 46. Geneva, Switzerland: International Labour Office, 168-176. (French)

Halasova E, Baska T, Kikura F, et al. 2005. Lung cancer in relation to occupational and environmental chromium exposure and smoking. *Neoplasma* 52(4):287-291.

\*Hallmark MA, Reynolds TH, DeSouza CA, et al. 1996. Effects of chromium on resistance training on muscle strength and body composition. *Med Sci Sports Exerc* 28:139-144.

\*Hamamy HA, Al-Hakkak ZS, Hussain AF. 1987. Chromosome aberrations in workers in a tannery in Iraq. *Mutat Res* 189:395-398.

Hamdan S, Morse B, Reinhold D. 1999. Nickel subsulfide is similar to potassium dichromate in protecting normal human fibroblasts from the mutagenic effects of benzo[a]pyrene diol epoxide. *Environ Mol Mutagen* 33:211-218.

Hanaoka T, Yamano Y, Katsuno N, et al. 1997. Elevated serum levels of p53 proteins in chromium workers. *Scand J Work Environ Health* 23:37-40.

Hanna PM, Kadiiska MB, Jordan SJ, et al. 1993. Role of metallothionein in zinc(II) and chromium(III) mediated tolerance to carbon tetrachloride hepatotoxicity: Evidence against a trichloromethyl radical-scavenging mechanism. *Chem Res Toxicol* 6:711-717.

+\*Hansen MB, Johansen JD, Menne T. 2003. Chromium allergy: Significance of both Cr(III) and Cr(VI). *Contact Dermatitis* 49(4):206-212.

\*Hansen MB, Menne T, Johansen JD. 2006a. Cr(III) and Cr(VI) in leather and elicitation of eczema. *Contact Dermatitis* 54(5):278-282.

+\*Hansen MB, Menne T, Johansen JD. 2006b. Cr(III) reactivity and foot dermatitis in Cr(VI) positive patients. *Contact Dermatitis* 54(3):140-144.

+\*Hanslian L, Navratil J, Jurak J, et al. 1967. [Damage to the upper respiratory tract by a chromic acid aerosol]. *Pracovni Lekarstvi* 19:294-298. (Czechoslovakian)

Hanston P, Van Caenegem O, Decordier I, et al. 2005. Hexavalent chromium ingestion: Biological markers of nephrotoxicity and genotoxicity. *Clin Toxicol* 43(2):111-112.

\*Harnly JM, Patterson KY, Veillon C, et al. 1983. Comparison of electrothermal atomic absorption spectrometry and atomic emission spectrometry for determination of chromium in urine. *Anal Chem* 55:1417-1419.

Harreus U, Baumeister P, KleinSasser N, et al. 2007. Genotoxic effects of metals on human salivary gland tissue and lymphocytes as detected by the Comet assay. *Toxicol Environ Chem Rev* 89(2):205-214.

## 9. REFERENCES

- \*Hartford WH. 1979. Chromium compounds. In: Grayson M, ed. Kirk-Othmer encyclopedia of chemical technology. 3rd ed. Vol. 6. New York, NY: John Wiley and Sons, 82-120.
- Hartwig A. 1998. Carcinogenicity of metal compounds: Possible role of DNA repair inhibition. *Toxicol Lett* 102-103:235-239.
- \*Harzdorf C, Janser G. 1984. The determination of chromium(VI) in waste water and industrial effluents by differential pulse polarography. *Anal Chim Acta* 165:201-207.
- \*Hasan A. 2007. A case report: Ammonium dichromate poisoning. *Biomed Res* 18(1):35-37.
- Hasten DL, Hegsted M, Keenan MJ, et al. 1997. Effects of various forms of dietary chromium in growth and body composition in the rat. *Nutr Res* 17(2):283-294.
- \*Hasten DL, Rome EP, Franks BD, et al. 1992. Effects of chromium picolinate on beginning weight training students. *Int J Sport Nutr* 2:343-350.
- Havel PJ. 2004. A scientific review: The role of chromium in insulin resistance. Supplement to the diabetes educator.
- \*Haworth S, Lawlor T, Mortelmans K, et al. 1983. Salmonella mutagenicity test results for 250 chemicals. *Environ Mutagen Suppl* 1:3-142.
- Hayashi M, Sutou S, Shimada H, et al. 1989. Difference between intraperitoneal and oral gavage application in the micronucleus test. *Mutat Res* 223:329-344.
- Hayes RB. 1988. Review of occupational epidemiology of chromium chemicals and respiratory cancer. *Sci Total Environ* 71:331-339.
- Hayes RB. 1997. The carcinogenicity of metals in humans. *Cancer Causes Control* 8:371-385.
- +\*Hayes RB, Lilienfeld AM, Snell LM. 1979. Mortality in chromium chemical production workers: A prospective study. *Int J Epidemiol* 8(4):365-374.
- +\*Hayes RB, Sheffet A, Spirtas R. 1989. Cancer mortality among a cohort of chromium pigment workers. *Am J Ind Med* 16:127-133.
- \*HazDat. 2008. Chromium. HazDat Database: ATSDR's Hazardous Substance Release and Health Effects Database. Atlanta, GA: Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/hazdat.html>. May 02, 2008.
- \*He X, Lin GX, Chen MG, et al. 2007. Protection against chromium (VI)-induced oxidative stress and apoptosis by Nrf2. Recruiting Nrf2 into the nucleus and disrupting the nuclear Nrf2/Keap1 association. *Toxicol Sci* 98(1):298-309.
- Heitland P, Koster HD. 2006. Biomonitoring of 30 trace elements in urine of children and adults by ICP-MS. *Clin Chim Acta* 365(1-2):310-318.
- \*Hemminki K, Vainio H. 1984. Human exposure to potentially carcinogenic compounds. *IARC Scientific Publ No.* 59:37-45.

## 9. REFERENCES

- +\*Henderson RF, Rebar AH, Pickrell JA, et al. 1979. Early damage indicators in the lung. III. Biochemical and cytological response of the lung to inhaled metal salts. *Toxicol Appl Pharmacol* 50:123-136.
- \*Henshaw JM, Heithmar EM, Hinnert TA. 1989. Inductively coupled plasma mass spectrometric determination of trace elements in surface waters subject to acidic deposition. *Anal Chem* 61:335-342.
- Hernberg S. 1977. Incidence of cancer in population with exceptional exposure to metals. Cold Spring Harbor conference: Cell proliferation 4:147-157.
- +Hernberg S, Westerholm P, Schultz-Larsen K, et al. 1983. Nasal and sinonasal cancer: Connection with occupational exposures in Denmark, Finland and Sweden. *Scand J Work Environ Health* 9:315-326.
- Hewitt PJ. 1988. Accumulation of metals in the tissues of occupationally exposed workers. *Environ Geochem Health* 10:113-116.
- Higashi N, Taki H, Nishimura Y, et al. 1993. Chromium and tritiated thymidine releases from target cells are differential events in human monocyte/macrophage-mediated cytotoxicity. *Cell Immunol* 150:333-342.
- \*Higgins TE, Halloran AR, Petura JC. 1997. Traditional and innovative treatment methods for Cr(VI) in soil. *J Soil Contam* 6(6):767-797.
- Hilaski R, Katz S, Salem H. 1992. Inhalation toxicity of chromium from Whetlerite dust in rats. *Toxicol Lett* 62:25-31.
- +\*Hill WJ, Ferguson WS. 1979. Statistical analysis of epidemiological data from a chromium chemical manufacturing plant. *J Occup Med* 21:103-106.
- Hirose T, Kondo K, Takahashi Y, et al. 2002. Frequent microsatellite instability in lung cancer from chromate-exposed workers. *Mol Carcinog* 33(3):172-180.
- Hjollund NH, Bonde JP, Ernst E, et al. 2005. Spontaneous abortion in IVF couples-a folre of male welding exposure. *Hum Reprod* 20(7):1793-1797.
- Hjollund NH, Bonde JP, Jensen TK, et al. 2000. Male-mediated spontaneous abortion among spouses of stainless steel welders. *Scand J Work Environ Health* 26(3):187-192.
- +\*Hjollund NHI, Bonde JPE, Hansen KS. 1995. Male-mediated risk of spontaneous abortion with reference to stainless steel welding. *Scand J Work Environ Health* 21:272-276.
- Hjollund NHI, Bonde JPE, Jensen TK, et al. 1998. Semen quality and sex hormones with reference to metal welding. *Reprod Toxicol* 12(2):91-95.
- Hneihen AS, Standeven AM, Wetterhahn KE. 1993. Differential binding of chromium(VI) and chromium(III) complexes to salmon sperm nuclei and nuclear DNA and isolated calf thymus DNA. *Carcinogenesis* 14(9):1795-1803.
- Hodges NJ, Adam B, Lee AJ. 2001. Induction of DNA-strand breaks in human peripheral blood lymphocytes and A549 lung cells by sodium dichromate: Association with 8-oxo-2-deoxyguanosine formation and inter-individual variability. *Mutagenesis* 16(6):467-474.

## 9. REFERENCES

Hodges NJ, Smart D, Lee AJ, et al. 2004. Activation of c-Jun N-terminal kinase in A549 lung carcinoma cells by sodium dichromate: Role of dissociation of apoptosis signal regulating kinase-1 from its physiological inhibitor thioredoxin. *Toxicology* 197:101-112.

\*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.

Hofmann W, Balashazy I, Heistracher T, et al. 1996. The significance of particle deposition patterns in bronchial airway bifurcations for extrapolation modeling. *Aerosol Sci Technol* 25(3):305-327.

+\*Hojo Y, Satomi Y. 1991. In vivo nephrotoxicity induced in mice by chromium(VI): Involvement of glutathione and chromium(V). *Biol Trace Elem Res* 31:21-31.

\*Hojo Y, Nishiguchi K, Kawazoe S, et al. 1999. Comparison of susceptibility of liver and kidney to lipid peroxidation induction Cr(IV), Cr(V) and Cr(VI) compounds. *J Health Sci* 45(6):329-332.

\*Hojo Y, Nishiguchi K, Kawazoe S, et al. 2000. Enhancement of lipid peroxidation by chromium(IV) and chromium(V) is remarkable compared to that by chromium(VI) and is effectively suppressed by scavengers of reactive oxygen species. *J Health Sci* 46(2):75-80.

\*Holmes AL, Wise SS, Sandwick SJ, et al. 2006. The clastogenic effects of chronic exposure to particulate and soluble Cr(VI) in human lung cells. *Mutat Res* 610(1-2):8-13.

Holmes AL, Wise SS, Shuler JH, et al. 2003. Comparative genotoxicity of two particulate hexavalent chromium compounds in human bronchial cells. *Toxicologist* 72(S-1):218.

Holmes AL, Wise SS, Xie H, et al. 2005. Lead ions do not cause human lung cells to escape chromate-induced cytotoxicity. *Toxicol Appl Pharmacol* 203(2):167-176.

Hooper JW, Fields BN. 1996. Role of the  $\mu 1$  protein in reovirus stability and capacity to cause chromium release from host cells. *J Virol* 70(1):459-467.

+Hopkins LL. 1965. Distribution in the rat of physiological amounts of injected  $\text{Cr}^{51}$ (III) with time. *Am J Physiol* 209:731-735.

+Hopkins LL, Schwarz K. 1964. Chromium(III) binding to serum proteins, specifically siderophilin. *Biochim Biophys Acta* 90:484-491.

Hornig CJ, Lin SR. 1996. Determination of urinary zinc, chromium, and copper in steel production workers. *Biol Trace Elem Res* 55:307-314.

\*Hornig D. 1975. Distribution of ascorbic acid, metabolites and analogues in man and animals. *Ann N Y Acad Sci* 258:103-118.

\*Horowitz SB, Finley BL. 1993. Using human sweat to extract chromium from chromite ore processing residue: Applications to setting health-based cleanup levels. *J Toxicol Environ Health* 40:585-599.

Horowitz SB, Finley BL. 1994. Setting health-protective soil concentrations for dermal contact allergens: A proposed methodology. *Regul Toxicol Pharmacol* 19:31-47.



## 9. REFERENCES

- \*HSDB. 2008. Chromium. Hazardous Substances Data Bank. National Library of Medicine. <http://toxnet.nlm.nih.gov>. June 28, 2008.
- Hu W, Feng Z, Tang M. 2004. Chromium(VI) enhances (+/-)-anti-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene-induced cytotoxicity and mutagenicity in mammalian cells through its inhibitory effect on nucleotide excision repair. *Biochemistry* 43(44):14282-14289.
- Huang Y, Chen C, Sheu J, et al. 1999. Lipid peroxidation in workers exposed to hexavalent chromium. *J Toxicol Environ Health, A* 56:235-247.
- \*Hueper WC. 1955. Experimental studies in metal carcinogenesis. VII. Tissue reactions to parenterally introduced powdered metallic chromium and chromite ore. *J Natl Cancer Inst* 16:447-469.
- +\*Hueper WC. 1958. Experimental studies in metal carcinogenesis. *Arch Ind Health* 18:284-291.
- Hueper WC. 1961. Environmental carcinogenesis and cancers. *Cancer Res* 21:842-857.
- \*Hueper WC, Payne WW. 1959. Experimental cancers in rats produced by chromium compounds and their significance to industry and public health. *Ind Hyg J* 20:274-280.
- \*Hueper WC, Payne WW. 1962. Experimental studies in metal carcinogenesis. X. Cancerigenic effects of chromite ore roast deposited in muscle tissue and pleural cavity of rats. *Arch Environ Health* 5:51-68.
- Hughes LS, Cass GR, Gone J, et al. 1998. Physical and chemical characterization of atmospheric ultrafine particles in the Los Angeles area. *Environ Sci Technol* 32(9):1153-1161.
- Hunt CD, Stoecker BJ. 1996. Deliberations and evaluations of the approaches, endpoints, and paradigms for boron, chromium, and fluoride dietary recommendations. RDA Workshop: New approaches, endpoints and paradigms for RDAs of mineral elements, 2441S-S2451.
- +Hunter WC, Roberts JM. 1932. Experimental study of the effects of potassium bichromate on the monkey's kidney. *Am J Pathol* 9:133-147.
- \*Hurlbut CS, ed. 1971. Dana's manual of mineralogy. 18th ed. New York, NY: John Wiley and Sons, Inc., 346-347.
- \*Husgafvel-Pursiainen K, Kalliomaki PL, Sorsa M. 1982. A chromosome study among stainless steel workers. *J Occup Med* 24:762-766.
- +\*Huvinen M, Makitie A, Jarventaus H, et al. 2002b. Nasal cell micronuclei, cytology and clinical symptoms in stainless steel workers exposed to chromium. *Mutagenesis* 17(5):425-429.
- Huvinen M, Oksanen L, Kalliomaki K, et al. 1997. Estimation of individual dust exposure by magnetopneumography in stainless steel production. *Sci Total Environ* 199:133-139.
- +\*Huvinen M, Uitti J, Oksa P, et al. 2002a. Respiratory health effects of long-term exposure to different chromium species in stainless steel production. *Occup Med (Lond)*52(4):203-212.

## 9. REFERENCES

- +\*Huvinen M, Uitti J, Zitting A, et al. 1996. Respiratory health of workers exposed to low levels of chromium in stainless steel production. *Occup Environ Med* 53:741-747.
- \*Hyland JL, Snoots TR, Balthis WL. 1998. Sediment quality of estuaries in the southeastern U.S. *Environ Monit Assess* 51:331-343.
- +\*Hyodo K, Suzuki S, Furuya N, et al. 1980. An analysis of chromium, copper, and zinc in organs of a chromate worker. *Int Arch Occup Environ Health* 46:141-150.
- \*IARC. 1980. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Some metals and metallic compounds: Volume 23. Lyons, France: World Health Organization, 205-323.
- \*IARC. 1986a. Selected methods of analysis: Some metals. In: O'Neill IK, Schuller P, Fishbein L, eds. Vol. 8: IARC Scientific Publications No. 71. Lyon, France: International Agency for Research on Cancer, World Health Organization 141-158; 291-317; 433-440.
- IARC. 1986b. Sources of exposure and biological effects of chromium. International Agency for Research on Cancer. *IARC Sci Publ.* (71):63-77.
- IARC. 1987. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: Overall evaluations of carcinogenicity. Vol. 1 to 42: Supplement 7: An updating of IARC monographs. Lyons, France: International Agency for Research on Cancer, World Health Organization.
- \*IARC. 1990. IARC monographs on the evaluation of carcinogenic risks to humans. Chromium, nickel and welding. Vol. 49. Lyons, France: International Agency for Research on Cancer, World Health Organization 49-256.
- \*IARC. 1997. Vol 49. Chromium, nickel and welding. Summary of data reported and evaluation. International Agency for Research on Cancer. World Health Organization. <http://monographs.iarc.fr/ENG/Monographs/vol49/volume49.pdf>. May 02, 2008.
- \*IARC. 2008. 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>. April 24, 2008.
- \*Iarmarcovai G, Sari-Minodier I, Chaspoul F, et al. 2005. Risk assessment of welders using analysis of eight metals by ICP-MS in blood and urine and DNA damage evaluation by the comet and micronucleus assays; influence of XRCC1 and XRCC3 polymorphisms. *Mutagenesis* 20(6):425-432.
- \*ICRP. 1994. Human respiratory tract model for radiological protection. Pergamon Press, Oxford: International Commission on Radiological Protection. ICRP publication 66.
- \*ICSH. 1980. Recommended method for radioisotope red-cell survival studies. *Br J Haematol* 45(4):659-666.
- +\*Iijima S, Matsumoto N, Lu C. 1983. Transfer of chromic chloride to embryonic mice and changes in the embryonic mouse neuroepithelium. *Toxicology* 26:257-265.
- Ikarashi Y, Ohno K, Tsuchiya T, et al. 1992. Differences of draining lymph node cell proliferation among mice, rats, and guinea pigs following exposure to metal allergens. *Toxicology* 76:283-292.

## 9. REFERENCES

- Ikarashi Y, Tsuchiya T, Nakamura A. 1992. Detection of contact sensitivity of metal salts using the murine local lymph node assay. *Toxicol Lett* 62:53-61.
- \*IMC. 2007. Chromium. Industrial Minerals Corporation. <http://www.industrialmineralscorp.com.au/index.php>. May 21, 2008.
- Ingber A, Gammelgaard B, David M. 1998. Detergents and bleaches are sources of chromium contact dermatitis in Israel. *Contact Dermatitis* 38:101-104.
- \*IOM. 2001. Chromium. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc (2000). A Report of the Panel on Micronutrients, subcommittees on upper reference levels of nutrients and of interpretation and uses of dietary reference intakes, and the standing committee on the scientific evaluation of dietary reference intakes. Washington, DC: Food and Nutrition Board. Institute of Medicine. National Academy Press, 197-223.
- \*IRIS. 2008. Chromium. Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. <http://www.epa.gov/iris/subst/index.html>. May 14, 2008.
- +\*Iseron KV, Banner W, Froede RC, et al. 1983. Failure of dialysis therapy in potassium dichromate poisoning. *J Emerg Med* 1:143-149.
- \*Ishikawa Y, Nakagawa K, Satoh Y, et al. 1994a. Characteristics of chromate workers' cancers, chromium lung deposition and precancerous bronchial lesions: An autopsy study. *Br J Cancer* 70(1):160-166.
- \*Ishikawa Y, Nakagawa K, Satoh Y, et al. 1994b. "Hot spots" of chromium accumulation at bifurcations of chromate workers' bronchi. *Cancer Res* 54(9):2342-2346.
- Itoh M, Nakamura M, Suzuki T, et al. 1995. Mechanism of chromium(VI) toxicity in *Escherichia coli*: Is hydrogen peroxide essential in Cr(VI) toxicity? *J Biochem* 117:780-786.
- \*Itoh S, Shimada H. 1996. Micronucleus induction by chromium and selenium, and suppression by metallothionein inducer. *Mutat Res* 367:233-236.
- \*Itoh S, Shimada H. 1997. Clastogenicity and mutagenicity of hexavalent chromium in lacZ transgenic mice. *Toxicol Lett* 91:229-233.
- \*Itoh S, Shimada H. 1998. Bone marrow and liver mutagenesis in lacZ transgenic mice treated with hexavalent chromium. *Mutat Res* 412:63-67.
- +\*Ivankovic S, Preussmann R. 1975. Absence of toxic and carcinogenic effects after administration of high doses of chromic oxide pigment in subacute and long-term feeding experiments in rats. *Food Cosmet Toxicol* 13:347-351.
- \*Iyengar V, Woittiez J. 1988. Trace elements in human clinical specimens: Evaluation of literature data to identify reference values. *Clin Chem* 34(3):474-481.
- Iyer VJ, Banerjee G, Govindram CB, et al. 2002. Role of different valence states of chromium in the elicitation of allergic contact dermatitis. *Contact Dermatitis* 47(6):357-360.

## 9. REFERENCES

- \*Izzotti A, Bagnasco M, Camoirano A, et al. 1998. DNA fragmentation, DNA-protein crosslinks, <sup>32</sup>P postlabeled nucleotide modifications, and 8-hydroxy-2'-deoxyguanosine in the lung but not in the liver of rats receiving intratracheal instillations of chromium(VI). Chemoprevention by oral N-acetylcysteine. *Mutat Res* 400:233-244.
- Izzotti A, Cartiglia C, Balansky R, et al. 2002. Selective induction of gene expression in rat lung by hexavalent chromium. *Mol Carcinog* 35(2):75-84.
- \*Jacquamet L, Sun Y, Hatfield J, et al. 2003. Characterization of chromodulin by x-ray absorption and electron paramagnetic resonance spectroscopies and magnetic susceptibility measurements. *J Am Chem Soc* 125:774-780.
- \*James BR, Petura JC, Vitale RJ, et al. 1997. Oxidation-reduction chemistry of chromium: Relevance to the regulation and remediation of chromate-contaminated soils. *J Soil Contam* 6(6):569-580.
- Jannetto PJ, Antholine WE, Myers CR. 2001. Cytochrome b5 plays a key role in human microsomal chromium(VI) reduction. *Toxicology* 159:119-133.
- +\*Jansen LH, Berrens L. 1968. Sensitization and partial desensitization of guinea pigs to trivalent and hexavalent chromium. *Dermatologica* 137:65-73.
- \*Jardine PM, Fendorf SE, Mayes MA, et al. 1999. Fate and transport of hexavalent chromium in undisturbed heterogeneous soil. *Environ Sci Technol* 33(17):2939-2944.
- \*Jeejeebhoy KN. 1999. The role of chromium in nutrition and therapeutics and as a potential toxin. *Nutr Rev* 57(11):329-335.
- \*Jeejeebhoy KN, Chu RC, Marliss EB, et al. 1977. Chromium deficiency, glucose intolerance, and neuropathy reversed by chromium supplementation in a patient receiving long-term total parenteral nutrition. *Am J Clin Nutr* 30:531-538.
- Jeng HA, Swanson J. 2006. Toxicity of metal oxide nanoparticles in mammalian cells. *J Environ Sci Health Part A* 41:2699-2711.
- \*Jennette KW. 1982. Microsomal reduction of the carcinogen chromate produced chromium(V). *J Am Chem Soc* 104:874-875.
- \*Jervis RE, Landsberger S, Aufreiter S, et al. 1983. Trace elements in wet atmospheric deposition: Application and comparison of PIXE, INAA, and graphite-furnace AAS techniques. *Int J Environ Anal Chem* 15:89-106.
- \*Johanson CE. 1980. Permeability and vascularity of the developing brain: Cerebellum vs cerebral cortex. *Brain Res* 190:3-16.
- Johansson A, Curstedt T, Jarstrand C, et al. 1992. Alveolar macrophages and lung lesions after combined exposure to nickel, cobalt, and trivalent chromium. *Environ Health Perspect* 97:215-219.
- +\*Johansson A, Robertson B, Curstedt, et al. 1986a. Rabbit lung after inhalation of hexa- and trivalent chromium. *Environ Res* 41:110-119.

## 9. REFERENCES

- +\*Johansson A, Wiernik A, Jarstrand C, et al. 1986b. Rabbit alveolar macrophages after inhalation of hexa- and trivalent chromium. *Environ Res* 39:372-385.
- \*Johnson J, Schewel L, Graedel TE. 2006. The contemporary anthropogenic chromium cycle. *Environ Sci Technol* 40:7060-7069.
- Joudah L, Moghaddas S, Bose RN. 2002. DNA oxidation by peroxo-chromium(v) species: Oxidation of guanosine to guanidinohydantoin. *Chem Commun* :1742-1743.
- +\*Junaid M, Murthy RC, Saxena DK. 1996a. Embryo- and fetotoxicity of chromium in pregestationally exposed mice. *Bull Environ Contam Toxicol* 57:327-334.
- +\*Junaid M, Murthy RC, Saxena DK. 1996b. Embryotoxicity of orally administered chromium in mice: Exposure during the period of organogenesis. *Toxicol Lett* 84:143-148.
- +\*Kaaber K, Veien NK. 1977. The significance of chromate ingestion in patients allergic to chromate. *Acta Derm Venereol* 57:321-323.
- Kaats GR, Blum K, Fisher JA, et al. 1996. Effects of chromium picolinate supplementation on body composition: A randomized double-masked placebo-controlled study. *Curr Ther Res* 57:747-756.
- \*Kaats GR, Wise JA, Blum K, et al. 1992. The short-term therapeutic efficacy of beating obesity with a plan of improved nutrition and moderate calorie restriction. *Curr Ther Res* 51:261-274.
- Kaczmarek M, Timofeeva OA, Karaczyn A, et al. 2007. The role of ascorbate in the modulation of HIF-1 $\alpha$  protein and HIF-dependent transcription by chromium(VI) and nickel(II). *Free Radic Biol Med* 42(8):1246-1257.
- Kadiiska MB, Morrow JD, Awad JA, et al. 1998. Identification of free radical formation and F<sub>2</sub>-isopropanes in vivo by acute Cr(VI) poisoning. *Chem Res Toxicol* 11:1516-1520.
- Kadiiska MB, Xiang Q-H, Mason RP. 1994. In vivo free radical generation by chromium(VI): An electron spin resonance spin-trapping investigation. *Chem Res Toxicol* 7:800-805.
- +\*Kalahasthi R, Rao RHR, Krishna murthy RB, et al. 2007. Effect of chromium (VI) exposure on serum amylase activity in chromium plating workers. *Environ Sci Indian J* 2(1):1-6.
- Kalahasthi RB, Rao RH, Murthy RB, et al. 2006. Effect of chromium(VI) on the status of plasma lipid peroxidation and erythrocyte antioxidant enzymes in chromium plating workers. *Chem Biol Interact* 164(3):192-199.
- +Kalliomaki PL, Aitio A, Hyvarinen HK, et al. 1986. Lung clearance, transportation, and excretion of metals in rats after intratracheal instillation of activated welding fumes. In: Stern RM, ed. *International conference on health hazards and biological effects of welding fumes and gases*, International Congress Series Vol. 676. New York, NY: Excerpta Medica, Elsevier Science Publ. Co., 345-348.
- Kaltreider RC, Pesce CA, Ihnat MA, et al. 1999. Differential effects of arsenic(III) and chromium(IV) on nuclear transcription factor binding. *Mol Carcinog* 25:219-229.
- Kamaludeen SPB, Megharaj M, Juhasz AL, et al. 2003. Chromium-microorganism interactions in soils: Remediation implications. *Rev Environ Contam Toxicol* 178:93-164.

## 9. REFERENCES

- Kamath SM, Stoecker BJ, Davis-Whitenack ML. 1997. Absorption, retention and urinary excretion of chromium-51 in rats pretreated with indomethacin and dosed with dimethylprostaglandin E<sub>2</sub>, misoprostal or prostacyclin. *J Nutr* 127:478-482.
- Kamburova M. 1997. Neotetrazolium chloride - A new analytical reagent for determination of chromium. *Anal Lett* 30:305-316.
- \*Kanematsu N, Hara M, Kada T. 1980. REC assay and mutagenicity studies on metal compounds. *Mutat Res* 77:109-116.
- +\*Kanojia RK, Junaid M, Murthy RC. 1996. Chromium induced teratogenicity in female rat. *Toxicol Lett* 89:207-213.
- +\*Kanojia RK, Junaid M, Murthy RC. 1998. Embryo and fetotoxicity of hexavalent chromium: A long-term study. *Toxicol Lett* 95:165-172.
- +\*Kaplan I, Zeligman I. 1962. Occupational dermatitis of railroad workers. *Arch Dermatol* 85:135-142.
- +\*Kargacin B, Squibb KS, Cosentino S, et al. 1993. Comparison of the uptake and distribution of chromate in rats and mice. *Biol Trace Elem Res* 36:307-318.
- Karstadt M. 1998. Availability of epidemiologic data for chemicals known to cause cancer in animals: An update. *Am J Ind Med* 34:519-525.
- Kasprzak KS. 1991. The role of oxidative damage in metal carcinogenicity. *Chem Res Toxicol* 4:604-615.
- Katabami M, Dosaka-Akita H, Mishina T, et al. 2000. Frequent cyclin D1 expression in chromate-induced lung cancers. *Hum Pathol* 31(8):973-979.
- Katsarou A, Baxevanis C, Armenaka M, et al. 1997. Study of persistence and loss of patch test reactions to dichromate and cobalt. *Contact Dermatitis* 36:87-90.
- Katsiki M, Trougakos IP, Chondrogianni N, et al. 2004. Alterations of senescence biomarkers in human cells by exposure to CrVI in vivo and in vitro. *Exp Gerontol* 39(7):1079-1087.
- Katz AJ. 1998. Modulation by temperature of the genotoxic potency of cisplatin on *Drosophila* wing spot assay. *Teratog Carcinog Mutagen* 18:93-100.
- Katz AJ, Chiu A, Beaubier J, et al. 2001. Combining *Drosophila melanogaster* somatic-mutation-recombination and electron-spin-resonance-spectroscopy data to interpret epidemiologic observations on chromium carcinogenicity. *Mol Cell Biochem* 222(1-2):61-68.
- Katz SA. 1991. The analytical biochemistry of chromium. *Environ Health Perspect* 92:13-16.
- Katz SA, Salem H. 1993. The toxicology of chromium with respect to its chemical speciation: A review. *J Appl Toxicol* 13:217-224.
- +\*Kaufman DB, DiNicola W, McIntosh R. 1970. Acute potassium dichromate poisoning: Treated by peritoneal dialysis. *Am J Dis Child* 119:374-376.

## 9. REFERENCES

- Kawanishi S, Inoue S, Yamamoto K. 1989. Hydroxyl radical and singlet oxygen production and DNA damage induced by carcinogenic metal compounds and hydrogen peroxide. *Biol Trace Elem Res* 21:367-372.
- Kawanishi S, Inoue S, Yamamoto K. 1994. Active oxygen species in DNA damage induced by carcinogenic metal compounds. *Environ Health Perspect* 102 Suppl 3:17-20.
- \*Kaya B, Creus A, Velazquez A, et al. 2002. Genotoxicity is modulated by ascorbic acid studies using the wing spot test in *Drosophila*. *Mutat Res* 520:93-101.
- Kegley EB, Spears JW, Brown TT. 1996. Immune response and disease resistance of calves fed chromium nicotinic acid complex or chromium chloride. *J Dairy Sci* 79:1278-1283.
- Kegley EB, Spears JW, Eisemann JH. 1997. Performance and glucose metabolism in calves fed a chromium-nicotinic acid complex or chromium chloride. *J Dairy Sci* 80:1744-1750.
- Keith RL, Gandolfi AJ, McIntyre LC, et al. 1999. Analysis of heavy metal deposition in renal tissue by sectional mapping using PIXE. *Nucl Instr Meth Phys Res B* 149:168-175.
- +\*Kelly WF, Ackrill P, Day JP, et al. 1982. Cutaneous absorption of trivalent chromium: Tissue levels and treatment by exchange transfusion. *Br J Ind Med* 39:397-400.
- +\*Kerger BD, Finley BL, Corbett GE, et al. 1997. Ingestion of chromium(VI) in drinking water by human volunteers: Absorption, distribution, and excretion of single and repeated doses. *J Toxicol Environ Health* 50:67-95.
- +\*Kerger BD, Paustenbach DJ, Corbett GE, et al. 1996a. Absorption and elimination of trivalent and hexavalent chromium in humans following ingestion of a bolus dose in drinking water. *Toxicol Appl Pharmacol* 141:145-158.
- \*Kerger BD, Richter RO, Chute SM, et al. 1996b. Refined exposure assessment for ingestion of tapwater contaminated with hexavalent chromium: Consideration of exogenous and endogenous reducing agents. *J Expo Anal Environ Epidemiol* 6(2):163-179.
- +\*Keskinen H, Kalliomaki P, Alanko K. 1980. Occupational asthma due to stainless steel welding fumes. *Clin Allergy* 10:151-159.
- Khengarot BS, Rathore RS, Tripathi DM. 1999. Effects of chromium on humoral and cell-mediated immune responses and host resistance to disease in a freshwater catfish, *Saccobranhus fossilis* (bloch). *Ecotoxicol Environ Saf* 43:11-20.
- Kiilunen M. 1997. Occupational exposure to chromium and nickel in the 1980s in Finland. *Sci Total Environ* 199:91-101.
- \*Kiilunen M, Jarvisalo J, Mäkitie O, et al. 1987. Analysis, storage stability and reference values for urinary chromium and nickel. *Int Arch Occup Environ Health* 59:43-56.
- +\*Kiilunen M, Kivisto H, Ala-Laurila P, et al. 1983. Exceptional pharmacokinetics of trivalent chromium during occupational exposure to chromium lignosulfonate dust. *Scand J Work Environ Health* 9:265-271.

## 9. REFERENCES

- \*Kilburn KH, Warshaw R, Boylen CT, et al. 1990. Cross-shift and chronic effects of stainless-steel welding related to internal dosimetry of chromium and nickel. *Am J Ind Med* 17:607-615.
- Kim E, Na KJ. 1990. Acute toxic effect of sodium dichromate on metabolism. *Arch Toxicol* 64:644-649.
- \*Kim G, Yurkow EJ. 1996. Chromium induces a persistent activation of mitogen-activated protein kinases by a redox-sensitive mechanism in H4 rat hepatoma cells. *Cancer Res* 56:2045-2051.
- +\*Kim HY, Lee SB, Jang BS. 2004. Subchronic inhalation toxicity of soluble hexavalent chromium trioxide in rats. *Arch Toxicol* 78:363-368.
- Kim Y, An S, Oyama T, et al. 2003. Oxidative stress, hogg1 expression and NF-kappaB activity in cells exposure to low level chromium. *J Occup Health* 45(5):271-277.
- \*Kimberly MM, Paschal DC. 1985. Screening for selected toxic elements in urine by sequential-scanning inductively-coupled plasma atomic emission spectrometry. *Anal Chim Acta* 174:203-210.
- \*Kimbrough DE, Cohen Y, Winer AM, et al. 1999. A critical assessment of chromium in the environment. *Crit Rev Environ Sci* 29(1):1-46.
- \*King LD. 1988. Retention of metals by several soils of the southeastern United States. *J Environ Qual* 17(2):239-246.
- Kiran SB, Irene D, Devi KR. 1999. Mutagenicity of chromium in bone marrow cells of mice. *Trends Life Sci* 14(2):93-96.
- Kirkpatrick DC, Coffin DE. 1975. Trace metal content of chicken eggs. *J Food Sci Agric* 26:99-103.
- \*Kirpnick-Sobol Z, Reliene R, Schiestl RH. 2006. Carcinogenic Cr(VI) and the nutritional supplement Cr(III) induce DNA deletions in yeast and mice. *Cancer Res* 66(7):3480-3484.
- Kist AA, Zhuk LI, Danilova EA, et al. 1998. Mapping of ecologically unfavorable territories based on human hair composition. *Biol Trace Elem Res* 64:1-12.
- Kitagawa S, Seki H, Kametani F, et al. 1982. Uptake of hexavalent chromium by bovine erythrocytes and its interaction with cytoplasmic components; the role of glutathione. *Chem Biol Interact* 40:265-274.
- +\*Kitamura F, Yokoyama K, Araki S, et al. 2003. Increase of olfactory threshold in plating factory workers exposed to chromium in Korea. *Ind Health* 41(3):279-285.
- Kitchalong L, Fernandez JM, Bunting LD, et al. 1995. Influence of chromium tipicolinate on glucose metabolism and nutrient partitioning in growing lambs. *J Anim Sci* 73:2694-2705.
- \*Klein LA, Lang M, Nash N, et al. 1974. Sources of metals in New York City wastewater. *J Water Pollut Control Fed* 46(12):2653-2662.
- Klein RM, Dahmen M, Putz H, et al. 1998. Workplace exposure during laser machining. *J Laser Appl* 10(3):99-105.



## 9. REFERENCES

- +\*Kleiner AM, Stolbun BM, Likhacheva YI, et al. 1970. [Indices of the functional status of the myocardium and hemodynamics in chronic occupational poisoning with chromium compounds.] *Gig Tr Prof Zabol* 14:7-10. (Russian)
- +\*Kleinfeld M, Rosso A. 1965. Ulcerations of the nasal septum due to inhalation of chromic acid mist. *Ind Med Surg* 24:242-243.
- Knauf W. 1993. Magenlymphom nach exposition gegenüber chrom und nickel? *Dtsch Med Wochenschr* 118(12):438.
- Knudsen I. 1980. The mammalian spot test and its use for the testing of potential carcinogenicity of welding fume particles and hexavalent chromium. *Acta Pharmacol Toxicol* 47:66-70.
- Knudsen LE, Boisen T, Christensen JM, et al. 1992. Biomonitoring of genotoxic exposure among stainless steel welders. *Mutat Res* 279:129-143.
- Knutsson A, Damber L, Jarvholm B. 2000. Cancers in concrete workers: Results of a cohort study of 33,688 workers. *Occup Environ Med* 57:264-267.
- +\*Kollmeier H, Seemann J, Rothe G, et al. 1990. Age, sex, and region adjusted concentrations of chromium and nickel in lung tissue. *Br J Ind Med* 47:682-687.
- \*Komori K, Toda K, Ohtake H. 1990a. Effects of oxygen stress on chromate reduction in *Enterobacter cloacae* strain HO1. *J Ferment Bioeng* 69(1):67-69.
- \*Komori M, Nishio K, Kitada M, et al. 1990b. Fetus-specific expression of a form of cytochrome P-450 in human liver. *Biochemistry* 29:4430-4433.
- Kondo K, Takahashi Y, Hirose Y, et al. 2006. The reduced expression and aberrant methylation of p16INK4a in chromate workers with lung cancer. *Lung Cancer* 53(3):295-302.
- \*Korallus U. 1986a. Biological activity of chromium(VI) - against chromium(III) compounds: New aspects of biological monitoring. In: Serrone DM, ed. *Chromium symposium 1986: An update*. Pittsburgh, PA: Industrial Health Foundation Inc., 210-230.
- \*Korallus U. 1986b. Chromium compounds: Occupational health, toxicological and biological monitoring aspects. *Toxicol Environ Chem* 12:47-59.
- +\*Korallus U, Ehrlicher H, Wustefeld E. 1974b. [Trivalent chromium compounds. Results of a study in occupational medicine. Part 2. Disease status analysis.] *Arb Soz Prev* 9:76-79. (German)
- Korallus U, Ehrlicher H, Wustefeld E. 1974c. [Trivalent chromium compounds. Results of an industrial medicine study. Part 3: Clinical studies.] *Arb Soz Prev* 9:248-252. (German)
- \*Korallus U, Harzdorf C, Lewalter J. 1984. Experimental bases for ascorbic acid therapy of poisoning by hexavalent chromium compounds. *Int Arch Occup Environ Health* 53:247-256.
- +\*Korallus U, Ehrlicher H, Wustefeld E, et al. 1974a. [Trivalent chromium compounds - results of a study in occupational medicine.] *Arb Soz Prev* 9:51-54. (German)

## 9. REFERENCES

- +\*Korallus U, Lange H, Neiss A, et al. 1982. Relationships between hygienic measures and the bronchial carcinoma mortality in the chromate producing industry. *Arb Soz Prev* 17:159-167.
- \*Kornhauser C, Wrobel K, Wrobel K, et al. 2002. Possible adverse effect of chromium in occupational exposure of tannery workers. *Ind Health* 40(2):207-213.
- Kortenkamp A. 1996. Pharmacokinetic modeling in chromium risk assessment: A prediction of chromium (III) accumulation in humans from chromium dietary supplements. *Human Exp Toxicol* 15(7):601-602.
- Kortenkamp A, O'Brien P. 1991. Studies of the binding of chromium(III) complexes to phosphate groups of adenosine triphosphate. *Carcinogenesis* 12:921-926.
- Kortenkamp A, Casadevall M, Faux SP, et al. 1996a. A role for molecular oxygen in the formation of DNA damage during the reduction of the carcinogen chromium(VI) by glutathione. *Arch Biochem Biophys* 329(2):199-207.
- \*Kortenkamp A, Casadevall M, Fresco PDC. 1996b. The reductive conversion of the carcinogen chromium(VI) and its role in the formation of DNA lesions. *Ann Clin Lab Sci* 26(2):160-175.
- Kortenkamp A, Curran B, O'Brien P. 1992. Defining conditions for the efficient in vitro cross-linking of proteins to DNA by chromium(III) compounds. *Carcinogenesis* 13(2):307-308.
- \*Koshi K. 1979. Effects of fume particles from stainless steel welding on sister chromatid exchanges and chromosome aberrations in cultured Chinese hamster cells. *Ind Health* 17:39-49.
- \*Koshi K, Iwasaki K. 1983. Solubility of low-solubility chromates and their clastogenic activity in cultured cells. *Ind Health* 21:57-65.
- Koshi K, Serita F, Sawatari K, et al. 1987. Cytogenetic analysis of bone marrow cells and peripheral blood lymphocytes from rats exposed to chromium fumes by inhalation. *Mutat Res* 181:365.
- \*Koshi K, Yagami T, Nakanishi Y. 1984. Cytogenetic analysis of peripheral blood lymphocytes from stainless steel welders. *Ind Health* 22:305-318.
- \*Kowalski LA, Tsang SS, Davison AJ. 1996. Arsenic and chromium enhance transformation of bovine papillomavirus DNA-transfected C3H/10T1/2 cells. *Cancer Lett* 103:65-69.
- Kozlowski CA. 2007. Kinetics of chromium(VI) transport from mineral acids across cellulose triacetate (CTA) plasticized membranes immobilized by tri-n-octylamine. *Ind Eng Chem Res* 46:5420-5428.
- Kozuh N, Stupar J, Gorenc B. 2000. Reduction and oxidation processes of chromium in soils. *Environ Sci Technol* 34:112-119.
- Kreider RB. 1999. Dietary supplements and the promotion of muscle growth with resistance exercise. *Sports Med* 27(2):97-110.
- Krepkiy D, Antholine WE, Myers C, et al. 2001. Model reactions of Cr(VI) with DNA mediated by thiol species. *Mol Cell Biol* 22:213-219.

## 9. REFERENCES

- \*Krishnan K, Andersen ME. 1994. Physiologically-based pharmacokinetic modeling in toxicology. In: Hayes W, ed. Principles and methods of toxicology. 3rd edition, New York, NY: Raven Press, Ltd, 149-188.
- \*Krishnan K, Andersen ME, Clewell HJ, et al. 1994. Physiologically-based pharmacokinetic modeling of chemical mixtures. In: Yang RSA, ed. Toxicology of chemical mixtures. New York, NY: Academic Press, 399-437.
- \*Krull IS, Panaro KW, Gershman LL. 1983. Trace analysis and speciation for Cr(VI) and Cr(III) via HPLC-direct current plasma emission spectroscopy (HPLC-DCP). J Chromatogr Sci 21:460-472.
- Kucharz EJ, Sierakowski SJ. 1987. Immunotoxicity of chromium compounds: Effect of sodium dichromate on the T cell activation *in vitro*. Arch Gig Rada Toksikol 38:239-243.
- +\*Kumar A, Rana SVS. 1982. Lipid accumulation in chromium-poisoned rats. Int J Tissue React 4(4):291-295.
- +\*Kumar A, Rana SVS. 1984. Enzymological effects of hexavalent chromium in the rat kidney. Int J Tissue React 6(2):135-139.
- \*Kumar A, Rana SVS, Prakash R. 1985. Dysenzymuria induced by hexavalent chromium. Int J Tissue React 7(4):333-338.
- Kumar S, Mehdi F, Raza T. 2007. Genotoxicity of chromium in exposed human subjects suffering from lung problems [Abstract]. Toxicol Lett 172:S171-S172.
- \*Kumar S, Sathwara NG, Gautam AK, et al. 2005. Semen quality of industrial workers occupationally exposed to chromium. J Occup Health 47(5):424-430.
- \*Kumpulainen J. 1984. Chromium. In: Vercruyse A, ed. Techniques and instrumentation in analytical chemistry. Vol. 4. Evaluation of analytical methods in biological systems. Part B: Hazardous metals in human toxicology. Amsterdam, The Netherlands: Elsevier Science Publishers, 253-277.
- \*Kumpulainen JT, Wolf WR, Veillon C, et al. 1979. Determination of chromium in selected United States diets. J Agric Food Chem 27(3):490-494.
- Kundu R, Lakshmi R, Mansuri AP. 1995. Effects of Cr(VI) on ATPases in the brain and muscle of mudskipper, *Boleophthalmus dentates*. Bull Environ Contam Toxicol 55:723-729.
- Kuo CY, Wong RH, Lin JY, et al. 2006. Accumulation of chromium and nickel metals in lung tumors from lung cancer patients in Taiwan. J Toxicol Environ Health A 69(14):1337-1344.
- +\*Kuo HW, Wu ML. 2002. Effects of chromic acid exposure on immunological parameters among electroplating workers. Int Arch Occup Environ Health 75(3):186-190.
- Kuo HW, Chang SF, Wu KY, et al. 2003. Chromium(VI) induced oxidative damage to DNA: Increase of urinary 8-hydroxydeoxyguanosine concentrations (8-OHdG) among electroplating workers. Occup Environ Med 60(8):590-594.
- +\*Kuo HW, Lai JS, Lin TI. 1997a. Nasal septum lesions and lung function in workers exposed to chromic acid in electroplating factories. Int Arch Occup Environ Health 70:272-276.

## 9. REFERENCES

- Kuo HW, Lai JS, Lin TI. 1997b. Concentration and size distribution of airborne hexavalent chromium in electroplating factories. *Am Ind Hyg Assoc J* 58:29-32.
- Kurokawa Y, Matsushima M, Imazaawa T, et al. 1985. Promoting effect of metal compounds on rat renal tumorigenesis. *J Am Coll Toxicol* 4:321-331.
- +\*Kuykendall JR, Kerger BD, Jarvi EJ, et al. 1996. Measurement of DNA-protein cross-links in human leukocytes following acute ingestion of chromium in drinking water. *Carcinogenesis* 17(9):1971-1977.
- +Laborda R, Diaz-Mayans J, Nunez A. 1986. Nephrotoxic and hepatotoxic effects of chromium compound in rats. *Bull Environ Contam Toxicol* 36:332-336.
- \*Lai JS, Kuo HW, Liao FC, et al. 1998. Sister chromatid exchange induced by chromium compounds in human lymphocytes. *Int Arch Occup Environ Health* 71:550-5532.
- Lalaoui A, Henderson C, Kupper C, et al. 2007. The interaction of chromium (VI) with macrophages: Depletion of glutathione and inhibition of glutathione reductase. *Toxicology* 236:76-81.
- Lamson DS, Plaza SM. 2002. The safety and efficacy of high-dose chromium. *Altern Med Rev* 7(3):218-235.
- \*Landsberger S, Jervis RE, Kajrys G, et al. 1983. Characterization of trace elemental pollutants in urban snow using proton induced X-ray emission and instrumental neutron activation analysis. *Int J Environ Anal Chem* 16:95-130.
- Lane BP, Mass MJ. 1977. Carcinogenicity and cocarcinogenicity of chromium carbonyl in heterotopic tracheal grafts. *Cancer Res* 37:1476-1479.
- +\*Langård S. 1980. A survey of respiratory symptoms and lung function in ferrochromium and ferrosilicon workers. *Int Arch Occup Environ Health* 46:1-9.
- Langård S. 1982. Absorption, transport and excretion of chromium in man and animals. In: Langard S, ed. *Biological and environmental aspects of chromium*. Elsevier Biomedical Press, 149-169.
- Langård S. 1988. Chromium carcinogenicity: A review of experimental animal data. *Sci Total Environ* 71:341-350.
- Langård S. 1990. One hundred years of chromium and cancer: A review of epidemiological evidence and selected case reports. *Am J Ind Med* 17:189-215.
- Langård S. 1993. Role of chemical species and exposure characteristics in cancer among persons occupationally exposed to chromium compounds. *Scand J Work Environ Health* 19(Suppl 1):1:81-89.
- +\*Langård S, Norseth T. 1975. A cohort study of bronchial carcinomas in workers producing chromate pigments. *Br J Ind Med* 32:62-65.
- Langård S, Norseth T. 1979. Chromium. In: Friberg L, Nordberg GF, Vouk VB, eds. *Handbook on the toxicology of metals*. Amsterdam: Elsevier/North-Holland Biomedical Press, 383-397.

## 9. REFERENCES

Langård S, Norseth T. 1986. Chromium. In: Friberg L, Nordberg GF, Vouk VB, eds. Handbook on the toxicology of metals. Vol. II. Specific metals. 2nd ed. Amsterdam: Elsevier Science Publishers B.V., 185-210.

+\*Langård S, Vigander T. 1983. Occurrence of lung cancer in workers in producing chromium pigments. *Br J Ind Med* 40:71-74.

+\*Langård S, Andersen A, Gylseth B. 1980. Incidence of cancer among ferrochromium and ferrosilicon workers. *Br J Ind Med* 37:114-120.

+\*Langård S, Andersen A, Ravnstad J. 1990. Incidence of cancer among ferrochromium and ferrosilicon workers: An extended observation period. *Br J Ind Med* 47:14-19.

+\*Langård S, Gundersen N, Tsalev DL, et al. 1978. Whole blood chromium level and chromium excretion in the rat after zinc chromate inhalation. *Acta Pharmacol Toxicol* 42:142-149.

Lange JH. 2003. Cement: A common cancer agent? (Comment on: *Toxicol Ind Health* 18:321-331). *Toxicol Ind Health* 19:183.

Lansdown ABG. 1995. Physiological and toxicological changes in the skin resulting from the action and interaction of metal ions. *Crit Rev Toxicol* 25(5):397-462.

Larsen EH, Rasmussen L. 1991. Chromium, lead and cadmium in Danish milk products and cheese determined by Zeeman graphite furnace atomic adsorption spectrometry after direct injection or pressurized ahsing. *Z Lebensm Unters Forsch* 192:136-141.

\*Laskin S, Kuschner M, Drew RT. 1970. Studies in pulmonary carcinogenesis. In: Hanna MG, Nettesheim P, Gilbert JR, eds. Inhalation carcinogenesis. U.S. Atomic Energy Commission symposium series no. 18. Oak Ridge, TN: Division of Technical Information Extension, U.S. Atomic Energy Commission, 321-351.

Lauwerys RR. 1989. Metals — Epidemiological and experimental evidence for carcinogenicity. *Arch Toxicol Suppl* 13:21-27.

\*LaVelle JM. 1986a. Chromium(VI) comutagenesis: Characterization of the interaction of  $K_2CrO_4$  with azide. *Environ Mutagen* 87:717-725.

\*LaVelle JM. 1986b. Potassium chromate potentiates frameshift mutagenesis in *E. coli* and *S. typhimurium*. *Mutat Res* 171:1-10.

Lay PA, Levina A. 1998. Activation of molecular oxygen during the reactions of chromium(VI/V/IV) with biological reductants: Implications for chromium-induced genotoxicities. *J Am Chem Soc* 120:6704-6714.

\*Le Curieux F, Marzin D, Erb F. 1992. Genotoxic activity of three carcinogens in peripheral blood erythrocytes of the newt *Pleurodeles waltl*. *Mutat Res* 283:157-160.

Le Curieux F, Marzin D, Erb F. 1993. Comparison of three short-term assays: Results on seven chemicals; Potential contribution to the control of water genotoxicity. *Mutat Res* 319:223-236.

## 9. REFERENCES

- Lee BG, Luoma SN. 1998. Influence of microalgal biomass on absorption efficiency of Cd, Cr, and Zn by two bivalves from San Francisco Bay. *Limnol Oceanogr* 43(7):1455-1466.
- Lee CR, Yoo CI, Kang SK. 2002. Nasal septum perforation of welders. *Ind Health* 40(3):286-289.
- +\*Lee HS, Goh CL. 1988. Occupational dermatosis among chrome platers. *Contact Dermatitis* 18:89-93.
- +\*Lee KP, Ulrich CE, Geil RG, et al. 1989. Inhalation toxicity of chromium dioxide dust to rats after two years exposure. *Sci Total Environ* 86:83-108.
- \*Lee NA, Reasner CA. 1994. Beneficial effect of chromium supplementation on serum triglyceride levels in NIDDM. *Diabetes Care* 17(12):1449-1452.
- Lee SH, Brennan FR, Jacobs JJ, et al. 1997. Human monocyte/macrophage response to cobalt-chromium corrosion products and titanium particles in patients with total joint replacements. *J Orthop Res* 15:40-49.
- Lee TY, Lam TH. 1991. Contact dermatitis due a Chinese herbal orthopaedic tincture, Zheng Gu Shui. *Contact Dermatitis* 24:64-65.
- \*Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: Implications for practice. *Pediatr Clin North Am* 44:55-77.
- Lees PSJ. 1991. Chromium and disease: Review of epidemiological studies with particular reference to etiologic information provided by measures of exposure. *Environ Health Perspect* 92:93-104.
- \*Leikin JB, Paloucek FP, eds. 2002. In: Leikin and Paloucek's poisoning and toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp, Inc., 372-379.
- Lendinez E, Lopez MC, Cabrera C, et al. 1998. Determination of chromium in wine and other alcoholic beverages consumed in Spain by electrothermal atomic absorption spectrometry. *J Aoac Int* 8(5):1043-1047.
- Leónard A, Bernard A. 1993. Biomonitoring exposure to metal compounds with carcinogenic properties. *Environ Health Perspect* 101(3):127-133.
- Leónard A, Lauwerys RR. 1980. Carcinogenicity and mutagenicity of chromium. *Mutat Res* 76:227-239.
- Leonard S, Wang S, Zang L, et al. 2000. Role of molecular oxygen in the generation of hydroxyl and superoxide anion radicals during enzymatic Cr(VI) reduction and its implication to Cr(VI)-induced carcinogenesis. *J Environ Pathol Toxicol Oncol* 19(1-2):49-60.
- +\*Leroyer C, Dewitte JD, Bassanets A, et al. 1998. Occupational asthma due to chromium. *Respiration* 65:403-405.
- +\*Letterer E. 1939. [Examination of a chromium-silicotic lung.] *Arch Gewerbepatnol Gewerbe Hyg* 9:498-508. [Abstract] *J Ind Hyg Toxicol* 21:215-216. (German)
- \*Leung H. 1993. Physiologically-based pharmacokinetic modeling. In: Ballantine B, Marro T, Turner T, eds. *General and applied toxicology*. Vol. I. New York, NY: Stockton Press, 153-164.

## 9. REFERENCES

- +\*Levin HM, Brunner MJ, Rattner H. 1959. Lithographer's dermatitis. *J Am Med Assoc* 169:566-569.
- \*Levina A, Lay PA. 2005. Mechanistic studies of relevance to the biological activities of chromium. *Coord Chem Rev* 249(3-4):281-298.
- \*Levine RA, Streeten DHP, Doisy RJ, et al. 1968. Effects of oral chromium supplementation on the glucose tolerance of elderly human subjects. *Metabolism* 17:114-125.
- Levis AG, Bianchi V. 1982. Mutagenic and cytogenetic effects of chromium compounds. In: Lang S, ed. *Biological and environmental aspects of chromium*. Amsterdam: Elsevier Biomedical Press, 171-208.
- Levis AG, Buttignol M. 1977. Effects of potassium dichromate on DNA synthesis in hamster fibroblasts. *Br J Cancer* 35:496-499.
- \*Levis AG, Majone F. 1979. Cytotoxic and clastogenic effects of soluble chromium compounds on mammalian cell cultures. *Br J Cancer* 40:523-533.
- Levis AG, Buttignol M, Bianchi V, et al. 1978. Effects of potassium dichromate on nucleic acid and protein syntheses and on precursor uptake in BHK fibroblasts. *Cancer Res* 38:110-116.
- Levy LS, Venitt S. 1975. Carcinogenic and mutagenic activity of chromium containing materials. *Br J Cancer* 32:254-255.
- +\*Levy LS, Martin PA, Bidstrup PL. 1986. Investigation of the potential carcinogenicity of a range of chromium containing materials on rat lung. *Br J Ind Med* 43:243-256.
- \*Lewalter J, Korallus U, Harzdorf C, et al. 1985. Chromium bond detection in isolated erythrocytes: A new principle of biological monitoring of exposure to hexavalent chromium. *Int Arch Occup Environ Health* 55:305-318.
- \*Li H, Chen Q, Li S, et al. 2001. Effect of Cr(VI) exposure on sperm quality: Human and animal studies. *Ann Occup Hyg* 45(7):505-511.
- Lide DR. 1994. *CRC handbook of chemistry and physics*. 74th ed. Boca Raton, FL: CRC Press.
- \*Lide DR. 1998. Chromium. In: Lide DR, ed. *CRC handbook of chemistry and physics*. 79th ed. Boca Raton, FL: CRC Press, 4-8.
- +\*Liden S, Lundberg E. 1979. Penetration of chromium in intact human skin in vivo. *J Invest Dermatol* 72:42-45.
- \*Lieber M, Perlmutter NM, Frauenthal HL. 1964. Cadmium and hexavalent chromium in Nassau County groundwater. *J Am Water Works Assoc* 56:739-747.
- +\*Lieberman H. 1941. Chrome ulcerations of the nose and throat. *New Engl J Med* 225:132-133.
- Liggins J, Furth AJ. 1995. Fructation induced cross-linking of  $\beta$ -lactoglobulin and lysozyme. *Biochem Soc Trans* 23:240S-241S.

## 9. REFERENCES

- Lilien DL, Spivak JL, Goldman ID. 1970. Chromate transport in human leukocytes. *J Clin Invest* 49:1551-1557.
- +\*Lim TH, Sargent T, Kusubov N. 1983. Kinetics of trace element chromium(III) in the human body. *Am J Physiol* 244(4):445-454.
- \*Lin KY, Chang BV, Wang Y-S. 1996. Mobility of copper, zinc and chromium with municipal solid waste leachate in soils. *Proc Natl Sci Coun Repub China B* 20(1):19-25.
- \*Lin X, Zhuang Z, Costa M. 1992. Analysis of residual amino acid-DNA crosslinks induced in intact cells by nickel and chromium compounds. *Carcinogenesis* 3(10):1763-1768.
- +\*Lindberg E, Hedenstierna G. 1983. Chrome plating: Symptoms, findings in the upper airways, and effects on lung function. *Arch Environ Health* 38:367-374.
- \*Lindberg E, Vesterberg O. 1983a. Monitoring exposure to chromic acid in chromeplating by measuring chromium in urine. *Scand J Work Environ Health* 9:333-340.
- +\*Lindberg E, Vesterberg O. 1983b. Urinary excretion of proteins in chromeplaters, exchromeplaters and referents. *Scand J Work Environ Health* 9:505-510.
- Lindemann MD, Wood CM, Harper AF, et al. 1995. Dietary chromium picolinate additions improve gain: Feed and carcass characteristics in growing-finishing pigs and increase litter size in reproducing sows. *J Anim Sci* 73:457-465.
- \*Little MC, Gawkrödger DJ, Macneil S. 1996. Chromium- and nickel-induced cytotoxicity in normal and transformed human keratinocytes: An investigation of pharmacological approaches to the prevention of Cr(VI)-induced cytotoxicity. *Br J Dermatol* 134:199-207.
- +\*Littorin M, Welinder H, Hultberg B. 1984. Kidney function in stainless steel welders. *Int Arch Occup Environ Health* 53:279-282.
- \*Littorin M, Hogstedt B, Stromback B, et al. 1983. No cytogenetic effects in lymphocytes of stainless steel welders. *Scand J Work Environ Health* 9:259-264.
- \*Liu JK, Morris JS. 1978. Relative chromium response as an indicator of chromium status. *Am J Clin Nutr* 31:972-976.
- \*Liu KJ, Shi X. 2001. *In vivo* reduction of chromium (VI) and its related free radical generation. *Mol Cell Biochem* 222:41-47.
- Liu S, Dixon K. 1996. Induction of mutagenic DNA damage by chromium(VI) and glutathione. *Environ Mol Mutagen* 28:71-79.
- +\*Liu CS, Kuo HW, Lai JS, et al. 1998. Urinary N-acetyl-B-glucosaminidase as an indicator of renal dysfunction in electroplating workers. *Int Arch Occup Environ Health* 71:348-352.
- \*Liu KJ, Shi X, Dalal NS. 1997b. Synthesis of Cr(IV)-GSH, its identification and its free hydroxyl radical generation: A model compound for Cr(VI) carcinogenicity. *Biochem Biophys Res Commun* 235:54-58.



## 9. REFERENCES

- +\*Liu KJ, Jiang J, Swartz HM, et al. 1994. Low-frequency EPR detection of chromium(V) formation by chromium(VI) reduction in whole live mice. *Arch Biochem Biophys* 313(2):248-252.
- +\*Liu KJ, Mäder K, Shi X, et al. 1997a. Reduction of carcinogenic chromium(VI) on the skin of living rats. *MRM* 38:524-526.
- \*Liu KJ, Shi X, Jiang JJ, et al. 1995. Chromate-induced chromium(V) formation in live mice and its control by cellular antioxidants: An L-band electron paramagnetic resonance study. *Arch Biochem Biophys* 323(1):33-39.
- Liu W, Chaspoul F, Lefranc DB, et al. 2007. Microcalorimetry as a tool for Cr(VI) toxicity evaluation of human dermal fibroblasts. *J Therm Anal Calorim* 89(1):21-24.
- Liu X, Lu J, Liu S. 1999. Synergistic induction of hydroxyl radical-induced DNA single-strand breaks by chromium(VI) compound and cigarette smoke solution. *Mutat Res* 440:109-117.
- \*Livingston AL. 1978. Forage plant estrogens. *J Toxicol Environ Health* 4:301-324.
- \*Llagostera M, Garrido S, Guerrero R, et al. 1986. Induction of SOS genes of *Escherichia coli* by chromium compounds. *Environ Mutagen* 8:571-577.
- Llobet JM, Granero S, Schuhmacher M, et al. 1998a. Biological monitoring of environmental pollution and human exposure to metals in Tarragona, Spain. II. Levels in autopsy tissues. *Trace Elem Electrolytes* 15(1):44-49.
- Llobet JM, Granero S, Schumacher M, et al. 1998b. Biological monitoring of environmental pollution and human exposure to metals in Tarragona, Spain. IV. Estimation of the dietary intake. *Trace Elem Electrolytes* 15(3):136-141.
- \*Lo FB, Arai DK. 1988. Determination by atomic spectrometry of chromium on air sampling filters in the presence of iron. *Am Ind Hyg Assoc J* 49(5):207-212.
- Loeb LA, Sirover MA, Agarwal SS. 1978. Infidelity of DNA synthesis as related to mutagenesis and carcinogenesis. *Adv Exp Med Biol* 91:103-115.
- Lofroth G. 1978. The mutagenicity of hexavalent chromium is decreased by microsomal metabolism. *Naturwissenschaften* 65:207-208.
- Lofroth G, Ames BN. 1977. Mutagenicity of inorganic compounds in *Salmonella typhimurium*: Arsenic, chromium and selenium. *Mutat Res* 53:65-66.
- Losi ME, Amrhein C, Frankenberger WT. 1994. Environmental biochemistry of chromium. *Rev Environ Contam Toxicol* 136:91-121.
- +\*Loubieres Y, de Lassence A, Bernier M, et al. 1999. Acute, fatal, oral chromic acid poisoning. *J Toxicol Clin Toxicol* 37(3):333-336.
- +\*Lovrincevic I, Leung FY, Alfieri MAH, et al. 1996. Can elevated chromium induce somatopsychic responses? *Biol Trace Elem Res* 55:163-171.

## 9. REFERENCES

- Low KS, Lee CK, Lee PL. 1997. Chromium(III) sorption enhancement through NTA-modification of biological materials. *Bull Environ Contam Toxicol* 58:380-386.
- \*Loyaux-Lawniczak S, Lecomte P, Ehrhardt J. 2001. Behavior of hexavalent chromium in a polluted groundwater: Redox Processes and immobilization in soils. *Environ Sci Technol* 35:1350-1357.
- Lu YY, Yang JL. 1995. Long-term exposure to chromium(VI) oxide leads to defects in sulfate transport system in Chinese hamster ovary cells. *J Cell Biochem* 57:655-665.
- +\*Lucas JB, Kramkowski RS. 1975. Health hazard evaluation determination report number 74-87-221. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Center for Disease Control, National Institute for Occupational Safety and Health.
- Lucia-Jandris P, Hooper JW, Fields BN. 1993. Reovirus M2 gene is associated with chromium release from mouse L cells. *J Virol* 67(9):5339-5345.
- Luciani S, Dal Toso R, Rebellato AM, et al. 1979. Effects of chromium compounds on plasma membrane  $Mg^{2+}$ -ATPase activity of BHK cells. *Chem Biol Interact* 27:29-67.
- \*Luippold RS, Mundt KA, Austin RP, et al. 2003. Lung cancer mortality among chromate production workers. *Occup Environ Med* 60(6):451-457.
- \*Lukanova A, Toniolo P, Zhitkovich A, et al. 1996. Occupational exposure to Cr(VI): Comparison between chromium levels in lymphocytes, erythrocytes, and urine. *Int Arch Occup Environ Health* 69:39-44.
- Lukaski HC. 1999. Chromium as a supplement. *Annu Rev Nutr* 19:279-302.
- \*Lukaski HC, Bolonchuk WW, Siders WA, et al. 1996. Chromium supplementation and resistance training: Effects on body composition, strength, and trace element status of men. *Am J Clin Nutr* 63:954-965.
- \*Luo H, Lu Y, Shi X, et al. 1996. Chromium(IV)-mediated Fenton-like reaction causes DNA damage: Implication to genotoxicity of chromate. *Ann Clin Lab Sci* 26(2):185-191.
- Lutton JD, Abraham NG, Drummond GS, et al. 1997. Zinc porphyrins: Potent inhibitors of hematopoiesis in animal and human bone marrow. *Proc Natl Acad Sci USA* 94:1432-1436.
- Lytle CM, Lytle FW, Yang N, et al. 1998. Reduction of Cr(VI) to Cr(III) by wetland plants: Potential for in situ heavy metal detoxification. *Environ Sci Technol* 32:3087-3093.
- +\*Machle W, Gregorius F. 1948. Cancer of the respiratory system in the United States chromate-producing industry. *Public Health Rep* 63:114-127.
- Mackenzie RD, Anwar RA, Byerrum RU, et al. 1959. Absorption and distribution of Cr51 in the albino rat. *Arch Biochem Biophys* 79:200-205.
- +\*MacKenzie RD, Byerrum RU, Decker CF, et al. 1958. Chronic toxicity studies: II. Hexavalent and trivalent chromium administered in drinking water to rats. *Arch Ind Health* 18:232-234.

## 9. REFERENCES

- \*MacRae WD, Whiting RF, Stich HF. 1979. Sister chromatid exchanges induced in cultured mammalian cells by chromate. *Chem Biol Interact* 26:281-286.
- Maeng SH, Chung HW, Yu IJ, et al. 2003. Changes of 8-OH dG levels in DNA and its base excision repair activity in rat lungs after inhalation exposure to hexavalent chromium. *Mutat Res* 539:109-116.
- \*Maiti B, Desai SR. 1986. High-performance liquid chromatographic separation of beryllium, cobalt, nickel and chromium as the  $\beta$ -isopropyltropolone complexes and its application to the determination of chromium in air samples. *Analyst* 111:809-811.
- \*Majone F, Levis AG. 1979. Chromosomal aberrations and sister-chromatid exchanges in Chinese hamster cells treated in vitro with hexavalent chromium compounds. *Mutat Res* 67:231-238.
- +\*Major RH. 1922. Studies on a case of chromic acid nephritis. *Johns Hopkins Hosp Bull* 33:56-61.
- Majumder S, Ghoshal K, Summers D, et al. 2003. Chromium(VI) down-regulates heavy metal-induced metallothionein gene transcription by modifying transactivation potential of the key transcription factor, metal-responsive transcription factor 1. *J Biol Chem* 278(28):26216-26226.
- +\*Mali JW, Malten K, Van Neer FCJ. 1966. Allergy to chromium. *Arch Dermatol* 93:41-44.
- \*Mali JWH, Van Kooten WJ, VanNeer FCJ. 1963. Some aspects of the behavior of chromium compounds in the skin. *J Invest Dermatol* 41:111-122.
- \*Malinski T, Fish J, Matusiewicz H. 1988. Determining ultratrace metal concentrations by inductively coupled plasma emission spectrometry. *Am Water Works Assoc J* 80:81-85.
- \*Malm O, Pfeiffer WC, Fiszman M, et al. 1988. Transport and availability of heavy metals in the Paraiba Do Sul-Guandu river system, Rio de Janeiro State, Brazil. *Sci Total Environ* 75:201-209.
- \*Malsch PA, Proctor DM, Finley BL. 1994. Estimation of chromium inhalation reference concentration using the benchmark dose method: A case study. *Regul Toxicol Pharmacol* 20:58-82.
- Maltoni C. 1976. Predictive value of carcinogenesis bioassays. *Ann NY Acad Sci* 271:431-433.
- +\*Mancuso TF. 1951. Occupational cancer and other health hazards in a chromate plant: A medical appraisal: II. Clinical and toxicologic aspects. *Ind Med Surg* 20:393-407.
- +\*Mancuso TF. 1975. Consideration of chromium as an industrial carcinogen. In: Hutchinson TC, ed. *Proceedings of the international conference on heavy metals in the environment*. Toronto, Canada: Toronto Institute for Environmental Studies, 343-356.
- +\*Mancuso TF. 1997a. Chromium as an industrial carcinogen: Part I. *Am J Ind Med* 31:129-139.
- +\*Mancuso TF. 1997b. Chromium as an industrial carcinogen: Part II. Chromium in human tissues. *Am J Ind Med* 31:140-147.
- \*Mancuso TF, Hueper WC. 1951. Occupational cancer and other health hazards in a chromate plant: A medical appraisal: I. Lung cancers in chromate workers. *Ind Med Surg* 20:358-363.

## 9. REFERENCES

- \*Manning FCR, Xu J, Patierno SR. 1992. Transcriptional inhibition by carcinogenic chromate: Relationship to DNA damage. *Mol Carcinog* 6:270-279.
- \*Manygoats KR, Yazzie M, Stearns DM. 2002. Ultrastructural damage in chromium picolinate-treated cells: A TEM study. *J Biol Inorg Chem* 7:791-798.
- +\*Manzo L, Di Nucci A, Edel J, et al. 1983. Biliary and gastrointestinal excretion of chromium after administration of Cr-III and Cr-VI in rats. *Res Commun Chem Pathol Pharmacol* 42(1):113-125.
- Manzoori JL, Sorouraddin MH, Shemiran F. 1996. Preconcentration and spectrophotometric determination of chromium(VI) and total chromium in drinking water by the sorption of chromium diphenylcarbazone with surfactant coated alumina. *Anal Lett* 29:2007-2014.
- \*Mao Y, Zang L, Shi X. 1995. Generation of free radicals by Cr(IV) from lipid hydroperoxides and its inhibition by chelators. *Biochem Mol Biol Int* 36(2):327-337.
- Marini F, Ferré, MP, Gross H. 1995. Does welding stainless steel cause cancer? *Scand J Work Environ Health* 21:65-68.
- Mariscal A, Garcia A, Carnero M, et al. 1995. Evaluation of the toxicity of several heavy metals by a fluorescent bacterial bioassay. *J Appl Toxicol* 15(2):103-107.
- \*Martin WR, Fuller RE. 1998. Suspected chromium picolinate-induced rhabdomyolysis. *Pharmacotherapy* 18(4):860-862.
- +\*Maruyama Y. 1982. The health effect of mice given oral administration of trivalent and hexavalent chromium over a long-term. *Acta Scholae Medicinalis Universitatis in Gifu* 31:24-46.
- +Mason RW, Edwards IR. 1989. Acute toxicity of combinations of sodium dichromate, sodium arsenate and copper sulphate in the rat. *Comp Biochem Physiol* 93C:121-125.
- Matczak W, Chmielnicka J. 1993. Relation between various chromium compounds and some other elements in fumes from manual metal arc stainless steel welding. *Br J Ind Med* 50:244-251.
- \*Mathur AK. 2005. Effects of dermal application of chromium and linear alkylbenzene sulphonate alone and in combination in guinea pigs. *Toxicol Int* 12(1):9-12.
- Mathur AK, Gupta BN. 1998. Dermal toxicity of linear alkylbenzene sulfonate, chromium, and nickel in guinea pigs. *J Toxicol Cutaneous Ocul Toxicol* 17(4):191-196.
- +Mathur AK, Chandra SV, Tandon SK. 1977. Comparative toxicity of trivalent and hexavalent chromium to rabbits: II. Morphological changes in some organs. *Toxicology* 8:53-61.
- \*Matsui S. 1980. Evaluation of a *Bacillus subtilis* rec-assay for the detection of mutagens which may occur in water environments. *Water Res* 14:1613-1619.
- +\*Matsumoto N, Iijima S, Katsunuma H. 1976. Placental transfer of chromic chloride and its teratogenic potential in embryonic mice. *J Toxicol Sci* 2(2):1-13.

## 9. REFERENCES

- \*Mattagajasingh SN, Misra HP. 1996. Mechanisms of the carcinogenic chromium(VI)-induced DNA-protein cross-linking and their characterization in cultured intact human cells. *J Biol Chem* 271(52):33550-33560.
- Mattagajasingh SN, Misra HP. 1999. Analysis of EDTA-chelatable proteins from DNA-protein crosslinks induced by a carcinogenic chromium (VI) in cultured intact human cells. *Mol Cell Biochem* 199(1-2):149-162
- Mayebzadeh A, Dufresne A, Harvie S, et al. 1999. Mineralogy of lung tissue in dental laboratory technicians' pneumoconiosis. *Am Ind Hyg Assoc J* 60:349-353.
- \*Mayr U, Butsch A, Schneider S. 1992. Validation of two in vitro test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. *Toxicology* 74:135-149.
- \*McAughey JJ, Samuel AM, Baxter PJ, et al. 1988. Biological monitoring of occupational exposure in the chromate pigment production industry. *Sci Total Environ* 71:317-322.
- McCarty MF. 1993. Homologous physiological effects of phenformin and chromium picolinate. *Med Hypotheses* 41:316-324.
- McCarty MF. 1994. Longevity effect of chromium picolinate - "rejuvenation" of hypothalamic function? *Med Hypotheses* 43:253-265.
- McCarty MF. 1995. Inhibition of citrate lyase may aid aerobic endurance. *Med Hypotheses* 45:247-254.
- McCarty MF. 1996. Chromium and other insulin sensitizers may enhance glucagon secretion: Implications for hypoglycemia and weight control. *Med Hypotheses* 46:77-80.
- McCarty MF. 1997a. Over-the-counter chromium and renal failure. *Ann Intern Med* 127(8):654-655.
- McCarty MF. 1997b. Subtoxic intracellular trivalent chromium is not mutagenic: Implications for safety of chromium supplementation. *Med Hypotheses* 48:263-269.
- McGregor DB, Martin R, Cattanaach P, et al. 1987. Responses of the L5178Y tk<sup>+</sup>/tk<sup>-</sup> mouse lymphoma cell forward mutation assay to coded chemicals. I: Results for nine compounds. *Environ Mutagen* 9:143-160.
- McKay GC, Macnair R, MacDonald C, et al. 1996. Interactions of orthopaedic metals with an immortalized rat osteoblast cell line. *Biomaterials* 17(13):1339-1344.
- McKenna IM, Ramakrishna G, Diwan BA, et al. 2001. K-ras mutations in mouse lung tumors of extreme age: Independent of paternal preconceptional exposure to chromium(III) but significantly more frequent in carcinomas than adenomas. *Mutat Res* 490:57-65.
- \*Medeiros MG, Rodrigues AS, Batoreu MC, et al. 2003a. Elevated levels of DNA-protein crosslinks and micronuclei in peripheral lymphocytes of tannery workers exposed to trivalent chromium. *Mutagenesis* 18(1):19-24.
- \*Medeiros MG, Rodrigues AS, Batoreu MC, et al. 2003b. Biomarkers of chromium exposure and cytogenetic damage in leather tanning and welding industry workers. In: Cebulska-Wasilewska A, Au WW, Sram RJ, eds. *Human monitoring for genetic effects*. Washington, DC: IOS Press, 132-141.

## 9. REFERENCES

- Medina-Campos ON, Barrera D, Segoviano-Murillo S, et al. 2007. S-allylcysteine scavenges singlet oxygen and hypochlorous acid and protects LLC-PK1 cells of potassium dichromate-induced toxicity. *Food Chem Toxicol* 45(10):2030-2039.
- Mehra R, Bhalla S. 1998. Determination of chromium, manganese, iron and nickel content of hair for evaluating exposure to metals in occupational environment. *Oriental J Chem* 14(1):117-120.
- Mehra R, Juneja M. 2005. Fingernails as biological indices of metal exposure. *J Biosci* 30(2):253-257.
- \*Meranger JC, Subramanian KS, Chalifoux C. 1979. A national survey for cadmium, chromium, copper, lead, zinc, calcium and magnesium in Canadian drinking water supplies. *Environ Sci Technol* 13(6):707-711.
- \*Merian E. 1984. Introduction on environmental chemistry and global cycles of chromium, nickel, cobalt, beryllium, arsenic, cadmium and selenium, and their derivatives. *Toxicol Environ Chem* 8:9-38.
- Merk O, Reiser K, Speit G. 2000. Analysis of chromate-induced DNA-protein crosslinks with the comet assay. *Mutat Res* 471(1-2):71-80.
- +\*Merkur'eva RV, Koganova ZI, Gabdullina MK, et al. 1982. [Comparison of metabolic reactions in the bodies of experimental animals exposed to hexavalent chromium with different paths of penetration]. *Gig Sanit* 8:75-76. (Russian)
- +Merritt K, Crowe TD, Brown SA. 1989. Elimination of nickel, cobalt, and chromium following repeated injections of high dose metal salts. *J Biomed Mater Res* 23:845-862.
- \*Mertz W. 1969. Chromium occurrence and function in biological systems. *Physiol Rev* 49(2):163-239.
- Mertz W. 1974. The newer essential trace elements, chromium, tin, vanadium, nickel and silicon. *Proc Nutr Soc* 33:307-131.
- Mertz W. 1995. Risk assessment of essential trace elements: New approaches to setting recommended dietary allowances and safety limits. *Nutr Rev* 53(7):179-185.
- +\*Mertz W, Roginski EE, Feldman FJ, et al. 1969. Dependence of chromium transfer into the rat embryo on the chemical form. *J Nutr* 99:363-367.
- \*Messer J, Reynolds M, Stoddard L, et al. 2006. Causes of DNA single-strand breaks during reduction of chromate by glutathione in vitro and in cells. *Free Radic Biol Med* 40(11):1981-1992.
- +\*Meyers JB. 1950. Acute pulmonary complications following inhalation of chromic acid mist. *Ann Ind Hyg Occup Med* 2:742-747.
- Michaels D, Lurie P, Monforton C. 2006a. Lung cancer mortality in the German chromate industry. (Comment on: *J Occup Environ Med* 48(4):426-433). *J Occup Environ Med* 48(10):995-997.
- Michaels D, Monforton C, Lurie P. 2006b. Selected science: An industrial campaign to undermine an OSHA hexavalent chromium standard. *Environ Health* 5(5):1-8.

## 9. REFERENCES

\*Michel R, Loer F, Nolte M, et al. 1987. Neutron activation analysis of human tissues, organs and body fluids to describe the interaction of orthopaedic implants made of cobalt-chromium alloy with the patients organisms. *J Radioanal Nucl Chem* 113(1):83-96.

Michels PE. 1999. [Nickel and chromium(VI) aerosols in the air at electroplating facilities]. *Galvanotechnik* 90(5):1280-1286.

+\*Mignini F, Streccioni V, Baldo M, et al. 2004. Individual susceptibility to hexavalent chromium of workers of shoe, hide, and leather industries. Immunological pattern of HLA-B8,DR3-positive subjects. *Prev Med* 39(4):767-775.

Mikalsen A, Capellmann M, Alexander J. 1995. The role of iron chelators and oxygen in the reduced nicotinamide adenine dinucleotide phosphate-cytochrome P450 oxidoreductase-dependent chromium(VI) reduction. *Analyst* 120:935-938.

\*Mikalsen A, Alexander J, Andersen RA, et al. 1989. Reduction of hexavalent chromium in a reconstituted system of cytochrome P-450 and cytochrome b<sub>5</sub>. *Chem Biol Interact* 71:213-221.

\*Mikalsen SO. 1990. Effects of heavy metal ions on intercellular communication in Syrian hamster embryo cells. *Carcinogenesis* 11(9):1621-1626.

Miksche LW, Lewalter J. 1997. Health surveillance and biological effect monitoring for chromium-exposed workers. *Regul Toxicol Pharmacol* 26:S94-S99.

\*Milford JB, Davidson CI. 1985. The sizes of particulate trace elements in the atmosphere — a review. *J Air Pollut Control Assoc* 35:1249-1260.

\*Miller CA, Cohen MD, Costa M. 1991. Complexing of actin and other nuclear proteins to DNA by cis-diamminedichloroplatinum(II) and chromium compounds. *Carcinogenesis* 12(2):269-276.

+\*Minoia C, Cavalleri A. 1988. Chromium in urine, serum and red blood cells in the biological monitoring of workers exposed to different chromium valency states. *Sci Total Environ* 71:323-327.

\*Mirsalis JC, Hamilton CM, O'Loughlin KG, et al. 1996. Chromium(VI) at plausible drinking water concentrations is not genotoxic in the in vivo bone marrow micronucleus or liver unscheduled DNA synthesis assays. *Environ Mol Mutagen* 28:60-63.

Misra M, Alcedo JA, Wetterhahn KE. 1994. Two pathways for chromium(VI)-induced DNA damage in 14 day chick embryos: Cr-DNA binding in liver and 8-oxo-2'-deoxyguanosine in red blood cells. *Carcinogenesis* 15(12):2911-2917.

Moghaddas S, Gelerinter E, Bose RN. 1995. Mechanisms of formation and decomposition of hypervalent chromium metabolites in the glutathione-chromium(VI) reaction. *J Inorg Biochem* 57:135-146.

+\*Mohamedshah FY, Moser-Veillon PB, Yamini S, et al. 1998. Distribution of a stable isotope of chromium (<sup>53</sup>Cr) in serum, urine, and breast milk in lactating women. *Am J Clin Nutr* 67:1250-1255.

+\*Moller DR, Brooks SM, Bernstein DI, et al. 1986. Delayed anaphylactoid reaction in a worker exposed to chromium. *J Allergy Clin Immunol* 77(3):451-456.

## 9. REFERENCES

- \*Molyneux MJ, Davies MJ. 1995. Direct evidence for hydroxyl radical-induced damage to nucleic acids by chromium(VI)-derived species: Implications for chromium carcinogenesis. *Carcinogenesis* 16(4):875-882.
- \*Montaldi A, Zentilin L, Zordan M, et al. 1987. Chromosomal effects of heavy metals (Cd, Cr, Hg, Ni and Pb) on cultured mammalian cells in the presence of nitrilotriacetic acid (NTA). *Toxicol Environ Chem* 14:183-200.
- Moore JW, Maher MA, Banz WJ, et al. 1997. Chromium picolinate modulates rat vascular smooth muscle cell intracellular calcium metabolism. *J Nutr* 128:180-184.
- +\*Mor S, Ben-Efraim S, Leibovici J, et al. 1988. Successful contact sensitization to chromate in mice. *Int Arch Allergy Appl Immunol* 85:452-457.
- Mor S, Ravindra K, Dahiya RP, et al. 2006. Leachate characterization and assessment of groundwater pollution near municipal solid waste landfill site. *Environ Monit Assess* 118:435-456.
- \*Morris B, MacNeil S, Fraser R, et al. 1995b. Increased urine chromium excretion in normal pregnancy. *Clin Chem* 41(10):1544-1545.
- Morris BW, Gray TA, MacNeil S. 1993a. Glucose-dependent uptake of chromium in human and rat insulin-sensitive tissues. *Clin Sci* 84:477-482.
- Morris BW, Gray T, MacNeil S. 1995a. Evidence for chromium acting as an essential trace element in insulin-dependent glucose uptake in cultured mouse myotubes. *J Endocrinol* 144:135-141.
- Morris BW, MacNeil S, Stanley K, et al. 1993b. The inter-relationship between insulin and chromium in hyperinsulinaemic euglycaemic clamps in healthy volunteers. *J Endocrinol* 139:339-345.
- Morselli L, Cecchini M, Grandi E, et al. 1999. Heavy metals in atmospheric surrogate dry deposition. *Chemosphere* 38(4):899-907.
- \*Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants. *Clin Pharmacokin* 5:485-527.
- \*Moschandreas DJ, Karuchit S, Berry MR, et al. 2002. Exposure apportionment: Ranking food items by their contribution to dietary exposure. *J Expo Anal Environ Epidemiol* 12:233-243.
- Moukarzel AA, Song MK, Buchman AL, et al. 1992. Excessive chromium intake in children receiving total parenteral nutrition. *Lancet* 339:385-388.
- +\*Moulin JJ, Wild P, Mantout B, et al. 1993. Mortality from lung cancer and cardiovascular diseases among stainless-steel producing workers. *Cancer Causes Control* 4:75-81.
- \*Moxon AL, DuBois KP. 1939. The influence of arsenic and certain other elements on the toxicity of seleniferous grains. *J Nutr* 18:447-457.
- \*Mudroch A, Sarazin L, Lomas T. 1988. Report: Summary of surface and background concentrations of selected elements in the Great Lakes sediments. *J Great Lakes Res* 14(2):241-251.
- Mukherjee AB. 1998. Chromium in the environment of Finland. *Sci Total Environ* 217:9-19.



## 9. REFERENCES

- Mukherjee S, Palmer LJ, Kim JY, et al. 2004. Smoking status and occupational exposure affects oxidative DNA injury in boilerworkers exposed to metal fume and residual oil fly ash. *Cancer Epidemiol Biomarkers Prev* 13(3):454-460.
- Mukherjee S, Rodrigues E, Aeschliman DB, et al. 2005. Urinary metal and polycyclic aromatic hydrocarbon biomarkers in boilerworkers exposed to metal fume and residual oil fly ash. *Am J Ind Med* 47(6):484-493.
- \*Munch D. 1993. Concentration profiles of arsenic, cadmium, chromium, copper, lead, mercury, nickel, zinc, vanadium and polynuclear aromatic hydrocarbons (PAH) in forest soil beside an urban road. *Sci Total Environ* 138:47-55.
- \*Mundt KA, Dell LD. 1997. Carcinogenicity of trivalent and hexavalent chromium. *OEM Report* 11(11):95-100.
- Murgia N, Muzi G, Dell'omo M, et al. 2006. Induced sputum, exhaled breath condensate and nasal lavage fluid in electroplating workers exposed to chromium. *Int J Immunopathol Pharmacol* 19(4):67-71.
- +\*Murthy RC, Junaid M, Saxena DK. 1996. Ovarian dysfunction in mice following chromium (VI) exposure. *Toxicol Lett* 89:147-154.
- +Murthy RC, Saxena DK, Gupta SK, et al. 1991. Ultrastructural observations in testicular tissue of chromium-treated rats. *Reprod Toxicol* 5:443-447.
- \*Muttamara S, Leong ST. 2004. Health implication among occupational exposed workers in a chromium alloy factory, Thailand. *J Environ Sci* 16(2):181-186.
- +\*Mutti A, Cavatorta A, Borghi L, et al. 1979. Distribution and urinary excretion of chromium: Studies on rats after administration of single and repeated doses of potassium dichromate. *Med Lav* 3:171-179.
- +\*Mutti A, Lucertini S, Valcavi P, et al. 1985a. Urinary excretion of brush-border antigen revealed by monoclonal antibody: Early indicator of toxic nephropathy. *Lancet* 2(8461):914-917.
- \*Mutti A, Pedroni C, Arfini G, et al. 1985b. Biological monitoring of occupational exposure to different chromium compounds at various valency states. In: Merian E, Frei RW, Hardi W, et al., eds. *Carcinogenic and mutagenic metal compounds: Environmental and analytical chemistry and biological effects*. London: Gordon and Breach Science Publishers, 119-125.
- \*Myers CR, Myers JM. 1998. Iron stimulates the rate of reduction of hexavalent chromium by human microsomes. *Carcinogenesis* 19(6):1029-1038.
- Myers CR, Porgilsson B, Carstens BP, et al. 1999. Naphthoquinones stimulate the rate of reduction of hexavalent chromium by human microsomes. *Toxic Subst Mech* 18(3):103-128.
- Myers MJ, Farrell DE, Evock-Clover CM, et al. 1997. Effect of growth hormone or chromium picolinate on swine metabolism and inflammatory cytokine production after endotoxin challenge exposure. *Am J Vet Res* 58(6):594-598.

## 9. REFERENCES

- \*Nadig RJ. 1994. Cadmium and other metals and metalloids. In: Goldfrank LR, Weisman RS, Flomenbaum NE, et al., eds. Goldfrank's toxicologic emergencies. 5th ed. Norwalk, CT: Appleton and Lange, 1063-1069.
- \*Nagaya T. 1986. No increase in sister-chromatid exchange frequency in lymphocytes of chromium platers. *Mutat Res* 170:129-132.
- \*Nagaya T, Ishikawa N, Hata H, et al. 1991. Sister-chromatid exchanges in lymphocytes from 12 chromium platers: A 5-year follow-up study. *Toxicol Lett* 58:329-335.
- \*Nakamura S, Oda Y, Shimada T, et al. 1987. SOS-inducing activity of chemical carcinogens and mutagens in *Salmonella typhimurium* TA1535/pSK1002: Examination with 151 chemicals. *Mutat Res* 192:239-246.
- \*Nakamuro K, Yoshikawa K, Sayato Y, et al. 1978. Comparative studies of chromosomal aberration and mutagenicity of trivalent and hexavalent chromium. *Mutat Res* 58:175-181.
- \*NAS/NRC. 1989. Biologic markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.
- Nasu T, Ooyama I, Shibata H. 1993. Inhibitory effects of hexavalent chromium ions on the contraction in ileal longitudinal smooth muscle of guinea-pig. *Comp Biochem Physiol* 104C(1):97-102.
- \*Nestmann ER, Matula TI, Douglas GR, et al. 1979. Detection of the mutagenic activity of lead chromate using a battery of microbial tests. *Mutat Res* 66:357-365.
- +\*Nethercott J, Paustenbach D, Adams R, et al. 1994. A study of chromium induced allergic contact dermatitis with 54 volunteers: Implications for environmental risk assessment. *Occup Environ Med* 51:371-380.
- +\*Nettesheim P, Szakal AK. 1972. Morphogenesis of alveolar bronchiolization. *Lab Invest* 26(2):210-219.
- +\*Nettesheim P, Hanna MG, Doherty DG, et al. 1971. Effect of calcium chromate dust, influenza virus, and 100 R whole-body X-radiation on lung tumor incidence in mice. *J Natl Cancer Inst* 47(5):1129-1144.
- \*Newbold RF, Amos J, Connell JR. 1979. The cytotoxic, mutagenic and clastogenic effects of chromium-containing compounds on mammalian cells in culture. *Mutat Res* 67:55-63.
- Newhook R, Hirtle H, Byrne K, et al. 2003. Releases from copper smelters and refineries and zinc plants in Canada: Human health exposure and risk characterization. *Sci Total Environ* 301:23-41.
- +\*Newhouse ML. 1963. A cause of chromate dermatitis among assemblers in an automobile factory. *Br J Ind Med* 20:199-203.
- Ng TB, Liu WK. 1990. Toxic effect of heavy metals on cells isolated from the rat adrenal and testis. *In Vitro Cell Dev Biol* 26:24-28.
- Ng WK, Wilson RP. 1997. Chromic oxide inclusion in the diet does not affect glucose utilization or chromium retention by channel catfish, *Ictalurus punctatus*. *J Nutr* 127:2357-2362.

## 9. REFERENCES

Ning J, Grant MH. 2000. The role of reduced glutathione and glutathione reductase in the cytotoxicity of chromium (VI) in osteoblasts. *Toxicol In Vitro* 14:329-335.

NIOSH. 1975. Criteria for a recommended standard...occupational exposure to chromium(VI). Washington, DC: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. HEW (NIOSH) publication no. 76-129.

NIOSH. 1987a. Registry of toxic effects of chemical substances. 1985-86 ed. Washington, DC: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. 106, 1590-1598.

NIOSH. 1987b. Manual of analytical methods, 3rd ed. Methods: 7024, 7600, 7604, 8005, 8310. Washington, DC: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

\*NIOSH. 1989. National occupation exposure survey. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. March 29, 1989.

\*NIOSH. 1992. NIOSH recommendations for occupational safety and health. Compendium of Policy Documents and Statements. Categories of Pesticides. Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. <http://www.cdc.gov/niosh/92-100.html>. April 29, 2008.

\*NIOSH. 1994a. Elements in blood or tissue. Method: 8005. In: NIOSH manual of analytical methods. 4th ed. Cincinnati, OH: Department of Health and Human Services, National Institute of Occupational Safety and Health. DHHS publication no. 94-113.

\*NIOSH. 1994b. Metals in urine. Method: 8310. In: NIOSH manual of analytical methods. 4th ed. Cincinnati, OH: Department of Health and Human Services, National Institute of Occupational Safety and Health. DHHS publication no. 94-113.

\*NIOSH. 1994c. Chromium and chromium compounds, as Cr. Method: 7024. In: NIOSH manual of analytical methods. 4th ed. Cincinnati, OH: Department of Health and Human Services, National Institute of Occupational Safety and Health. DHHS publication no. 94-113.

\*NIOSH. 1994d. Elements by ICP. Method: 7300. In: NIOSH manual of analytical methods. 4th ed. Cincinnati, OH: Department of Health and Human Services, National Institute of Occupational Safety and Health. DHHS publication no. 94-113.

\*NIOSH. 1994e. Chromium, hexavalent. Method: 7600. In: NIOSH manual of analytical methods. 4th ed. Cincinnati, OH: Department of Health and Human Services, National Institute of Occupational Safety and Health. DHHS publication no. 94-113.

\*NIOSH. 1994f. Chromium, hexavalent. Method: 7604. In: NIOSH manual of analytical methods. 4th ed. Cincinnati, OH: Department of Health and Human Services, National Institute of Occupational Safety and Health. DHHS publication no. 94-113.

## 9. REFERENCES

- \*NIOSH. 2005. Chromium. 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/>. April 24, 2008.
- \*NIOSH. 2008. International chemical safety cards. U.S. national Version. National Institute for Occupational Safety and Health. <http://www.cdc.gov/niosh/ipcsneng/neng0029.html>. May 22, 2008.
- \*Nishioka H. 1975. Mutagenic activities of metal compounds in bacteria. *Mutat Res* 31:185-189.
- +Nomiya K, Nomiya H, Yotoriyama M. 1982. Low-molecular-weight proteins in urine from rabbits given nephrotoxic compounds. *Ind Health* 20:1-10.
- Norseth T. 1981. The carcinogenicity of chromium. *Environ Health Perspect* 40:121-130.
- \*Norseth T. 1986. The carcinogenicity of chromium and its salts. *Br J Ind Med* 43:649-651.
- +\*Norseth T, Alexander J, Aaseth J, et al. 1982. Biliary excretion of chromium in the rat: A role of glutathione. *Acta Pharmacol Toxicol* 51:450-455.
- Nour AM, El-Tablawy N, El Allaway RMM. 2000. Beneficial role of L-thyroxine on hepato-renal toxicity induced by amikacin and potassium dichromate. *J Drug Res* 23:277-289.
- Nouri AME, Mansouri M, Hussain RF, et al. 1995. Super-sensitive epithelial cell line and colorimetric assay to replace the conventional K562 target and chromium release assay for assessment of non-MHC-restricted cytotoxicity. *J Immunol Methods* 180:63-68.
- +\*Novey HS, Habib M, Wells ID. 1983. Asthma and IgE antibodies induced by chromium and nickel salts. *J Allergy Clin Immunol* 72(4):407-412.
- Nowak B. 1998. Contents and relationship of elements in human hair for a non-industrialised population in Poland. *Sci Total Environ* 209:59-68.
- NRC. 1989. National Research Council. Recommended dietary allowances. 10th ed. Washington, DC: National Academy of Sciences, 241-243.
- \*NRC. 1993. Pesticides in the diets of infants and children. Washington DC: National Academy Press, National Research Council.
- \*NRCC. 1976. Effects of chromium in the Canadian environment. Ottawa, Canada: Subcommittee on Heavy Metals and Certain Other Compounds, National Research Council of Canada, 92.
- \*Nriagu JO. 1979. Copper in the atmosphere and precipitation. In: Nriagu JO, ed. Copper environment. New York, NY: John Wiley and Sons, 43-75.
- \*Nriagu JO, Pacyna JM. 1988. Quantitative assessment of worldwide contamination of air, water and soils by trace metals. *Nature* 333:134-139.
- +\*NTP. 1996a. Final report on the reproductive toxicity of potassium dichromate (hexavalent) (CAS No. 7778-50-9) administered in diet to SD rats. National Institute of Environmental Health Sciences, National Toxicology Program. PB97125355.

## 9. REFERENCES

- +\*NTP. 1996b. Final report on the reproductive toxicity of potassium dichromate (hexavalent) (CAS No. 7778-50-9) administered in diet to BALB/c mice. National Institute of Environmental Health Sciences, National Toxicology Program. PB97125363.
- +\*NTP. 1997. Final report on the reproductive toxicity of potassium dichromate (CAS No. 7778-50-9) administered in diet to BALB/c mice. National Institute of Environmental Health Sciences, National Toxicology Program. PB97144919.
- NTP. 1998. Report on carcinogens, Eighth edition: Summary 1998. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institute of Environmental Health Sciences, National Toxicology Program, 29-31.
- NTP. 2002. Report on carcinogens. 10th ed. Bethesda, MD: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. <http://ehp.niehs.nih.gov/roc/toc10/html>. March 24, 2008.
- \*NTP. 2005. Report on carcinogens. 11th ed. 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>. April 24, 2008.
- +\*NTP. 2007. NTP technical report on the toxicity studies of sodium dichromate dihydrate (CAS No. 7789-12-0) administered in drinking water to male and female F344/N rats and B6C3F1 mice and male BALB/c and *am3-C57BL/6* mice. Washington, DC: National Toxicology Program. Toxicity Report Series Number 72. [http://ntp.niehs.nih.gov/ntp/htdocs/ST\\_rpts/TOX72.pdf](http://ntp.niehs.nih.gov/ntp/htdocs/ST_rpts/TOX72.pdf). October 7, 2008
- +\*NTP. 2008a. NTP technical report on the toxicology and carcinogenesis studies of sodium dichromate dihydrate (CAS No. 7789-12-0) in F344/N rats and B6C3F1 mice (drinking water studies). Washington, DC: National Toxicology Program. NTP TR 546. [http://ntp.niehs.nih.gov/files/546\\_web\\_FINAL.pdf](http://ntp.niehs.nih.gov/files/546_web_FINAL.pdf). August 13, 2008.
- +\*NTP. 2008b. NTP technical report on the toxicology and carcinogenesis studies of chromium picolinate monohydrate (CAS No. 27882-76-4) in F344/N rats and B6C3F1 mice (feed studies). Scheduled peer review date: February 27-28, 2008. Washington, DC: National Toxicology Program. NTP TR 556. [http://ntp.niehs.nih.gov/files/TR556board\\_webRev.pdf](http://ntp.niehs.nih.gov/files/TR556board_webRev.pdf). May 21, 2008.
- \*O'Brien TJ, Brooks BR, Patierno SR. 2005. Nucleotide excision repair functions in the removal of chromium-induced DNA damage in mammalian cells. *Mol Cell Biochem* 279:85-95.
- \*O'Brien TJ, Ceryak S, Patierno SR. 2003. Complexities of chromium carcinogenesis: Role of cellular response, repair and recovery mechanisms. *Mutat Res* 533(1-2):3-36.
- \*Offenbacher EG, Pi-Sunyer FX. 1980. Beneficial effect of chromium-rich yeast on glucose tolerance and blood lipids in elderly subjects. *Diabetes* 29:919-925.
- O'Flaherty EJ. 1993a. A pharmacokinetic model for chromium. *Toxicol Lett* 68:145-158.
- O'Flaherty EJ. 1993b. Chromium as an essential and toxic metal. *Scand J Work Environ Health* 19(1):124-124.
- \*O'Flaherty EJ. 1993c. Physiologically based models for bone-seeking elements. IV. Kinetics of lead disposition in humans. *Toxicol Appl Pharmacol* 118:16-29.

## 9. REFERENCES

- \*O'Flaherty EJ. 1995. Physiologically based models for bone-seeking elements. V. Lead absorption and disposition in childhood. *Toxicol Appl Pharmacol* 131:297-308.
- \*O'Flaherty EJ. 1996. A physiologically based model of chromium kinetics in the rat. *Toxicol Appl Pharmacol* 138:54-64.
- O'Flaherty EJ. 1998. Physiologically based models of metal kinetics. *Crit Rev Toxicol* 28(3):271-317.
- \*O'Flaherty EJ, Kerger BD, Hays SM, et al. 2001. A physiologically based model for the ingestion of chromium(III) and chromium(VI) by humans. *Toxicol Sci* 60:196-213.
- Ogawa M, Nakajima Y, Endo Y. 2007. Four cases of chemical burns thought to be caused by exposure to chromic acid mist. *J Occup Health* 49(5):402-404.
- \*Ohanian EV. 1986. Health effects of corrosion products in drinking water. *Trace Subst Environ Health* 20:122-138.
- \*O'Hara KA, Klei LR, Barchowsky A. 2003. Selective activation of Src family kinases and JNK by low levels of chromium(VI). *Toxicol Appl Pharmacol* 190(3):214-223.
- \*O'Hara KA, Vaghjiani RJ, Nemec AA, et al. 2007. Cr(VI)-stimulated STAT3 tyrosine phosphorylation and nuclear translocation in human airway epithelial cells requires Lck. *Biochem J* 402(2):261-269.
- \*Ohno H, Hanaoka F, Yamada MA. 1982. Inducibility of sister-chromatid exchanges by heavy-metal ions. *Mutat Res* 104:141-145.
- +\*Ohsaki Y, Abe S, Kimura K, et al. 1978. Lung cancer in Japanese chromate workers. *Thorax* 33:372-374.
- Okada S, Tsukada H, Tezuka M. 1989. Effect of chromium(III) on nucleolar RNA synthesis. *Biol Trace Elem Res* 21:35-39.
- +\*Okubo T, Tsuchiya K. 1977. An epidemiological study on lung cancer among chromium plating workers. *Keio J Med* 26:171-177.
- +\*Okubo T, Tsuchiya K. 1979. Epidemiological study of chromium platers in Japan. *Biol Trace Elem Res* 1:35-44.
- +\*Olaguibel JM, Basomba A. 1989. Occupational asthma induced by chromium salts. *Allergol Immunopathol (Madr)* 17(3):133-136.
- Oliveira H, Santos TM, Ramalho-Santos J, et al. 2006. Histopathological effects of hexavalent chromium in mouse kidney. *Bull Environ Contam Toxicol* 76(6):977-983.
- \*Olivier P, Marzin D. 1987. Study of the genotoxic potential of 48 inorganic derivatives with the SOS chromotest. *Mutat Res* 189:263-269.
- \*Olvera O, Zimmering S, Arceo C, et al. 1993. The protective effects of chlorophyllin in treatment with chromium(VI) oxide in somatic cells of *Drosophila*. *Mutat Res* 301:201-204.

## 9. REFERENCES

Ondov JM, Choquette CE, Zoller WH, et al. 1989. Atmospheric behavior of trace elements on particles emitted from a coal-fired power plant. *Atmos Environ* 23(10):2193-1104.

\*O'Neil MJ, Heckelman PE, Koch CB, et al., eds. 2006. *The Merck index*. 14th ed. Whitehouse Station, NJ: Merck & Co., Inc., 370, 372.

Ortega R, Deves G, Bonnin-Mosbah M, et al. 2001. Chromium mapping in male mice reproductive glands exposed to CrCl<sub>3</sub> using proton and x-ray synchrotron radiation microbeams. *Nucl Instrum Methods Phys Res B* 181:485-488.

Ortega R, Deves G, Fayard B, et al. 2003. Combination of synchrotron radiation x-ray microprobe and nuclear microprobe for chromium and chromium oxidation states quantitative mapping in single cells. *Nucl Instrum Methods Phys Res B* 210:325-329.

\*OSHA. 1998a. Air contaminants; final rule. U.S. Department of Labor. Occupational Safety and Health Administration. *Fed Regist* 54:2930.

OSHA. 1998b. Industry group seeks updated data on hex chrome exposure. Occupational Safety and Health Administration. *Inside OSHA*. August 24, 1998.

OSHA 1999a. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000.

OSHA 1999b. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000.

OSHA 1999c. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55.

OSHA. 2001. Method ID-109-SG: Aluminum oxide in workplace atmospheres. Sampling and analytical methods. Occupational Safety and Health Administration. U.S. Department of Labor. <http://www.osha.gov/dts/sltc/methods/inorganic/t-id109sg-pv-02-0110-m/t-id109sg-pv-02-0110-m.html>. March 07, 2006.

\*OSHA. 2007a. Air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000, Table Z 1. <http://www.osha.gov/comp-links.html>. April 24, 2008.

OSHA. 2007b. Gases, vapors, fumes, dusts, and mists. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55, Appendix A. <http://www.osha.gov/comp-links.html>. April 24, 2008.

OSHA. 2007c. Limits for air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000. <http://www.osha.gov/comp-links.html>. April 24, 2008.

\*OSHA. 2007d. Chromium (VI). Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.26. [http://edocket.access.gpo.gov/cfr\\_2007/julqtr/pdf/29cfr1910.1026.pdf](http://edocket.access.gpo.gov/cfr_2007/julqtr/pdf/29cfr1910.1026.pdf). October 07, 2008.

\*OSHA. 2007e. Chromium (VI). Code of Federal Regulations. Occupational Safety and Health Administration. 29 CFR 1915.1026. [http://edocket.access.gpo.gov/cfr\\_2007/julqtr/pdf/29cfr1915.1026.pdf](http://edocket.access.gpo.gov/cfr_2007/julqtr/pdf/29cfr1915.1026.pdf). October 07, 2008.

## 9. REFERENCES

- \*OSHA. 2007f. Safety and health regulations for construction. Chromium (VI). Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.1126. [http://edocket.access.gpo.gov/cfr\\_2007/julqtr/pdf/29cfr1926.1126.pdf](http://edocket.access.gpo.gov/cfr_2007/julqtr/pdf/29cfr1926.1126.pdf). October 07, 2008.
- \*Osim EE, Tandayi M, Chinyanga HM, et al. 1999. Lung function, blood gases, pH and serum electrolytes of small-scale miners exposed to chrome ore dust on the Great Dyke in Zimbabwe. *Trop Med Int Health* 4(9):621-628.
- Oster-Jorgensen E, Gerner T, Pedersen SA. 1991. The determination of gastric emptying rate. *Euro J Surg* 157:31-43.
- \*OTA. 1990. Neurotoxicology: Identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment, OTA-BA-438.
- \*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: Saunders, 222-238.
- \*Oygard JK, Mage A, Gjengedal E. 2004. Estimation of the mass-balance of selected metals in four sanitary landfills in Western Norway, with emphasis on the heavy metal content of the deposited waste and the leachate. *Water Res* 38:2851-2858.
- \*Pacyna JM, Ottar B. 1985. Transport and chemical composition of the summer aerosol in the Norwegian Arctic. *Atmos Environ* 19(12):2109-2120.
- \*Pacyna JM, Pacyna EG. 2001. An assessment of global and regional emissions of trace metals to the atmosphere from anthropogenic sources worldwide. *Environ Rev* 9(4):269-298.
- Paddle GM. 1997. Metaanalysis as an epidemiological tool and its application to studies of chromium. *Regul Toxicol Pharmacol* 26:S42-S50.
- Palmer CD, Wittbrodt PR. 1991. Processes affecting the remediation of chromium-contaminated sites. *Environ Health Perspect* 92:25-40.
- \*Papp JF, Lipin BR. 2001. Chromium and chromium alloys. In: *Kirk-Othmer encyclopedia of chemical technology*. John Wiley & Sons, Inc, 468-526. <http://mrw.interscience.wiley.com/emrw/9780471238966/kirk/article/chrowest.a01/current/pdf>. May 21, 2008.
- +\*Park RM, Stayner LT. 2006. A search for thresholds and other nonlinearities in the relationship between hexavalent chromium and lung cancer. *Risk Anal* 26(1):79-88.
- +\*Park RM, Bena JF, Stayner LT, et al. 2004. Hexavalent chromium and lung cancer in the chromate industry: A quantitative risk assessment. *Risk Anal* 24(5):1099-1108.
- \*Parks JL, McNeill L, Frey M, et al. 2004. Determination of total chromium in environmental water samples. *Water Res* 38(12):2827-2838.
- +\*Partington CN. 1950. Acute poisoning with potassium bichromate. *Br Med J* 2(4688):1097-1098.
- Pascal LE, Tessier DM. 2004. Cytotoxicity of chromium and manganese to lung epithelial cells in vitro. *Toxicol Lett* 147(2):143-151.



## 9. REFERENCES

- +\*Pascale LR, Waldstein SS, Engbring G, et al. 1952. Chromium intoxication with special reference to hepatic injury. *J Am Med Assoc* 149:1385-1389.
- \*Paschin YV, Zacepilova TA, Kozchenko VI. 1982. Induction of dominant lethal mutations in male mice by potassium dichromate. *Mutat Res* 103:345-347.
- +\*Pastides H, Austin R, Lemeshow S, et al. 1994. A retrospective-cohort study of occupational exposure to hexavalent chromium. *Am J Ind Med* 25:663-675.
- \*Pattison DI, Davies MJ, Levina A, et al. 2001. Chromium(VI) reduction by catechol(amine)s results in DNA cleavage in vitro: Relevance to chromium genotoxicity. *Chem Res Toxicol* 14(5):500-510.
- \*Paustenbach DJ, Finley BL, Mowat FS, et al. 2003. Human health risk and exposure assessment of chromium(VI) in tap water. *J Toxicol Environ Health A* 66(14):1295-1339.
- +\*Paustenbach DJ, Hays SM, Brien BA, et al. 1996. Observation of steady state in blood and urine following human ingestion of hexavalent chromium in drinking water. *J Toxicol Environ Health* 49:453-461.
- Paustenbach DJ, Meyer DM, Sheehan PJ, et al. 1991. An assessment and quantitative uncertainty analysis of the health risks to workers exposed to chromium contaminated soils. *Toxicol Ind Health* 7(3):159-196.
- \*Paustenbach DJ, Panko JM, Fredrick MM, et al. 1997. Urinary chromium as a biological marker of environmental exposure: What are the limitations? *Regul Toxicol Pharmacol* 26:S23-S34.
- \*Paustenbach DJ, Sheehan PJ, Paull JM, et al. 1992. Review of the allergic contact dermatitis hazard posed by chromium-contaminated soil: Identifying a "safe" concentration. *J Toxicol Environ Health* 37:177-207.
- +Payne WW. 1960. Production of cancers in mice and rats by chromium compounds. *Arch Ind Health* 21:530-535.
- Pedersen NB. 1982. The effects of chromium on the skin. In: Langard S, ed. *Biological and environmental aspects of chromium*. Amsterdam: Elsevier Biomedical Press, 249-275.
- \*Pellerin C, Booker SM. 2000. Reflections on hexavalent chrom. Health hazards of an industrial heavyweight. *Environ Health Perspect* 108(9):A403-A407.
- +\*Peltonen L, Fraki J. 1983. Prevalence of dichromate sensitivity. *Contact Dermatitis* 9:190-194.
- Penefsky ZJ, Elwood JC. 1996. Mechanical responses of chromium-deficient developing rat heart. *Comp Biochem Physiol* 114A(2):175-187.
- Pereira ML, das Neves RP, Oliveira H, et al. 2005. Effect of Cr(V) on reproductive organ morphology and sperm parameters: An experimental study in mice. *Environ Health* 4(9):1-6.
- \*Perrault G, Dufresne A, Strati G, et al. 1995. Physico-chemical fate of chromium compounds in the sheep lung model. *J Toxicol Environ Health* 44:247-262.

## 9. REFERENCES

- Persson D, Osterberg R, Bjursell G. 1986. Mechanism of chromium carcinogenesis. *Acta Pharmacol Toxicol* 59:260-263.
- Petersen R, Thomsen JF, Jorgensen NK, et al. 2000. Half life of chromium in serum and urine in a former plasma cutter of stainless steel. *Occup Environ Med* 57(2):140-142.
- \*Petit A, Mwale F, Zukor DJ, et al. 2004. Effect of cobalt and chromium ions on bcl-2, bax, caspase-3, and caspase-8 expression in human U937 macrophages. *Biomaterials* 25(11):2013-2018.
- Petrilli FL, De Flora S. 1978a. Metabolic deactivation of hexavalent chromium mutagenicity. *Mutat Res* 54:139-147.
- \*Petrilli FL, De Flora S. 1978b. Oxidation of inactive trivalent chromium to the mutagenic hexavalent form. *Mutat Res* 58:167-173.
- Petrilli FL, De Flora S. 1987. Correspondence. Carcinogenicity of chromium and its salts. *Br J Ind Med* 44:355.
- \*Petrilli FL, Camoirano A, Bennicelli C, et al. 1985. Specificity and inducibility of the metabolic reduction of chromium(VI) mutagenicity by subcellular fractions of rat tissues. *Cancer Res* 45:3179-3187.
- \*Petrilli FL, Romano M, Bennicelli C, et al. 1986a. Metabolic reduction and detoxification of hexavalent chromium. In: Serrone DM, ed. *Chromium symposium 1986: An update*. Pittsburgh, PA: Industrial Health Foundation Inc., 112-130.
- \*Petrilli FL, Rossi GA, Camoirano A, et al. 1986b. Metabolic reduction of chromium by alveolar macrophages and its relationships to cigarette smoke. *J Clin Invest* 77:1917-1924.
- \*Petruzzelli G, Lubrano L, Cervelli S. 1987. Heavy metal uptake by wheat seedlings grown in fly ash-amended soils. *Water Air Soil Pollut* 32:389-395.
- Phan BC, Peyser YM, Reisler E, et al. 1997. Effect of complexes of ADP and phosphate analogs on the conformation of the Cys707-Cys697 region of myosin subfragment 1. *Eur J Biochem* 243:636-642.
- +\*PHS. 1953. *Health of workers in chromate producing industry: A study*. Washington, DC: U.S. Public Health Service. Publication no. 192.
- Piela Z, Kiec-Swierczynska M. 1998. [Skin reactivity in subjects sensitive to different concentrations of nickel, chromium, and cobalt.] *Med Pr* 49(5):457-463. (Polish)
- \*Pilliere F, Levy F, Renier A, et al. 1992. Induction of DNA-repair synthesis (UDS) in rat pleural mesothelial cells by urine of subjects exposed to genotoxic agents. *Clin Toxicol* 30(2):223-238.
- +\*Pippard EC, Acheson ED, Winter PD. 1985. Mortality of tanners. *Br J Ind Med* 42:285-287.
- \*Pi-Sunyer F, Offenbacher EG. 1984. Chromium. In: *Present knowledge in nutrition*. 5th ed. Washington, DC: The Nutrition Foundation, Inc., 571-586.
- \*Plantz MR, Fritz JS, Smith FG, et al. 1989. Separation of trace metal complexes for analysis of samples of high salt content by inductively coupled plasma mass spectrometry. *Anal Chem* 61:149-153.

## 9. REFERENCES

- \*Polprasert C, Charnpratheep K. 1989. Heavy metal removal in attached-growth waste stabilization ponds. *Water Research* 23(5):625-632.
- Popper HH, Grygar E, Ingolic E, et al. 1993. Cytotoxicity of chromium(III) and (VI) compounds. I. In vitro studies using different cell culture systems. *Inhal Toxicol* 5:345-369.
- Porter R, Jachymova M, Martasek P, et al. 2005. Reductive activation of Cr(VI) by nitric oxide synthase. *Chem Res Toxicol* 18(5):834-843.
- Post GB, Stern AH. 2006. Comments on article "Toxicity and carcinogenicity of chromium compounds in humans" by Costa and Klein. *Crit Rev Toxicol* 36(9):777-778.
- Pourahmad J, Rabiei M, Jokar F, et al. 2005. A comparison of hepatocyte cytotoxic mechanisms for chromate and arsenite. *Toxicology* 206(3):449-460.
- \*Powers WJ, Gad SC, Siino KM, et al. 1986. Effects of therapeutic agents on chromium-induced acute nephrotoxicity. In: Serrone DM, ed. *Chromium symposium 1986: An update*. Pittsburgh, PA: Industrial Health Foundation, Inc., 79-86.
- Prabakaran G, Mohan M, Vijayalaksmi N. 2005. Impact of chromium toxicity in dyeing industry workers. *Pollut Res* 24(3):625-628.
- \*Pratt PF, Myers CR. 1993. Enzymatic reduction of chromium(VI) by human hepatic microsomes. *Carcinogenesis* 14(10):2051-2057.
- \*Press RI, Geller J, Evans GW. 1990. The effect of chromium picolinate on serum cholesterol and apolipoprotein fractions in human subjects. *West J Med* 152:41-45.
- Preuss HG, Gondal JA, Bustos E, et al. 1995. Effects of chromium and guar on sugar-induced hypertension in rats. *Clin Nephrol* 44(3):170-177.
- Preuss HG, Grojec PL, Lieberman S, et al. 1997. Effects of different chromium compounds on blood pressure and lipid peroxidation in spontaneously hypertensive rats. *Clin Nephrol* 47(5):325-330.
- Preuss HG, Jarrell ST, Scheckenbach R, et al. 1998. Comparative effects of chromium, vanadium and gymnema sylvestre on sugar-induced blood pressure elevations in SHR. *J Am Coll Nutr* 17(2):116-123.
- Pritchard DE, Ceryak S, Ramsey KE, et al. 2005. Resistance to apoptosis, increased growth potential, and altered gene expression in cells that survived genotoxic hexavalent chromium [Cr(VI)] exposure. *Mol Cell Biochem* 279(1-2):169-181.
- Pritchard KA, Ackerman A, Kalyanaraman B. 2000. Chromium (VI) increases endothelial cell expression of ICAM-1 and decreases nitric oxide activity. *J Environ Pathol Toxicol Oncol* 19(3):251-260.
- \*Proctor DM, Fredrick MM, Scott PK, et al. 1998. The prevalence of chromium allergy in the United States and its implications for setting soil cleanup: A cost-effectiveness case study. *Regul Toxicol Pharmacol* 28:27-37.

## 9. REFERENCES

- \*Proctor DM, Otani JM, Finley BL, et al. 2002. Is hexavalent chromium carcinogenic via ingestion? A weight-of-evidence review. *J Toxicol Environ Health A* 65(10):701-746.
- Proctor DM, Panko JP, Liebig EW, et al. 2004. Estimating historical occupational exposure to airborne hexavalent chromium in a chromate production plant: 1940-1972. *J Occup Environ Hyg* 1(11):752-767.
- \*Pulido MD, Parrish AR. 2003. Metal-induced apoptosis: Mechanisms. *Mutat Res* 533:227-241.
- \*Qi W, Reiter RJ, Tan DX, et al. 2000. Chromium(III)-induced 8-hydroxydeoxyguanosine in DNA and its reduction by antioxidants: Comparative effects of melatonin, ascorbate, and vitamin E. (Comment in: *Environ Health Perspect* 109(6):A250). *Environ Health Perspect* 108(5):399-402.
- \*Qi WB, Zhu LZ. 1986. Spectrophotometric determination of chromium in waste water and soil. *Talanta* 33(8):694-696.
- \*Quievryn G, Goulart M, Messer J, et al. 2001. Reduction of Cr (VI) by cysteine: Significance in human lymphocytes and formation of DNA damage in reactions with variable reduction rates. *Mol Cell Biochem* 222(1-2):107-118.
- Quievryn G, Peterson E, Messer J, et al. 2003. Genotoxicity and mutagenicity of chromium(VI)/ascorbate-generated DNA adducts in human and bacterial cells. *Biochemistry* 42(4):1062-1070.
- Quievryn G, Peterson E, Zhitkovich A. 2004. Mutagenic DNA damage generated by chromium(VI) during its reductive activation with ascorbic acid. In: Cser MA, Sziklai Laszlo I, Etienne JC, et al., eds. *Metal ions in biology and medicine*. 8th ed. Paris: John Libbey Eurotext, 246-249.
- +\*Quinteros FA, Poliandri AHB, Machiavelli LI, et al. 2007. *In vivo* and *in vitro* effects of chromium VI on anterior pituitary hormone release and cell viability. *Toxicol Appl Pharmacol* 218:79-87.
- \*Radivojevic S, Cooper PA. 2008. Extraction of hexavalent chromium from chromated copper arsenate treated wood under alkaline conditions. *Environ Sci Technol* 42:3739-3744.
- Rafael AI, Almeida A, Parreira I, et al. 2006. An *in vivo* study on the effects of hexavalent chromium contaminated drinking water on rat livers. In: Alpoim MC, Morais PV, Santos MA, et al., eds. *Metal ions in biology and medicine*. Vol. 9. Paris: John Libbey Eurotext, 315-318.
- +\*Rafael AI, Almeida A, Santos P, et al. 2007. A role for transforming growth factor-beta apoptotic signaling pathway in liver injury induced by ingestion of water contaminated with high levels of Cr(VI). *Toxicol Appl Pharmacol* 224:163-173.
- \*Raffetto G, Parodi S, Parodi C, et al. 1977. Direct interaction with cellular targets as the mechanism for chromium carcinogenesis. *Tumori* 63:503-512.
- +Rafnsson V, Johannesdottir SG. 1986. Mortality among masons in Iceland. *Br J Ind Med* 43:522-525.
- Rafnsson V, Gunnarsdottir H, Kiilunen M. 1997. Risk of lung cancer among masons in Iceland. *Occup Environ Med* 54:184-188.
- \*Raithel HJ, Ebner G, Schaller KH. 1987. Problems in establishing norm values for nickel and chromium concentrations in human pulmonary tissue. *Am J Ind Med* 12:55-70.

## 9. REFERENCES

- Raithel HJ, Schaller KH, Kraus T, et al. 1993. Biomonitoring of nickel and chromium in human pulmonary tissue. *Int Arch Occup Environ Health* 65:S197-S200.
- Rajaram R, Balachandran UN, Ramasami T. 1995. Chromium(III)-induced abnormalities in human lymphocyte cell proliferation: Evidence for apoptosis. *Biochem Biophys Res Commun* 210(2):434-440.
- Ralph S, Petras M. 1998. Caged amphibian tadpoles and in situ genotoxicity monitoring of aquatic environments with the alkaline single cell gel electrophoresis (comet) assay. *Mutat Res* 413:235-250.
- Ramana VV, Sastry KS. Chromium toxicity in *Neurospora Crassa*. *J Inorg Biochem* 56:87-95.
- \*Ramelow GJ, Maples RS, Thompson RL, et al. 1987. Periphyton as monitors for heavy metal pollution in the Calcasieu River estuary. *Environ Pollut* 43:247-263.
- \*Ramelow GJ, Webre CL, Mueller CS, et al. 1989. Variations of heavy metals and arsenic in fish and other organisms from the Calcasieu River and Lake, Louisiana. *Arch Environ Contam Toxicol* 18:804-818.
- \*Randall JA, Gibson RS. 1987. Serum and urine chromium as indices of chromium status in tannery workers. *Proc Soc Exp Biol Med* 185:16-23.
- \*Randall JA, Gibson RS. 1989. Hair chromium as an index of chromium exposure to tannery workers. *Br J Ind Med* 46:171-175.
- \*Rao MV, Parekh SS, Chawla SL. 2006. Vitamin-E supplementation ameliorates chromium-and/or nickel induced oxidative stress *in vivo*. *J Health Sci* 52(2):142-147.
- \*Räsänen L, Sainio H, Lehto M, et al. 1991. Lymphocyte proliferation test as a diagnostic aid in chromium contact sensitivity. *Contact Dermatitis* 25:25-29.
- \*Rasmuson A. 1985. Mutagenic effects of some water-soluble metal compounds in a somatic eye-color test system in *Drosophila melanogaster*. *Mutat Res* 157:157-162.
- Rastogi SC, Pritzi G. 1996. Migration of some toxic metals from crayons and water colors. *Bull Environ Contam Toxicol* 56:527-533.
- Ratnasooriya WD, Balasuriya R. 1992. Effects of trivalent chromium on gestation in rat. *Med Sci Res* 20:475-476.
- \*Reddy KR, Chinthamreddy S. 1999. Electrokinetic remediation of heavy metal-contaminated soils under reducing environments. *Waste Manag* 19:269-282.
- \*\*\*Reichelderfer TE. 1968. Accidental death of an infant caused by ingestion of ammonium dichromate. *South Med J* 61:96-97.
- Rengasamy A, Kommineni C, Jones JA, et al. 1999. Effects of hard metal on nitric oxide pathways and airway reactivity to methacholine in rat lungs. *Toxicol Appl Pharmacol* 157:178-191.
- \*Reynolds M, Zhitkovich A. 2007. Cellular vitamin C increases chromate toxicity via a death program requiring mismatch repair but not p53. *Carcinogenesis* 28(7):1613-1620.

## 9. REFERENCES

- Reynolds M, Stoddard L, Bespalov I, et al. 2007. Ascorbate acts as a highly potent inducer of chromate mutagenesis and clastogenesis: Linkage to DNA breaks in G2 phase by mismatch repair. *Nucleic Acids Res* 35(2):465-476.
- \*Rhodes MC, Hebert CD, Herbert RA, et al. 2005. Absence of toxic effects in F344/N rats and B6C3F1 mice following subchronic administration of chromium picolinate monohydrate. *Food Chem Toxicol* 43(1):21-29.
- \*Richelmi P, Baldi C, Minoia C. 1984. Blood levels of hexavalent chromium in rats. *in vitro* and *in vivo* experiments. *Int J Environ Anal Chem* 17(3-4):181-186.
- \*Riedel GF, Sanders JG. 1998. Trace element speciation and behavior in the tidal Delaware River. *Estuaries* 21(1):78-90.
- \*Rifkin E, Gwinn P, Bouwer E. 2004. Chromium and sediment toxicity. *Environ Sci Technol* 38(14):267A-271A.
- \*Robson M. 2003. Methodologies for assessing exposures to metals: Human host factors. *Ecotoxicol Environ Saf* 56:104-109.
- \*Rodriguez-Arnaiz R, Martinez RFM. 1986. Genetic effects of potassium dichromate and chromium trioxide in *Drosophila melanogaster*. *Cytologia* 51:421-425.
- +\*Roe FJC, Carter RL. 1969. Chromium carcinogenesis: Calcium chromate as a potent carcinogen for the subcutaneous tissues of the rat. *Br J Cancer* 23:172-176.
- Roeback JR, Hla KM, Chambless LE, et al. 1991. Effects of chromium supplementation on serum high-density lipoprotein cholesterol levels in men taking beta-blockers: A randomized, controlled trial. *Ann Intern Med* 115:917-924.
- Rogers CE, Tomita AV, Trowbridge PR, et al. 1997. Hair analysis does not support hypothesized arsenic and chromium exposure from drinking water in Woburn, Massachusetts. *Environ Health Perspect* 105(10):1090-1097.
- \*Roginski EE, Mertz W. 1969. Effects of chromium(III) supplementation on glucose and amino acid metabolism in rats fed a low protein diet. *J Nutr* 97:525-530.
- Romaguera C, Vilaplana J. 1998. Contact dermatitis in children: 6 years experience (1992-1997). *Contact Dermatitis* 39:227-280.
- \*Rosas I, Belmont R, Baez A, et al. 1989. Some aspects of the environmental exposure to chromium residues in Mexico. *Water Air Soil Pollut* 48:463-476.
- Rosenman KD. 1990. Mortality among former chromium smelter workers (human). U.S. DHHS, Public Health Services, National Institutes of Health, National Institute for Occupational Safety and Health. CRISP Database, July 1990.
- +\*Rosenman KD, Stanbury M. 1996. Risk of lung cancer among former chromium smelter workers. *Am J Ind Med* 29:491-500.

## 9. REFERENCES

- \*Roto P, Sainio H, Reunala T, et al. 1996. Addition of ferrous sulfate to cement and risk of chromium dermatitis among construction workers. *Contact Dermatitis* 34:43-50.
- Routledge PA, Bialas MC, Babar I, et al. 1998. Blood arsenic and chromium concentrations after dermal exposure to tannalysing fluid and the use of DMPs. *J Toxicol Clin Toxicol* 36(5):494-495.
- +\*Royle H. 1975a. Toxicity of chromic acid in the chromium plating industry (1). *Environ Res* 10:39-53.
- +\*Royle H. 1975b. Toxicity of chromic acid in the chromium plating industry (2). *Environ Res* 10:141-163.
- \*Rubin MA, Miller JP, Ryan AS, et al. 1998. Acute and chronic resistive exercise increase urinary chromium excretion in men as measured with an enriched chromium stable isotope. *J Nutr* 128:73-78.
- Rudolf E, Cervinka M. 2006. The role of intracellular zinc in chromium(VI)-induced oxidative stress, DNA damage and apoptosis. *Chem Biol Interact* 162(3):212-227.
- Rudolf E, Cervinka M, Cerman J. 2005a. Zinc has ambiguous effects on chromium (VI)-induced oxidative stress and apoptosis. *J Trace Elem Med Biol* 18(3):251-260.
- Rudolf E, Cervinka M, Cerman J, et al. 2005b. Hexavalent chromium disrupts the actin cytoskeleton and induces mitochondria-dependent apoptosis in human dermal fibroblasts. *Toxicol In Vitro* 19(6):713-723.
- Rungby J, Ernst E. 1991. Experimentally induced lipid peroxidation after exposure to chromium, mercury or silver: Interactions with carbon tetrachloride. *Pharmacol Toxicol* 70:205-207.
- \*Russo P, Catassi A, Cesario A, et al. 2005. Molecular mechanisms of hexavalent chromium-induced apoptosis in human bronchoalveolar cells. *Am J Respir Cell Mol Biol* 33(6):589-600.
- Ryberg D, Alexander J. 1990. Mechanisms of chromium toxicity in mitochondria. *Chem Biol Interact* 75:141-151.
- Saha M, Sarkar SK, Bhattacharya B. 2006. Interspecific variation in heavy metal body concentrations in biota of Sunderban mangrove wetland, northeast India. *Environ Int* 32:203-207.
- \*Sahuquillo A, Rigol A, Rauret G. 2003. Overview of the use of leaching/extraction tests for risk assessment of trace metals in contaminated soils and sediments. *TrAC Trends Anal Chem* 22(3):152-159.
- Sakai K, Uchida R. 1992. Comparative effects of potassium dichromate on the mutagenicity of some nitrohydrocarbons and methylating agents. *Bull Environ Contam Toxicol* 48:541-548.
- \*Saleh FY, Parkerton TF, Lewis RV, et al. 1989. Kinetics of chromium transformations in the environment. *Sci Total Environ* 86:25-41.
- Salnikow K, Zhitkovich A. 2008. Genetic and epigenetic mechanisms in metal carcinogenesis and cocarcinogenesis: Nickel, arsenic, and chromium. *Chem Res Toxicol* 21(1):28-44.
- Salnikow K, Zhitkovich A, Costa M. 1992. Analysis of the binding sites of chromium to DNA and protein *in vitro* and in intact cells. *Carcinogenesis* 13(12):2341-2346.

## 9. REFERENCES

- \*Saltzman BE, Cholak J, Schafer LJ, et al. 1985. Concentration of six metals in the air of eight cities. *Environ Sci Technol* 19:328-333.
- Samet JM, Graves LM, Quay J, et al. 1998. Activation of MAPKs in human bronchial epithelial cells exposed to metals. *Am J Physiol* 275(3):L551-L558.
- +\*Samitz MH. 1970. Ascorbic acid in the prevention and treatment of toxic effects from chromates. *Acta Derm Venereol* 50:59-64.
- +\*Samitz MH, Epstein E. 1962. Experimental cutaneous chrome ulcers in guinea pigs. *Arch Environ Health* 5:69-74.
- +\*Samitz MH, Shrager J. 1966. Patch test reactions to hexavalent and trivalent chromium compounds. *Arch Dermatol* 94:304-306.
- +Samitz MH, Gross S, Katz S. 1962. Inactivation of chromium ion in allergic eczematous dermatitis. *J Invest Dermatol* 38:5-12.
- +Sander JK, Camp CD. 1939. Chromium poisoning in infancy. *Am J Med Sci* 198:551-554.
- Sanderson CJ. 1976. The uptake and retention of chromium by cells. *Transplantation* 21:526-529.
- \*Saner G, Yuzbasiyan V, Cigdem S. 1984. Hair chromium concentration and chromium excretion in tannery workers. *Br J Ind Med* 41:263-266.
- Saraswathy CP, Usharani MV. 2007. Monitoring of cellular enzymes in the serum of electroplating workers at Coimbatore. *J Environ Biol* 28(2):287-290.
- +Sargent T, Lim TH, Jenson R. 1979. Reduced chromium retention in patients with hemochromatosis, a possible basis of hemochromatotic diabetes. *Metabolism* 28:70-79.
- \*Sarkar D, Sharma A, Talukder G. 1993. Differential protection of chlorophyllin against clastogenic effects of chromium and chlordane in mouse bone marrow in vivo. *Mutat Res* 301:33-38.
- \*Sarto F, Levis AG, Paulon C. 1980. Clastogenic activity of hexavalent and trivalent chromium in cultured human lymphocytes. *Caryologia* 33:239-250.
- \*Sarto F, Cominato I, Bianchi V, et al. 1982. Increased incidence of chromosomal aberrations and sister chromatid exchanges in workers exposed to chromic acid (CrO<sub>3</sub>) in electroplating factories. *Carcinogenesis* 3(9):1011-1016.
- +\*Saryan LA, Reedy M. 1988. Chromium determinations in a case of chromic acid ingestion. *J Anal Toxicol* 12:162-164.
- +\*Sassi C. 1956. [Occupational pathology in a chromate plant.] *Med Lav* 47(5):314-327. (Italian)
- Sastre J, Fernandez-Nieto M, Maranon F, et al. 2001. Allergenic cross-reactivity between nickel and chromium salts in electroplating-induced asthma. *J Allergy Clin Immunol* 108(4):650-651.



## 9. REFERENCES

- \*Sata F, Araki S, Murata K, et al. 1998. Behavior of heavy metals in human urine and blood following calcium disodium ethylenediamine tetraacetate injection: Observations in metal workers. *J Toxicol Environ Health, A* 54:167-178.
- \*Sathwara NG, Patel KG, Vyas JB, et al. 2007. Chromium exposure study in chemical based industry. *J Environ Biol* 28(2):405-408.
- Sato H, Murai K, Kanda T, et al. 2003. Association of chromium exposure with multiple primary cancers in the nasal cavity. *Auris Nasus Larynx* 30(1):93-96.
- +\*Sato K, Fukuda Y, Torrii K, et al. 1981. Epidemiological study of workers engaged in the manufacture of chromium compounds. *J Occup Med* 23(12):835-838.
- +\*Sato N, Fukuda S, Takizawa M, et al. 1994. Chromium-induced carcinoma in the nasal region. A report of four cases. *Rhinology* 32:47-50.
- Satsuma S, Scudamore RA, Cooke TDV, et al. 1993. Toxicity of complement for chondrocytes. A possible source of cartilage degradation in inflammatory arthritis. *Rheumatol Int* 13:71-75.
- Savery LC, Grlickova-Duzevik E, Wise SS, et al. 2007. Role of the Fancg gene in protecting cells from particulate chromate-induced chromosome instability. *Mutat Res* 626(1-2):120-127.
- \*Sawatari K. 1986. Sampling filters and dissolution methods for differential determination of water-soluble chromium(VI) and chromium(III) in particulate substances. *Ind Health* 24:111-116.
- +\*Saxena DK, Murthy RC, Jain VK, et al. 1990a. Fetoplacental-maternal uptake of hexavalent chromium administered orally in rats and mice. *Bull Environ Contam Toxicol* 45:430-435.
- Saxena DK, Murthy RC, Lal B, et al. 1990b. Effect of hexavalent chromium on testicular maturation in the rat. *Reprod Toxicol* 4:223-228.
- +\*Sayato Y, Nakamuro K, Matsui S, et al. 1980. Metabolic fate of chromium compounds. I. Comparative behavior of chromium in rat administered with  $\text{Na}_2^{51}\text{CrO}_4$  and  $^{51}\text{CrCl}_3$ . *J Pharm Dyn* 3:17-23.
- \*Schaller H, Neeb R. 1987. Gas-chromatographic elemental analysis via di(trifluoroethyl)dithiocarbamate-3 chelates X. Capillary gas chromatography at the pg-level determination of Co and Cr[VI] besides Cr[III] in river water. *Fresenius Z Analytical Chemistry* 327:170-174.
- Schmid M, Zimmermann S, Krug HG, et al. 2007. Influence of platinum, palladium and rhodium as compared with cadmium, nickel and chromium on cell viability and oxidative stress in human bronchial epithelial cells. *Environ Int* 33(3):385-390.
- \*Schmidt JA, Andren AW. 1984. Deposition of airborne metals into the Great Lakes: An evaluation of past and present estimates. *Adv Environ Sci Technol* 14:81-103.
- Schnekenburger M, Talaska G, Puga A. 2007. Chromium cross-links histone deacetylase 1-DNA methyltransferase 1 complexes to chromatin, inhibiting histone-remodeling marks critical for transcriptional activation. *Mol Cell Biol* 27(20):7089-7101.

## 9. REFERENCES

- \*Schonwald S. 2004. Chromium. In: Dart RC, ed. Medical toxicology. 3rd ed. Philadelphia, PA: Lippicott Williams & Wilkins, 415-1417.
- +\*Schroeder HA, Balassa JJ, Tipton IH. 1962. Abnormal trace metals in man — Chromium. *J Chron Dis* 15:941-964.
- +\*Schroeder HA, Balassa JJ, Vinton WH. 1964. Chromium, lead, cadmium, nickel and titanium in mice: Effect on mortality, tumors and tissue levels. *J Nutr* 83:239-250.
- +\*Schroeder HA, Balassa JJ, Vinton WH. 1965. Chromium, cadmium and lead in rats: Effects on life span, tumors and tissue levels. *J Nutr* 86:51-66.
- +Schroeder HA, Vinton WH, Balassa JJ. 1963. Effect of chromium, cadmium and other trace metals on the growth and survival of mice. *J Nutr* 80:39-47.
- \*Schroeder WH, Dobson M, Kane DM, et al. 1987. Toxic trace elements associated with airborne particulate matter: A review. *J Air Pollut Control Assoc* 37(11):1267-1285.
- \*Schuhmacher M, Domingo JL, Llobet JM, et al. 1993. Chromium, copper, and zinc concentrations in edible vegetables grown in Tarragona Province, Spain. *Bull Environ Contam Toxicol* 50:514-521.
- Schwarz Y, Kivity S, Fischbein A, et al. 1998. Evaluation of workers exposed to dust containing hard metals and aluminum oxide. *Am J Ind Med* 34:177-182.
- 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. 2007. Effects of vanadium(V) and/or chromium(III) on L-ascorbic acid and glutathione as well as iron, zinc, and copper levels in rat liver and kidney. *J Toxicol Environ Health A* 70(8):696-704.
- \*Scott PK, Proctor DM. 1997. Evaluation of 10% minimum elicitation threshold for Cr(VI)-induced allergic contact dermatitis using benchmark dose methods. *J Soil Contam* 6(6):707-731.
- \*Scott PK, Finley BL, Harris MA, et al. 1997a. Background air concentrations of Cr(VI) in Hudson County, New Jersey: Implications for setting health-based standards for Cr(VI) in soil. *J Air Waste Manage Assoc* 47:592-600.
- \*Scott PK, Finley BL, Sung HM, et al. 1997b. Identification of an accurate soil suspension/dispersion modeling method for use in estimating health-based soil cleanup levels of hexavalent chromium in chromite ore processing residues. *J Air Waste Manage Assoc* 47:753-765.
- Seaborn CD, Cheng N, Adeleye B, et al. 1994. Chromium and chronic ascorbic acid depletion effects on tissue ascorbate, manganese, and <sup>14</sup>C retention from <sup>14</sup>C-ascorbate in guinea pigs. *Biol Trace Elem Res* 41:279-294.
- \*Sedman RM, Beaumont J, McDonald TA, et al. 2006. Review of the evidence regarding the carcinogenicity of hexavalent chromium in drinking water. *J Environ Sci Health Part C Environ Carcinogen Rev* 24(1):155-182.

## 9. REFERENCES

Seel EA, Zaebs DD, Hein MJ, et al. 2007. Inter-rater agreement for a retrospective exposure assessment of asbestos, chromium, nickel and welding fumes in a study of lung cancer and ionizing radiation. *Ann Occup Hyg* 51(7):601-610.

\*Seigneur C, Constantinos E. 1995. Chemical kinetic mechanism for atmospheric chromium. *Environ Sci Technol* 29:222-231.

Seldén AI, Persson B, Bornberger-Dankvardt SI, et al. 1995. Exposure to cobalt chromium dust and lung disorders in dental technicians. *Thorax* 50:769-772.

Sen P, Conway K, Costa M. 1987. Comparison of the localization of chromosome damage induced by calcium chromate and nickel compounds. *Cancer Res* 47:2142-2147.

\*Seoane AI, Dulout FN. 1999. Contribution to the validation of the anaphase-telophase test: Aneugenic and clastogenic effects of cadmium sulfate, potassium dichromate and nickel chloride in Chinese hamster ovary cells. *Genet Mol Biol* 22(4):551-555.

Seoane AI, Dulout FN. 2001. Genotoxic ability of cadmium, chromium and nickel salts studied by kinetochore staining in the cytokinesis-blocked micronucleus assay. *Mutat Res* 490(2):99-106.

\*Setchell BP, Waites GMH. 1975. The blood testis barrier. In: Creep RO, Astwood EB, eds. *Handbook of physiology: Endocrinology V*. Washington, DC: American Physiological Society. 143-172.

\*Shah M, Palmer IR. 2002. An ultrastructural study of chronic chromate hand dermatitis. *Acta Derm Venereol* 82(4):254-259.

\*Shanker AK, Cervantes C, Loza-Tavera H, et al. 2005. Chromium toxicity in plants. *Environ Int* 31: 739-753.

+\*Shara M, Kincaid AE, Limpach AL, et al. 2007. Long-term safety evaluation of a novel oxygen-coordinated niacin-bound chromium (III) complex. *J Inorg Biochem* 101(7):1059-1069.

+\*Shara M, Yasmin T, Kincaid AE, et al. 2005. Safety and toxicological evaluation of a novel niacin-bound chromium (III) complex. *J Inorg Biochem* 99(11):2161-2813.

Sharma VK, Chakrabarti A. 1998. Common contact sensitizers in Chandigarh, India. *Contact Dermatitis* 38:127-131.

+\*Sharma BK, Singhal PC, Chugh KS. 1978. Intravascular haemolysis and acute renal failure following potassium dichromate poisoning. *Postgrad Med J* 54:414-415.

Sheehan HE. 1995. An urban community faces an environmental hazard: "Let them eat chromium"? *Mt Sinai J Med* 62(5):332-338.

\*Sheehan P, Ricks R, Ripple S, et al. 1992. Field evaluation of a sampling and analytical method for environmental levels of airborne hexavalent chromium. *Am Ind Hyg Assoc J* 53(1):57-68.

Sheehan PJ, Meyer DM, Sauer MM, et al. 1991. Assessment of the human health risks posed by exposure to chromium-contaminated soils. *J Toxicol Environ Health* 32:161-201.

## 9. REFERENCES

- +\*Sheffet A, Thind I, Miller AM, et al. 1982. Cancer mortality in a pigment plant utilizing lead and zinc chromates. *Arch Environ Health* 37:44-52.
- \*Shelnutt SR, Goad P, Belsito DV. 2007. Dermatological toxicity of hexavalent chromium. *Crit Rev Toxicol* 37(5):375-387.
- \*Sheppard MI, Thibault DH. 1991. A four-year mobility study of selected trace elements and heavy metals. *J Environ Qual* 20:101-114.
- \*Sheppard SC, Evenden WG, Schwartz WJ. 1995. Heavy metals in the environment: Ingested soil: Bioavailability of sorbed lead, cadmium, cesium, iodine, and mercury. *J Environ Qual* 24:498-505.
- \*Sheridan PJ, Zoller WH. 1989. Elemental composition of particulate material sampled from the Arctic haze aerosol. *J Atmospher Chem* 9:363-381.
- Shi X, Chiu A, Chen CT, et al. 1999a. Reduction of chromium(VI) and its relationship to carcinogenesis. *J Toxicol Environ Health* 2(part B):87-104.
- \*Shi X, Dalal NS, Kasprzak KS. 1993. Generation of free radicals from hydrogen peroxide and lipid hydroperoxides in the presence of Cr(III). *Arch Biochem Biophys* 302(1):294-291.
- Shi X, Ding M, Ye J, et al. 1999b. Cr(VI) causes activation of nuclear transcription factor-KB, DNA strand breaks and dG hydroxylation via free radical reactions. *J Inorg Biochem* 75:37-44.
- \*Shi X, Dong Z, Dalal NS, et al. 1994. Chromate-mediated free radical generation from cysteine, penicillamine, hydrogen peroxide, and lipid hydroperoxides. *Biochim Biophys Acta* 1226:65-72.
- \*Shi X, Leonard SS, Liu KJ, et al. 1998. Cr(III)-mediated hydroxyl radical generation via Haber-Weiss cycle. *J Inorg Biochem* 69:263-268.
- Shiao YH, Crawford EB, Anderson LM, et al. 2005. Allele-specific germ cell epimutation in the spacer promoter of the 45S ribosomal RNA gene after Cr(III) exposure. *Toxicol Appl Pharmacol* 205:290-296.
- +Shimkin MB, Leiter J. 1940. Induced pulmonary tumors in mice. III. The role of chronic irritation in the production of pulmonary tumors in strain A mice. *J Natl Cancer Inst* 1:241-254.
- \*Shindo Y, Toyoda Y, Kawamura K, et al. 1989. Micronucleus test with potassium chromate(VI) administered intraperitoneally and orally to mice. *Mutat Res* 223:403-406.
- \*Shmitova LA. 1978. [The course of pregnancy in women engaged in the production of chromium and its compounds.] *Vliy Prof Fakt Spet Funk Zhensk Organ, Sverd* 108-111. (Russian)
- +\*Shmitova LA. 1980. [Content of hexavalent chromium in the biological substrates of pregnant women and women in the immediate post-natal period engaged in the manufacture of chromium compounds.] *Gig Trud Prof Zabol* 2:33-35. (Russian)
- Shrivastava R, Kannan A, Upreti RK, et al. 2005. Effects of chromium on the resident gut bacteria of rat. *Toxicol Mech Methods* 15(3):211-218.
- \*Shrivastava R, Upreti RK, Seth PK, et al. 2002. Effects of chromium on the immune system. *FEMS Immunol Med Microbiol* 34:1-7.

## 9. REFERENCES

- +\*Shubochkin LN, Pokhodzie YI. 1980. Toxic properties of strontium chromate. *Gig Sanit* 45:76-77.
- Shumilla JA, Barchowsky A. 1999. Inhibition of protein synthesis by chromium(VI) differentially affects expression of urokinase and its receptor in human type II pneumocytes. *Toxicol Appl Pharmacol* 158:288-295.
- Shumilla JA, Broderick RJ, Wang Y, et al. 1999. Chromium(VI) inhibits the transcriptional activity of nuclear factor- $\kappa$ B by decreasing the interaction of p65 with cAMP-responsive element-binding protein-binding protein. *J Biol Chem* 274(51):36207-36212.
- \*Shumilla JA, Wetterhahn KE, Barchowsky A. 1998. Inhibition of NF- $\kappa$ B binding to DNA by chromium, cadmium, mercury, zinc, and arsenite *in vitro*: Evidence of a thiol mechanism. *Arch Biochem Biophys* 349(2):356-362.
- Shupack SI. 1991. The chemistry of chromium and some resulting analytical problems. *Environ Health Perspect* 92:7-11.
- +\*Siegel NJ, Gaudio KM, Katz LA, et al. 1984. Beneficial effect of thyroxin on recovery from toxic acute renal failure. *Kidney Int* 25:906-911.
- +\*Silverstein M, Mirer F, Kotelchusk D, et al. 1981. Mortality among workers in a die-casting and electroplating plant. *Scand J Work Environ Health* 7(suppl 4):156-165.
- \*Simonoff M, Llabador Y, Hamon C, et al. 1984. Extraction procedure for the determination of trace chromium in plasma by proton-induced x-ray emission spectrometry. *Anal Chem* 56:454-457.
- +\*Simpson JR, Gibson RS. 1992. Hair, serum, and urine chromium concentrations in former employees of the leather tanning industry. *Biol Trace Elem Res* 32:155-159.
- \*Singh I. 1983. Induction of reverse mutation and mitotic gene conversion by some metal compounds in *Saccharomyces cerevisiae*. *Mutat Res* 117:149-152.
- \*Singh J, Carlisle DL, Pritchard DE, et al. 1998a. Chromium-induced genotoxicity and apoptosis: Relationship to chromium carcinogenesis (review). *Oncology Reports* 5:1307-1318.
- \*Singh J, McLean JA, Pritchard DE, et al. 1998b. Sensitive quantitation of chromium-DNA adducts by inductively coupled plasma mass spectrometry with a direct injection high-efficiency nebulizer. *Toxicological Sciences* 46:260-265.
- \*Singh J, Pritchard DE, Carlisle DL, et al. 1999. Internalization of carcinogenic lead chromate particles by cultured normal human lung epithelial cells: Formation of intracellular lead-inclusion bodies and induction of apoptosis. *Toxicol Appl Pharmacol* 161:240-248.
- +\*Sipowicz MA, Anderson LM, Utermahlen WE, et al. 1997. Uptake and tissue distribution of chromium(III) in mice after a single intraperitoneal or subcutaneous administration. *Toxicol Lett* 93:9-14.
- Sirover MA, Loeb LA. 1976. Infidelity of DNA synthesis *in vitro*: Screening for potential metal mutagens or carcinogens. *Science* 194:1434-1436.

## 9. REFERENCES

- +Sjogren B. 1980. A retrospective cohort study of mortality among stainless steel welders. *Scand J Work Environ Health* 6:197-200.
- +\*Sjogren B, Gustavsson A, Hedstrom L. 1987. Mortality in two cohorts of welders exposed to high- and low-levels of hexavalent chromium. *Scand J Work Environ Health* 13:247-251.
- \*Sjogren B, Hedstrom L, Ulfvarson U. 1983. Urine chromium as an estimator of air exposure to stainless steel welding fumes. *Int Arch Occup Environ Health* 51:347-354.
- +\*Sluis-Cremer GK, du Toit RSJ. 1968. Pneumoconiosis in chromite miners in South Africa. *Br J Ind Med* 25:63-67.
- Smailyte G, Kurtinaitis J, Andersen A. 2004. Mortality and cancer incidence among Lithuanian cement producing workers. *Occup Environ Med* 61:529-534.
- Smith AH. 2008. Hexavalent chromium, yellow water, and cancer: A convoluted saga. (Comment on: *Epidemiology* 19(1):12-23). *Epidemiology* 19(1):24-26.
- +\*Smith AR. 1931. Chrome poisoning with manifestation of sensitization. *J Am Med Assoc* 97(2):95-98.
- \*Smith, RA, Alexander RB, Wolman MG. 1987. Water-quality trends in the nation's rivers. *Science* 235:1607-1615.
- +\*Smyth HF, Carpenter CP, Weil CS, et al. 1969. Range finding toxicity data: List VII. *Am Ind Hyg Assoc J* 30:470-476.
- \*Snow ET. 1991. A possible role of chromium(III) in genotoxicity. *Environ Health Perspect* 92:75-81.
- \*Snow ET, Xu SL. 1989. Effects of chromium(III) on DNA replication in vitro. *Biological Trace Element Res* 21:61-71.
- +\*Snyder CA, Valle CD. 1991. Immune function assays as indicators of chromate exposure. *Environ Health Perspect* 92:83-86.
- +Snyder CA, Sellakumar A, Waterman S. 1997. An assessment of the tumorigenic properties of a Hudson County soil sample heavily contaminated with hexavalent chromium. *Arch Environ Health* 52(3):220-226.
- +\*Snyder CA, Udasin I, Waterman SJ, et al. 1996. Reduced IL-6 levels among individuals in Hudson County, New Jersey, an area contaminated with chromium. *Arch Environ Health* 51(1):26-28.
- Soko L, Cukrowska E, Chimuka L. 2002. Extraction and preconcentration of Cr(VI) from urine using supported liquid membrane. *Anal Chim Acta* 474(1-2):59-68.
- Solano-Serena F, Marchal R, Ropars M, et al. 1999. Biodegradation of gasoline: Kinetics, mass balance and fate of individual hydrocarbons. *J Appl Microbiol* 86(6):1008-1016.
- +\*Sorahan T, Burges DCL, Hamilton L, et al. 1998. Lung cancer mortality in nickel/chromium platers, 1946-95. *Occup Environ Med* 55:236-242.

## 9. REFERENCES

- +\*Sorahan T, Burges DCL, Waterhouse JAH. 1987. A mortality study of nickel/chromium platers. *Br J Ind Med* 44:250-258.
- +Sparrow S, Magos L, Snowden R. 1988. The effect of sodium chromate pretreatment on mercuric chloride-induced nephrotoxicity. *Arch Toxicol* 61:440-443.
- Spengler JD, Koutrakis P, Dockery DW, et al. 1996. Health effects of acid aerosols on North American children: Air pollution exposures. *Environ Health Perspect* 104(5):492-499.
- Spicer MT, Stoecker BJ, Chen T, et al. 1998. Maternal and fetal insulin-like growth factor system and embryonic survival during pregnancy in rats: Interaction between dietary chromium and diabetes. *J Nutr* 128:2341-2347.
- \*Spruit D, van Neer FCJ. 1966. Penetration of Cr(III) and Cr(VI). *Dermatologica* 132:179-182.
- \*SRI. 1997. Directory of chemical producers: United States of America. Menlo Park, CA: Stanford Research Institute International, 518-519.
- \*SRI. 2007. 2007 Directory of chemical producers. Menlo Park, CA: SRI Consulting. Access Intelligence, LLC., 526-527.
- +Srivastava L, Jain VK, Kachru DN, et al. 1985. Comparative toxicity of trivalent and hexavalent chromium(V): Enzymatic alterations in rat liver and kidneys. *Ind Health* 23:89-94.
- Srivastava S, Shanker K, Prakash S, et al. 1999. Bioavailability of chromium: An interactive aspect. *J Environ Biol* 20(1):49-54.
- \*Stackhouse RA, Benson WH. 1989. The effect of humic acid on the toxicity and bioavailability of trivalent chromium. *Ecotoxicol Environ Safety* 17:105-111.
- Stackpole MM, Wise SS, Goodale BC, et al. 2007. Homologous recombination repair protects against particulate chromate-induced chromosome instability in Chinese hamster cells. *Mutat Res* 625(1-2):145-154.
- State of California. 1991. Memorandum from Lauren Zeise, Reproductive and Cancer Hazard Assessment Section to Steven A. Book, Health Hazard Assessment Division. Department of Health Services, State of California, June 11, 1991.
- \*Stearns DM. 2000. Is chromium a trace essential metal? *Biofactors* 11(3):149-162.
- Stearns DM, Wetterhahn KE. 1997. Intermediates produced in the reaction of chromium(VI) with dehydroascorbate cause single-strand breaks in plasmid DNA. *Chem Res Toxicol* 10:271-278.
- +\*Stearns DM, Belbruno JJ, Wetterhaun KE. 1995a. A prediction of chromium(III) accumulation in humans from chromium dietary supplements. *FASEB J* 9:1650-1657.
- \*Stearns DM, Courtney KD, Giangrande PH, et al. 1994. Chromium (VI) reduction by ascorbate: Role of reactive intermediates in DNA damage in vitro. *Environ Health Perspect* 102:21-25.

## 9. REFERENCES

- \*Stearns DM, Silveira SM, Wolf KK, et al. 2002. Chromium(III) tris(picolinate) is mutagenic at the hypoxanthine (guanine) phosphoribosyltransferase locus in Chinese hamster ovary cells. *Mutat Res* 513(1-2):135-142.
- \*Stearns DM, Wise JP, Patierno SR, Wetterhahn KE. 1995b. Chromium(III) picolonate produces chromosome damage in Chinese hamster ovary cells. *FASEB J* 9:1643-1649.
- \*Steenland K, Loomis D, Shy C, et al. 1996. Review of occupational lung carcinogens. *Am J Ind Med* 29:474-490.
- +\*Steffee CH, Baetjer AM. 1965. Histopathologic effects of chromate chemicals. *Arch Environ Health* 11:66-75.
- +\*Steinhoff D, Gad SC, Hatfield GK, et al. 1986. Carcinogenicity studies with sodium dichromate in rats. *Exp Pathol* 30:129-141.
- \*Stella M, Montaldi A, Rossi R, et al. 1982. Clastogenic effects of chromium on human lymphocytes in vitro and in vivo. *Mutat Res* 101:151-164.
- +\*Stereckova NP, Zeleneva NI, Solomina SN et al. 1978. [Gastric pathology in the workers of chromium salts industries.] *Gig Trud Prof Zabol* 3:19-23. (Russian)
- +\*Stern AH, Bagdon RE, Hazen RE, et al. 1993. Risk assessment of the allergic dermatitis potential of environmental exposure to hexavalent chromium. *J Toxicol Environ Health* 40:613-641.
- Stern AH, Fagliano JA, Savrin JE, et al. 1998. The association of chromium in household dust with urinary chromium in residences adjacent to chromate production waste sites. *Environ Health Perspect* 106(12):833-839.
- +\*Stern FB, Beaumont JJ, Halperin WE, et al. 1987. Mortality of chrome leather tannery workers and chemical exposures in tanneries. *Scand J Work Environ Health* 13:108-117.
- Stern RM. 1981. Process-dependent risk of delayed health effects for welders. *Environ Health Perspect* 41:235-253.
- \*Stern RM. 1982. Chromium compounds: Production and occupational exposure. In: Langard S, ed. *Biological and environmental aspects of chromium*. New York, NY: Elsevier Biomedical Press, 5-47.
- \*Stern RM, Thomsen E, Furst A. 1984. Cr(VI) and other metallic mutagens in fly ash and welding fumes. *Toxicol Environ Chem* 8:95-108.
- Stift A, Friedl J, Laengle F. 1998. Liver transplantation for potassium dichromate poisoning. *N Engl J Med* 338(11):766-767.
- \*Stilwell DE, Gorny KD. 1997. Contamination of soil with copper, chromium, and arsenic under decks built from pressure treated wood. *Bull Environ Contam Toxicol* 58:22-29.
- Stohs SJ, Bagchi D, Hassoun E, et al. 2000. Oxidative mechanisms in the toxicity of chromium and cadmium ions. *J Environ Pathol Toxicol Oncol* 19(3):201-213.



## 9. REFERENCES

- Stohs SJ, Bagchi D, Hassoun E, et al. 2001. Oxidative mechanisms in the toxicity of chromium and cadmium ions. *J Environ Pathol Toxicol Oncol* 20(2):77-88.
- Stokes DL, Lacapare JJ. 1994. Conformation of Ca<sup>2+</sup>-ATPase in two crystal forms. *J Biol Chem* 269(15):11606-11613.
- \*Stokinger HE. 1981. Chromium, Cr. In: Clayton GD, Clayton FE, eds. *Patty's industrial hygiene and toxicology*. Vol. IIA, 3rd ed. New York, NY: John Wiley & Sons, 1589-1605.
- \*Stridsklev IC, Schaller K, Langard S. 2004. Monitoring of chromium and nickel in biological fluids of stainless steel welders using the flux-cored-wire (FCW) welding method. *Int Arch Occup Environ Health* 77(8):587-591.
- Stridsklev IC, Schaller K, Langard S. 2007. Monitoring of chromium and nickel in biological fluids of grinders grinding stainless steel. *Int Arch Occup Environ Health* 80(5):450-454.
- Striffler JS, Law JS, Polansky MM, et al. 1995. Chromium improves insulin response to glucose in rats. *Metabolism* 44(10):1314-1320.
- Štupar J, Dolinšek F. 1996. Determination of chromium, manganese, lead and cadmium in biological samples including hair using direct electrothermal atomic absorption spectrometry. *Spectrochim Acta Part B* 51:665-683.
- Stupar J, Vrtovec M, Kocijancic A, et al. 1999. Chromium status of tannery workers in relation to metabolic disorders. *J Appl Toxicol* 19:437-446.
- Subiyatno A, Mowat DN, Yang WZ. 1996. Metabolite and hormonal responses to glucose or propionate infusions in periparturient dairy cows supplemented with chromium. *J Dairy Sci* 79:1436-1445.
- +\*Subramanian S, Rajendiran G, Sekhar P, et al. 2006. Reproductive toxicity of chromium in adult bonnet monkeys (*Macaca radiata* Geoffrey). Reversible oxidative stress in the semen. *Toxicol Appl Pharmacol* 215:237-249.
- Sugden KD, Stearns DM. 2000. The role of chromium(V) in the mechanism of chromate-induced oxidative DNA damage and cancer. *J Environ Pathol Toxicol Oncol* 19(3):215-230.
- Sugden KD, Wetterhahn KE. 1997. Direct and hydrogen peroxide-induced chromium(V) oxidation of deoxyribose in single-stranded and double-stranded calf thymus DNA. *Chem Res Toxicol* 10:1397-1406.
- \*Sugden KD, Burris RB, Rogers SJ. 1990. An oxygen dependence in chromium mutagenesis. *Mutat Res* 244:239-244.
- Sugden KD, Geer RD, Rogers SJ. 1992. Oxygen radical-mediated DNA damage by redox-active Cr(III) complexes. *Biochemistry* 31:11626-11631.
- Sugden KD, Rigby KM, Martin BD. 2004. Oxidative activation of the human carcinogen chromate by arsenite: A model for synergistic metal activation leading to oxidative DNA damage. *Toxicol In Vitro* 18(6):741-748.
- Sugiyama M. 1989. Effects of vitamin E and vitamin B<sub>2</sub> on chromate-induced DNA lesions. *Biol Trace Elem Res* 21:399-404.

## 9. REFERENCES

- \*Sugiyama M. 1991. Effects of vitamins on chromium(VI)-induced damage. *Environ Health Perspect* 92:63-70.
- \*Sugiyama M, Tsuzuki K. 1994. Effect of glutathione depletion on formation of paramagnetic chromium in Chinese hamster V-79 cells. *FEBS Lett* 341:273-276.
- Sugiyama M, Ando A, Nakao K, et al. 1989. Influence of vitamin B<sub>2</sub> on formation of chromium(V), alkali-labile sites, and lethality of sodium chromate(VI) in Chinese hamster V-70 cells. *Cancer Res* 49:6180-6184.
- Sugiyama M, Ando A, Ogura R. 1989. Effect of vitamin E on survival, glutathione reductase and formation of chromium(V) in Chinese hamster V-79 cells treated with sodium chromate(VI). *Carcinogenesis* 10:737-741.
- \*Sugiyama M, Patierno SR, Cantoni O, et al. 1986a. Characterization of DNA lesions induced by CaCrO<sub>4</sub> in synchronous and asynchronous cultured mammalian cells. *Mol Pharmacol* 29:606-613.
- Sugiyama M, Tsuzuki K, Haramaki N. 1993. Influence of o-phenanthroline on DNA single-strand breaks, alkali-labile sites, glutathione reductase, and formation of chromium(V) in Chinese hamster V-79 cells treated with sodium chromate(VI). *Arch Biochem Biophys* 305(2):261-266.
- Sugiyama M, Wang XW, Costa M. 1986b. Comparison of DNA lesions and cytotoxicity induced by calcium chromate in human, mouse, and hamster cell lines. *Cancer Res* 46:4547-4551.
- +\*Sullivan MF, Miller BM, Goebel JC. 1984. Gastrointestinal absorption of metals (<sup>51</sup>Cr, <sup>65</sup>Zn, <sup>95m</sup>Tc, <sup>109</sup>Cd, <sup>113</sup>Sn, <sup>147</sup>Pm, and <sup>238</sup>Pu) by rats and swine. *Environ Res* 35:439-453.
- Sullivan PA, Eisen EA, Woskie SR, et al. 1998. Mortality studies of metalworking fluid exposure in the automobile industry: VI. A case-control study of esophageal cancer. *Am J Ind Med* 34:36-48.
- Sunderman FW. 1976. A review of the carcinogenicities of nickel, chromium and arsenic compounds in man and animals. *Prev Med* 5:279-294.
- \*Sunderman FW, Hopfer SM, Swift T, et al. 1989. Cobalt, chromium, and nickel concentrations in body fluids of patients with porous-coated knee or hip prostheses. *J Orthop Res* 7:307-315.
- Susa N, Ueno S, Furukawa Y, et al. 1997a. Potent protective effect of melatonin on chromium(VI)-induced DNA single-strand breaks, cytotoxicity, and lipid peroxidation in primary cultures of rat hepatocytes. *Toxicol Appl Pharmacol* 144:377-384.
- Susa N, Ueno S, Furukawa Y, et al. 1997b. Protective effect of deferoxamine on chromium(VI)-induced DNA single-strand breaks, cytotoxicity, and lipid peroxidation in primary cultures of rat hepatocytes. *Arch Toxicol* 71:345-350.
- Susa N, Ueno S, Furukawa Y, et al. 1998. Protective effect of diethyldithiocarbamate pretreatment on chromium(VI)-induced cytotoxicity, and lipid peroxidation in primary cultures of rat hepatocytes. *J Vet Med Sci* 60(1):71-76.
- Suzuki Y. 1988. Reduction of hexavalent chromium by ascorbic acid in rat lung lavage fluid. *Arch Toxicol* 62:116-122.

## 9. REFERENCES

- Suzuki Y. 1990. Synergism of ascorbic acid and glutathione in the reduction of hexavalent chromium in vitro. *Ind Health* 28:9-19.
- +\*Suzuki Y, Fukuda K. 1990. Reduction of hexavalent chromium by ascorbic acid and glutathione with special reference to the rat lung. *Arch Toxicol* 64:169-176.
- \*Suzuki Y, Serita F. 1985. Simultaneous determination of water-soluble trivalent and hexavalent chromium by anion exchange high-pressure liquid chromatography. *Ind Health* 23:207-220.
- +\*Suzuki Y, Homma K, Minami M, et al. 1984. Distribution of chromium in rats exposed to hexavalent chromium and trivalent chromium aerosols. *Ind Health* 22:261-267.
- \*Swaine DJ, Mitchell RL. 1960. Trace-element distribution in soil profiles. *J Soil Sci* 11(2):347-368.
- \*Tagliari KC, Cecchini R, Vargas VMF. 2004. Mutagenicity of chromium (VI) using the Salmonella microsuspension bioassay. *Rev Bras Toxicol* 17(2):45-50.
- Taioli E, Zhitkovich A, Kinney P, et al. 1995. Increased DNA-protein crosslinks in lymphocytes of residents living in chromium-contaminated areas. *Biol Trace Elem Res* 50:175-180.
- +\*Takagi Y, Matsuda S, Imai S, et al. 1986. Trace elements in human hair: An international comparison. *Bull Environ Contam Toxicol* 36:793-800.
- +\*Takagi Y, Matsuda S, Imai S, et al. 1988. Survey of trace elements in human nails: An international comparison. *Bull Environ Contam Toxicol* 41:683-689.
- Takahashi A, Ikehara T, Hosokawa K, et al. 1995. Properties of Ca<sup>2+</sup>-dependent K<sup>+</sup> channels of human gingival fibroblasts. *J Dent Res* 74(8):1507-1512.
- +\*Takahashi K, Okubo T. 1990. A prospective cohort study of chromium plating workers in Japan. *Arch Environ Health* 45(2):107-111.
- Takahashi Y, Kondo K, Hirose T, et al. 2005. Microsatellite instability and protein expression of the DNA mismatch repair gene, hMLH1, of lung cancer in chromate-exposed workers. *Mol Carcinog* 42(3):150-158.
- Tamino G, Peretta L, Levis AG. 1981. Effects of trivalent and hexavalent chromium on the physicochemical properties of mammalian cell nucleic acids and synthetic polynucleotides. *Chem Biol Interact* 37:309-319.
- +\*Tandon SK, Behari JR, Kachru DN. 1979. Distribution of chromium in poisoned rats. *Toxicology* 13:29-34.
- +Tandon SK, Saxena DK, Gaur JS, et al. 1978. Comparative toxicity of trivalent and hexavalent chromium. *Environ Res* 15:90-99.
- +\*Taylor FH. 1966. The relationship of mortality and duration of employment as reflected by a cohort of chromate workers. *Am J Public Health* 56(2):218-229.

## 9. REFERENCES

- Taylor MD, Roberts JR, Leonard SS, et al. 2003. Effects of welding fumes of differing composition and solubility on free radical production and acute lung injury and inflammation in rats. *Toxicol Sci* 75(1):181-191.
- Tel H, Altas Y, Taner MS. 2004. Adsorption characteristics and separation of Cr(III) and Cr(VI) on hydrous titanium(IV) oxide. *J Hazard Mater* 112(3):225-231.
- +\*Teraoka H. 1981. Distribution of 24 elements in the internal organs of normal males and the metallic workers in Japan. *Arch Environ Health* 36(4):155-164.
- \*Tezuka M, Keiko M, Toshiyuki E, et al. 1991. Protective effect of chromium (III) on acute lethal toxicity of carbon tetrachloride in rats and mice. *J Inorg Biochem* 42(1):1-8.
- \*Tezuka M, Sadanobu S, Gomi K, et al. 1995. *In vitro* effect of chromium and other trace metals on mouse hepatotoxicity induced by carbon tetrachloride exposure. *Biol Pharm Bull* 18(2):256-261.
- \*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 VL, Gropper SS. 1996. Effect of chromium nicotinic acid supplementation on selected cardiovascular disease risk factors. *Biol Trace Elem Res* 55:297-305.
- \*Thompson RC, Hollis OL. 1958. Irradiation of the gastrointestinal tract of the rat by ingested ruthenium-106. *Am J Physiol* 194(2):308-312.
- +\*Thomson WE. 1903. Note on a case of vesication of the cornea by potassium bichromate. *Ophthalmoscope* 1:214-216.
- Tisch M, Maier H. 1996. Plattenepithelkarzinom der zunge nach beruflicher exposition gegenüber chrom-VI-verbindungen. *Laryngol Rhino Otol* 75:455-458.
- Tkeshelashvili LK, Shearman CW, Zakour RA, et al. 1980. Effects of arsenic, selenium, and chromium on the fidelity of DNA synthesis. *Cancer Res* 40:2455-2460.
- \*Tola S, Kilpio J, Virtamo M, et al. 1977. Urinary chromium as an indicator of the exposure of welders to chromium. *Scand J Work Environ Health* 3:192-202.
- \*Torgrimsen T. 1982. Analysis of chromium. In: Langård S, ed. *Biological and environmental aspects of chromium*. New York, NY: Elsevier Biomedical Press, 65-99.
- +\*Tossavainen A, Nurminen P, Mutanen P, et al. 1980. Application of mathematical modeling for assessing the biological half-times of chromium and nickel in field studies. *Br J Ind Med* 37:285-291.
- Travacio M, Polo JM, Llesuy S. 2000. Chromium(VI) induces oxidative stress in the mouse brain. *Toxicology* 150:137-146.
- Travacio M, Polo JM, Llesuy S. 2001. Chromium(VI) induces oxidative stress in the mouse brain (Corrected and republished from 2000). *Toxicology* 162:139-148.

## 9. REFERENCES

- \*Trent LK, Thieding-Cancel D. 1995. Effects of chromium picolinate on body composition. *J Sports Med Phys Fitness* 35:273-280.
- \*TRI06. 2008. 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/>. February 27, 2008.
- +\*Triebig G, Zschiesche W, Schaller KH, et al. 1987. Studies on the nephrotoxicity of heavy metals in iron and steel industries. In: Foa V, Emmett EA, Maroni M, Colombi A, eds. Occupational and environmental chemical hazards. Cellular and biochemical indices for monitoring toxicity. Chichester, UK: Ellis Horwood Limited, 334-338.
- Tripathi RM, Raghunath R, Kumar AV, et al. 1998. Intake of chromium by the adult population of Mumbai City. *Environ Monit Assess* 53:379-389.
- +\*Trivedi B, Saxena DK, Murthy RC, et al. 1989. Embryotoxicity and fetotoxicity of orally administered hexavalent chromium in mice. *Reprod Toxicol* 3:275-278.
- \*Trzeciak A, Kowalik J, Malecka-Panas E, et al. 2000. Genotoxicity of chromium in human gastric mucosa cells and peripheral blood lymphocytes evaluated by the single cell gel electrophoresis (comet assay). *Med Sci Monit* 6(1):24-29.
- Tsapakos MJ, Hampton TH, Jennette KW. 1981. The carcinogen chromate induces DNA cross-links in rat liver and kidney. *J Biol Chem* 256:3623-3626.
- \*Tsapakos MJ, Hampton TH, Sinclair PR, et al. 1983a. The carcinogen chromate causes DNA damage and inhibits drug-mediated induction of porphyrin accumulation and glucuronidation in chick embryo hepatocytes. *Carcinogenesis* 4(8):959-966.
- \*Tsapakos MJ, Hampton TH, Wetterhahn KE. 1983b. Chromium(VI)-induced DNA lesions and chromium distribution in rat kidney, liver, and lung. *Cancer Res* 43:5662-5667.
- Tsou TC, Yang JL. 1996. Formation of reactive oxygen species and DNA strand breakage during interaction of chromium(III) and hydrogen peroxide in vitro: Evidence for a chromium(III)-mediated Fenton-like reaction. *Chem Biol Interact* 102:133-153.
- \*Tsou TC, Chen CL, Liu TY, et al. 1996. Induction of 8-hydroxydeoxyguanosine in DNA by chromium(III) plus hydrogen peroxide and its prevention by scavengers. *Carcinogenesis* 17(1):103-108.
- Tsuchiya K. 1965. The relation of occupation to cancer, especially cancer of the lung. *Cancer* 18:136-144.
- Tsuda H, Kato K. 1976. Potassium dichromate-induced chromosome aberrations and its control with sodium sulfite in hamster embryonic cells in vitro. *Gann* 67:469-470.
- \*Tsuda H, Kato K. 1977. Chromosomal aberrations and morphological transformation in hamster embryonic cells treated with potassium dichromate in vitro. *Mutat Res* 46:87-94.

## 9. REFERENCES

- Tully DB, Collins BJ, Overstreet JD, et al. 2000. Effects of arsenic, cadmium, chromium, and lead on gene expression regulated by a battery of 13 different promoters in recombinant HepG2 cells. *Toxicol Appl Pharmacol* 168:79-90.
- Turel I, Leban I, Klintschar G, et al. 1997. Synthesis, crystal structure, and characterization of two metal-quinolone compounds. *J Inorg Biochem* 66(2):77-82.
- Turk K, Rietschel RL. 1993. Effect of processing cement to concrete on hexavalent chromium levels. *Contact Dermatitis* 28:209-211.
- Twardowska I. 1993. Pathways of chromium in the terrestrial and aquatic environment in the area of a long-lasting emission. *Sci Total Environ* 134(Suppl 1):173-184.
- \*Uddin AN, Burns FJ, Rossman TG, et al. 2007. Dietary chromium and nickel enhance UV-carcinogenesis in skin of hairless mice. *Toxicol Appl Pharmacol* 221(3):329-338.
- \*Ueno S, Kashimoto T, Susa N, et al. 2001. Detection of dichromate (VI)-induced DNA strand breaks and formation of paramagnetic chromium in multiple mouse organs. *Toxicol Appl Pharmacol* 170:56-62.
- \*Ueno S, Sugiyama M, Nobuyuki S, et al. 1995a. Effect of dimethylthiourea on chromium(VI)-induced DNA single-strand breaks in Chinese hamster V-79 cells. *Mutat Res* 346:247-253.
- +Ueno S, Susa N, Furukawa Y, et al. 1988. The relationship between the development of toxicity and lipid peroxidation induced by chromium compounds in rats. *Kitasato Arch of Exp Med* 61:137-147.
- Ueno S, Susa N, Furukawa Y, et al. 1989. Cellular injury and lipid peroxidation induced by hexavalent chromium in isolated rat hepatocytes. *Jpn J Vet Sci* 51:137-145.
- \*Ueno S, Susa N, Furukawa Y, et al. 1995b. Formation of paramagnetic chromium in liver of mice treated with dichromate(VI). *Toxicol Appl Pharmacol* 135:165-171.
- \*Umeda M, Nishimura M. 1979. Inducibility of chromosomal aberrations by metal compounds in cultured mammalian cells. *Mutat Res* 67:221-229.
- Upreti RK, Shrivastava R, Chaturvedi UC. 2004. Gut microflora & toxic metals: Chromium as a model. *Indian J Med Res* 119(2):49-59.
- Upreti RK, Shrivastava R, Kannan A, et al. 2005. A comparative study on rat intestinal epithelial cells and resident gut bacteria: (I) Effect of hexavalent chromium. *Toxicol Mech Methods* 15(5):331-338.
- \*Urasa IT, Nam SH. 1989. Direct determination of chromium(III) and chromium(VI) with ion chromatography using direct current plasma emission as element-selective detector. *J Chromatogr Sci* 27:30-37.
- \*USDI. 1988a. Mineral yearbook: Chromium. U.S. Department of the Interior, Bureau of Mines, Pittsburgh, PA.
- USDI. 1988b. Mineral commodity summaries. Pittsburgh, PA: U.S. Department of the Interior, Bureau of Mines, 36.

## 9. REFERENCES

- \*USGS. 1984. Element concentrations in soils and other surficial materials of the conterminous United States. United States Geological Survey. USGS Professional Paper 1270. Washington, DC: U.S. Government Printing Office.
- \*USGS. 1989. Concentrations of nine trace metals in ground water at the Idaho National Engineering Laboratory, Idaho. U.S. Geological Survey. Idaho Falls, Idaho: U.S. Geological Service, U.S. Department of Energy. DE88015177.
- USGS. 1998. Chromium. USGS minerals information: 1998. Mineral commodities summaries. United States Geological Survey. <http://minerals.usgs.gov/minerals/pubs/mcs/1998>.
- \*USGS. 2008a. Chromium. In: Mineral commodity summaries 2008. U.S. Geological Survey, 48-49. <http://minerals.usgs.gov/minerals/pubs/mcs/2008/mcs2008.pdf>. May 22, 2008.
- \*USGS. 2008b. 2006 Minerals yearbook. Chromium. U.S. Geological Survey. <http://minerals.usgs.gov/minerals/pubs/commodity/chromium/myb1-2006-chrom.pdf>. May 22, 2008.
- Uyama T, Monden Y, Tsuyuguchi M, et al. 1989. Lung cancer in chromate workers: High-risk group for multiple lung cancer. *J Surg Oncol* 41:213-218.
- \*Vaglenov A, Nosko M, Georgieva R, et al. 1999. Genotoxicity and radioresistance in electroplating workers exposed to chromium. *Mutat Res* 446(1):23-34.
- Vallier HA, Rodgers PA, Stevenson DK. 1993. Inhibition of heme oxygenase after oral vs. intraperitoneal administration of chromium porphyrins. *Life Sci* 52:79-84.
- Van Faassen A, Borm PJA. 1991. Composition and health hazards of water-based construction paints: Results from a survey in the Netherlands. *Environ Health Perspect* 92:147-154.
- Van Heugten E, Spears JW. 1997. Immune response and growth of stressed weanling pigs fed diets supplemented with organic or inorganic forms of chromium. *J Anim Sci* 75:409-416.
- \*Vasant C, Rajaram R, Ramasami T. 2003. Apoptosis of lymphocytes induced by chromium(VI/V) is through ROS-mediated activation of Src-family kinases and caspases-3. *Free Radic Biol Med* 35(9):1082-1100.
- Vasconcelos MTSD, Taveres HMF. 1998. Atmospheric metal pollution (Cr, Cu, Fe, Mn, Ni, Pb and Zn) in Oporto City derived from results for low-volume aerosol samplers and for the moss *Sphagnum auriculatum* bioindicator. *Sci Total Environ* 212:11-20.
- Vashishat RK, Vasudeva M. 1987. Genotoxic potential of chromium salts in *Saccharomyces cerevisiae*. *Ind J Microbiol* 27:35-36.
- \*Veillon C. 1989. Analytical chemistry of chromium. *Sci Total Environ* 86:65-68.
- \*Veillon C, Patterson KY, Bryden NA. 1982. Direct determination of chromium in human urine by electrothermal atomic absorption spectrometry. *Anal Chim Acta* 136:233-241.
- \*Venier P, Montaldi A, Majone F, et al. 1982. Cytotoxic, mutagenic and clastogenic effects of industrial chromium compounds. *Carcinogenesis* 3(11):1331-1338.

## 9. REFERENCES

- \*Venier P, Montini R, Zordan M, et al. 1989. Induction of SOS response in Escherichia coli strain PQ37 by 16 chemical compounds and human urine extracts. *Mutagenesis* 4(1):51-57.
- \*Venitt S, Levy LS. 1974. Mutagenicity of chromates in bacteria and its relevance to chromate carcinogenesis. *Nature* 250:493-495.
- Verhage AH, Cheong WK, Jeejeebhoy KN. 1996. Neurological symptoms due to possible chromium deficiency in long-term parenteral nutrition that closely mimic metronidazole-induced syndromes. *J Parenter Enter Nutr* 20(2):123-127.
- +\*Vernot EH, MacEwen JD, Haun CC, et al. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. *Toxicol Appl Pharmacol* 42:417-423.
- +\*Verschoor MA, Bragt PC, Herber RFM, et al. 1988. Renal function of chrome-plating workers and welders. *Int Arch Occup Environ Health* 60:67-70.
- Versieck J. 1985. Trace elements in human body fluids and tissues. *CRC Crit Rev Clin Lab Sci* 22:97-184.
- Viccellio P, Bania T, Brent J, et al, eds. 1998. *Emergency toxicology*. 2nd ed. Philadelphia, PA: Lippincott-Raven, 448-449, 470, 1141.
- \*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* 238:476-483.
- Vijayram K, Geraldine P. 1996. Regulation of essential heavy metals (Cu, Cr, and Zn) by the freshwater prawn *Macrobrachium malcolmsonii* (Milne Edwards). *Bull Environ Contam Toxicol* 56:335-342.
- +\*Visek WJ, Whitney IB, Kuhn USC, et al. 1953. Metabolism of Cr<sup>51</sup> by animals as influenced by chemical state. *Proc Soc Exp Biol Med* 84:610-615.
- Vitale RJ, Mussoline GR, Rinehimer KA. 1997. Environmental monitoring of chromium in air, soil, and water. *Regul Toxicol Pharmacol* 26:S80-S85.
- Wacker WEC, Vallee BL. 1959. Nucleic acids and metals I. Chromium, manganese, nickel, iron and other metals in ribonucleic acid from diverse biological sources. *J Biol Chem* 234:3257-3262.
- \*Wagley D, Schmiedel G, Mainka E, et al. 1989. Direct determination of some essential and toxic elements in milk and milk powder by graphite furnace atomic absorption spectrometry. *Atmos Spectrosc* 10(4):106-111.
- +\*Wahba A, Cohen T. 1979. Chrome sensitivity in Israel. *Contact Dermatitis* 5:101-107.
- +Wahlberg JE. 1965. Percutaneous toxicity of metal compounds: A comparative investigation in guinea pigs. *Arch Environ Health* 11:201-204.
- \*Wahlberg JE. 1970. Percutaneous absorption of trivalent and hexavalent chromium (<sup>51</sup>Cr) through excised human and guinea pig skin. *Dermatologica* 141:288-296.
- +\*Wahlberg JE, Skog E. 1965. Percutaneous absorption of trivalent and hexavalent chromium. *Arch Dermatol* 92:315-318.



## 9. REFERENCES

- Wakeman TP, Wyczechowska D, Xu B. 2005. Involvement of the p38 MAP kinase in Cr(VI)-induced growth arrest and apoptosis. *Mol Cell Biochem* 279:69-73.
- Walter Z, Mankiewicz J, Wozniak K, et al. 2000. Does potassium dichromate induce apoptosis in lymphocytes? *Int J Occup Environ Health* 13(3):205-213.
- \*Wang J, Ashley K, Kennedy ER, et al. 1997a. Determination of hexavalent chromium in industrial samples using ultrasonic extraction and flow injection analysis. *Analyst* 122(11):1307-1312.
- Wang JF, Bashir M, Engelsberg BN, et al. 1997b. High mobility group proteins 1 and 2 recognize chromium-damaged DNA. *Carcinogenesis* 18(2):371-375.
- \*Wang JY, Tsukayama DT, Wicklund BH, et al. 1996a. Inhibition of T and B cell proliferation by titanium, cobalt, and chromium: Role of IL-2 and IL-6. *J Biomed Mater Res* 32:655-661.
- Wang JY, Wicklund BH, Gustilo RB, et al. 1996b. Titanium, chromium and cobalt ions modulate the release of bone-associated cytokines by human monocytes/macrophages *in vitro*. *Biomaterials* 17:2233-2240.
- \*Wang X, Xing M, Shen Y, et al. 2006. Oral administration of Cr(VI) induced oxidative stress, DNA damage and apoptotic cell death in mice. *Toxicology* 228(1):16-23.
- +Wang XW, Davies JWL, Sirvent RLZ, et al. 1985. Chromic acid burns and acute chromium poisoning. *Burns* 11:181-184.
- \*Wani S, Weskamp C, Marple J, et al. 2006. Acute tubular necrosis associated with chromium picolinate-containing dietary supplement. *Ann Pharmacother* 40:563-566.
- \*Warren G, Schultz P, Bancroft D, et al. 1981. Mutagenicity of a series of hexacoordinate chromium(III) compounds. *Mutat Res* 90:111-118.
- \*Wasser WG, Feldman NS, D'Agati VD. 1997. Chronic renal failure after ingestion of over-the-counter chromium picolinate. *Ann Intern Med* 126(5):410.
- \*Watanabe K, Sakamoto K, Sasaki T. 1998a. Comparisons on chemically-induced mutation among four bacterial strains, *Salmonella typhimurium* TA102 and TA2638, and *Escherichia coli* WP2/pKM101 and WP2 *uvrA*/pKM101: Collaborative study II. *Mutat Res* 412:17-31.
- Watanabe K, Sasaki T, Kawakami K. 1998b. Comparisons of chemically-induced mutation among four bacterial strains, *Salmonella typhimurium* TA102 and TA2638, and *Escherichia coli* WP2/pKM101 and WP2 *uvrA*/pKM101: Collaborative study III and evaluation of the usefulness of these strains. *Mutat Res* 416:169-181.
- Waters MD, Gardner DE, Arany C, et al. 1975. Metal toxicity for rabbit alveolar macrophages *in vitro*. *Environ Res* 9:32-47.
- Wei Y, Tepperman K, Huang M, et al. 2004. Chromium inhibits transcription from polycyclic aromatic hydrocarbon-inducible promoters by blocking the release of histone deacetylase and preventing the binding of p300 to chromatin. *J Biol Chem* 279(27):4110-4119.

## 9. REFERENCES

- \*Weast RC, ed. 1985. CRC handbook of chromium and physics. 66th ed. Boca Raton, FL: CRC Press, Inc., B-70, B-88-89, B-106, B-127, B-142, B-147, B-159, D-215.
- +\*Weber H. 1983. Long-term study of the distribution of soluble chromate-51 in the rat after a single intratracheal administration. *J Toxicol Environ Health* 11:749-764.
- Wedeen RP, Qian L. 1991. Chromium-induced kidney disease. *Environ Health Perspect* 92:71-74.
- +\*Wedeen RP, Haque S, Udasin I, et al. 1996. Absence of tubular proteinuria following environmental exposure to chromium. *Arch Environ Health* 51(4):321-323.
- Wendt PH, Van Dolah RF, Bobo MY, et al. 1996. Wood preservative leachates from docks in an estuarine environment. *Arch Environ Contam Toxicol* 31:24-37.
- \*Werfel U, Langen V, Eickhoff I, et al. 1998. Elevated DNA single-strand breakage frequencies in lymphocytes of welders exposed to chromium and nickel. *Carcinogenesis* 19(3):413-418.
- \*West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. *J Pediatrics* 32a:10-18.
- \*Westbrook JH. 1979. Chromium and chromium alloys. In: Grayson M, ed. *Kirk-Othmer encyclopedia of chemical technology*, Vol. 6, 3rd ed. New York, NY: John Wiley and Sons, 54-82
- Wetterhahn KE, Hamilton JW. 1989. Molecular basis of hexavalent chromium carcinogenicity: Effect on gene expression. *Sci Total Environ* 86:113-129.
- White MA, Sabbioni E. 1998. Trace element reference values in tissues from inhabitants of the European Union. X. A study of 13 elements in blood and urine of a United Kingdom population. *Sci Total Environ* 216:253-270.
- \*Whiting RF, Stich HF, Koropatnick DJ. 1979. DNA damage and DNA repair in cultured human cells exposed to chromate. *Chem Biol Interact* 26:267-280.
- \*Whittaker P, San RHC, Clarke JJ, et al. 2005. Mutagenicity of chromium picolinate and its components in *Salmonella typhimurium* and L5178Y mouse lymphoma cells. *Food Chem Toxicol* 43(11):1619-1625.
- Whittemore AS. 1978. Quantitative theories of oncogenesis. *Adv Cancer Res* 27:55-87.
- \*WHO. 1988. Chromium. *Environmental Health Criteria* 61. Geneva: United Nations Environment Programme. International Labour Organisation. World Health Organization. <http://www.inchem.org/documents/ehc/ehc/ehc61.htm>. April 23, 2008.
- \*WHO. 2000. Air quality guidelines. 2nd ed. Geneva, Switzerland: World Health Organization. [http://www.euro.who.int/document/aicq/6\\_4chromium.pdf](http://www.euro.who.int/document/aicq/6_4chromium.pdf). May 14, 2008.
- \*WHO. 2003. Chromium in drinking water. Background document for development of WHO guidelines for drinking water quality. Geneva: World Health Organization.
- \*WHO. 2004. Guidelines for drinking-water quality. Vol. 1. Recommendations. 3rd ed. Geneva, Switzerland: World Health Organization. [http://www.who.int/water\\_sanitation\\_health/dwq/gdwq3/en/](http://www.who.int/water_sanitation_health/dwq/gdwq3/en/). March 08, 2006.

## 9. REFERENCES

- \*Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Felix F, eds. Mineral metabolism: An advanced treatise Volume II, The elements part A. New York, NY: Academic Press.
- \*Wiegand HJ, Ottenwalder H, Bolt HM. 1984. The reduction of chromium(VI) to chromium(III) by glutathione: An intracellular redox pathway in the metabolism of the carcinogen chromate. *Toxicology* 33:341-348.
- \*Wiegand HJ, Ottenwalder H, Bolt HM. 1985. Fast uptake kinetics *in vitro* of <sup>51</sup>Cr (VI) by red blood cells of man and rat. *Arch Toxicol* 57(1):31-34.
- +\*Wiegand HJ, Ottenwalder H, Bolt HM. 1987. Bioavailability and metabolism of hexavalent chromium compounds. *Toxicol Environ Chem* 14:263-275.
- \*Wiegand HJ, Ottenwalder H, Bolt HM. 1988. Recent advances in biological monitoring of hexavalent chromium compounds. *Sci Total Environ* 71:309-315.
- \*Wiersema JM, Wright L, Rogers B, et al. 1984. Human exposure to potentially toxic elements through ambient air in Texas. In: Proceedings of the 77th meeting of Air Pollution Control Association, Vol. Austin, TX, 2-15.
- Wilcox AJ, Savitz DA, Samet JM. 2008. A tale of two toxicants: Lessons from Minamata and Liaoning. (Comment on: *Epidemiology* 19(1):12-23). *Epidemiology* 19(1):1-2.
- \*Wild D. 1978. Cytogenetic effects in the mouse of 17 chemical mutagens and carcinogens evaluated by the micronucleus test. *Mutat Res* 56:319-327.
- +Williams MW, Hoeschele JD, Turner JE, et al. 1982. Chemical softness and acute metal toxicity in mice and *Drosophila*. *Toxicol Appl Pharmacol* 63:461-469.
- \*Winder C, Carmody M. 2002. The dermal toxicity of cement. (Comment in: *Toxicol Ind Health* 19:183). *Toxicol Ind Health* 18:321-331.
- Windholz, M, ed. 1983. The Merck index. 10th ed. Rahway, NJ: Merck and Co., Inc., 316-317.
- +\*Winston JR, Walsh EN. 1951. Chromate dermatitis in railroad employees working with diesel locomotives. *J Am Med Assoc* 147:1133-1134.
- \*Wise JP, Orenstein JM, Patierno SR. 1993. Inhibition of lead chromate clastogenesis by ascorbate: Relationship to particle dissolution and uptake. *Carcinogenesis* 14(3):429-434.
- Wise JP, Stearns DM, Wetterhaun KE, et al. 1994. Cell-enhanced dissolution of carcinogenic lead chromate particles: The role of individual dissolution products in clastogenesis. *Carcinogenesis* 15(10):2249-2254.
- \*Wise JP, Wise SS, Little JE. 2002. The cytotoxicity and genotoxicity of particulate and soluble hexavalent chromium in human lung cells. *Mutat Res* 517:221-229.
- \*Wise SS, Holmes AL, Ketterer ME, et al. 2004. Chromium is the proximate clastogenic species for lead chromate-induced clastogenicity in human bronchial cells. *Mutat Res* 560:79-89.

## 9. REFERENCES

- \*Wise SS, Holmes AL, Ketterer M, et al. 2003. Chromium is the proximate genotoxic species in lead chromate-induced genotoxicity in human bronchial cells. *Toxicologist* 72(S-1):217.
- Wise SS, Holmes AL, Moreland JA, et al. 2005. Human lung cell growth is not stimulated by lead ions after lead chromate-induced genotoxicity. *Mol Cell Biochem* 279(1-2):75-84.
- \*Wise SS, Holmes AL, Wise JP. 2006b. Particulate and soluble hexavalent chromium are cytotoxic and genotoxic to human lung epithelial cells. *Mutat Res* 610(1-2):2-7.
- \*Wise SS, Holmes AL, Xie H, et al. 2006a. Chronic exposure to particulate chromate induces spindle assembly checkpoint bypass in human lung cells. *Chem Res Toxicol* 19:1492-1498.
- \*Wise SS, Kraus S, Shaffiey F, et al. 2008. Hexavalent chromium is cytotoxic and genotoxic to the North Atlantic right whale (*Eubalaena glacialis*) lung and testes fibroblasts. *Mutat Res* 650:30-38.
- Wise SS, Schuler JH, Katsifis SP, et al. 2003. Barium chromate is cytotoxic and genotoxic to human lung cells. *Environ Mol Mutagen* 42(4):274-278.
- Witmer C, Cooper K, Kelly J. 1982. Effects of plating efficiency and lowered concentration of salts on mutagenicity assays with Ames; Salmonella strains. *Adv Exp Med Biol* 136B:1271-1284.
- +\*Witmer C, Faria E, Park H-S, et al. 1994. *In vivo* effects of chromium. *Environ Health Perspect* 102(3):169-176.
- +\*Witmer CM, Harris R, Shupack SI. 1991. Oral bioavailability of chromium from a specific site. *Environ Health Persp* 92:105-110.
- +\*Witmer CM, Park HS, Shupack SI. 1989. Mutagenicity and disposition of chromium. *Sci Total Environ* 86:131-148.
- Wolf T, Bolt HM, Ottenwalder H. 1989. Nick translation studies on DNA strand breaks in pBR322 plasmid induced by different chromium species. *Toxicol Lett* 47:295-301.
- Wolf T, Kasemann R, Ottenwalder H. 1989. Differing effects of chromium(III) and chromium(VI) on nucleotides and DNA. *Arch Toxicol Suppl* 13:48-51.
- Wolf T, Wiegand HJ, Ottenwalder H. 1989. Different molecular effects on nucleotides by interaction with Cr(III) and Cr(VI): A <sup>31</sup>P-NMR study in vitro. *Toxicol Environ Chem* 23:108.
- Wong PK. 1988. Mutagenicity of heavy metals. *Bull Environ Contam Toxicol* 40:597-603.
- \*Wong SS, Chan MT, Gan SL, et al. 1998. Occupational chromate allergy in Singapore: A study of 87 patients and a review from 1983 to 1995. *Am J Contact Dermatitis* 9(1):1-5.
- +Woolliscroft J, Barbosa J. 1977. Analysis of chromium induced carbohydrate intolerance in the rat. *J Nutr* 107(9):1702-1706.
- \*Wrońska-Nofer T, Wisniewska-Knypl J, Wszyńska K. 1999. Prooxidative and genotoxic effect of transition metals (cadmium, nickel, chromium, and vanadium) in mice. *Trace Elem Electrolytes* 15(2):87-92.

## 9. REFERENCES

- Wrobel K, Garay-Sevilla ME, Malacara JM, et al. 1999. Effect of chromium on glucose tolerance, serum cholesterol and triglyceride levels in occupational exposure to trivalent species in type 2 diabetic patients and in control subjects. *Trace Elem Electrolytes* 16(4):199-205.
- Wu F, Tsai F, Kuo H, et al. 2000. Cytogenic study of workers exposed to chromium compounds. *Mutat Res* 464:289-296.
- \*Wu F, Wu W, Kuo H, et al. 2001. Effect of genotoxic exposure to chromium among electroplating workers in Taiwan. *Sci Total Environ* 279:21-28.
- Xie H, Holmes AL, Wise SS, et al. 2004. Lead chromate-induced chromosome damage requires extracellular dissolution to liberate chromium ions but does not require particle internalization or intracellular dissolution. *Chem Res Toxicol* 17(10):1362-1367.
- Xie H, Holmes AL, Wise SS, et al. 2007. Neoplastic transformation of human bronchial cells by lead chromate particles. *Am J Respir Cell Mol Biol* 37(5):544-552.
- Xie H, Wise SS, Wise JP. 2008. Deficient repair of particulate hexavalent chromium-induced DNA double strand breaks leads to neoplastic transformation. *Mutat Res* 649:230-238.
- \*Xu J, Bubleby GJ, Detrick B, et al. 1996. Chromium(VI) treatment of normal human lung cells results in guanine-specific DNA polymerase arrest, DNA-DNA cross-links and S-phase blockade of cell cycle. *Carcinogenesis* 17(7):1511-1517.
- Yadav J, Yadav A, Sharma T. 2001. Chromosome damage in nickel-chrome electroplaters. *J Hum Ecol* 12(3):185-189.
- +\*Yamaguchi S, Sano K, Shimojo N. 1983. On the biological half-time of hexavalent chromium in rats. *Ind Health* 21:25-34.
- Yamamoto A, Honma R, Sumita M. 1998. Cytotoxicity evaluation of 43 metal salts using murine fibroblasts and osteoblastic cells. *J Biomed Mater Res* 39:331-340.
- \*Yamamoto A, Kohyama Y, Hanawa T. 2002. Mutagenicity evaluation of forty-one metal salts by the umu test. *J Biomed Mater Res* 59:176-183.
- \*Yang JL, Hsieh YC, Wu CW, et al. 1992. Mutational specificity of chromium(VI) compounds in the hprt locus of Chinese hamster ovary-K1 cells. *Carcinogenesis* 13(11):2053-2057.
- Yargicoglu P, Agar A, Oguz Y, et al. 1997. The effect of developmental exposure to cadmium (Cd) on visual evoked potentials (EEPs) and lipid peroxidation. *Neurotoxicol Teratol* 19(3):213-219.
- Yavorsky M, Almaden P, King CG. 1934. The vitamin C content of human tissues. *J Biol Chem* 106(2):525-529.
- Ye J, Shi X. 2001. Gene expression profile in response to chromium-induced cell stress in A549 cells. *Mol Cell Biochem* 222:189-197.
- \*Ye J, Zhang X, Young HA, et al. 1995. Chromium(VI)-induced nuclear factor- $\kappa$ B activation in intact cells via free radical reactions. *Carcinogenesis* 16(10):2401-2405.

## 9. REFERENCES

- \*Yeadley RB, Lazorchak JM, Paulsen SG. 1998. Elemental fish tissue contamination in Northeastern U.S. lakes: Evaluation of an approach to regional assessment. *Environ Toxicol Chem* 17(9):1875-1884.
- +\*Yousef MI, El-Demerdash FM, Kamil KI, et al. 2006. Ameliorating effect of folic acid on chromium(VI)-induced changes in reproductive performance and seminal plasma biochemistry in male rabbits. *Reprod Toxicol* 21(3):322-328.
- Yu IJ, Song KS, Chang HK, et al. 2001. Lung fibrosis in Sprague-Dawley rats, induced by exposure to manual metal arc-stainless steel welding fumes. *Toxicol Sci* 63:99-106.
- Yu W, Sipowicz MA, Diwan BA, et al. 1998. Preconception exposure of male mice to urethane or chromium: Increased tumors in multiple organs of offspring. *Proc Am Assoc Cancer Res* 39:21.
- Zabulyte D, Uleckiene S, Kalibatas J, et al. 2006. Investigation of combined effect of chromium (VI) and nitrate in experiments on rats. *Trace Elem Electrolytes* 23(4):287-291.
- Zachariae COC, Agner T, Menne T. 1996. Chromium allergy in consecutive patients in a country where ferrous sulfate has been added to cement since 1981. *Contact Dermatitis* 35:83-85.
- Zagrodzki P, Debecki L, Radkowski A, et al. 2007. Association of occupational exposure to chromium with tumour markers and selected biochemical parameters. *Pol J Environ Stud* 16(2):275-281.
- +\*Zahid ZR, Al-Hakkak ZS, Kadhim AHH, et al. 1990. Comparative effects of trivalent and hexavalent chromium on spermatogenesis of the mouse. *Toxicol Environ Chem* 25:131-136.
- Zak LJ, Cosgrove JR, Aherne FX, et al. 1997. Pattern of feed intake and associated metabolic and endocrine change differentially affect postweaning fertility in primiparous lactating sows. *J Anim Sci* 75:208-216.
- \*Zatka VJ. 1985. Speciation of hexavalent chromium in welding fumes interference by air oxidation of chromium. *Am Ind Hyg Assoc J* 46(6):327-331.
- Zha L, Xu Z, Wang M, et al. 2007. Effects of chromium nanoparticle dosage on growth, body consumption, serum hormones and tissue chromium in Sprague-Dawley rats. *J Zhejiang Univ Sci B* 8(5):323-330.
- \*Zhang J, Li S. 1997. Cancer mortality in a Chinese population exposed to hexavalent chromium in water. (Comment in: *J Occup Environ Med* 48(7):749). *J Occ Env Med* 39(4):315-319.
- +\*Zhang J, Li X. 1987. Chromium pollution of soil and water in Jinzhou. *J Chinese Prev Med* 21:262-264.
- Zhang Z, Leonard SS, Wang S, et al. 2001. Cr(VI) induces cell growth arrest through hydrogen peroxide-mediated reactions. *Mol Cell Biochem* 222:77-83.
- \*Zhitkovich A. 2005. Importance of chromium-DNA adducts in mutagenicity and toxicity of chromium(VI). *Chem Res Toxicol* 18:3-11.

## 9. REFERENCES

Zhitkovich A, Shrager S, Messer J. 2000. Reductive metabolism of Cr(VI) by cystein leads to the formation of binary and ternary Cr-DNA adducts in the absense of oxidative DNA damage. *Chem Res Toxicol* 13:1114-1124.

Zhitkovich A, Voitkun V, Costa M. 1995. Gluathione and free amino acids from stable complexes with DNA following exposure of intact mammalian cells to chromate. *Carcinogenesis* 16(4):907-913.

\*Zhitkovich A, Voitkun V, Costa M. 1996. Formation of the amino acid-DNA complexes by hexavalent and trivalent chromium *in vitro*: Importance of trivalent chromium and the phosphate group. *Biochemistry* 35:7275-7282.

\*Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. *Pediatr Res* 12:29-34.

\*Zimmering S, Mason JM, Valencia R, et al. 1985. Chemical mutagenesis testing in *Drosophila*. II. Results of 20 coded compounds tested for the National Toxicology Program. *Environ Mutagen* 7:87-100.

9. REFERENCES

This page is intentionally blank.



## 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<sub>10</sub> 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.

## 10. GLOSSARY

**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.

## 10. GLOSSARY

**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<sub>(LO)</sub> (LC<sub>LO</sub>)**—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

**Lethal Concentration<sub>(50)</sub> (LC<sub>50</sub>)**—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<sub>(LO)</sub> (LD<sub>LO</sub>)**—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<sub>(50)</sub> (LD<sub>50</sub>)**—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time<sub>(50)</sub> (LT<sub>50</sub>)**—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.

## 10. GLOSSARY

**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.

## 10. GLOSSARY

**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  $\mu\text{g/L}$  for water,  $\text{mg/kg/day}$  for food, and  $\mu\text{g/m}^3$  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  $\text{mg/m}^3$  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.

## 10. GLOSSARY

**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<sub>(50)</sub> (TD<sub>50</sub>)**—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.

## 10. GLOSSARY

**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

10. GLOSSARY

This page is intentionally blank.



## 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.

## APPENDIX A

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-32, Atlanta, Georgia 30333.

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical name: Chromium(VI) aerosols and mists  
CAS number: 18540-29-9  
Date: October 2008  
Profile status: Final Draft Pre-Public Comment  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to figure: 11, 29  
Species: Human

Minimal Risk Level:  $5 \times 10^{-6}$  mg chromium(VI)/m<sup>3</sup> for dissolved hexavalent chromium aerosols and mists.

Reference: Lindberg E, Hedenstierna G. 1983. Chrome plating: Symptoms, findings in the upper airways, and effects on lung function. Arch Environ Health 38:367-374.

Experimental design: Eighty-five male and 19 female chrome-plating workers exposed to chromic acid were assessed for nose, throat, and chest symptoms, were inspected for effects in nasal passages, and were given pulmonary function tests. Study participants were compared to a reference group of 119 auto mechanics who were not exposed to chromium. The length of worker exposures to chromic acid ranged from 0.1 to 36 years, spanning intermediate- and chronic-exposure durations. Since the study population included workers exposed for both intermediate and chronic durations, data are considered appropriate for derivation of the intermediate- and chronic-duration inhalation MRLs. Chromium exposures were measured using personal air samplers and stationary equipment positioned close to the baths containing chromic acid. The exposure categories were defined as high average daily concentrations  $>0.002$  mg chromium(VI)/m<sup>3</sup>, low (average daily concentrations  $<0.002$  mg chromium(VI)/m<sup>3</sup>), and mixed category (chromium(VI) was  $<0.002$  mg chromium(VI)/m<sup>3</sup>, with exposure to other acids and metallic salts). Correlations with nasal irritation and respiratory functions were also determined for peak exposures. Statistical analyses were performed using the chi-square test with Yate's correction when comparing nasal findings, and the Student's two tail t-test was used when comparing lung function findings.

Effects noted in study and corresponding doses: Nasal irritation ( $p < 0.05$ ), mucosal atrophy ( $p < 0.05$ ), and ulceration ( $p < 0.01$ ), and decreases in spirometric parameters (forced vital capacity, forced expired volume in 1 second, and forced mid-expiratory flow) were observed in workers occupationally exposed to  $\geq 0.002$  mg chromium(VI)/m<sup>3</sup> as chromic acid with a median exposure period of 2.5 years. About 60% of the exposed subjects were smokers, but no consistent association between exposure and cigarette smoking was observed. Short-term peak exposures to chromic acid correlated better with nasal septum damage than with 8-hour mean concentrations.

Dose end point used for MRL derivation: 0.002 mg chromium(VI)/m<sup>3</sup> (nasal irritation, mucosal atrophy, decreased FVC, FEP<sub>1</sub>, and FEV)

NOAEL  LOAEL  benchmark concentration (BMC)

The LOAEL of 0.002 mg chromium(VI)/m<sup>3</sup> for upper respiratory effects was selected as the point of departure for derivation of the intermediate- and chronic-duration inhalation MRLs for dissolved hexavalent chromium aerosols and mists. The LOAEL was duration-adjusted to a LOAEL<sub>ADJ</sub> of 0.0005 mg chromium(VI)/m<sup>3</sup> for continuous exposure. The intermediate- and chronic-duration inhalation MRLs of 0.000005 mg chromium(VI)/m<sup>3</sup> for dissolved hexavalent chromium aerosols and mists were

## APPENDIX A

derived by dividing the  $LOAEL_{ADJ}$  of 0.0005 mg chromium(VI)/m<sup>3</sup> by a composite uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

Uncertainty factors used in MRL derivation:

- 10 for use of a LOAEL
- 10 for extrapolation from animals to humans
- 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: No. Not applicable.

Was a conversion used from intermittent to continuous exposure? Yes, the LOAEL of 0.002 mg chromium(VI)/m<sup>3</sup> was multiplied by 8 hour/24 hour and by 5 days/7 days to yield a duration-adjusted LOAEL ( $LOAEL_{ADJ}$ ) of 0.0005 mg chromium(VI)/m<sup>3</sup>.

Other additional studies or pertinent information that lend support to this MRL: The respiratory tract is the major target of inhalation exposure to chromium(VI) compounds in humans and animals. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. In workers exposed to dissolved hexavalent chromium aerosols and mists (as chromium trioxide mist) for intermediate durations, nasal irritation, ulceration, and mucosal atrophy and rhinorrhea have been reported, with LOAEL values ranging from 0.09 to 0.1 mg chromium(VI)/m<sup>3</sup> (Gibb et al. 2000a; Gomes 1972; Kleinfeld and Rosso 1965). Similarly, studies in rats and mice have shown that the upper respiratory tract is a primary target of exposure to inhaled chromium trioxide mist, with LOAEL values ranging from 0.49 to 3.63 mg chromium(VI)/m<sup>3</sup> (Adachi 1987; Adachi et al. 1986; Kim et al. 2004). In addition, numerous intermediate- and chronic-duration exposure studies of workers to chromium(VI) compounds in general identify the respiratory tract as the primary target of exposure, with reports of epistaxis, chronic rhinorrhea, nasal itching and soreness, nasal mucosal atrophy, perforations and ulceration of the nasal septum, bronchitis, pneumoconiosis, decreased pulmonary function, and pneumonia (Bovet et al. 1977; Cohen et al. 1974; Davies et al. 1991; Gomes 1972; Greater Tokyo Bureau of Hygiene 1989; Hanslian et al. 1967; Keskinen et al. 1980; Kleinfeld and Rosso 1965; Lee and Goh 1988; Letterer 1939; Lieberman 1941; Lindberg and Hedenstierna 1983; Lucas and Kramkowski 1975; Mancuso 1951; Meyers 1950; Novey et al. 1983; Pastides et al. 1991; PHS 1953; Royle 1975b; Sassi 1956; Sluis-Cremer and du Toit 1968; Sorahan et al. 1987; Taylor 1966).

Agency Contact (Chemical Manager): Sharon Wilbur

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical name: Chromium(VI) particulates  
CAS number: 18540-29-9  
Date: October 2008  
Profile status: Final Draft Pre-Public Comment  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to figure: 14  
Species: Rat

Minimal Risk Level: 0.0003 mg chromium (VI)/m<sup>3</sup> for hexavalent chromium particulate compounds

Reference: Glaser U, Hochrainer D, Steinhof D. 1990. Investigation of irritating properties of inhaled CrVI with possible influence on its carcinogenic action. Environ Hyg 2:235-245.

Experimental design: Eight-week-old male Wistar rats (30 animals in each group) were exposed 22 hours/day, 7 days/week to 0, 0.05, 0.1, 0.2, or 0.4 mg chromium(VI)/m<sup>3</sup> as sodium dichromate aerosol particulates. Groups of 10 animals were sacrificed after 30 or 90 days of exposure or after 90 days of exposure and a 30-day recovery period. The respective mass median mean diameters (MMAD) and geometric standard deviation were 0.28 µm and 1.63 for the 0.5 and 0.1 mg chromium(VI)/m<sup>3</sup> concentrations and 0.39 µm and 1.72 for the 0.2 and 0.4 mg chromium(VI)/m<sup>3</sup> concentrations. Hematological, clinical chemistry, and urinalysis tests were performed. Gross and histological examinations were limited to the upper airway epithelia, left lung lobes, and the kidneys. In addition, lung lavage fluid was analyzed for total protein, albumin, lactate dehydrogenase, and β-glucuronidase activities.

Effects noted in study and corresponding doses: No deaths or abnormal clinical signs occurred at any of the exposures. Body weight was significantly (p<0.001) decreased at 0.2 and 0.4 mg chromium(VI)/m<sup>3</sup> for 30 days, at 0.4 mg chromium(VI)/m<sup>3</sup> for 90 days (p<0.05), and at 0.2 (p<0.01) and 0.4 mg chromium(VI)/m<sup>3</sup> (p<0.05) in the recovery group. No differences in urinary protein and no exposure-related histopathological lesions were noted. No differences were seen in analysis of serum levels or activities of alanine aminotransferase, alkaline phosphatase, glucose, urea, total bilirubin, total cholesterol, or phospholipids. There were no hematological effects on red blood cells, but the white blood cell counts increased significantly in a dose-related manner at ≥0.1 mg chromium(VI)/m<sup>3</sup> after 30 days and at ≥0.05 mg chromium(VI)/m<sup>3</sup> after 90 days. White blood cells counts were not increased in 90 day exposure plus 30-day observation group.

Obstructive respiratory dyspnea occurred at ≥0.2 mg chromium(VI) chromium(VI)/m<sup>3</sup> after 30 and 90 days. Mean lung weight was increased in all exposure groups and was statistically increased at ≥0.05 mg chromium(VI)/m<sup>3</sup> for 30 days, and at ≥0.1 mg chromium(VI)/m<sup>3</sup> for 90 days and in the 90-day plus recovery period group. Histological examination revealed slight hyperplasia in high incidence at ≥0.05 mg chromium(VI)/m<sup>3</sup> at 30 days. With longer exposure, the incidence declined, indicating repair. Lung fibrosis occurred at ≥0.1 mg chromium(VI)/m<sup>3</sup> for 30 days, but was not seen in rats exposed for 90 days. Accumulation of macrophages was observed in all exposed rats, regardless of exposure concentration or duration. This histiocytosis probably accounts for the increased lung weight. Histology of upper airways revealed focal inflammation. Results of bronchoalveolar lavage (BAL) analysis provided further information of the irritation effect. Total protein in BAL fluid was significantly increased in all exposed groups, but declined in the recovery period. Albumin in BAL fluid increased in a dose-related manner at all concentrations in the 30-day group, but recovery started during 90-day exposure and continued during the 30-day observation period. The activities of lactate dehydrogenase

## APPENDIX A

and  $\beta$ -glucuronidase, measures of cytotoxicity, were elevated at 0.2 and 0.4 mg chromium(VI)/m<sup>3</sup> for 30 and 90 days, but returned to control values during the recovery period. The number of macrophages in the BAL fluid had significantly increased after 30 and 90 days, but normalized during the recovery period. The macrophages were undergoing cell division or were multinucleate and larger. This activation of macrophages was not observed in the recovered rats. The study authors concluded that inflammation is essential for the induction of most chromium inhalation effects and may influence the carcinogenicity of chromium(VI) compounds.

Dose end point used for MRL derivation: 0.016 mg/m<sup>3</sup> (alterations in lactate dehydrogenase levels in bronchoalveolar lavage), converted to a BMCL<sub>HEC</sub> of 0.010 mg chromium(VI)/m<sup>3</sup>

NOAEL  LOAEL  benchmark concentration (BMC)

The Agency adopted the benchmark concentration (BMC) analysis of the Glaser et al. (1990) data conducted by Malsch et al. (1994) for deriving an intermediate-duration inhalation MRL for hexavalent chromium particulate compounds. Using the 90-day exposure data (as described above), Malsch et al. (1994) developed BMCLs for lung weight and BAL fluid levels of lactate dehydrogenase, protein, and albumin. Prior to conducting the benchmark analysis, Malsch et al. (1994) adjusted the dose-response data for intermittent exposure. Duration-adjusted data were then fitted to a polynomial mean response regression model by the maximum likelihood method to derive BMCLs (defined as the 95% lower confidence limit on the concentration corresponding to a 10% relative change in the end point compared to the control). The BMCL values for lung weight, lactate dehydrogenase in the BAL fluid, protein in BAL fluid, and albumin in BAL fluid were 0.067, 0.016, 0.035, and 0.031 mg chromium(VI)/m<sup>3</sup>, respectively. The lowest BMCL, 0.016 mg chromium(VI)/m<sup>3</sup> for alterations in lactate dehydrogenase levels in BAL fluid, was selected to derive the intermediate-duration inhalation MRL. The BMCL of 0.016 mg chromium(VI)/m<sup>3</sup> was converted to a human equivalent concentration (BMCL<sub>HEC</sub>) of 0.010 mg chromium(VI)/m<sup>3</sup>, as described below. The intermediate-duration inhalation MRL of 0.0003 mg chromium(VI)/m<sup>3</sup> for hexavalent chromium particulate compounds was derived by dividing the BMCL<sub>HEC</sub> of 0.010 mg chromium(VI)/m<sup>3</sup> by a composite uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

Uncertainty factors used in MRL derivation:

10 for use of a LOAEL  
 3 for extrapolation from animals to humans, with dosimetric adjustments  
 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.  
 Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:  
 The BMCL of 0.016 mg chromium(VI)/m<sup>3</sup> was converted to a human equivalent concentration (BMCL<sub>HEC</sub>) of 0.010 mg chromium(VI)/m<sup>3</sup> using the RDDR (regional deposited dose ratio) program (EPA 1994c) as follows:

$$\text{BMCL}_{\text{HEC}} = \text{BMCL} \times \text{RDDR}$$

$$\text{BMCL}_{\text{HEC}} = 0.016 \text{ mg chromium(VI)/m}^3 \times 0.630 = 0.010 \text{ mg chromium(VI)/m}^3$$

where

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

## APPENDIX A

multiplier of 0.630 for the thoracic region tract was determined using the default subchronic body weight of 217 g for male Wistar rats (EPA 1988d) and a particle size MMAD $\pm$ GSD of 0.5 $\pm$ 1.63  $\mu$ m reported in the Glaser et al. (1984) study. Although the actual mean particle size reported in the critical study was 0.28  $\mu$ m, the RDDR program (EPA 1994c) can only run for particle sizes ranging from 0.5 to 30  $\mu$ m; therefore, 0.5  $\mu$ m was used as the default particle size to calculate the RDDR. Since the critical study did not report body weight, the default subchronic body weight of 217 g for male Wistar rats was used.

Was a conversion used from intermittent to continuous exposure? Yes. Animals were exposed for 22 hours/day, 7 days/week. Prior to conducting the benchmark analysis, Malsch et al. (1994) adjusted the dose-response data for intermittent exposure (22 hours/day) by multiplying data points for all outcome measures by 22 hours/24 hours.

Other additional studies or pertinent information that lend support to this MRL: The findings in this study are supported by another 90-day study conducted by the same group (Glaser et al. 1985). In this study, groups of 20 male Wistar rats were exposed to 0, 0.025, 0.05, 0.1, or 0.2 mg chromium(VI)/m<sup>3</sup> as sodium dichromate for 22 hours/day, 7 days/week for 90 days. No deaths occurred at any of the exposures. All exposed animals showed normal histologic findings in lung, kidney, liver, stomach, and gonads. Lung and spleen weights were increased significantly at doses above 0.025 mg chromium(VI)/m<sup>3</sup>. Serum levels of triglycerides and phospholipid were increased in rats exposed to 0.2 mg chromium(VI)/m<sup>3</sup>. Serum contents of total immunoglobulins were significantly increased in the 0.05 and 0.1 mg chromium(VI)/m<sup>3</sup> groups. At 0.025 and 0.2 mg chromium(VI)/m<sup>3</sup>, serum immunoglobulin contents were no different than controls. The SRBC antibody response was increased in all dosed groups over control values. Chromium treatment at 0.2 mg chromium(VI)/m<sup>3</sup> also enhanced the mitogenic-stimulation of splenic Concanavalin T-lymphocytes. At 0.025 mg chromium(VI)/m<sup>3</sup>, there were significant increases in polynuclear macrophages and the number of macrophages in telophase, and increases in lymphocytes in bronchoalveolar lavage samples. At 0.05 and 0.2 mg chromium(VI)/m<sup>3</sup>, there were significant decreases in total numbers of macrophages. The percentages of polynuclear macrophages, lymphocytes, and granulocytes were increased at chromium exposures of 0.05 mg chromium(VI)/m<sup>3</sup>, but at 0.2 mg chromium(VI)/m<sup>3</sup>, the percentage of granulocytes cells was lower than control values. At 0.025 and 0.05 mg chromium(VI)/m<sup>3</sup> exposures, phagocytosis of latex particles by alveolar macrophages was increased over controls. However, at 0.2 mg chromium(VI)/m<sup>3</sup>, the phagocytic activity was less than controls and there was a decrease in lung clearance of iron oxide particulates.

Agency Contact (Chemical Manager): Sharon Wilbur

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: Chromium(VI)  
CAS Numbers: 18540-29-9  
Date: October 2008  
Profile status: Final Draft Pre-Public Comment  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Graph Key: 45  
Species: Rat

Minimal Risk Level: 0.005  mg chromium(VI)/kg/day  ppm

Reference: NTP. 2008a. NTP technical report on the toxicology and carcinogenesis studies of sodium dichromate dihydrate (CAS No. 7789-12-0) in F344/N rats and B6C3F1 mice (drinking water studies). Washington, DC: National Toxicology Program. NTP TR 546.  
[http://ntp.niehs.nih.gov/files/546\\_web\\_FINAL.pdf](http://ntp.niehs.nih.gov/files/546_web_FINAL.pdf). August 13, 2008.

Experimental design: Male F344/N rats (6–7 weeks old) were exposed to sodium dichromate dihydrate in drinking water in a 2-year toxicology and carcinogenicity study. Male rats (50/group) were exposed to drinking water concentrations of 0, 14.3, 57.3, 172, or 516 mg sodium dichromate dihydrate/L. In a subgroup of 10 male rats, blood was collected from the retroorbital sinus after exposure durations of 4 days, 22 days, 3 months, 6 months, and 1 year and evaluated for hematology (Hct; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; erythrocyte and platelet morphology; MCV; MCH; MCHC; and leukocyte count and differentials) and clinical chemistry (urea nitrogen, creatinine, total protein, albumin, ALT, AP, creatine kinase, SDH, and bile acids). Clinical signs of toxicity were assessed over the course of exposure. NTP calculated mean daily doses of sodium dichromate dihydrate in male rats of 0, 0.6, 2.2, 6, or 17 mg/kg (equivalent to 0, 0.21, 0.77, 2.1, or 5.9 mg chromium(VI)/kg/day, respectively) over the course of the 2-year study. Since observations were made at various time points during the chronic study (e.g., 22 days to 1 year), rather than using different dosage scales for each observation and outcome in the dose-response modeling, time-averaged dosages for the chronic duration (i.e., 101 weeks) were used to represent the dosage received during the intermediate- (i.e., >2–<52 weeks) and chronic- (>2–101 weeks) duration periods. This is an approximation of the actual dosages received, which varied as a function of body weight, and therefore, time of observation, with the differences most pronounced at the earliest periods of the intermediate-duration exposure (e.g., 3–12 weeks). The rationale for this simplification of the dose-response analysis is as follows: (1) outcomes observed at specific time points in the study (e.g., blood effects) after the acute period (>2 weeks) were considered to be relevant to the entire intermediate-duration period (>2–<52 weeks), if observed at multiple observation times during the intermediate-duration period; (2) chronic duration dosages were nearly identical to the time-averaged dosages for intermediate-duration exposure (e.g., <12% difference in the rat study); and (3) the possible bias introduced into estimates of BMDLs as a result of using chronic-duration dosages to represent intermediate-duration dosages is small (<12%) and conservative (i.e., BMDLs based on the chronic-duration dosages may be slightly lower than BMDLs based on actual intermediate-duration dosages).

Effect noted in study and corresponding doses: No treatment-related clinical signs of toxicity were observed in rats over the course of this study. Hematological effects consistent with microcytic, hypochromic anemia were observed at all intermediate-duration time points (22 days to 6 months) in male rats exposed to sodium dichromate dihydrate in drinking water; severity exhibited dose-dependence. At the 22-day assessment in rats, decreases were observed in Hct, Hgb, MCV, and MCH at  $\geq 0.77$  mg chromium(VI)/kg/day; effects at higher doses included decreased MCHC and platelet count at  $\geq 2.1$  mg chromium(VI)/kg/day, and decreased erythrocyte and reticulocyte counts, and increased nucleated



## APPENDIX A

erythrocytes at 5.9 mg chromium(VI)/kg/day). At the 3-month assessment in rats, decreases were observed for MCV and MCH at  $\geq 0.77$  mg chromium(VI)/kg/day; effects at higher doses included decreased Hgb at  $\geq 2.1$  mg chromium(VI)/kg/day and decreased Hct and increased erythrocyte, reticulocyte, platelet, leukocyte, and segmented neutrophil counts at  $\geq 5.9$  mg chromium(VI)/kg/day. Increases in cell counts indicate a compensatory hematopoietic response to anemia. At 6 months in rats, decreased MCV, MCH, and MCHC were observed at  $\geq 0.77$  mg chromium(VI)/kg/day; at 5.9 mg chromium(VI)/kg/day, decreased Hgb was observed. For all intermediate-duration exposures (22 days to 6 months), NOAEL and LOAEL values in male rats for hematological effects were 0.21 and 0.77 mg chromium(VI)/kg/day, respectively. Although effects in rats were similar at the 22-day and 3-month assessments, NTP (2008a) concluded that effects were more severe at 22 days than at 3 months based on the magnitude of changes and the number of parameters affected in rats exposed to 0.77 mg chromium(VI)/kg/day. Effects at 6 months were less severe than those observed at the 22-day and 3-month assessments. Although the magnitude of the decreases in hematological parameters was small at 0.77 mg chromium(VI)/kg/day compared to the control group (6.1–10.6%), there is clear indication of damage to the hematological system and this dose level was considered a minimal LOAEL. At the next highest dose (2.1 mg chromium(VI)/kg/day), these parameters were 16–25% lower than controls. As defined by ATSDR, an effect that enhances the susceptibility of an organism to the deleterious effects of other chemical, physical, microbiological, or environmental influences should be considered adverse. Thus, the slight, but statistically significant, decrease in hematological parameters at 0.77 mg chromium(VI)/kg/day was considered minimally adverse.

Evaluation of clinical chemistry parameters in male rats showed significant alterations in serum liver enzyme activities, although changes were not consistent over all intermediate-duration exposures. At the 22-day assessment, increases were observed for ALT ( $\geq 0.77$  mg chromium(VI)/kg/day) and AP (5.9 mg chromium(VI)/kg/day), but no change was observed for SDH. At 3 months, ALT was increased ( $\geq 0.77$  mg chromium(VI)/kg/day), but AP was decreased ( $\geq 0.21$  mg chromium(VI)/kg/day) and no change was observed for SDH. At 6 months, increases were observed for ALT and SDH ( $\geq 2.1$  mg chromium(VI)/kg/day), but AP was decreased (0.77 mg chromium(VI)/kg/day). Due to the inconsistent changes in serum liver enzyme activities, NTP (2008a) concluded that alterations in liver enzymes (specifically ALT) were suggestive of enzyme induction, rather than hepatocellular damage. Thus, altered serum liver enzyme activities were not considered indicative of an adverse effect on the liver.

Dose and end point used for MRL derivation: 0.52 mg chromium(VI)/kg/day (microcytic, hypochromic anemia)

NOAEL  LOAEL  benchmark dose (BMD)

Exposure to sodium dichromate dihydrate in drinking water resulted in microcytic, hypochromic anemia in male rats at all intermediate-duration exposures (22 days to 6 months). The severity was greatest at the 22-day assessment compared to the 3- and 6-month assessments; therefore, microcytic, hypochromic anemia observed at the 22-day assessment was identified as the critical effect for derivation of the intermediate-duration oral MRL. In male rats, decreases in Hct, Hgb, MCV, and MCH were the most sensitive measures of hematological effects, with NOAEL and LOAEL values of 0.21 and 0.77 mg chromium(VI)/kg/day, respectively; data sets for these end points are summarized in Table A-1.

## APPENDIX A

**Table A-1. Hematological Effects in Male F/344 Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days**

	Dose (mg chromium(VI)/kg/day)				
	0	0.21	0.77	2.1	5.9
Male rats					
Hematocrit (percent)	46.0±1.1 <sup>a</sup>	44.4±0.4	43.2±0.6 <sup>b</sup>	38.7±0.6 <sup>c</sup>	33.5±0.8 <sup>c</sup>
Hemoglobin (g/dL)	15.5±0.3	15.1±0.2	14.2±0.2 <sup>c</sup>	12.0±0.3 <sup>c</sup>	10.1±0.2 <sup>c</sup>
MCV (fL)	59.5±0.4	58.6±0.5	54.9±0.5 <sup>c</sup>	47.4±0.4 <sup>c</sup>	45.0±0.7 <sup>c</sup>
MCH (pg)	19.8±0.1	19.5±0.2	17.7±0.2 <sup>c</sup>	14.8±0.2 <sup>c</sup>	16.3±0.5 <sup>c</sup>

<sup>a</sup>Mean±standard error: number of rats/group=10; number of mice/group=10

<sup>b</sup>Significantly different ( $p \leq 0.05$ ) from the control group by Dunn's or Shirley's test

<sup>c</sup>Significantly different ( $p \leq 0.01$ ) from the control group by Dunn's or Shirley's test

MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume

Source: NTP 2008a

To determine the point of departure for derivation of the intermediate-duration oral MRL, available continuous-variable models in the EPA BMDs (version 1.4.1) were fit to the data for Hct, Hgb, MCV, and MCH in male rats (NTP 2008a; Table A-1). The BMD and the 95% lower confidence limit (BMDL) calculated is an estimate of the doses associated with a change of 2 standard deviations from the control (BMDL<sub>2sd</sub>); the use of 2 standard deviations takes into consideration of the normal variability in the population and decreases the possibility of misclassifying a small change as anemia. The model-fitting procedure for continuous data is as follows. The simplest model (linear) is applied to the data while assuming constant variance. If the data are consistent with the assumption of constant variance ( $p \geq 0.1$ ), then the other continuous models (polynomial, power, and Hill models) are applied to the data. Among the models providing adequate fits to the means ( $p \geq 0.1$ ), the one with the lowest AIC for the fitted model is selected for BMD derivation. If the test for constant variance is negative, the linear model is run again while applying the power model integrated into the BMDs to account for nonhomogenous variance. If the nonhomogenous variance model provides an adequate fit ( $p \geq 0.1$ ) to the variance data, then the other continuous models are applied to the data. Among the models providing adequate fits to the means ( $p \geq 0.1$ ), the one with the lowest AIC for the fitted model is selected for BMD derivation. If the tests for both constant and nonconstant variance are negative, then the data set is considered not to be suitable for BMD modeling.

A summary of the BMDs and BMDLs for the best fitting models for each hematological end point are shown in Table A-2. For male rats, BMDL<sub>2sd</sub> values ranged from 0.37 mg chromium(VI)/kg/day for MCH to 0.71 mg chromium(VI)/kg/day for hemoglobin. None of the models provided adequate fit to the data, even with the two highest doses dropped from the analysis, for Hct. Additional details of the benchmark dose analysis for each data set modeled are presented in the last section of this worksheet. Because several hematological parameters are used to define the clinical picture of anemia, the BMDL<sub>2sd</sub> values for hemoglobin, MCV, and MCH were averaged resulting in a BMDL<sub>2sd</sub> of 0.52 mg chromium(VI)/kg/day. The intermediate-duration MRL of 0.005 mg chromium(VI)/kg/day was derived by dividing the average BMDL<sub>2sd</sub> by a composite uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

## APPENDIX A

**Table A-2. Summary of BMDs and BMDLs From the Best Fitting Models for Hematological End Points in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days**

End point	Model	Number of doses	BMD <sub>2sd</sub> (mg/kg/day) <sup>b</sup>	BMDL <sub>2sd</sub> (mg/kg/day) <sup>b</sup>
Hematocrit (percent) <sup>a</sup>	—	—	—	—
Hemoglobin (g/dL)	Polynomial (2-degree)	5	0.88	0.71
MCV (fL)	Hill	4	0.63	0.49
MCH (pg)	Linear	4	0.44	0.37

<sup>a</sup>None of the models provided an adequate fit to the data.

<sup>b</sup>Units of BMD<sub>1sd</sub> and BMDL<sub>1sd</sub> are mg chromium(VI)/kg/day.

BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; 2sd = a 2 standard deviation change from the control

Uncertainty Factors used in MRL derivation:

- [ ] 10 for use of a LOAEL
- [X] 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. Daily doses for each exposure group based on measured body weight and drinking water intake were reported by study authors (NTP 2008a). Additional information on daily doses used for intermediate-duration exposure is discussed in the experimental design section above.

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: Identification of anemia, as defined by significant alterations in hematocrit, hemoglobin, MCH, and MCV, as the critical end point for deriving an intermediate-duration oral MRL is supported by results of a 22-day study in female mice (NTP 2008a), 3-month drinking water study on sodium dichromate dihydrate in rats and mice (NTP 2007), and dietary studies on potassium dichromate in rats and mice (NTP 1996a, 1996b, 1997). In the 3-month sodium dichromate dihydrate drinking water study in male and female F344/N rats (NTP 2007), blood was collected for hematology assessments after 23 days and after 3 months of exposure; for B6C3F1 mice, hematological assessments were conducted only after 3 months. Dose-dependent hematological effects consistent with microcytic, hypochromic anemia, including decreased Hct, Hgb, MCV, and MCH, were observed in rats at the 23-day and 14-week hematological assessments; the LOAEL value at both time points in males and females was 1.7 mg chromium(VI)/kg/day (a NOAEL was not established). Hematological effects were more severe at the 23-day assessment compared to the 14 week assessment. Similar hematological effects were observed in male and female B6C3F1 mice and male BALB/c and C57BL/6 mice exposed to sodium dichromate dihydrate in drinking water for 14 weeks, with a LOAEL value of 3.1 mg chromium(VI)/kg/day (a NOAEL was not established). Results of the 3-month study in rats and mice (NTP 2007) were not selected as the basis for the

## APPENDIX A

intermediate-duration MRL because a lower LOAEL value (0.77 mg chromium(VI)/kg/day) was observed for intermediate-duration exposures in the 2-year study (NTP 2008a). In a dietary studies on potassium dichromate, microcytic, hypochromic anemia was observed in male and female Sprague-Dawley rats exposed for 9 weeks, with NOAEL and LOAEL values in males of 2.1 and 8.4 mg chromium(VI)/kg/day, respectively, and of 2.5 and 9.8 mg chromium(VI)/kg/day, respectively, in females (NTP 1996b). Similar hematological effects were observed in male and female BALB/c mice exposed to potassium dichromate in the diet for 9 weeks with NOAEL and LOAEL values in males of 7.3 and 32.2 mg chromium(VI)/kg/day, respectively, and in females of 12 and 48 mg chromium(VI)/kg/day, respectively (NTP 1996a). In a multigeneration study on dietary potassium dichromate in BALB/c mice, a LOAEL value of 7.8 for hematological effects was reported (a NOAEL was not established) (NTP 1997). Compared to the LOAEL values for hematological effects at 22 days and 3 months in male rats (0.77 mg chromium(VI)/kg/day) and female mice (0.38 mg chromium(VI)/kg/day) observed in the critical study on sodium dichromate dihydrate in drinking water, higher LOAEL values were reported in the 9-week dietary study on potassium dichromate in rats (8.4 and 9.8 mg chromium(VI)/kg/day in males and females, respectively) (EPA 1996b) and mice (32.2 and 48 mg chromium(VI)/kg/day in males and females, respectively) (NTP 1996a). The reason for the differences in LOAEL values has not been established, but could be due to different exposure media (drinking water versus feed) or differences in strain sensitivity (rats).

The erythrocyte has a high capacity for chromium(VI) uptake and binding. Chromium(VI) enters the erythrocyte through a sulfate ion channel; once inside the cell, it is rapidly reduced to reactive intermediates (chromium(V) and chromium(IV)) and binds to hemoglobin and other ligands. The chromium-hemoglobin complex is stable and remains sequestered within the cell over the life-span of the erythrocyte (Paustenbach et al. 2003). Thus, chromium(VI) uptake and subsequent sequestration as a chromium-Hgb complex by erythrocytes provides supporting information regarding the plausibility of adverse hematological effects following intermediate-duration oral exposure to chromium(VI).

#### **Details of Benchmark Dose Analysis for the Intermediate-duration Oral MRL**

***Hematocrit in Male Rats.*** The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did not provide an adequate fit (as assessed by the p-value for variance) to the data (Table A-3). The linear model was applied to the data again while applying the power model integrated into the BMDS to account for nonhomogenous variance. The nonconstant variance model also did not provide an adequate fit (as assessed by the p-value for variance). In an attempt to achieve an adequate fitting model, the highest doses were dropped from the data set. As with the full data set, statistical tests indicated that the variances were not constant across exposure groups without the highest doses. Similar to the full data set, applying the nonhomogenous variance model also did not provide an adequate fit (as assessed by the p-value for variance); therefore, the data set is considered not suitable for benchmark dose modeling.

## APPENDIX A

**Table A-3. Model Predictions for Changes in Hematocrit (Percent) in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days**

Model	Variance p-value <sup>a</sup>	p-Value for the means <sup>a</sup>	AIC	BMD <sub>2sd</sub> (mg/kg/day)	BMDL <sub>2sd</sub> (mg/kg/day)
All doses					
Linear <sup>b,c</sup>	0.03	0.02	145.49	—	—
Linear <sup>c,d</sup>	0.01	0.02	147.49	—	—
Polynomial (1-degree) <sup>c,d</sup>	0.01	0.02	147.49	—	—
Polynomial (2-degree) <sup>c,d</sup>	0.01	0.02	147.49	—	—
Polynomial (3-degree) <sup>c,d</sup>	0.01	0.02	147.49	—	—
Polynomial (4-degree) <sup>c,d</sup>	0.01	0.02	147.49	—	—
Power <sup>d</sup>	0.01	0.02	147.49	—	—
Hill <sup>d</sup>	0.01	0.28	142.76	—	—
Highest dose dropped					
Linear <sup>b,c</sup>	0.01	0.64	109.33	—	—
Linear <sup>c,d</sup>	0.02	0.43	109.21	—	—
Polynomial (1-degree) <sup>c,d</sup>	0.02	0.43	109.21	—	—
Polynomial (2-degree) <sup>c,d</sup>	0.02	0.43	109.21	—	—
Polynomial (3-degree) <sup>c,d</sup>	0.02	0.43	109.21	—	—
Power <sup>d</sup>	0.02	0.43	109.21	—	—
Hill <sup>d</sup>	0.02	0.21	111.09	—	F <sup>e</sup>
Two highest doses dropped					
Linear <sup>b,c</sup>	0.01	0.37	86.65	—	—
Linear <sup>c,d</sup>	0.02	0.15	85.61	—	—
Polynomial (1-degree) <sup>c,d</sup>	0.02	0.15	85.61	—	—
Polynomial (2-degree) <sup>c,d</sup>	0.02	0.15	85.61	—	—
Power <sup>d</sup>	0.02	0.15	85.61	—	—
Hill <sup>d</sup>	NA <sup>f</sup>				

<sup>a</sup>Values <0.1 fail to meet conventional goodness-of-fit criteria.

<sup>b</sup>Constant variance

<sup>c</sup>Restriction = non-positive

<sup>d</sup>Nonconstant variance

<sup>e</sup>F = BMDL computation failed

<sup>f</sup>NA = model failed to generate output

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; 2sd = a 2 standard deviation change from the control

Source: NTP 2008a

**Hemoglobin in Male Rats.** The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did provide an adequate fit (as assessed by the p-value for variance) to the data. The polynomial, power, and Hill models were then fit to the data with constant variance assumed. Only the Hill model provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-4); however, the model failed to generate a figure. Without a visual representation of the model, an assessment of model fit is not complete. In order to obtain an appropriate

## APPENDIX A

assessment for model fit adequacy, the highest dose was dropped from the dataset. After dropping the highest dose from the dataset, all models provided an adequate fit to the constant variance model and to the means (as assessed by the p-values for variance and means). Most models, with the exception of the Hill model, took the form of a linear model. Comparing across models, the best fitting model is generally determined by the lowest AIC. As assessed by the AIC, the linear model provides the best fit to the data. The predicted BMD<sub>2sd</sub> and BMDL<sub>2sd</sub> for the data are 0.88 and 0.71 mg chromium(VI)/kg/day (Figure A-1).

**Table A-4. Model Predictions for Changes in Hemoglobin (g/dL) in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days**

Model <sup>a</sup>	Variance p-value <sup>b</sup>	p-Value for the means <sup>b</sup>	AIC	BMD <sub>2sd</sub> (mg/kg/day)	BMDL <sub>2sd</sub> (mg/kg/day)
Linear <sup>c</sup>	0.40	<0.0001	46.98	—	—
Polynomial (1-degree) <sup>c</sup>	0.40	<0.0001	46.98	—	—
Polynomial (2-degree) <sup>c</sup>	0.40	<0.0001	46.98	—	—
Polynomial (3-degree) <sup>c</sup>	0.40	<0.0001	46.98	—	—
Polynomial (4-degree) <sup>c</sup>	0.40	<0.0001	46.98	—	—
Power	0.40	<0.0001	46.98	—	—
Hill	0.40	0.51	24.37	0.83	0.55
Highest dose dropped					
<b>Linear</b>	<b>0.36</b>	<b>0.99</b>	<b>20.37</b>	<b>0.88</b>	<b>0.71</b>
Polynomial (1-degree) <sup>c</sup>	0.36	0.99	20.37	0.88	0.71
Polynomial (2-degree) <sup>c</sup>	0.36	0.99	20.37	0.88	0.71
Polynomial (3-degree) <sup>c</sup>	0.36	0.99	20.37	0.88	0.71
Power	0.36	0.99	20.37	0.88	0.71
Hill	0.36	0.99	22.36	0.87	0.57

<sup>a</sup>Constant variance assumed for all models

<sup>b</sup>Values <0.1 fail to meet conventional goodness-of-fit criteria.

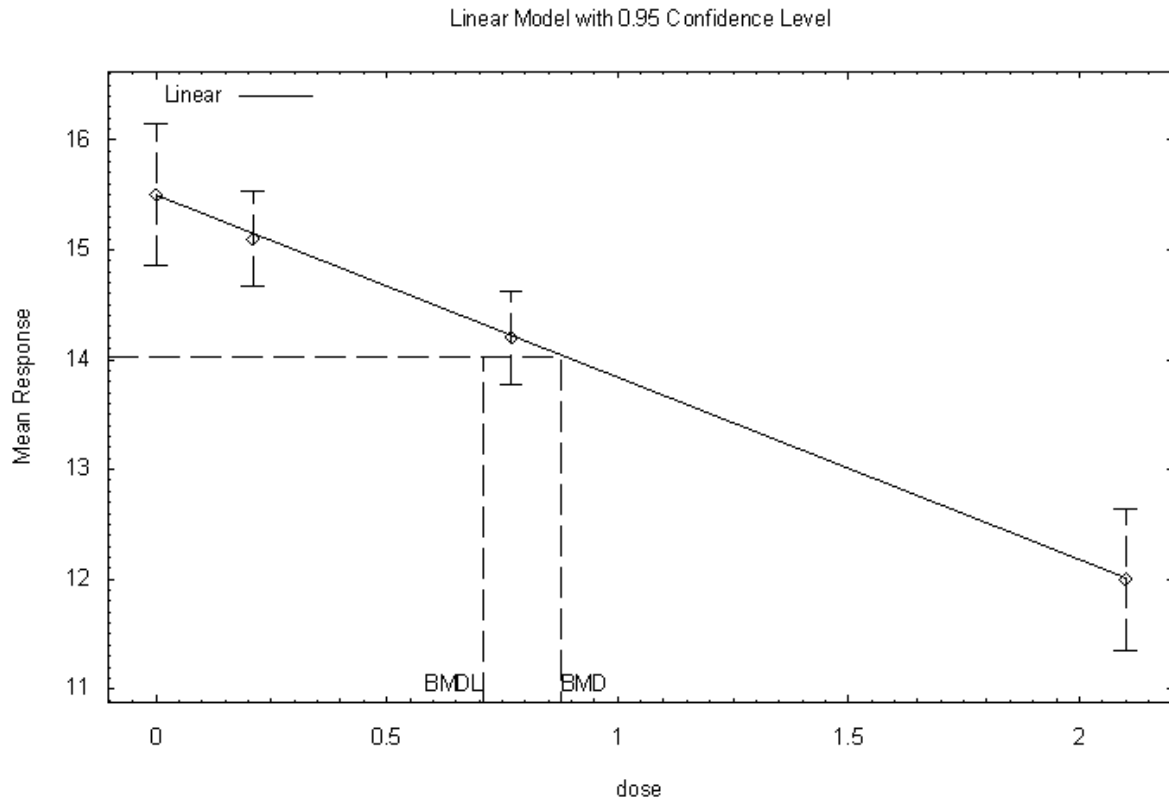
<sup>c</sup>Restriction = non-positive

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; 2sd = a 2 standard deviation change from the control

Source: NTP 2008a

## APPENDIX A

**Figure A-1. Predicted and Observed Changes in Hemoglobin in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days\***



\*BMDs and BMDLs indicated are associated with a 2 standard deviation change from the control, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

**Mean Cell Volume in Male Rats.** The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did provide an adequate fit (as assessed by the p-value for variance) to the data. The polynomial, power, and Hill models were then fit to the data with constant variance assumed. The Hill model was the only model which provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-5). Using the constant-variance Hill model, the  $BMD_{2sd}$  and  $BMDL_{2sd}$  are 0.63 mg chromium(VI)/kg and 0.49 mg chromium(VI)/kg, respectively (Figure A-2).

## APPENDIX A

**Table A-5. Model Predictions for Changes in MCV (fL) in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days**

Model <sup>a</sup>	Variance p-value <sup>b</sup>	p-Value for the means <sup>b</sup>	AIC	BMD <sub>2sd</sub> (mg/kg/day)	BMDL <sub>2sd</sub> (mg/kg/day)
Linear <sup>c</sup>	0.41	<0.0001	168.50	—	—
Polynomial (1-degree) <sup>c</sup>	0.41	<0.0001	168.50	—	—
Polynomial (2-degree) <sup>c</sup>	0.41	<0.0001	168.50	—	—
Polynomial (3-degree) <sup>c</sup>	0.41	<0.0001	168.50	—	—
Polynomial (4-degree) <sup>c</sup>	0.41	<0.0001	168.50	—	—
Power	0.41	<0.0001	168.50	—	—
<b>Hill</b>	<b>0.41</b>	<b>0.41</b>	<b>104.52</b>	<b>0.63</b>	<b>0.49</b>

<sup>a</sup>Constant variance assumed for all models

<sup>b</sup>Values <0.1 fail to meet conventional goodness-of-fit criteria.

<sup>c</sup>Restriction = non-positive

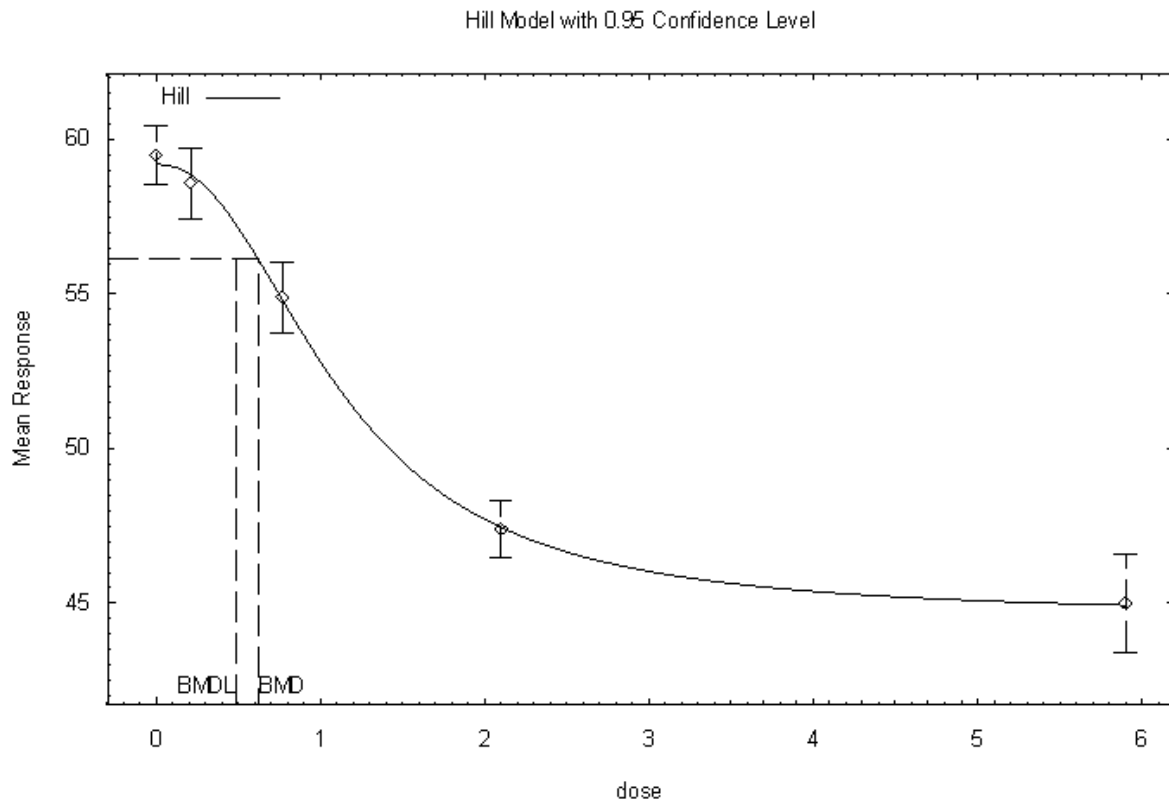
AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; 2sd = a 2 standard deviation change from the control

Source: NTP 2008a



## APPENDIX A

**Figure A-2. Predicted and Observed Changes in MCV in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days\***



\*BMDs and BMDLs indicated are associated with a 2 standard deviation change from the control, and are in units of mg chromium(VI)/kg/day

Source: NTP 2008a

**Mean Cell Hemoglobin in Male Rats.** The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did not provide an adequate fit (as assessed by the p-value for variance) to the data. The linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. The nonconstant variance model also did not provide an adequate fit (as assessed by the p-value for variance). In an attempt to achieve an adequate fitting model, the highest dose was dropped from the data-set. Unlike the full data-set, statistical tests indicated that the variances were constant across exposure groups without the highest dose. All of the models reverted to the linear model and provided an adequate fit to the means (Table A-6). Using the constant-variance Linear model (without the highest dose), the  $BMD_{2sd}$  and  $BMDL_{2sd}$  are 0.44 and 0.37 mg chromium(VI)/kg, respectively (Figure A-3).

## APPENDIX A

**Table A-6. Model Predictions for Changes in MCH (pg) in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days**

Model	Variance p-value <sup>b</sup>	p-Value for the means <sup>b</sup>	AIC	BMD <sub>2sd</sub> (mg/kg/day)	BMDL <sub>2sd</sub> (mg/kg/day)
All doses					
Linear <sup>b,c</sup>	<0.0001	<0.0001	107.27	—	—
Linear <sup>c,d</sup>	0.00	<0.0001	57.60	—	—
Polynomial (1-degree) <sup>c,d</sup>	0.00	<0.0001	57.60	—	—
Polynomial (2-degree) <sup>c,d</sup>	0.00	<0.0001	57.60	—	—
Polynomial (3-degree) <sup>c,d</sup>	0.00	<0.0001	57.60	—	—
Polynomial (4-degree) <sup>c,d</sup>	0.00	<0.0001	57.60	—	—
Power <sup>d</sup>	0.00	<0.0001	57.60	—	—
Hill <sup>d</sup>	0.00	0.02	34.64	—	—
Highest dose dropped (four doses)					
<b>Linear<sup>b,c</sup></b>	<b>0.14</b>	<b>0.15</b>	<b>-3.57</b>	<b>0.44</b>	<b>0.37</b>
Polynomial (1-degree) <sup>b,c</sup>	0.14	0.15	-3.57	0.44	0.37
Polynomial (2-degree) <sup>b,c</sup>	0.14	0.15	-3.57	0.44	0.37
Polynomial (3-degree) <sup>b,c</sup>	0.14	0.15	-3.57	0.44	0.37
Power <sup>b</sup>	0.14	0.15	-3.57	0.44	0.37
Hill <sup>b</sup>	0.14	NA <sup>e</sup>	-3.39	0.46	0.32

<sup>a</sup>Values <0.1 fail to meet conventional goodness-of-fit criteria.

<sup>b</sup>Constant variance

<sup>c</sup>Restriction = non-positive

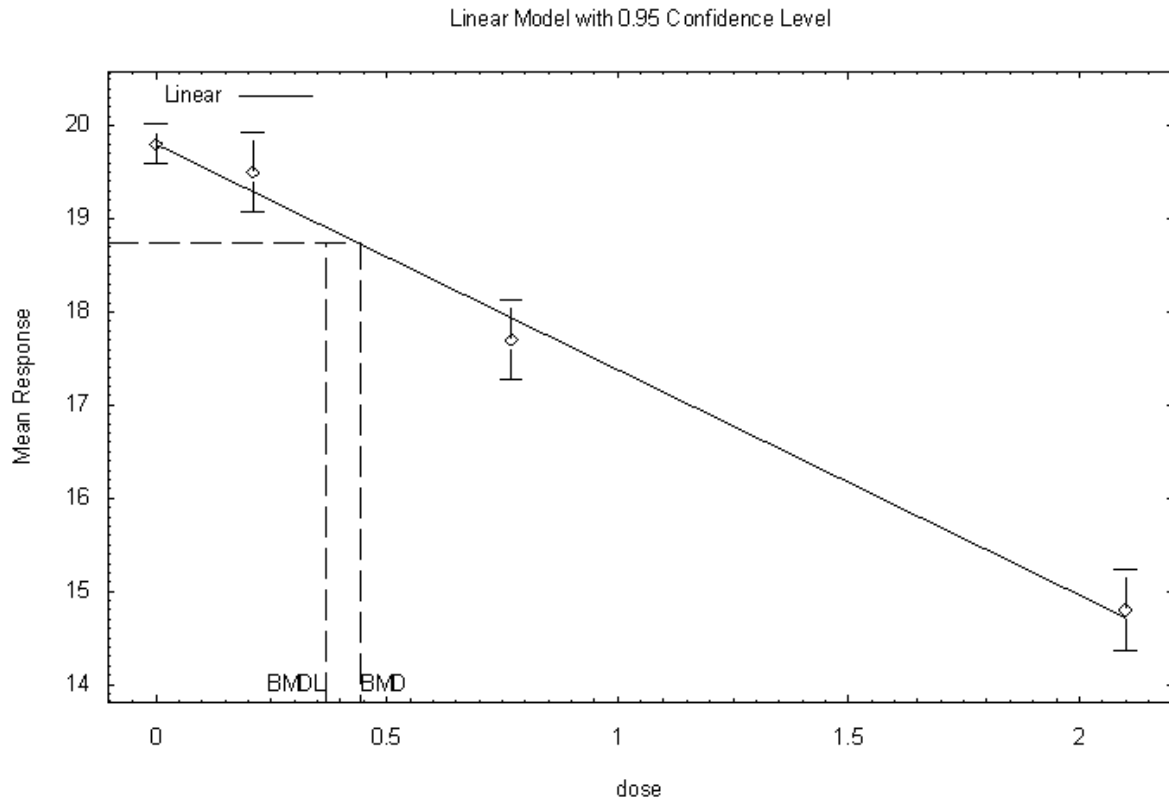
<sup>d</sup>Nonconstant variance

<sup>e</sup>NA = degrees of freedom are ≤0; the Chi-Square test for fit is not valid.

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; 2sd = a 2 standard deviation change from the control

Source: NTP 2008a

## APPENDIX A

**Figure A-3. Predicted and Observed Changes in MCH in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days\***

14:14 09/26 2008

\*BMDs and BMDLs indicated are associated with a 2 standard deviation change from the control, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

Agency Contact (Chemical Manager): Sharon Wilbur

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: Chromium(VI)  
CAS Numbers: 18540-29-9  
Date: October 2008  
Profile status: Final Draft Pre-Public Comment  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Graph Key: 95  
Species: Mouse

Minimal Risk Level: 0.001  mg chromium(VI)/kg/day  ppm

Reference: NTP. 2008a. NTP technical report on the toxicology and carcinogenesis studies of sodium dichromate dihydrate (CAS No. 7789-12-0) in F344/N rats and B6C3F1 mice (drinking water studies). Washington, DC: National Toxicology Program. NTP TR 546.  
[http://ntp.niehs.nih.gov/files/546\\_web\\_FINAL.pdf](http://ntp.niehs.nih.gov/files/546_web_FINAL.pdf). August 13, 2008.

Experimental design: Groups of F344/N rats (50/sex/group) and B6C3F1 mice (50/sex/group) were exposed to sodium dichromate dihydrate in drinking water in a 2-year toxicology and carcinogenicity study. Rats and female mice were exposed to drinking water concentrations of 0, 14.3, 57.3, 172, or 516 mg sodium dichromate dihydrate/L. NTP (2008a) calculated mean daily doses of sodium dichromate dihydrate in male rats of 0, 0.6, 2.2, 6, or 17 mg/kg (equivalent to 0, 0.21, 0.77, 2.1, or 5.9 mg chromium(VI)/kg/day, respectively), in female rats of 0, 0.7, 2.7, 7, or 20 mg/kg (equivalent to 0, 0.24, 0.94, 2.4, and 7.0 mg chromium(VI)/kg/day, respectively), and in female mice of 0, 1.1, 3.9, 9, or 25 mg/kg (equivalent to 0, 0.38, 1.4, 3.1, or 8.7 mg chromium(VI)/kg/day, respectively) over the course of the 2-year study. Male mice were exposed to 0, 14.3, 28.6, 85.7, or 257.4 mg sodium dichromate dihydrate/L. NTP (2008a) calculated mean daily doses of sodium dichromate dihydrate in male mice of 1.1, 2.6, 7, or 17 mg/kg (equivalent to 0, 0.38, 0.91, 2.4, and 5.9 mg chromium(VI)/kg/day, respectively). Mortality, clinical signs of toxicity, body weight, and water intake were assessed over the course of exposure. In a subgroup of 10 male rats and 10 female mice, blood was collected from the retroorbital sinus after exposure durations of 4 days (rats only), 22 days, 3 months, 6 months, and 1 year and evaluated for hematology (Hct; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; erythrocyte and platelet morphology; MCV; MCH; MCHC; and leukocyte count and differentials) in rats and mice and clinical chemistry (urea nitrogen, creatinine, total protein, albumin, ALT, AP, creatine kinase, SDH, and bile acids) in rats only. Blood for hematology and clinical chemistry was not obtained at the end of the 2-year treatment period. At the end of the 2-year treatment period, necropsies and histopathological assessment of comprehensive tissues, gross lesions and tissue masses were performed on all animals. No data on organ weights were presented in the study report (NTP 2008a).

Effect noted in study and corresponding doses: Study results presented in the following discussion are noncancer findings associated with chronic-duration exposures only; results of hematological and clinical chemistry assessments conducted at 4 days and from 22 days to 6 months are described in the acute- and intermediate-duration MRL worksheets, respectively; carcinogenic effects are reviewed in Section 3.2.2.7 (Oral Exposure, Cancer). In rats, no treatment-related effects were observed on survival and no clinical signs of toxicity were observed. Final body weight was significantly decreased by 12% in male and 11% in females exposed to the highest drinking water concentration. Study authors attributed alterations in body weight to decreased water intake (due to decreased palatability) rather than to a toxicological effect. Hematological assessments conducted in male rats at 1-year showed dose-dependent effects indicative of microcytic, hypochromic anemia: decreased MCH ( $\geq 0.77$  mg chromium(VI)/kg/day), decreased MCV and MCHC ( $\geq 2.1$  mg chromium(VI)/kg/day), and decreased Hgb (5.9 mg chromium(VI)/kg/day). No

## APPENDIX A

hematological effects were observed at 2.1 mg chromium(VI)/kg/day. Other hematological effects observed were decreased leukocyte (5.9 mg chromium(VI)/kg/day) and segmented neutrophil counts ( $\geq 0.77$  mg chromium(VI)/kg/day). Alterations in clinical chemistry parameters observed after 1 year of exposure were increased ALT and decreased AP ( $\geq 0.77$  mg chromium(VI)/kg/day), increased BUN and creatine kinase ( $\geq 2.1$  mg chromium(VI)/kg/day), and decreased total protein (5.9 mg chromium(VI)/kg/day). Regarding the toxicological significance of elevated ALT, as discussed below, histopathological assessment of the liver showed minimal-to-mild chronic inflammation in males ( $\geq 2.1$  mg chromium(VI)/kg/day) and females ( $\geq 0.24$  mg chromium(VI)/kg/day). However, since serum activities of AP, SDH, or bile acids were not increased, elevated serum ALT activity may have resulted from enzyme induction rather than hepatocellular injury. Histopathological evaluations revealed an increased incidence of nonneoplastic lesions in the liver (males and females), small intestine (males and females), mesenteric lymph nodes (males and females), pancreatic lymph nodes (females only) and salivary gland (females only). Hepatic lesions observed in male rats included minimal-to-mild chronic inflammation ( $\geq 0.77$  mg chromium(VI)/kg/day) and histiocytic cellular infiltration (5.9 mg chromium(VI)/kg/day); hepatic lesions in females included chronic inflammation ( $\geq 0.24$  mg chromium(VI)/kg/day), histiocytic cellular infiltration ( $\geq 0.94$  mg chromium(VI)/kg/day) and fatty change ( $\geq 0.94$  mg chromium(VI)/kg/day). Although chronic hepatic inflammation is commonly observed in aging rats, the incidence was significantly enhanced by exposure. Histiocytic cellular infiltration (minimal-to-mild) of the duodenum, was observed in males ( $\geq 0.77$  mg chromium(VI)/kg/day) and females ( $\geq 2.4$  mg chromium(VI)/kg/day). Nonneoplastic lesions of lymph nodes included the following: histiocytic cellular infiltration of mesenteric lymph nodes in males and females at  $\geq 0.77$  and  $\geq 2.4$  mg chromium(VI)/kg/day, respectively; hemorrhage of mesenteric lymph nodes in males and females at  $\geq 0.77$  and  $\geq 7.0$  mg chromium(VI)/kg/day, respectively; and histiocytic cellular infiltration of pancreatic lymph nodes in females at  $\geq 2.4$  mg chromium(VI)/kg/day only. The incidence of salivary gland atrophy was significantly increased in female rats at 2.4 mg chromium(VI)/kg/day; although the incidence was also increased at 7.0 mg chromium(VI)/kg/day, the change was not significantly different from control. Salivary atrophy was not observed in male rats. No data on organ weights were presented in the study report (NTP 2008a).

In mice, no treatment-related effects on survival or signs of toxicity were observed. Final body weight was significantly decreased by 15% in male and 8% in females exposed to the highest drinking water concentration. The study authors attributed the alterations in body weight to decreased water intake (due to decreased palatability) rather than to a toxicological effect. Hematological assessments conducted in female mice at 1 year showed dose-dependent effects indicative of microcytic, hypochromic anemia and compensatory erythropoiesis: decreased MCV and MCH ( $\geq 3.1$  mg chromium(VI)/kg/day) and increased erythrocyte count at  $\geq 3.1$  mg chromium(VI)/kg/day. Platelet count and segmented neutrophil count were decreased at 8.7 mg chromium(VI)/kg/day. Severity of hematological effects on mice was less than in rats. Clinical chemistry was not evaluated in male or female mice. Histopathological evaluations revealed an increased incidence of nonneoplastic lesions in the liver (females), small intestine (male and females), and mesenteric and pancreatic lymph nodes (males and females). Histiocytic cellular infiltration of the liver was observed in all treatment groups, with incidence and severity exhibiting dose-dependence. Chronic inflammation of the liver was also observed in females at  $\geq 3.1$  mg chromium(VI)/kg/day. In males, only pre-neoplastic (clear cell and eosinophilic foci) lesions were observed at the highest dose tested. Diffuse epithelial hyperplasia of the duodenum was observed in all treatment groups in males and females ( $\geq 0.38$  mg chromium(VI)/kg/day), with histiocytic cellular infiltration of the duodenum in males and females at  $\geq 2.4$  and 3.1 mg chromium(VI)/kg/day, respectively. Histiocytic cellular infiltration was observed in mesenteric lymph nodes in all treatment groups in males and females ( $\geq 0.38$  mg chromium(VI)/kg/day) and in pancreatic lymph nodes at  $\geq 2.4$  and  $\geq 3.1$  mg chromium(VI)/kg/day in males and females, respectively. Increased incidence of cytoplasm alteration of the pancreas (depletion of zymogen granules from acinar epithelial cells) was observed in males at

## APPENDIX A

$\geq 2.4$  mg chromium(VI)/kg/day and in females in all treatment groups ( $\geq 0.38$  mg chromium(VI)/kg/day); the toxicological significance of this finding is not clear.

Dose and end point used for MRL derivation: 0.09 mg chromium(VI)/kg/day (diffuse epithelial hyperplasia of the duodenum)

[ ] NOAEL [ ] LOAEL [X] benchmark dose (BMD)

Chronic-duration exposure of rats and mice to sodium dichromate dihydrate in drinking water resulted in microcytic, hypochromic anemia and nonneoplastic lesions of the liver, duodenum, mesenteric and pancreatic lymph nodes, pancreas and salivary gland. Based on comparison of LOAEL values (Table A-7), the lowest LOAELs were observed for histopathological changes of the liver (chronic inflammation in female rats and histiocytic cellular infiltration in female mice), duodenum (diffuse epithelial hyperplasia in male and female mice), mesenteric lymph node (histiocytic cellular infiltration in male and female mice) and pancreas (cytoplasm cellular alteration of acinar epithelial cells in female mice), with effects occurring in all treatment groups. Therefore, all effects with LOAEL values of the lowest dose tested were considered as the possible the critical effect for derivation of the chronic-duration oral MRL. Incidence data for these lesions are summarized in Table A-8.

**Table A-7. NOAEL and LOAEL Values for Effects in Rats and Mice Exposed to Sodium Dichromate Dihydrate in Drinking Water for 1–2 Years**

Effect or tissue with lesion	NOAEL/LOAEL value (mg chromium(VI)/kg/day)			
	Male rats	Female rats	Male mice	Female mice
Hematological effects	0.21/0.77	N/A	N/A	1.4/3.1
Liver	0.21/0.77	0.24 <sup>a</sup>	2.4/5.9 <sup>c</sup>	0.38 <sup>a</sup>
Duodenum	0.21/0.77	0.94/2.4	0.38 <sup>a</sup>	0.38 <sup>a</sup>
Mesenteric lymph node	0.21/0.77	0.94/2.4	0.38 <sup>a</sup>	0.38 <sup>a</sup>
Pancreatic lymph node	N/O	0.94/2.4	0.91/2.4	1.4/3.1
Pancreas	N/O	N/O	0.91/2.4	0.38 <sup>a</sup>
Salivary gland	N/O	2.4 <sup>b</sup>	N/O	N/O

<sup>a</sup>No NOAEL value was identified; effects occurred in all treatment groups

<sup>b</sup>Not observed at other doses

<sup>c</sup>Pre-neoplastic lesions

LOAEL = lowest-observed-adverse-effect level; N/A = not assessed; N/O = effect not observed; NOAEL = no-observed-adverse-effect level

Source: NTP 2008a

## APPENDIX A

**Table A-8. Incidence Data for Nonneoplastic Lesions<sup>a</sup> Occurring in All Treatment Groups of Female F/344 Rats and Male and Female B6C3F1 Mice Exposed to Sodium Dichromate Dihydrate in Drinking Water for 2 Years**

	Dose (mg chromium(VI)/kg/day)				
	0	0.24	0.94	2.4	7.0
<b>Female rats</b>					
Liver, chronic inflammation	12/50 <sup>b</sup> (1.3)	21/50 <sup>c</sup> (1.2)	28/50 <sup>d</sup> (1.3)	35/50 <sup>d</sup> (1.6)	39/50 <sup>d</sup> (2.1)
	Dose (mg chromium(VI)/kg/day)				
	0	0.38	0.91	2.4	5.9
<b>Male mice</b>					
Duodenum: diffuse epithelial hyperplasia	0/50	11/50 <sup>d</sup> (2.0)	18/50 <sup>d</sup> (1.6)	42/50 <sup>d</sup> (2.1)	32/50 <sup>c</sup> (2.1)
Mesenteric lymph node: histiocytic cellular infiltration	14/47 (1.2)	38/47 <sup>d</sup> (1.1)	31/49 <sup>d</sup> (1.2)	32/49 <sup>d</sup> (1.5)	42/46 <sup>c</sup> (2.5)
	Dose (mg chromium(VI)/kg/day)				
	0	0.38	1.4	3.1	8.7
<b>Female mice</b>					
Duodenum: diffuse epithelial hyperplasia	0/50	16/50 <sup>d</sup> (1.6)	35/50 <sup>d</sup> (1.7)	31/50 <sup>d</sup> (1.6)	42/50 <sup>d</sup> (2.2)
Mesenteric lymph node: histiocytic cellular infiltration	3/46 (1.0)	29/48 <sup>d</sup> (1.3)	26/46 <sup>d</sup> (1.1)	40/50 <sup>d</sup> (1.9)	42/50 <sup>d</sup> (2.7)
Liver: histiocytic cellular infiltration	2/49 (1.0)	15/50 <sup>d</sup> (1.1)	23/50 <sup>d</sup> (1.0)	32/50 <sup>d</sup> (1.0)	45/50 <sup>d</sup> (1.9)
Pancreas: acinus, cytoplasmic alteration	0/48	6/50 <sup>c</sup> (2.5)	6/49 <sup>c</sup> (2.0)	14/50 <sup>d</sup> (2.4)	32/50 <sup>d</sup> (2.6)

<sup>a</sup>Lesion severity (1=minimal, 2=mild, 3=moderate, 4=marked)

<sup>b</sup>Number of animals with lesions/number of animals examined

<sup>c</sup>Significantly different ( $p \leq 0.05$ ) from the control group by Dunn's or Shirley's test

<sup>d</sup>Significantly different ( $p \leq 0.01$ ) from the control group by Dunn's or Shirley's test

Source: NTP 2008a

To determine the specific end point for derivation of the chronic-duration oral MRL, all available dichotomous models in the EPA (version 1.4.1) were fit to the incidence data for selected end points in female rats and male and female mice exposed to sodium dichromate dihydrate in drinking water for 2 years (NTP 2008a) (Table A-8). To provide potential points of departure for MRL derivation, 10% extra risk was selected as the benchmark response in accordance with U.S. EPA (2000) technical guidance for benchmark dose analysis to select a response level near the lower range of detectable observations. The  $BMD_{10s}$  and  $BMDL_{10s}$  from the best fitting models for nonneoplastic lesions of the liver (female rats and mice), duodenum (male and female mice), mesenteric lymph nodes (male and female mice), and pancreas (female mice) are shown in Table A-9. For chronic inflammation of the liver in female rats, the log-logistic model provided the best fit, with  $BMD_{10}$  and  $BMDL_{10}$  values of 0.22 and 0.14 mg chromium(VI)/kg/day, respectively. For diffuse epithelial hyperplasia in male mice, the multistage and quantal linear models provided the best fit, with  $BMD_{10}$  and  $BMDL_{10}$  values of 0.16 and 0.13 mg chromium(VI)/kg/day, respectively. For diffuse epithelial hyperplasia in female mice, the best

## APPENDIX A

fit was provided by several models (gamma, multistage, quantal linear, and weibull) with BMD<sub>10</sub> and BMDL<sub>10</sub> values of 0.12 and 0.09 mg chromium(VI)/kg/day, respectively. For histiocytic alteration of the liver and cytoplasm alteration of the pancreas in female mice, the log-logistic model provided the best fit, with BMD<sub>10</sub> and BMDL<sub>10</sub> values of 0.17 and 0.12 mg chromium(VI)/kg/day, respectively, for liver lesions and of 0.68 and 0.52 mg chromium(VI)/kg/day, respectively, for pancreas lesions. For lesions of the mesenteric lymph nodes in male and female mice, none of the models provided adequate fit to the data, even with the two highest doses dropped from the analysis; thus, data sets for these lesions were considered not suitable for BMD analysis. Additional details of the benchmark dose analysis for each data set modeled are presented in the last section of this worksheet. Based on the lowest BMDL<sub>10</sub> value of 0.09 mg chromium(VI)/kg/day, diffuse epithelial hyperplasia of the duodenum in female mice was selected as the point of departure for derivation of the chronic-duration oral MRL. The chronic-duration oral MRL based on nonneoplastic lesions of the duodenum in female mice is expected to be protective for all other adverse effects observed in the 2-year drinking water study (e.g., hematological effects and lesions of the liver, lymph nodes, pancreas, and salivary gland). The chronic-duration MRL of 0.001 mg chromium(VI)/kg/day was derived by dividing the BMDL<sub>10</sub> by a composite uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

**Table A-9. Summary of BMD<sub>10</sub> and BMDL<sub>10</sub> from the Best Fitting Models for Nonneoplastic Lesions of the Liver, Duodenum, Mesenteric Lymph Nodes, and Pancreas in Female Rats and Male and Female Mice After Exposure to Sodium Dichromate Dihydrate in Drinking Water for 2 Years**

End point	Species/sex	Model	Number of doses	BMD <sup>a</sup> (mg/kg/day)	BMDL <sup>a</sup> (mg/kg/day)
Liver, chronic inflammation	Rat/female	Log-logistic	5	0.22	0.14
Duodenum: diffuse epithelial hyperplasia	Mouse/male	1-Degree polynomial multistage/quantal linear	4	0.16	0.13
Mesenteric lymph node: histiocytic cellular infiltration <sup>b</sup>	Mouse/male	—	—	—	—
<b>Duodenum: diffuse epithelial hyperplasia</b>	<b>Mouse/female</b>	<b>Gamma/Multistage/quantal linear/weibull</b>	<b>3</b>	<b>0.12</b>	<b>0.09</b>
Mesenteric lymph node: histiocytic cellular infiltration <sup>b</sup>	Mouse/female	—	—	—	—
Liver: histiocytic cellular infiltration	Mouse/female	Log-logistic	5	0.17	0.12
Pancreas: acinus, cytoplasmic alteration	Mouse/female	Log-logistic	5	0.68	0.52

<sup>a</sup>BMDs and BMDLs from dichotomous data are associated with a 10% extra risk; doses are in terms of mg chromium(VI)/kg/day.

<sup>b</sup>None of the models provided an adequate fit to the data.

BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a



## APPENDIX A

Uncertainty Factors used in MRL derivation:

- 10 for use of a LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No. Daily doses for each treatment group were reported by study authors (NTP 2008a) based on body weights and water intake over the 2-year exposure period.

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: Selection of nonneoplastic lesions of the duodenum in female mice is as the critical effect for the chronic-duration oral MRL is supported by observations from the same study showing adverse gastrointestinal effects in male mice (diffuse epithelial hyperplasia at  $\geq 0.38$  mg chromium(VI)/kg/day and histiocytic cellular infiltration at 5.9 mg chromium(VI)/kg/day) and in male and female rats (histiocytic cellular infiltration at  $\geq 0.77$  and  $\geq 0.94$  mg chromium(VI)/kg/day, respectively) exposed to sodium dichromate dihydrate in drinking water for 2 years (NTP 2008a). Although no other chronic-duration studies on oral chromium(VI) in animals were identified, a 3-month study on sodium dichromate dihydrate in drinking water revealed adverse gastrointestinal effects in rats and mice (including a comparative study in 3 mouse strains) (NTP 2007). Epithelial hyperplasia and histiocytic cellular infiltration of the duodenum was observed at  $\geq 3.1$  and  $\geq 5.9$  mg chromium(VI)/kg/day, respectively, in male and female B6C3F1 mice. Similar nonneoplastic lesions of the duodenum were also reported in the 3-month comparative study in male B6C3F1, BALB/c, and C57BL/6 mice, with epithelial hyperplasia at  $\geq 2.8$  mg chromium(VI)/kg/day in B6C3F1 and BALB/c strains and  $\geq 5.2$  in the C57BL/6 strain, and histiocytic cellular infiltration at  $\geq 2.8$  mg chromium(VI)/kg/day in B6C3F1 and C57BL/6 strains and  $\geq 5.2$  mg chromium(VI)/kg/day in the BALB/c strain. In male and female F344/N rats, histiocytic cellular infiltration was observed at  $\geq 3.5$  mg chromium(VI)/kg/day. At a higher daily dose (20.9 mg chromium(VI)/kg/day), ulcer, epithelial regenerative focal hyperplasia, and epithelial focal squamous metaplasia of the glandular stomach were observed.

**Details of Benchmark Dose Analysis for the Chronic-duration Oral MRL**

***Chronic Inflammation of the Liver in Female Rats.*** As assessed by the chi-square goodness-of-fit statistic, only the log-logistic model provided an adequate fit ( $X^2$  p-value  $\geq 0.1$ ) to the data (Table A-10). Based on the log-logistic model, the BMD associated with a 10% extra risk was 0.22 mg chromium(VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.14 mg chromium(VI)/kg/day (Figure A-4).

## APPENDIX A

**Table A-10. BMD<sub>10</sub> and BMDL<sub>10</sub> Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Chronic Inflammation of the Liver in Female Rats Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years**

Model	BMD <sub>10</sub> (mg/kg/day)	BMDL <sub>10</sub> (mg/kg/day)	$\chi^2$ p-value	AIC
Gamma <sup>a</sup>	0.51	0.37	0.04	317.97
Logistic	0.84	0.65	0.01	321.45
<b>Log-logistic<sup>b</sup></b>	<b>0.22</b>	<b>0.14</b>	<b>0.37</b>	<b>312.57</b>
Multi-stage <sup>c</sup>	0.51	0.37	0.04	317.97
Probit	0.88	0.70	0.01	321.80
Log-probit <sup>b</sup>	0.89	0.61	0.01	320.86
Quantal linear	0.51	0.37	0.04	317.97
Weibull <sup>a</sup>	0.51	0.37	0.04	317.97

<sup>a</sup>Restrict power  $\geq 1$

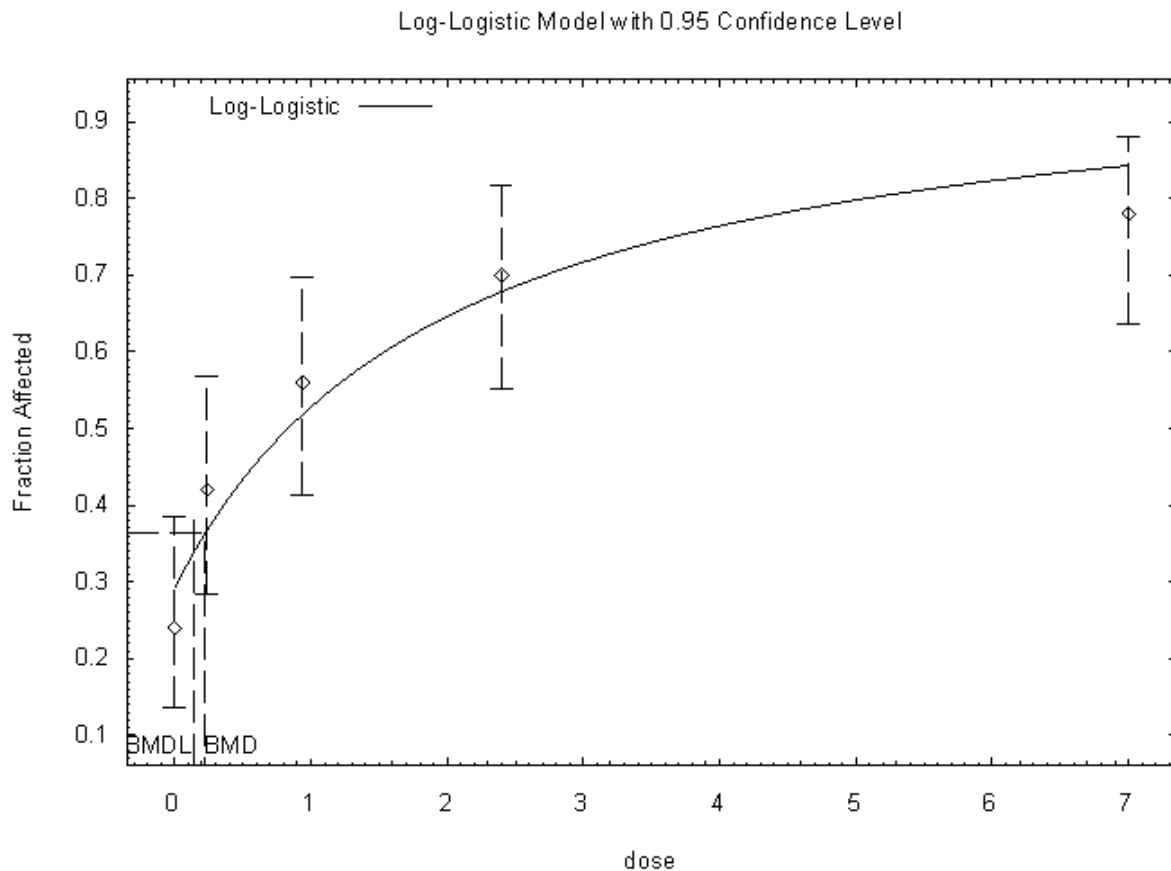
<sup>b</sup>Slope restricted to  $> 1$

<sup>c</sup>Restrict betas  $\geq 0$ ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

**Figure A-4. Predicted and Observed Incidence of Chronic Inflammation of the Liver in Female Rats Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years\***



13:34 04/08 2008

\*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

***Diffuse Epithelial Hyperplasia of the Duodenum in Male Mice.*** As assessed by the chi-square goodness-of-fit statistic, none of the models provided an adequate fit ( $X^2$  p-value  $\geq 0.1$ ) to the full dataset (Table A-11). In order to achieve a statistically fit model, the highest dose was dropped. This is determined to be appropriate, as the area of concern is with the low-dose region of the response curve. After dropping the highest dose, the gamma, log-logistic, multistage, log-probit, quantal linear, and weibull models provided adequate fits to the data ( $X^2$  p-value  $> 0.1$ ). Comparing across models, a better fit is generally indicated by a lower AIC (EPA 2000). As assessed by AIC, the 1-degree polynomial multistage model provided the best fit to the data (Figure A-5). Based on the multistage model, the BMD associated with a 10% extra risk was 0.16 mg chromium(VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.13 mg chromium(VI)/kg/day.

## APPENDIX A

**Table A-11. BMD<sub>10</sub> and BMDL<sub>10</sub> Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Diffuse Epithelial Hyperplasia in the Duodenum in Male Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years**

Model	BMD <sub>10</sub> (mg/kg/day)	BMDL <sub>10</sub> (mg/kg/day)	$\chi^2$ p-value	AIC
All doses				
Gamma <sup>a</sup>	0.31	0.25	0.00	270.99
Logistic	0.90	0.74	0.00	296.25
Log-logistic <sup>b</sup>	0.15	0.12	0.00	247.93
Multi-stage <sup>c</sup>	0.31	0.25	0.00	270.99
Probit	0.90	0.76	0.00	296.18
Log-probit <sup>b</sup>	0.48	0.36	0.00	274.38
Quantal linear	0.31	0.25	0.00	270.99
Weibull <sup>a</sup>	0.31	0.25	0.00	270.99
Highest dose dropped (four doses modeled)				
Gamma <sup>a</sup>	0.22	0.14	0.43	167.67
Logistic	0.47	0.39	0.03	177.09
Log-logistic <sup>b</sup>	0.26	0.15	0.20	169.23
Multi-stage <sup>d</sup>	0.16	<b>0.13</b>	<b>0.52</b>	<b>166.34</b>
Probit	0.45	0.37	0.04	176.19
Log-probit <sup>b</sup>	0.28	0.23	0.33	167.41
Quantal linear	0.16	<b>0.13</b>	<b>0.52</b>	<b>166.34</b>
Weibull <sup>a</sup>	0.22	0.14	0.47	167.50

<sup>a</sup>Restrict power  $\geq 1$

<sup>b</sup>Slope restricted to  $> 1$

<sup>c</sup>Restrict betas  $\geq 0$ ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.

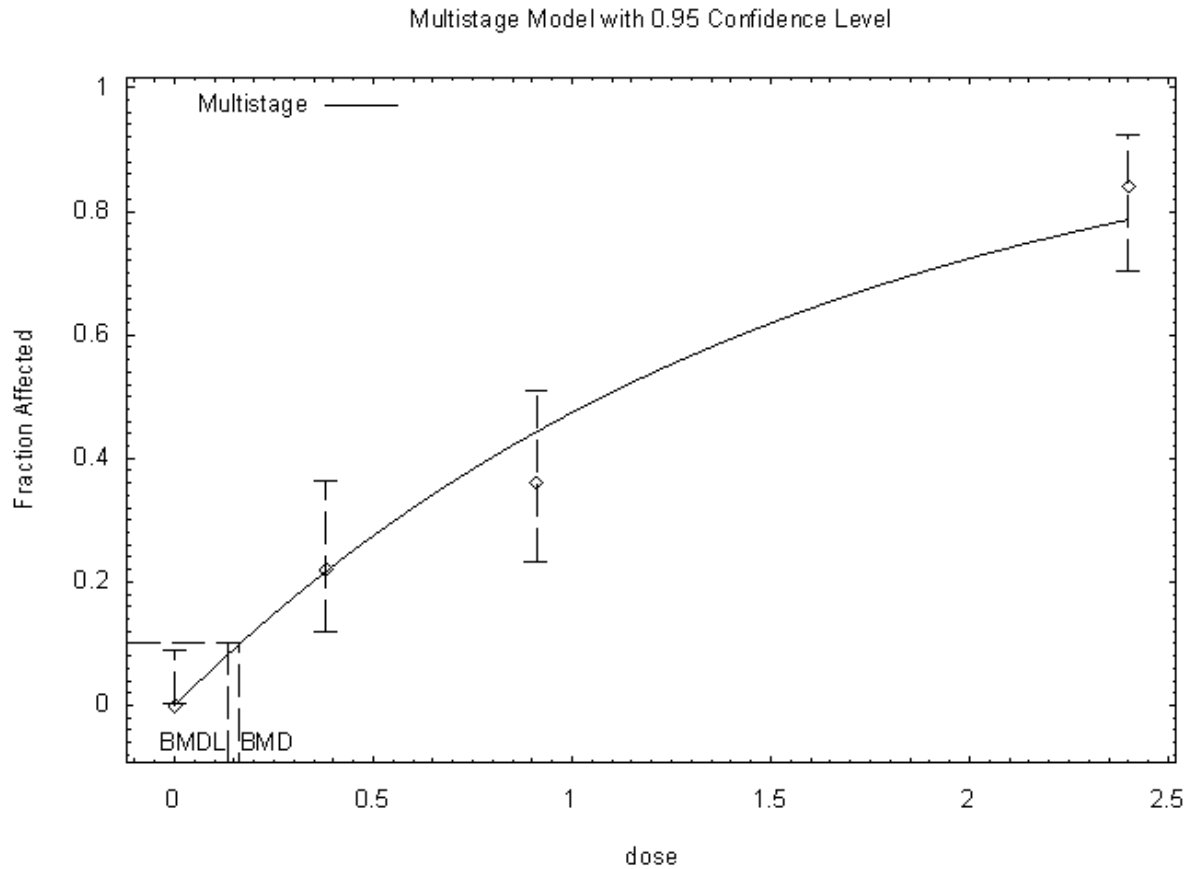
<sup>d</sup>Restrict betas  $\geq 0$ ; lowest degree polynomial (up to n-2) with an adequate fit is reported; degree polynomial = 1.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

## APPENDIX A

**Figure A-5. Predicted and Observed Incidence of Diffuse Epithelial Hyperplasia in the Duodenum of Male Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years\***



15:45 04/08 2008

\*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

***Histiocytic Cellular Infiltration of the Mesenteric Lymph Nodes in Male Mice.*** As assessed by the chi-square goodness-of-fit statistic, none of the models provided an adequate fit ( $X^2$  p-value  $\geq 0.1$ ) to the full dataset (Table A-12). In order to achieve a statistically fit model, the highest dose was dropped. This is determined to be appropriate, as the area of concern is with the low-dose region of the response curve. Dropping the highest dose did not result in adequately fitting models, nor did dropping the two highest doses. This dataset is considered not suitable for benchmark dose modeling.

## APPENDIX A

**Table A-12. BMD<sub>10</sub> and BMDL<sub>10</sub> Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Histiocytic Cellular Infiltration in Mesenteric Lymph Nodes of Male Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years**

Model	BMD <sub>10</sub> (mg/kg/day)	BMDL <sub>10</sub> (mg/kg/day)	$\chi^2$ p-value	AIC
All doses				
Gamma <sup>a</sup>	0.38	0.26	0.00	285.94
Logistic	0.53	0.39	0.00	286.38
Log-logistic <sup>b</sup>	0.16	0.08	0.00	284.48
Multi-stage <sup>c</sup>	0.43	0.26	0.00	287.88
Probit	0.56	0.43	0.00	286.35
Log-probit <sup>b</sup>	0.83	0.52	0.00	289.36
Quantal linear	0.38	0.26	0.00	285.94
Weibull <sup>a</sup>	0.38	0.26	0.00	285.94
Highest dose dropped (four doses modeled)				
Gamma <sup>a</sup>	0.47	0.24	0.00	258.50
Logistic	0.61	0.35	0.00	259.04
Log-logistic <sup>b</sup>	0.21	0.08	0.00	256.81
Multi-stage <sup>d</sup>	0.47	0.24	0.00	258.50
Probit	0.63	0.37	0.00	259.08
Log-probit <sup>b</sup>	1.24	0.56	0.00	261.28
Quantal linear	0.47	0.24	0.00	258.50
Weibull <sup>a</sup>	0.47	0.24	0.00	258.50
Two highest doses dropped (three doses modeled)				
Gamma <sup>a</sup>	0.11	0.07	0.00	187.77
Logistic	0.17	0.12	0.00	189.97
Log-logistic <sup>b</sup>	0.05	0.03	0.00	183.77
Multi-stage <sup>e</sup>	0.11	0.07	0.00	187.77
Probit	0.17	0.12	0.00	190.12
Log-probit <sup>b</sup>	0.17	0.11	0.00	190.37
Quantal linear	0.11	0.07	0.00	187.77
Weibull <sup>a</sup>	0.11	0.07	0.00	187.77

<sup>a</sup>Restrict power  $\geq 1$

<sup>b</sup>Slope restricted to  $> 1$

<sup>c</sup>Restrict betas  $\geq 0$ ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.

<sup>d</sup>Restrict betas  $\geq 0$ ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 2-degree polynomial is reported.

<sup>e</sup>Restrict betas  $\geq 0$ ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 1-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

## APPENDIX A

***Diffuse Epithelial Hyperplasia of the Duodenum in Female Mice.*** As assessed by the chi-square goodness-of-fit statistic, none of the models provided an adequate fit ( $X^2$  p-value  $\geq 0.1$ ) to the data (Table A-13). In order to achieve a statistically fit model, the highest dose was dropped. This is determined to be appropriate, as the area of concern is with the low-dose region of the response curve. After dropping the highest dose, an adequate fit was still not achieved. After dropping the two highest doses, all of the models except for the logistic and probit models provided an adequate fit ( $X^2$  p-value  $\geq 0.1$ ) to the data. Comparing across models, a better fit is generally indicated by a lower AIC (EPA 2000). As assessed by AIC, the gamma, multistage, quantal linear, and weibull models generated identical goodness of fit statistics and benchmark doses, as these models all took the form of a 1-degree polynomial multistage model which provides the best fit (Figure A-6). Based on these models, the BMD associated with a 10% extra risk was 0.12 mg chromium(VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.09 mg chromium(VI)/kg/day.

## APPENDIX A

**Table A-13. BMD<sub>10</sub> and BMDL<sub>10</sub> Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Diffuse Epithelial Hyperplasia in the Duodenum of Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years**

Model	BMD <sub>10</sub> (mg/kg/day)	BMDL <sub>10</sub> (mg/kg/day)	x <sup>2</sup> p-value	AIC
All doses				
Gamma <sup>a</sup>	0.34	0.27	0.00	275.34
Logistic	0.88	0.72	0.00	293.17
Log-logistic <sup>b</sup>	0.12	0.09	0.04	245.54
Multi-stage <sup>c</sup>	0.34	0.27	0.00	275.34
Probit	0.93	0.78	0.00	294.03
Log-probit <sup>b</sup>	0.52	0.38	0.00	279.54
Quantal linear	0.34	0.27	0.00	275.34
Weibull <sup>a</sup>	0.34	0.27	0.00	275.34
Highest dose dropped (four doses modeled)				
Gamma <sup>a</sup>	0.20	0.16	0.00	213.41
Logistic	0.55	0.46	0.00	236.10
Log-logistic <sup>b</sup>	0.11	0.08	0.04	200.07
Multi-stage <sup>d</sup>	0.20	0.16	0.00	213.41
Probit	0.54	0.45	0.00	235.61
Log-probit <sup>b</sup>	0.29	0.24	0.00	220.04
Quantal linear	0.20	0.16	0.00	213.41
Weibull <sup>a</sup>	0.20	0.16	0.00	213.41
Two highest doses dropped (three doses modeled)				
<b>Gamma<sup>a</sup></b>	<b>0.12</b>	<b>0.09</b>	<b>0.87</b>	<b>126.06</b>
Logistic	0.34	0.27	0.00	141.77
Log-logistic <sup>b</sup>	0.12	0.06	1.00	127.77
<b>Multi-stage<sup>e</sup></b>	<b>0.12</b>	<b>0.09</b>	<b>0.87</b>	<b>126.06</b>
Probit	0.32	0.26	0.00	140.65
Log-probit <sup>b</sup>	0.20	0.16	0.48	127.17
<b>Quantal linear</b>	<b>0.12</b>	<b>0.09</b>	<b>0.87</b>	<b>126.06</b>
<b>Weibull<sup>a</sup></b>	<b>0.12</b>	<b>0.09</b>	<b>0.87</b>	<b>126.06</b>

<sup>a</sup>Restrict power >=1

<sup>b</sup>Slope restricted to >1

<sup>c</sup>Restrict betas >=0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.

<sup>d</sup>Restrict betas >=0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 2-degree polynomial is reported.

<sup>e</sup>Restrict betas >=0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 1-degree polynomial is reported.

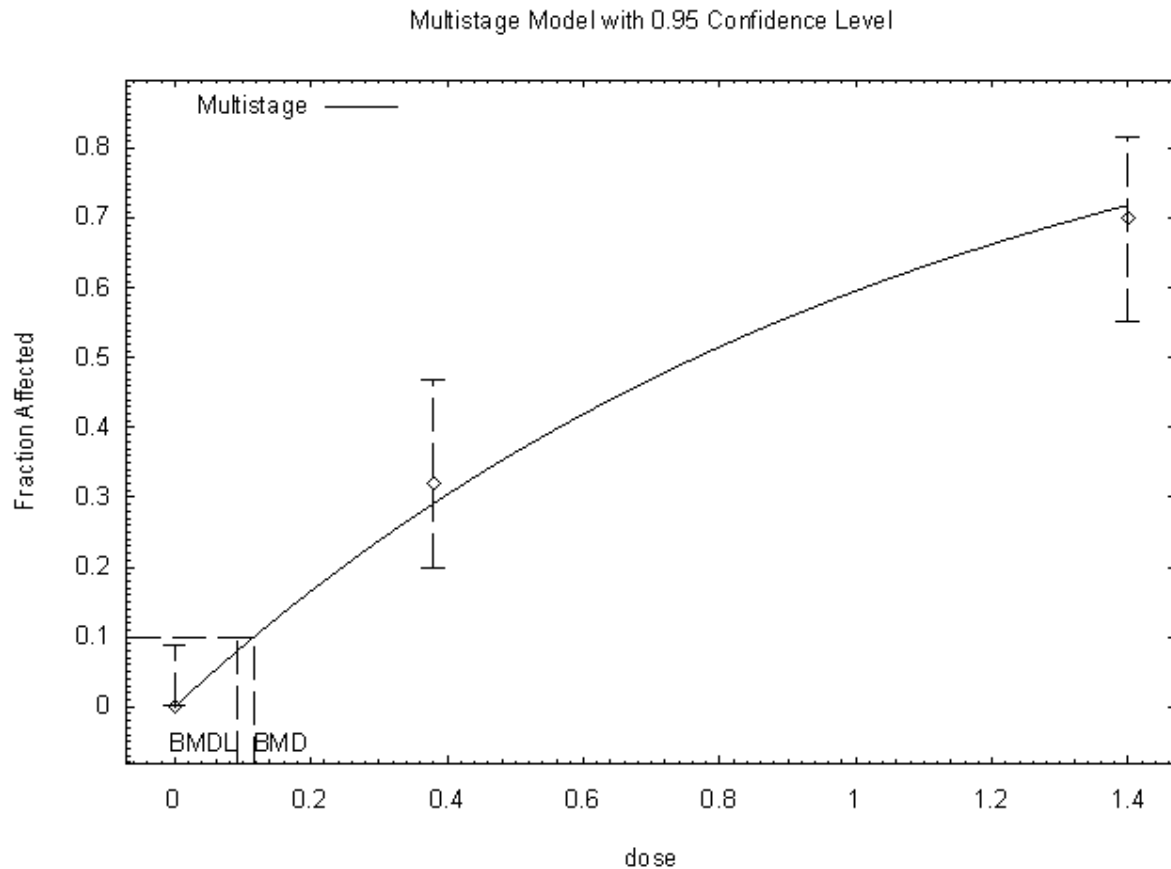
AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a



## APPENDIX A

**Figure A-6. Predicted and Observed Incidence of Diffuse Epithelial Hyperplasia in the Duodenum of Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years\***



\*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium (VI)/kg/day.

Source: NTP 2008a

***Histiocytic Cellular Infiltration of the Mesenteric Lymph Nodes in Female Mice.*** As assessed by the chi-square goodness-of-fit statistic, none of the models provided an adequate fit ( $X^2$  p-value  $\geq 0.1$ ) to the full dataset (Table A-14). In order to achieve a statistically fit model, the highest dose was dropped. This is determined to be appropriate, as the area of concern is with the low-dose region of the response curve. Dropping the highest dose did not result in adequately fitting models, nor did dropping the two highest doses. This dataset is not suitable for benchmark dose modeling.

## APPENDIX A

**Table A-14. BMD<sub>10</sub> and BMDL<sub>10</sub> Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Histiocytic Cellular Infiltration in Mesenteric Lymph Nodes of Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years**

Model	BMD <sub>10</sub> (mg/kg/day)	BMDL <sub>10</sub> (mg/kg/day)	x <sup>2</sup> p-value	AIC
All doses				
Gamma <sup>a</sup>	0.41	0.30	0.00	282.46
Logistic	0.77	0.61	0.00	290.18
Log-logistic <sup>b</sup>	0.09	0.06	0.00	263.55
Multi-stage <sup>c</sup>	0.41	0.30	0.00	282.46
Probit	0.85	0.69	0.00	291.41
Log-probit <sup>b</sup>	0.68	0.47	0.00	285.85
Quantal linear	0.41	0.30	0.00	282.46
Weibull <sup>a</sup>	0.41	0.30	0.00	282.46
Highest dose dropped (four doses modeled)				
Gamma <sup>a</sup>	0.20	0.15	0.00	224.84
Logistic	0.40	0.33	0.00	230.81
Log-logistic <sup>b</sup>	0.07	0.05	0.00	215.19
Multi-stage <sup>d</sup>	0.20	0.15	0.00	224.84
Probit	0.40	0.34	0.00	230.85
Log-probit <sup>b</sup>	0.37	0.24	0.00	231.76
Quantal linear	0.20	0.15	0.00	224.84
Weibull <sup>a</sup>	0.20	0.15	0.00	224.84
Two highest doses dropped (three doses modeled)				
Gamma <sup>a</sup>	0.14	0.10	0.00	172.32
Logistic	0.31	0.24	0.00	178.99
Log-logistic <sup>b</sup>	0.07	0.04	0.00	164.47
Multi-stage <sup>e</sup>	0.14	0.10	0.00	172.32
Probit	0.30	0.23	0.00	178.74
Log-probit <sup>b</sup>	0.21	0.15	0.00	178.11
Quantal linear	0.14	0.10	0.00	172.32
Weibull <sup>a</sup>	0.14	0.10	0.00	172.32

<sup>a</sup>Restrict power  $\geq 1$

<sup>b</sup>Slope restricted to  $> 1$

<sup>c</sup>Restrict betas  $\geq 0$ ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.

<sup>d</sup>Restrict betas  $\geq 0$ ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 2-degree polynomial is reported.

<sup>e</sup>Restrict betas  $\geq 0$ ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 1-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

## APPENDIX A

***Histiocytic Cellular Infiltration of the Liver in Female Mice.*** As assessed by the chi-square goodness-of-fit statistic, only the log-logistic model provided an adequate fit ( $X^2$  p-value  $\geq 0.1$ ) to the data (Table A-15). Based on the log-logistic model, the BMD associated with a 10% extra risk was 0.17 mg chromium(VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.12 mg chromium(VI)/kg/day (Figure A-7).

**Table A-15. BMD<sub>10</sub> and BMDL<sub>10</sub> Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Histiocytic Cellular Infiltration in the Liver of Female Rats Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years**

Model	BMD <sub>10</sub> (mg/kg/day)	BMDL <sub>10</sub> (mg/kg/day)	$\chi^2$ p-value	AIC
Gamma <sup>a</sup>	0.35	0.28	0.08	255.40
Logistic	0.85	0.70	0.00	267.56
<b>Log-logistic<sup>b</sup></b>	<b>0.17</b>	<b>0.12</b>	<b>0.44</b>	<b>251.36</b>
Multi-stage <sup>c</sup>	0.35	0.28	0.08	255.40
Probit	0.88	0.75	0.00	268.64
Log-probit <sup>b</sup>	0.62	0.48	0.01	260.00
Quantal linear	0.35	0.28	0.08	255.40
Weibull <sup>a</sup>	0.35	0.28	0.08	255.40

<sup>a</sup>Restrict power  $\geq 1$

<sup>b</sup>Slope restricted to  $>1$

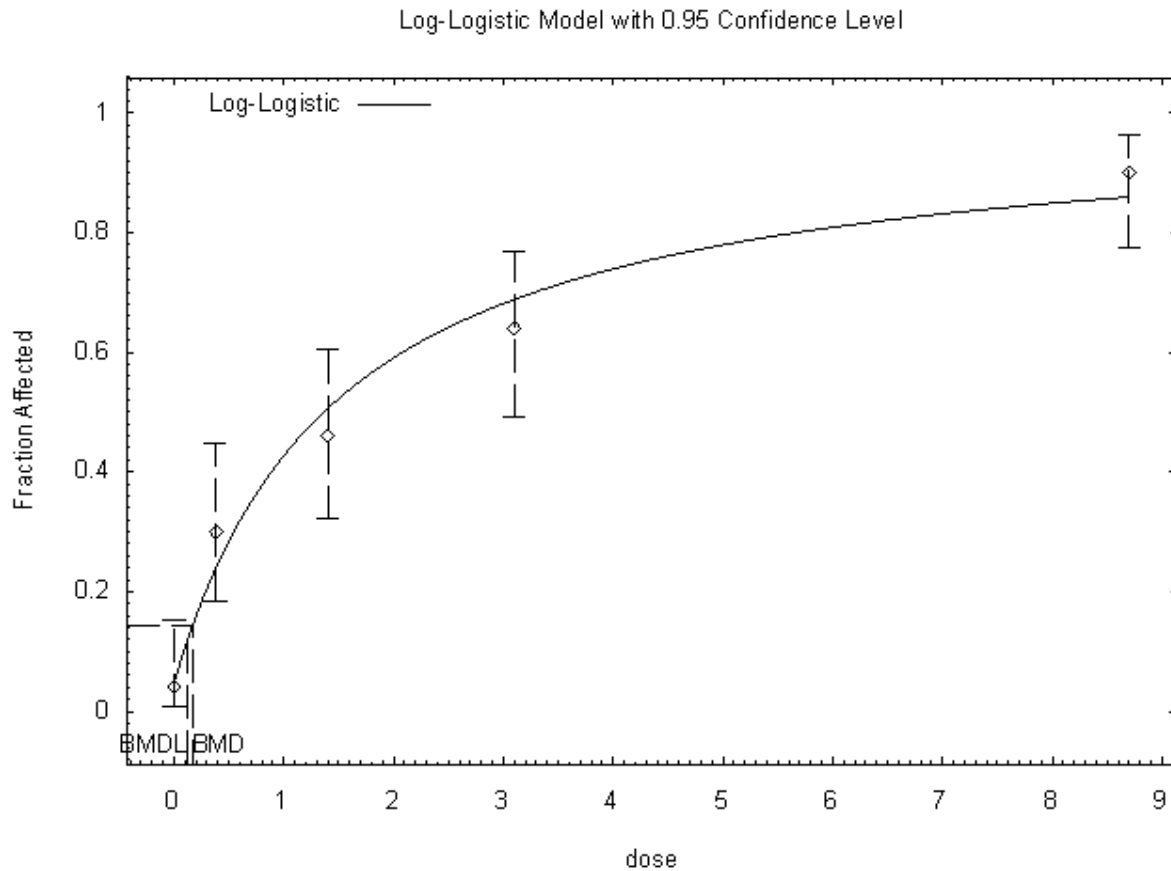
<sup>c</sup>Restrict betas  $\geq 0$ ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

## APPENDIX A

**Figure A-7. Predicted and Observed Incidence of Histiocytic Cellular Infiltration in the Livers of Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years\***



\*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium (VI)/kg/day.

Source: NTP 2008a

***Cytoplasmic Alteration of Acinar Epithelial Cells of the Pancreas in Female Mice.*** As assessed by the chi-square goodness-of-fit statistic, all of the models provide adequate fits ( $X^2$  p-value  $\geq 0.1$ ) to the data (Table A-16). Comparing across models, a better fit is generally indicated by a lower Akaike's Information Criteria (AIC) (EPA 2000). As assessed by AIC, the log-logistic model provides the best fit (Figure A-8). Based on the log-logistic model, the BMD associated with a 10% extra risk was 0.68 mg chromium (VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.52 mg chromium (VI)/kg/day.

## APPENDIX A

**Table A-16. BMD<sub>10</sub> and BMDL<sub>10</sub> Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Pancreas: Acinus, Cytoplasmic Alteration in Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years**

Model	BMD <sub>10</sub> (mg/kg/day)	BMDL <sub>10</sub> (mg/kg/day)	$\chi^2$ p-value	AIC
Gamma <sup>a</sup>	0.92	0.72	0.13	206.82
Logistic	2.43	2.03	0.09	211.78
<b>Log-logistic<sup>b</sup></b>	<b>0.68</b>	<b>0.52</b>	<b>0.19</b>	<b>205.22</b>
Multi-stage <sup>c</sup>	0.92	0.72	0.13	206.82
Probit	2.24	1.89	0.11	210.99
Log-probit <sup>b</sup>	1.77	1.40	0.11	209.99
Quantal linear	0.92	0.72	0.13	206.82
Weibull <sup>a</sup>	0.92	0.72	0.13	206.82

<sup>a</sup>Restrict power  $\geq 1$

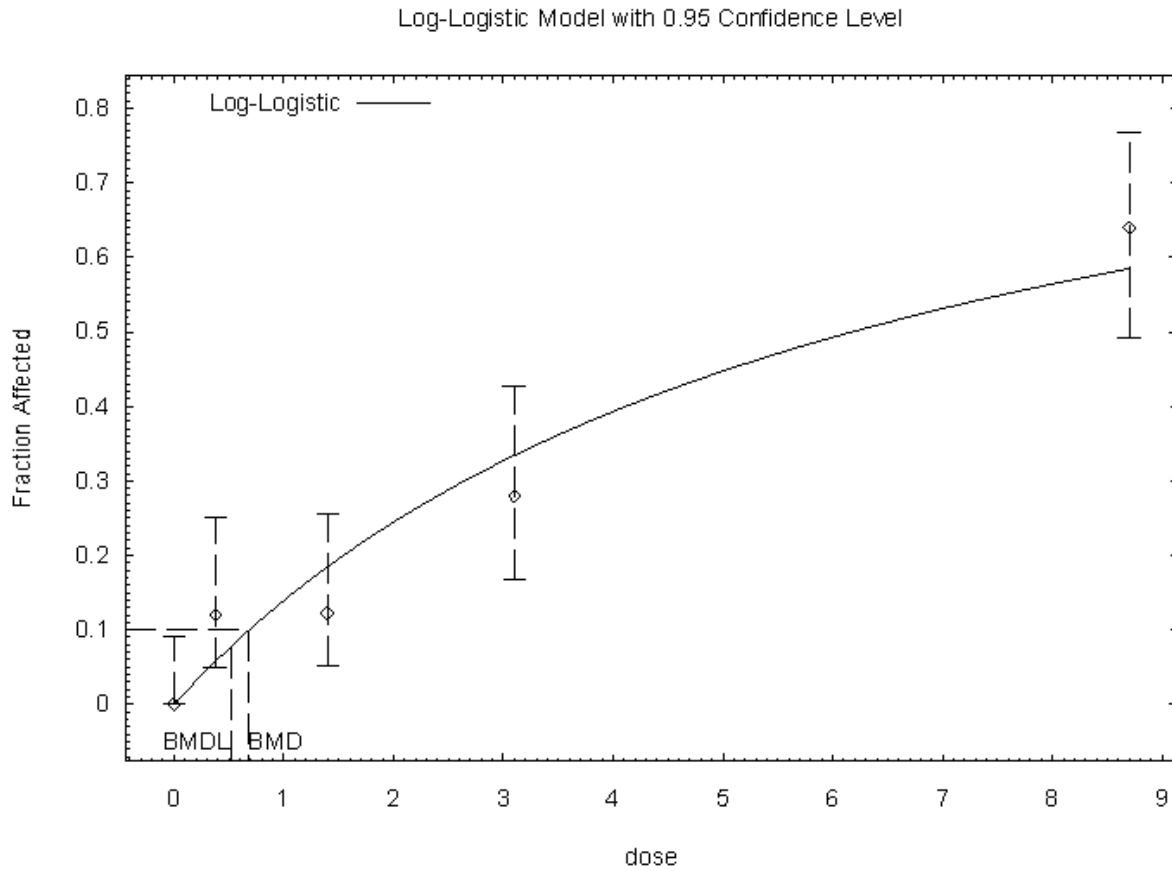
<sup>b</sup>Slope restricted to  $> 1$

<sup>c</sup>Restrict betas  $\geq 0$ ; lowest degree polynomial (up to n-2) with an adequate fit is reported; a 1-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

**Figure A-8. Predicted and Observed Incidence of Pancreas: Acinus, Cytoplasmic Alteration in Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years\***



11:41 04/09 2008

\*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium (VI)/kg/day.

Source: NTP 2008a

Agency Contact (Chemical Manager): Sharon Wilbur

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical name: Chromium(III) insoluble particulates  
CAS number: 16065-83-1  
Date: October 2008  
Profile status: Final Draft Pre-Public Comment  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to figure: 2  
Species: Rat

Minimal Risk Level: 0.005 mg chromium(III)/m<sup>3</sup> for insoluble trivalent chromium particulate compounds

Reference: Derelanko MJ, Rinehart WE, Hilaski RJ, et al. 1999. Thirteen-week subchronic rat inhalation toxicity study with a recovery phase of trivalent chromium compounds, chromic acid and basic chromium sulfate. Toxicol Sci 52(2):278-288.

Experimental design: Groups of 15 male and female CDF (Fisher 344/Crl BR VAF/Plus) rats were exposed to chromic oxide or basic chromium sulfate by nose-only inhalation to 0, 3, 10, or 30 mg chromium(III)/m<sup>3</sup> (measured concentrations) 6 hours/day, 5 days/week for 13 weeks. Mean particle sizes (in microns±GSD, based on 21 samples/test group evaluated over the 13-week exposure period) in the 3, 10, and 30 mg chromium(III)/m<sup>3</sup> groups, were 1.8±1.93, 1.9±1.84, and 1.9±1.78, respectively, for chromic oxide and 4.2±2.48, 4.2±2.37, and 4.5±2.50, respectively, for basic chromium sulfate; no chromium(VI) was detected in samples. Of these 15 rats/sex/group, 10 rats/sex/group were examined and sacrificed after 13 weeks of exposure and 5 rats/sex/group were examined and sacrificed after an additional 13-week recovery (e.g., no exposure) period. Throughout the exposure and recovery periods, rats were examined daily for mortality and clinical signs of toxicity; body weight was recorded weekly, but food consumption was not measured. Ophthalmoscopic examinations were conducted prior to treatment and before terminal sacrifice. At the end of the treatment and recovery phases, blood was analyzed for "standard" hematology and clinical chemistry, and urinalysis was conducted; specific outcome measures evaluated for these assessments were not reported. In five rats/sex/group, urine was also analyzed for β<sub>2</sub>-microglobulin. Gross necropsy was performed on all animals at terminal sacrifice and organ weights were recorded for heart, liver, lungs/trachea (combined), spleen, kidneys, brain, adrenal, thyroid/parathyroid, testes, and ovaries. Bone marrow was examined and differential cell counts of bone marrow were conducted. Microscopic examination of comprehensive tissues (described as "tissues typically harvested for subchronic studies") was conducted for all animals and the control and 30 mg chromium(III)/m<sup>3</sup> groups. For all animals in the 3 and 30 mg chromium(III)/m<sup>3</sup> groups, the following tissues were examined microscopically: kidneys, liver, nasal tissues, trachea, lungs, larynx, mediastinal and mandibular lymph nodes, and all tissues with gross lesions. Histopathological lesions were described, but no incidence data were reported. Sperm morphology, count, and motility were assessed in all males at the end of the 13-week treatment period only.

Effects noted in study and corresponding doses: The following study results are for rats exposed to chromic oxide only; detailed results of animals exposed to basic chromium sulfate are presented in the following intermediate-duration inhalation MRL worksheet for soluble chromium(III) compounds. No mortalities, clinical signs of toxicity, changes in body weight, findings on ophthalmologic examination, or alterations of sperm count, motility, or morphology were observed. Evaluations of hematology, clinical chemistry, and urinalysis did not reveal any treatment-related differences compared to controls; β<sub>2</sub>-microglobulin was not detected in urine of rats from any group. Absolute and relative lung/trachea weights were significantly increased by 12 and 13%, respectively, in males in the 30 mg

## APPENDIX A

chromium(III)/m<sup>3</sup> group compared to control. Lung weights were not increased in females. Other significant changes in organ weight changes were limited to small increases in absolute thyroid/parathyroid weight in females in the 10 mg chromium(III)/m<sup>3</sup> group and in relative thyroid/parathyroid weight (combined) in females in the 10 and 30 mg chromium(III)/m<sup>3</sup> groups. The study authors stated that the biological significance of changes in thyroid/parathyroid weight could not be determined; however, no histopathological changes were observed in these tissues in female rats exposed to 30 mg chromium(III)/m<sup>3</sup>. On necropsy, most animals (incidence not reported) in the chromic oxide group had green discoloration of the lungs and mediastinal lymph nodes; the degree of discoloration increased with exposure level and was presumed to represent deposition of the test material. Mediastinal lymph node enlargement was noted in the 30 mg chromium(III)/m<sup>3</sup> group. Microscopic examination of the lung revealed foci or aggregates of dark-pigmented (presumably the test material) macrophages within alveolar spaces adjacent to junctions of terminal bronchioles and alveolar ducts; black pigment was observed at the tracheal bifurcation and in peribronchial lymphoid tissue and the mediastinal lymph node in all chromic oxide treatment groups. These findings are consistent with normal physiological clearance mechanisms for particulates deposited in the lung and are not considered adverse. Lymphoid hyperplasia of the mediastinal node was observed in rats of all treatment groups (severity not reported). In rats exposed to 10 and 30 mg chromium(III)/m<sup>3</sup>, trace-to-mild chronic interstitial inflammation of the lung, characterized by inflammatory cell infiltration, was observed in alveolar septa, and hyperplasia of Type II pneumocytes (severity not reported) were observed. Histopathological changes were isolated to the lungs and respiratory lymphatic tissues and were not observed in other tissues, including nasal tissues and the larynx. Thus, for evaluations conducted at the end of the 13-week treatment period, a LOAEL of 3 mg chromium(III)/m<sup>3</sup> for hyperplasia of the mediastinal node was identified for both males and females; the severity of this effect was not reported. Following the 13-week recovery period, pigmented macrophages and black pigment were observed in peribronchial tissues and the mediastinal lymph node in animals from all treatment groups. Septal cell hyperplasia and chronic interstitial inflammation of the lung, both trace-to-mild in severity, were observed in males of all treatment groups and in females exposed to 10 and 30 mg chromium(III)/m<sup>3</sup>. For evaluations conducted at the 13-week posttreatment recovery period, a minimal LOAEL (classified as minimal based on severity) of 3 mg chromium(III)/m<sup>3</sup> for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats was identified.

Dose end point used for MRL derivation: 3 mg chromium(III)/m<sup>3</sup> (trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung), adjusted to 0.54 mg chromium(III)/m<sup>3</sup> for intermittent exposure and converted to a LOAEL<sub>HEC</sub> of 0.43 mg chromium(III)/m<sup>3</sup>

[ ] NOAEL [X] LOAEL

The LOAEL of 3 mg chromium(III)/m<sup>3</sup> for hyperplasia of the mediastinal node in males and females (observed at the end of the 13-week treatment period) and the minimal LOAEL (based on severity) of 3 mg chromium(III)/m<sup>3</sup> for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in males (observed at the end of the 13-week recovery period) were further evaluated as potential critical effects for derivation of the intermediate-duration inhalation MRL for insoluble trivalent chromium particulate compounds. A BMCL for these effects could not be determined since incidence data for lesions of the lung and respiratory lymphatic tissue were not reported; thus, a NOAEL/LOAEL approach was used. Following adjustment of LOAELs for intermittent exposure (LOAEL<sub>ADJ</sub>) and human equivalent concentrations (LOAEL<sub>HEC</sub>), as described below, trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats was selected as the critical effect, based on the lowest LOAEL<sub>HEC</sub> of 0.43 mg chromium(III)/m<sup>3</sup> (Table A-17). The intermediate-duration inhalation MRL for insoluble trivalent chromium particulate compounds of 0.005 mg chromium(III)/m<sup>3</sup> was derived by dividing the minimal LOAEL<sub>HEC</sub> of 0.43 mg chromium(III)/m<sup>3</sup> by a composite uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).



## APPENDIX A

**Table A-17. LOAEL Values (Expressed in Terms Of HEC) for Nonneoplastic Lesions in Rats Exposed to Chromic Oxide by Inhalation For 13 Weeks**

Species/sex	Lesion type (RDDR location)	RDDR multiplier	LOAEL <sub>ADJ</sub> (mg chromium(III)/m <sup>3</sup> ) <sup>a</sup>	LOAEL <sub>HEC</sub> (mg chromium(III)/m <sup>3</sup> ) <sup>b</sup>
Rat/male	Septal cell hyperplasia and chronic interstitial inflammation of the lung (thoracic)	0.789	0.54	0.43
Rat/male	Hyperplasia of the mediastinal node (tracheobronchial)	1.225	0.54	0.66
Rat/female	Hyperplasia of the mediastinal node (tracheobronchial)	1.084	0.54	0.59

<sup>a</sup>Duration-adjusted for intermittent exposure (LOAEL<sub>ADJ</sub> = LOAEL x 6 hours/24 hours x 5 days/7 days = 3 mg chromium(III)/m<sup>3</sup> x 6 hours/24 hours x 5 days/7 days = 0.54 mg chromium(III)/m<sup>3</sup>)

<sup>b</sup>LOAEL<sub>HEC</sub> = LOAEL<sub>ADJ</sub> x RDDR

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; RDDR = regional deposited dose ratio

Source: Derelanko et al. 1999

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: To determine the LOAEL<sub>HEC</sub>, the LOAEL<sub>ADJ</sub> in rats was multiplied by the RDDR multiplier determined for lesions in various areas of the respiratory tract in male and female rats (Table A-17). The RDDR computer program was used to determine the RDDR multipliers as follows.

For interstitial inflammation of the lung in male rats (specific location of lesion within the lung was not reported by study authors) observed after the 13-week recovery period, the thoracic region for the RDDR program was selected since the observed effect could occur in the both the tracheobronchial and pulmonary regions of the lung. The RDDR multiplier of 0.789 for the thoracic region of the respiratory tract in male rats was determined using the average body weight of 201 g for male rats in the control group in the basic chromium sulfate portion of the study (data for body weights of male rats in the chromic oxide portion of the study were not reported) and the average particle size (MMAD±GSD) of 1.9±1.85 reported in the Derelanko et al. (1999) study.

For hyperplasia of the mediastinal node in male and female rats observed at the end of the 13-week treatment period, the tracheobronchial region of the respiratory tract was selected for the RDDR program. Although the mediastinal lymph node is not a respiratory tissue, for the purposes of HEC conversions, it is considered part of the tracheobronchial region of the respiratory system rather than a systemic tissue;

## APPENDIX A

classification of the mediastinal lymph node as a systemic tissue is not appropriate, since the test material reaches the respiratory lymphatic tissues by the pulmonary macrophage clearance system and not by first entering the systemic circulation. For male rats, the RDDR multiplier of 1.225 for the tracheobronchial region of the respiratory tract in male rats was determined using the average body weight of 201 g for male rats in the control group in the basic chromium sulfate portion of the study (data for body weights of male rats in the chromic oxide portion of the study were not reported) and the average particle size MMAD±GSD of 1.9±1.85 reported in Derelanko et al. (1999). For female rats, the RDDR multiplier of 1.084 for the tracheobronchial region tract was determined using the default subchronic body weight of 124 g for female F344 rats (EPA 1988d) and the average particle size MMAD±GSD of 1.9±1.85 reported in the Derelanko et al. (1999) study; the default value for female body weights was used because female body weights were not reported in the critical study.

Was a conversion used from intermittent to continuous exposure? Rats were exposed for 6 hours/day, 5 days/week for 13 weeks.

$$\text{LOAEL}_{\text{ADJ}} = 3 \text{ mg chromium(III)/m}^3 \times 6 \text{ hours/24 hours} \times 5 \text{ days/7 days}$$
$$\text{LOAEL}_{\text{ADJ}} = 0.54 \text{ mg chromium(III)/m}^3$$

Other additional studies or pertinent information that lend support to this MRL: The respiratory tract is the major target of inhalation exposure to chromium(III) and chromium(VI) compounds in humans and animals. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. The available occupational studies for exposure to chromium(III) compounds include, or likely include, concomitant exposure to chromium(VI) compounds and other compounds that may produce respiratory effects (Langård 1980; Mancuso 1951; Osim et al. 1999). Thus, while the available data in humans suggest that respiratory effects occur following inhalation exposure to chromium(III) compounds, the respiratory effects of inhaled chromium(VI) and other compounds are confounding factors. Studies evaluating respiratory effects of intermediate-duration inhalation exposure of animals are limited to the critical study evaluating 13-week exposure to chromic oxide or basic chromium sulfate (Derelanko et al. 1999). Results of this study show that intermediate-duration inhalation exposure to chromic oxide or basic chromium sulfate produced adverse respiratory effects, as indicated by histopathological changes and increased lung weight. However, effects of chromic oxide were less severe and isolated to the lung and respiratory lymph tissues, whereas the effects of basic chromium sulfate were more severe and observed throughout the respiratory tract (e.g., nose, larynx, lung and respiratory lymph tissues). The authors suggest that differences in the respiratory toxicity of these compounds may be due to differences in chemical-physical properties (e.g., solubility, acidity). Based on the differences in respiratory toxicity between insoluble chromic oxide and soluble basic chromium sulfate, separate intermediate-duration inhalation MRLs were derived for insoluble and soluble trivalent chromium particulate compounds.

Agency Contact (Chemical Manager): Sharon Wilbur

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical name: Chromium(III) soluble particulates  
CAS number: 16065-83-1  
Date: October 2008  
Profile status: Final Draft Pre-Public Comment  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to figure: 3  
Species: Rat

Minimal Risk Level: 0.0001 mg chromium(III)/m<sup>3</sup> for soluble trivalent chromium particulate compounds

Reference: Derelanko MJ, Rinehart WE, Hilaski RJ, et al. 1999. Thirteen-week subchronic rat inhalation toxicity study with a recovery phase of trivalent chromium compounds, chromic acid and basic chromium sulfate. Toxicol Sci 52(2):278-288.

Experimental design: Groups of 15 male and female CDF (Fisher 344/Crl BR VAF/Plus) rats were exposed to chromic oxide or basic chromium sulfate by nose-only inhalation to 0, 3, 10, or 30 mg chromium(III)/m<sup>3</sup> (measured concentrations) 6 hours/day, 5 days/week for 13 weeks. Mean particle sizes (in microns±GSD, based on 21 samples/test group evaluated over the 13-week exposure period) in the 3, 10, and 30 mg chromium(III)/m<sup>3</sup> groups, were 1.8±1.93, 1.9±1.84, and 1.9±1.78, respectively, for chromic oxide and 4.2±2.48, 4.2±2.37, and 4.5±2.50, respectively, for basic chromium sulfate; no chromium(VI) was detected in samples. Of these 15 rats/sex/group, 10 rats/sex/group were examined and sacrificed after 13 weeks of exposure and 5 rats/sex/group were examined and sacrificed after an additional 13-week recovery (e.g., no exposure) period. Throughout the exposure and recovery periods, rats were examined daily for mortality and clinical signs of toxicity; body weight was recorded weekly but food consumption was not measured. Ophthalmoscopic examinations were conducted prior to treatment and before terminal sacrifice. At the end of the treatment and recovery phases, blood was analyzed for "standard" hematology and clinical chemistry, and urinalysis was conducted; specific outcome measures evaluated for these assessments were not reported. In five rats/sex/group, urine was also analyzed for β<sub>2</sub>-microglobulin. Gross necropsy was performed on all animals at terminal sacrifice and organ weights were recorded for heart, liver, lungs/trachea (combined), spleen, kidneys, brain, adrenal, thyroid/parathyroid, testes, and ovaries. Bone marrow was examined and differential cell counts of bone marrow were conducted. Microscopic examination of comprehensive tissues (described as "tissues typically harvested for subchronic studies") was conducted for all animals and the control and 30 mg chromium(III)/m<sup>3</sup> groups. For all animals in the 3 and 30 mg chromium(III)/m<sup>3</sup> groups, the following tissues were examined microscopically: kidneys, liver, nasal tissues, trachea, lungs, larynx, mediastinal and mandibular lymph nodes, and all tissues with gross lesions. Histopathological findings were described, but no incidence data were reported. Sperm morphology, count, and motility were assessed in all males at the end of the 13-week treatment period only.

Effects noted in study and corresponding doses: The following study results are for rats exposed to basic chromium sulfate only; detailed results of animals exposed to chromic oxide are presented in the preceding intermediate-duration inhalation MRL worksheet for insoluble chromium(III) compounds. No treatment-related mortalities were observed; one male rat in the 30 mg chromium(III)/m<sup>3</sup> group died on day 4 of exposure; the study authors did not attribute this death to treatment since no significant signs of toxicity were observed in this animals or in other animals in this treatment group. Females in the 30 mg chromium(III)/m<sup>3</sup> group exhibited sporadic labored breathing; no additional information on this observation was reported. No findings on ophthalmologic examination or alterations of sperm count, motility, or morphology were observed. At the end of the 13-week treatment period, body weight was

## APPENDIX A

significantly decreased in males in the 10 and 30 mg chromium(III)/m<sup>3</sup> groups and females in the 30 mg chromium(III)/m<sup>3</sup> group. The study authors stated that “most” hematological, clinical chemistry, and urinalysis values in all exposure groups were similar to controls, although data were not reported. A significant, dose-related increase in absolute and relative lung/trachea weights was observed in male rats in all treatment groups. Other organ weight changes in males were decreased absolute and increase relative brain weights (30 mg chromium(III)/m<sup>3</sup>), increased relative kidney weight (30 mg chromium(III)/m<sup>3</sup>), decreased absolute liver weight (30 mg chromium(III)/m<sup>3</sup>), increased relative thyroid/parathyroid weight (30 mg chromium(III)/m<sup>3</sup>), decreased relative spleen weight (10 and 30 mg chromium(III)/m<sup>3</sup>), and increased relative testes weight (30 mg chromium(III)/m<sup>3</sup>). In females, absolute and relative lungs weights were increased in a dose-dependent fashion in all treatment groups. Other organ weight changes in females were increased absolute and relative thyroid/parathyroid weight (30 mg chromium(III)/m<sup>3</sup>) and decreased absolute spleen weight (30 mg chromium(III)/m<sup>3</sup>). With the exception of increased absolute and relative lung weights in males and females, small changes in other organs weights were not considered adverse in the absence of histopathological changes. On necropsy, grey lung discoloration was observed in animals exposed to 10 and 30 mg chromium(III)/m<sup>3</sup>; the degree of discoloration increased with exposure level. Microscopic examination of the lung revealed the following changes in all treatment groups: chronic inflammation of the alveoli; alveolar spaces filled with macrophages, neutrophils, lymphocytes and cellular debris; foci of “intense” inflammation and thickened alveolar walls; chronic interstitial inflammation with cell infiltration; hyperplasia of Type II pneumocytes; and granulomatous inflammation, characterized by infiltration of macrophages and multinucleated giant cells. Macrophage infiltration and granulomatous inflammation of the larynx, acute inflammation and suppurative and mucoid exudates of nasal tissues, and histiocytosis and hyperplasia of peribronchial lymphoid tissues and the mediastinal lymph node were also observed in all treatment groups. Following the 13-week recovery period, enlargement of the mediastinal lymph node was observed on gross necropsy in all treatment groups. Microscopic examination of respiratory tissues showed changes to the lung (chronic alveolar inflammation, interstitial inflammation, septal cell hyperplasia, and granulomatous inflammation) in all treatment groups, larynx (granulomatous inflammation) in the 10 and 30 mg chromium(III)/m<sup>3</sup> groups, nasal tissues (trace suppurative exudates) in one to two animals in each groups, and mediastinal lymph node (histiocytosis and hyperplasia) in all treatment groups chromium(III)/m<sup>3</sup> groups. Following the 13-week recovery period, test material was observed in the respiratory tract on necropsy; however, incidence was decreased compared to observations made immediately following treatment (data not presented). In addition, chronic alveolar and interstitial inflammation and septal cell hyperplasia (all trace-to-moderate in severity) were observed in the 10 and 30 mg chromium(III)/m<sup>3</sup> groups, with severity similar to that observed immediately following treatment; in the 3 mg chromium(III)/m<sup>3</sup> group, severity was slightly reduced.

Dose end point used for MRL derivation: 3 mg chromium(III)/m<sup>3</sup> (nasal and larynx lesions), adjusted to 0.54 mg chromium(III)/m<sup>3</sup> for intermittent exposure and converted to a LOAEL<sub>HEC</sub> of 0.04 mg chromium(III)/m<sup>3</sup>

[ ] NOAEL [X] LOAEL

The respiratory tract was identified as the target for inhaled soluble trivalent chromium particulate compounds. Similar effects were observed in male and female rats exposed to inhaled basic chromium sulfate for 13 weeks, with histopathological changes to the nose, larynx, lung, and respiratory lymphatic tissues and increased relative lung weight occurring at  $\geq 3$  mg chromium(III)/m<sup>3</sup>. Therefore, data for histopathological changes in various regions of the respiratory tract and increased relative lung weights were further evaluated to determine the point of departure for derivation of the intermediate-duration MRL for soluble trivalent chromium particulate compounds.

## APPENDIX A

Benchmark dose analysis could not be conducted for respiratory tract lesions, since incidence data were not reported by Derelanko et al. (1999); therefore, a NOAEL/LOAEL approach was used. The LOAEL value of 3 mg chromium(III)/m<sup>3</sup> for lesions in different regions of the respiratory tract was further evaluated as a potential point of departure. LOAEL values were adjusted for intermittent exposure (LOAEL<sub>ADJ</sub>) and converted to a human equivalent concentration (LOAEL<sub>HEC</sub>), as shown in (Table A-18).

**Table A-18. LOAEL Values (Expressed in Terms of HEC) for Nonneoplastic Lesions in Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks**

Species/sex	Lesion type (RDDR location)	RDDR multiplier	LOAEL <sub>ADJ</sub> (mg chromium(III)/m <sup>3</sup> ) <sup>a</sup>	LOAEL <sub>HEC</sub> (mg chromium(III)/m <sup>3</sup> ) <sup>b</sup>
Rat/male	Granulomatous inflammation of larynx; inflammation of nasal tissue (extrathoracic)	0.129	0.54	0.07
Rat/male	Interstitial and alveolar inflammation; alveolar hyperplasia (thoracic)	0.470	0.54	0.25
Rat/female	Granulomatous inflammation of larynx; inflammation of nasal tissue (extrathoracic)	0.078	0.54	0.04
Rat/female	Interstitial and alveolar inflammation; alveolar hyperplasia (thoracic)	0.483	0.54	0.26

<sup>a</sup>Duration-adjusted for intermittent exposure (LOAEL<sub>ADJ</sub> = LOAEL x 6 hours/24 hours x 5 days/7 days = 3 mg chromium(III)/m<sup>3</sup> x 6 hours/24 hours x 5 days/7 days = 0.54 mg chromium(III)/m<sup>3</sup>)

<sup>b</sup>LOAEL<sub>HEC</sub> = LOAEL<sub>ADJ</sub> x RDDR

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; RDDR = regional deposited dose ratio

Soucre: Derelanko et al. 1999

To determine the BMC for increased lung weights, available continuous-variable models in the EPA Benchmark Dose (version 1.4.1) were fit to the data for relative lung weights in male and female rats (Derelanko et al. 1999; Table A-19). The BMC and the 95% lower confidence limit (BMCL) calculated is an estimate of the concentrations associated with a change of 1 standard deviation from the control (BMCL<sub>1sd</sub>). The model-fitting procedure for continuous data is as follows. The simplest model (linear) is applied to the data while assuming constant variance. If the data are consistent with the assumption of

## APPENDIX A

constant variance ( $p \geq 0.1$ ), then the other continuous models (polynomial, power, and Hill models) are applied to the data. Among the models providing adequate fits to the means ( $p \geq 0.1$ ), the one with the lowest Akaike's Information Criteria (AIC) for the fitted model is selected for BMC derivation. If the test for constant variance is negative, then the linear model is run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provides an adequate fit ( $p \geq 0.1$ ) to the variance data, then the other continuous models are applied to the data. Among the models providing adequate fits to the means ( $p \geq 0.1$ ), the one with the lowest AIC for the fitted model is selected for BMC derivation. If the tests for both constant and nonconstant variance are negative, then the data set is considered not to be suitable for BMC modeling. For male rats, the best model fit (Hill model) did not provide graphic output of the model; since model fit could not be evaluated by visual inspection, the  $BMDL_{1sd}$  from the Hill model was not selected. All other models took the form of a linear model (nonconstant variance), yielding predicted  $BMC_{1sd}$  and  $BMCL_{1sd}$  values of 2.89 and 2.05 mg chromium(III)/ $m^3$ , respectively. For female rats, the linear model (nonconstant variance) provided the best fit, with predicted  $BMC_{1sd}$  and  $BMCL_{1sd}$  values of 6.33 and 3.96 mg/ $m^3$ , respectively. Additional details of the benchmark dose analysis for each data set modeled are presented in the last section of this worksheet. The  $BMCL_{1sd}$  values for the best fitting models in male and female rats were adjusted for intermittent exposure ( $BMCL_{1sd, ADJ}$ ) and human equivalent concentrations ( $BMCL_{1sd, HEC}$ ), yielding  $BMCL_{1sd, HEC}$  values of 0.17 and 0.34 mg chromium(III)/ $m^3$  in males and females, respectively, as shown below (Table A-20).

**Table A-19. Relative Lung Weights<sup>a</sup> of CDF Rats<sup>b</sup> Exposed to Basic Chromium Sulfate by Nose-Only Inhalation 6 Hours/Day, 5 Days/Week for 13 Weeks**

Relative weight (percent x 10)	Concentrations (mg chromium(III)/ $m^3$ )			
	0	3	10	30
Basic chromium sulfate, males	4.42±0.187 <sup>c</sup>	5.60±0.271 <sup>d</sup>	7.15±0.252 <sup>d</sup>	10.69±0.688 <sup>d</sup>
Basic chromium sulfate, females	5.65±0.418	6.99±0.619 <sup>d</sup>	9.24±1.036 <sup>d</sup>	12.89±1.134 <sup>d</sup>

<sup>a</sup>Combined lung and trachea

<sup>b</sup>10 rat in all groups except male rats in the basic chromium sulfate 30 mg/ $m^3$  group (n=9)

<sup>c</sup>mean±Standard deviation

<sup>d</sup> $p < 0.01$

Source: Derelanko et al. 1999

## APPENDIX A

**Table A-20. BMCL<sub>1sd</sub> Values (Expressed in Terms of HEC) for Increased Relative Lung Weight in Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks**

Species/sex	RDDR multiplier <sup>a</sup>	Duration-adjusted BMCL <sub>1sd, ADJ</sub> (mg chromium(III)/m <sup>3</sup> ) <sup>b</sup>	BMCL <sub>1sd, HEC</sub> (mg chromium(III)/m <sup>3</sup> ) <sup>c</sup>
Rat/male	0.470	0.37	0.17
Rat/female	0.483	0.71	0.34

<sup>a</sup>For thoracic region

<sup>b</sup>Duration-adjusted for continuous exposure (BMCL<sub>1sd, ADJ</sub> = BMCL<sub>1sd</sub> x 6 hours/24 hours x 5 days/7 days); BMCL<sub>1sd</sub> for the best fitting models for male and female rats were 2.05 and 3.96 mg chromium(III)/m<sup>3</sup>, respectively.

<sup>c</sup>BMCL<sub>1sd, HEC</sub> = BMCL<sub>1sd, ADJ</sub> x RDDR

BMCL = lower confidence limit (95%) on the benchmark concentration; HEC = human equivalent concentration; RDDR = regional deposited dose ratio

Source: Derelanko et al. 1999

Based on comparison of LOAEL<sub>HEC</sub> values for respiratory tract lesions and BMCL<sub>1sd, HEC</sub> values for increased lung weight, the lowest value of 0.04 mg chromium(III)/m<sup>3</sup> (the LOAEL<sub>HEC</sub> for lesions of the larynx and nose in female rats) was selected as the point of departure. The intermediate-duration inhalation MRL for soluble trivalent chromium particulate compounds of 0.0001 mg chromium(III)/m<sup>3</sup> was derived by dividing the LOAEL<sub>HEC</sub> of 0.04 mg chromium(III)/m<sup>3</sup> by a composite uncertainty factor of 300 (10 for use of a LOAEL, 3 for pharmacodynamic variability between animals to humans, and 10 for human variability).

Uncertainty factors used in MRL derivation:

- [X] 10 for use of a LOAEL
- [X] 3 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? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: To determine human equivalent concentrations, LOAEL<sub>ADJ</sub> values for lesions in various areas of the respiratory tract (Table A-18) and BMCL<sub>1sd, ADJ</sub> values for changes in lung weights (Table A-20) were multiplied by the RDDR multiplier determined for lesions in various areas of the respiratory tract as follows.

For histopathological changes to the nose and larynx, the extrathoracic region for the RDDR program was selected. For male rats, the RDDR multiplier of 0.129 for the extrathoracic region of the respiratory tract was determined using the average body weight of 201 g for male rats in the control group in the basic chromium sulfate portion of the study and the average particle size (MMAD±GSD) of 4.3±2.45 reported in Derelanko et al. (1999). For female rats, the RDDR multiplier of 0.078 for the extrathoracic region of the respiratory tract was determined using the default subchronic body weight of 124 g for female F344 rats (EPA 1988d) and the average particle size MMAD±GSD of 4.3±2.45 reported in Derelanko et al. (1999); the default value for female body weights was used because female body weights were not reported in Derelanko et al. (1999).

## APPENDIX A

For histopathological changes to the lung and increased relative lung weight, the thoracic region (a combination of tracheobronchial and pulmonary regions) was selected. For male rats, the RDDR multiplier of 0.470 for the thoracic region of the respiratory tract was determined using the average body weight of 201 g for male rats in the control group in the basic chromium sulfate portion of the study and the average particle size (MMAD±GSD) of 4.3±2.45 reported in Derelanko et al. (1999). For female rats, the RDDR multiplier of 0.483 for the thoracic region of the respiratory tract was determined using the default subchronic body weight of 124 g for female F344 rats (EPA 1988d) and the average particle size MMAD±GSD of 4.3±2.45 reported in Derelanko et al. (1999); the default value for female body weights was used because female body weights were not reported in Derelanko et al. (1999).

Was a conversion used from intermittent to continuous exposure? Rats were exposed for 6 hours/day, 5 days/week for 13 weeks. The LOAEL and BMCL<sub>1sd</sub> values were adjusted for continuous exposure as follows:

$$\text{LOAEL}_{\text{ADJ}} \text{ or } \text{BMCL}_{1\text{sd}, \text{ADJ}} = \text{LOAEL or BMCL}_{1\text{sd}} \times 6 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days}$$

Other additional studies or pertinent information that lend support to this MRL: The respiratory tract is the major target of inhalation exposure to chromium(III) and chromium(VI) compounds in humans and animals. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. The available occupational studies for exposure to chromium(III) compounds include, or likely include, concomitant exposure to chromium(VI) compounds and other compounds that may produce respiratory effects (Langård 1980; Mancuso 1951; Osim et al. 1999). Thus, while the available data in humans suggest that respiratory effects occur following inhalation exposure to chromium(III) compounds, the respiratory effects of inhaled chromium(VI) and other compounds are confounding factors. Studies evaluating respiratory effects of intermediate-duration inhalation exposure of animals are limited to the critical study evaluating 13-week exposure to chromic oxide or basic chromium sulfate (Derelanko et al. 1999). Results of this study show that intermediate-duration inhalation exposure to chromic oxide or basic chromium sulfate produced adverse respiratory effects, as indicated by histopathological changes and increased lung weight. However, effects of chromic oxide were less severe and isolated to the lung and respiratory lymph tissues, whereas the effects of basic chromium sulfate were more severe and observed throughout the respiratory tract (e.g., nose, larynx, lung and respiratory lymph tissues). The authors suggest that differences in the respiratory toxicity of these compounds may be due to differences in chemical-physical properties (e.g., solubility, acidity). Based on the differences in respiratory toxicity between insoluble chromic oxide and soluble basic chromium sulfate, separate intermediate-duration inhalation MRLs were derived for insoluble and soluble trivalent chromium particulate compounds.

#### **Details of Benchmark Dose Analysis for the Intermediate-duration Inhalation MRL for Soluble Trivalent Chromium Particulates**

***Lung Weights in Male Rats.*** The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did not provide an adequate fit (as assessed by the p-value for variance) to the data. The linear model was applied to the data again while applying the power model integrated into the BMCs to account for nonhomogenous variance. The nonconstant variance model did provide an adequate fit (as assessed by the p-value for variance). The polynomial, power, and Hill models were then fit to the data with nonconstant variance assumed. All of the models provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-21). Comparing across models, a better fit is generally indicated by a lower AIC. As assessed by AIC, the Hill model provides the best fit to the data; however, the BMDS software did not generate the graph output needed to assess visual fit of the model to the data. All other models took the form of a linear model, so the



## APPENDIX A

nonconstant variance-linear model is selected for BMC derivation. The predicted  $BMC_{1sd}$  and  $BMCL_{1sd}$  for the data are 2.89 and 2.05 mg chromium(III)/m<sup>3</sup>, respectively (Figure A-9).

**Table A-21. Model Predictions for Changes in Relative Lung Weights of Male CDF Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks**

Model	Variance p-value <sup>a</sup>	p-Value for the means <sup>a</sup>	AIC	$BMC_{1sd}$ (mg chromium(III)/m <sup>3</sup> )	$BMCL_{1sd}$ (mg chromium(III)/m <sup>3</sup> )
Linear <sup>b,c</sup>	0.00	0.30	56.75	5.79	4.70
<b>Linear<sup>c,d</sup></b>	<b>0.40</b>	<b>0.10</b>	<b>44.09</b>	<b>2.89</b>	<b>2.05</b>
Polynomial (1-degree) <sup>c,d</sup>	0.40	0.10	44.09	2.89	2.05
Polynomial (2-degree) <sup>c,d</sup>	0.40	0.10	44.09	2.89	2.05
Polynomial (3-degree) <sup>c,d</sup>	0.40	0.10	44.09	2.89	2.05
Power <sup>d</sup>	0.40	0.10	44.09	2.89	2.05
Hill <sup>d</sup>	0.40	0.26	42.79	1.74	1.07

<sup>a</sup>Values <0.1 fail to meet conventional goodness-of-fit criteria.

<sup>b</sup>Constant variance assumed

<sup>c</sup>Restriction = non-negative

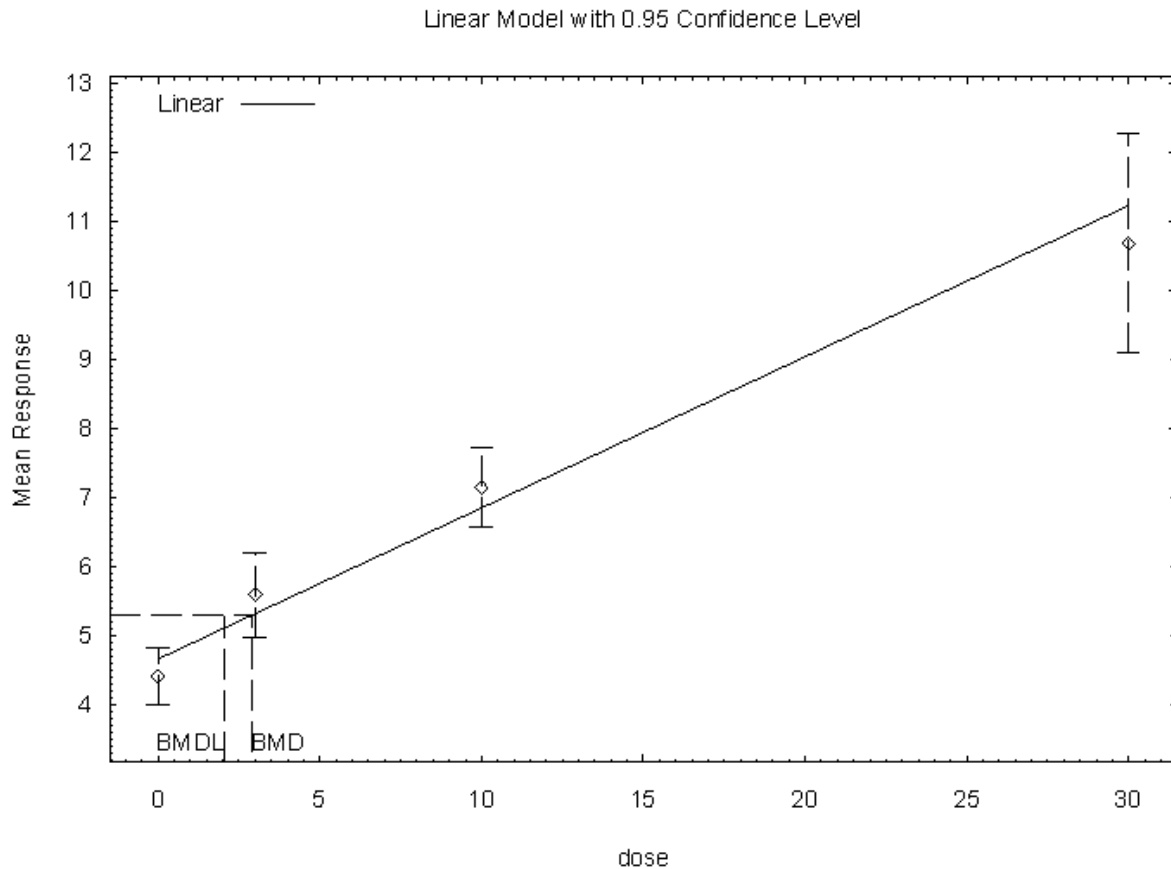
<sup>d</sup>Nonconstant variance model applied

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; 1sd = a 1 standard deviation change from the control

Source: Derelanko et al. 1999

## APPENDIX A

**Figure A-9. Predicted and Observed Changes in Relative Lung Weights in Male Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks\***



\*BMD=BMC; BMDL=BMCL; BMCs and BMCLs indicated are associated with a 1 standard deviation change from the control, and are in units of mg chromium(III)/m<sup>3</sup>.

Source: Derelanko et al. 1999

**Lung Weights in Female Rats.** The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did not provide an adequate fit (as assessed by the p-value for variance) to the data. The linear model was applied to the data again while applying the power model integrated into the BMDS to account for nonhomogenous variance. The nonconstant variance model did provide an adequate fit (as assessed by the p-value for variance). The polynomial, power, and Hill models were then fit to the data with nonconstant variance assumed. All of the models provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-22). Comparing across models, a better fit is generally indicated by a lower AIC. As assessed by AIC, the linear model provides the best fit to the data. The predicted BMC<sub>1sd</sub> and BMCL<sub>1sd</sub> for the data are 6.33 and 3.96 mg chromium(III)/m<sup>3</sup>, respectively (Figure A-10).

## APPENDIX A

**Table A-22. Model Predictions for Changes in Relative Lung Weights of Female CDF Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks**

Model	Variance p-value <sup>a</sup>	p-Value for the means <sup>a</sup>	AIC	BMC <sub>1sd</sub> (mg chromium(III)/m <sup>3</sup> )	BMCL <sub>1sd</sub> (mg chromium(III)/m <sup>3</sup> )
Linear <sup>b,c</sup>	0.01	0.51	122.61	11.28	8.59
<b>Linear<sup>c,d</sup></b>	<b>0.59</b>	<b>0.14</b>	<b>117.05</b>	<b>6.33</b>	<b>3.96</b>
Polynomial (1-degree) <sup>c,d</sup>	0.59	0.14	117.05	6.33	3.96
Polynomial (2-degree) <sup>c,d</sup>	0.59	0.14	117.05	6.33	3.96
Polynomial (3-degree) <sup>c,d</sup>	0.59	0.14	117.05	6.33	3.96
Power <sup>d</sup>	0.59	0.14	117.05	6.33	3.96
Hill <sup>d</sup>	0.59	NA <sup>e</sup>	117.13	2.84	1.32

<sup>a</sup>Values <0.1 fail to meet conventional goodness-of-fit criteria.

<sup>b</sup>Constant variance assumed

<sup>c</sup>Restriction = non-negative

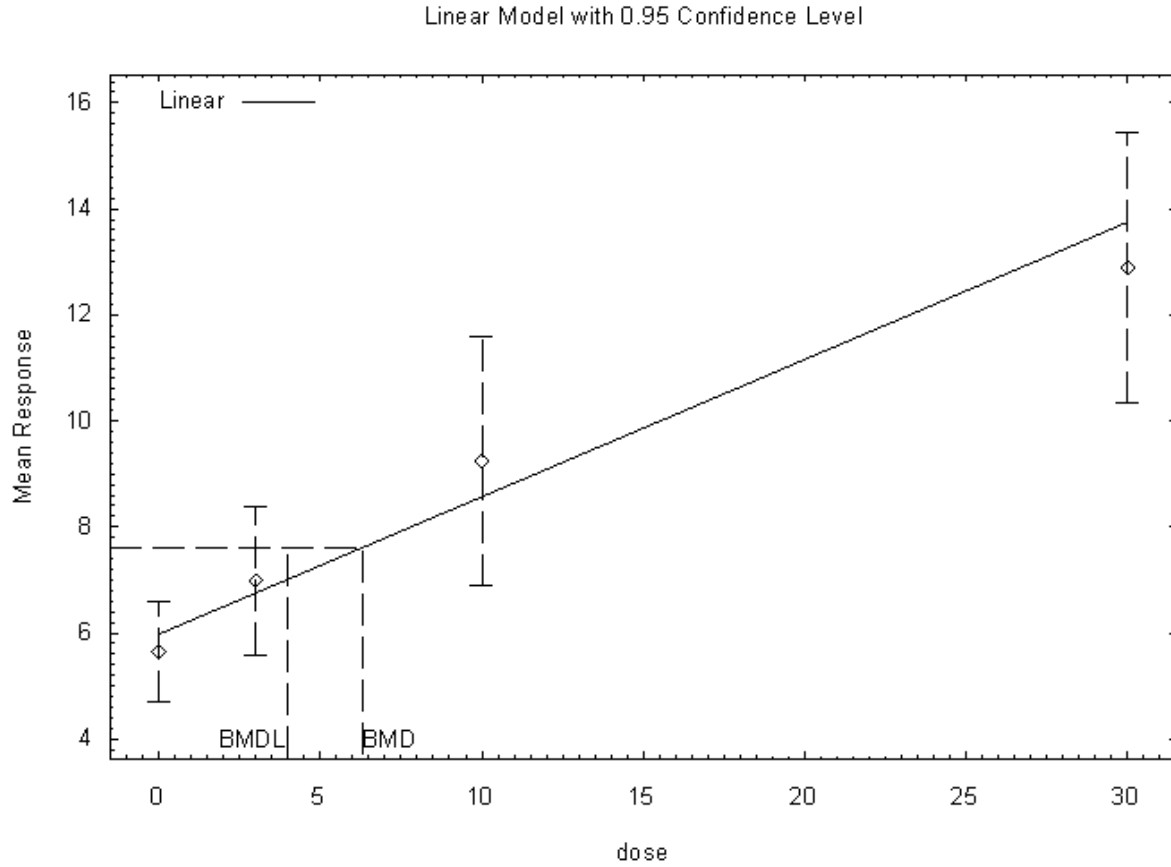
<sup>d</sup>Nonconstant variance model applied

<sup>e</sup>NA = degrees of freedom are  $\leq 0$ ; the Chi-Square test for fit is not valid.

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; 1sd = a 1 standard deviation change from the control

Source: Derelanko et al. 1999

**Figure A-10. Predicted and Observed Changes in Relative Lung Weights in Female Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks\***



14:47 04/17 2008

\*BMD=BMC; BMDL=BMCL; BMCs and BMCLs indicated are associated with a 1 standard deviation change from the control, and are in units of mg chromium(III)/m<sup>3</sup>.

Source: Derelanko et al. 1999

Agency Contact (Chemical Manager): Sharon Wilbur

## 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

## APPENDIX B

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.

## APPENDIX B

**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,

## APPENDIX B

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<sup>3</sup> 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.



## APPENDIX B

- (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 <sup>a</sup>	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
<b>INTERMEDIATE EXPOSURE</b>							
	5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓	↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3 <sup>b</sup>	10 (hyperplasia)	Nitschke et al. 1981
<b>CHRONIC EXPOSURE</b>							
	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 →

<sup>a</sup> The number corresponds to entries in Figure 3-1.

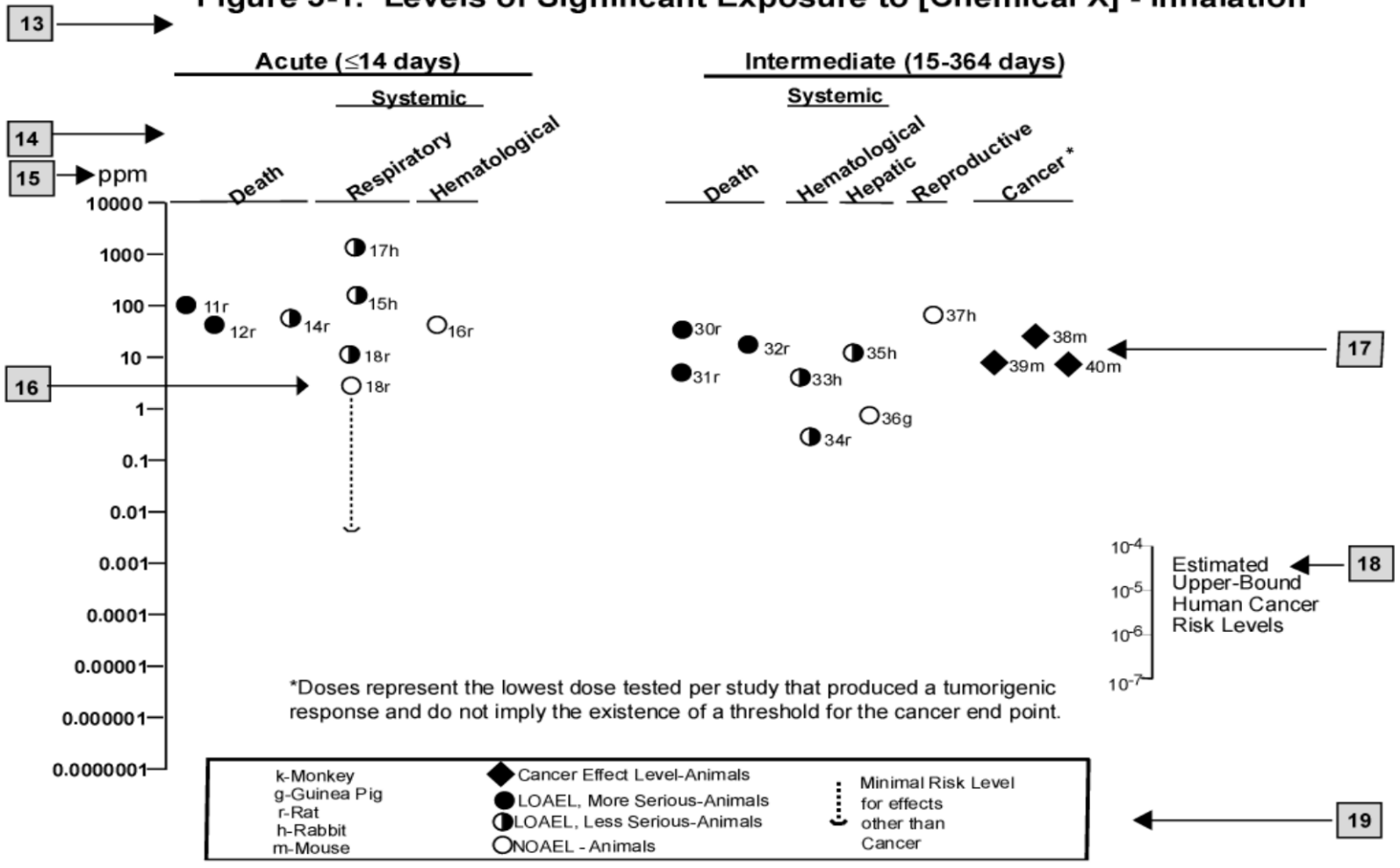
<sup>b</sup> Used to derive an intermediate inhalation Minimal Risk Level (MRL) of  $5 \times 10^{-3}$  ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

\*\*\*DRAFT FOR PUBLIC COMMENT\*\*\*

APPENDIX B

# SAMPLE

### Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



\*\*\*DRAFT FOR PUBLIC COMMENT\*\*\*

APPENDIX B

APPENDIX B

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
BMDX	dose that produces a X% change in response rate of an adverse effect
BMDLX	95% lower confidence limit on the BMDX
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

## APPENDIX C

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 <sub>1</sub>	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
K <sub>d</sub>	adsorption ratio
kg	kilogram
kkg	metric ton
K <sub>oc</sub>	organic carbon partition coefficient
K <sub>ow</sub>	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC <sub>50</sub>	lethal concentration, 50% kill
LC <sub>Lo</sub>	lethal concentration, low
LD <sub>50</sub>	lethal dose, 50% kill
LD <sub>Lo</sub>	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT <sub>50</sub>	lethal time, 50% kill
m	meter
MA	<i>trans,trans</i> -muconic acid

## APPENDIX C

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

## APPENDIX C

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 <sub>50</sub>	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization



## APPENDIX C

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q <sub>1</sub> *	cancer slope factor
-	negative
+	positive
(+)	weakly positive result
(-)	weakly negative result

APPENDIX C

This page is intentionally blank.

## APPENDIX D. INDEX

absorbed dose.....	11, 225, 275
acetylcholine .....	194
acetylcholinesterase .....	194
adenocarcinoma .....	106
adrenal gland.....	91, 166, 236
adrenals .....	91
adsorbed .....	349, 357, 378
adsorption.....	361, 392
aerobic.....	360, 361
alanine aminotransferase (see ALT) .....	33, 87, 162, 195
ALT (see alanine aminotransferase) .....	33, 162, 283, 294
ambient air .....	9, 347, 362, 369, 380
anaerobic .....	358, 359, 360, 361
anemia .....	4, 12, 16, 17, 34, 35, 36, 37, 159, 160, 194, 302, 395
aspartate aminotransferase (see AST).....	33, 162
AST (see aspartate aminotransferase).....	33, 162, 294
bioaccumulation.....	358
bioavailability .....	224, 230, 231, 232, 237, 253, 265, 288, 289, 314, 358, 373, 379
bioconcentration factor .....	358
biomarker .....	274, 275, 276, 279, 281, 282, 316, 383, 393
blood cell count.....	30, 85, 86, 158
body weight effects .....	50, 92, 167
breast milk.....	11, 225, 235, 236, 253, 255, 266, 273, 313, 315, 373, 374, 381
cancer .....	4, 21, 36, 50, 99, 100, 101, 102, 103, 104, 105, 106, 167, 181, 182, 202, 217, 234, 248, 272, 273, 281, 287, 296, 303, 309, 312, 374, 382, 397, 398
carcinogen.....	22, 403
carcinogenic .....	4, 22, 26, 48, 49, 99, 106, 183, 220, 268, 269, 287, 299, 303, 309, 403
carcinogenicity .....	22, 36, 37, 183, 184, 185, 220, 267, 299, 303, 403
carcinoma.....	22, 183, 184, 185, 195, 212, 216
cardiovascular .....	12, 23, 50, 82, 83, 154, 155, 193, 296, 299, 300
cardiovascular effects.....	82, 83, 154, 155, 193
cholinesterase.....	163, 194
chromosomal aberrations .....	211, 212, 217, 221, 268, 284, 304, 305, 310, 311
clearance .....	14, 79, 80, 89, 95, 224, 226, 228, 240, 248, 254, 255, 256, 260, 261, 262, 265, 266, 284, 288, 314
death.....	12, 16, 48, 50, 73, 77, 84, 101, 107, 154, 155, 181, 182, 234, 273, 283, 296, 299, 300, 315
deoxyribonucleic acid (see DNA).....	11, 207, 212, 216, 248
dermal effects.....	20, 91, 92, 166, 167, 170, 193, 195, 197, 245, 296
developmental effects .....	19, 25, 34, 43, 45, 99, 178, 180, 181, 202, 273, 299, 307, 315

## APPENDIX D

DNA (see deoxyribonucleic acid).....	11, 21, 173, 203, 204, 205, 207, 208, 210, 211, 212, 213, 215, 216, 217, 219, 220, 221, 222, 223, 224, 225, 248, 267, 268, 269, 275, 282, 284, 285, 292, 293, 294, 295, 304, 305, 310, 311, 312, 315, 317, 382, 393
elimination half-time.....	276
elimination rate .....	225
endocrine.....	23, 50, 91, 166, 270, 271
endocrine effects .....	90, 91, 166
erythema.....	15, 16, 27, 50, 93, 185, 198, 199
fetal tissue .....	239, 274, 314, 374, 381
fetus.....	271, 307
follicle stimulating hormone (see FSH).....	97
FSH (see follicle stimulating hormone).....	97
gastrointestinal effects .....	12, 14, 32, 35, 83, 84, 155, 156, 157, 193, 303
general population.....	3, 9, 104, 106, 249, 253, 312, 313, 349, 350, 369, 371, 375, 377, 380
genotoxic.....	21, 48, 217, 219, 220, 222, 223, 224, 252, 282, 284, 296, 299, 304, 305, 310, 312
genotoxicity.....	21, 202, 217, 220, 223, 224, 284, 294, 299, 304, 305, 310, 317
groundwater .....	3, 182, 349, 351, 359, 360, 365, 390, 402
half-life.....	226, 231, 251, 252, 266, 275, 279, 311, 359, 360, 379
hematological effects ..	16, 17, 28, 29, 34, 35, 37, 85, 158, 159, 160, 161, 194, 300, 302, 303, 395
hematopoietic .....	17, 35, 159
hepatic effects .....	87, 162, 163, 194, 282, 283
hydroxyl radical .....	223, 248, 293, 294
immune system .....	16, 95, 170, 301, 308
immunological .....	12, 23, 35, 48, 93, 96, 281, 287, 299
immunological effects.....	15, 20, 24, 35, 93, 96, 299
K <sub>ow</sub> .....	328, 329, 330, 331, 332, 333
LD <sub>50</sub> .....	108, 185, 242, 287, 300
leukemia.....	208, 212, 213, 216
leukopenia.....	85
lymphatic.....	35, 39, 40, 41, 170, 266
metabolic effects .....	169, 247
micronuclei .....	219, 220, 221, 284, 304, 305
milk .....	201, 235, 236, 253, 266, 273, 370, 384
mucociliary .....	224, 227, 260, 265, 266, 288, 314
musculoskeletal effects .....	23, 50, 86, 161, 194
neonatal .....	238, 375
neoplasm .....	184
neoplastic .....	22
neurobehavioral.....	171, 270
neurochemical .....	171
neurological effects.....	12, 96, 171, 202, 282, 289, 300
nuclear.....	269, 293
ocular effects.....	21, 91, 167, 198
odds ratio.....	78, 98
pharmacodynamic .....	42, 256

## APPENDIX D

pharmacokinetic .....	256, 257, 258, 269, 271, 274, 312, 307
placenta .....	11, 179, 225, 235, 239, 243, 273, 306, 307, 313, 315, 374, 381
rate constant .....	246, 260, 261, 262, 263
renal effects .....	37, 88, 89, 90, 164, 165, 195, 299
reproductive effects.....	17, 18, 23, 24, 25, 43, 44, 45, 97, 98, 172, 173, 174, 175, 176, 178, 181, 202, 296, 299, 302, 303, 306
respiratory effects.....	12, 13, 20, 23, 27, 28, 29, 30, 38, 39, 42, 50, 73, 74, 75, 76, 79, 81, 83, 154, 193, 195, 281, 299, 301, 302, 315, 395, 396
retention .....	11, 87, 195, 225, 227, 228, 229, 242, 251, 252, 263, 276
sequestered.....	16, 243, 251, 266, 277, 291
solubility .....	24, 39, 108, 224, 225, 226, 227, 264, 268, 284, 288, 319, 349, 358, 360, 377
spermatogonia .....	44, 173
systemic effects .....	16, 50, 154, 193, 272, 299, 300, 301, 396
thyroid .....	91, 166
thyroxine .....	295, 315
toxicokinetic.....	11, 47, 224
tumors .....	4, 22, 104, 106, 183, 283
volatilization .....	386

