DRAFT
TOXICOLOGICAL PROFILE FOR
ARSENIC

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

September 2005

1/537

ADMIN RECORD

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 Arsenic was released in 2000. This 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

INTENTIONALLY

LEFT 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

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 November 7, 2003 (68 FR 63098). 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); and October 25, 2001 (66 FR 54014). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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

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

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

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

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

Other Sections of Interest:

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

ATSDR Information Center

Phone:	1-888-42-ATSDR or (404) 498-0110	***Fax:***	(770) 488-4178
E-mail:	atsdric@cdc.gov	***Internet:***	http://www.atsdr.cdc.gov

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

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental*

Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity; and numerous chemical-specific case studies.

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

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

Other Agencies and Organizations

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

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

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

Referrals

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

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 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):

Selene Chou, Ph.D.
Carolyn Harper, Ph.D
ATSDR, Division of Toxicology and Environmental Medicine, Atlanta, GA

Mark Osier, Ph.D., D.A.B.T.
Marc Odin, M.S.
Lara Chappell, Ph.D.
Gloria Sage, 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 Research Implementation 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

INTENTIONALLY

LEFT BLANK

PEER REVIEW

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

1. Alan Hall, M.D., Toxicology Consulting and Medical Translating Services, Inc. (TCMTS, Inc.), Elk Mountain, Wyoming;

2. Gary Pascoe, Ph.D., Pascoe Environmental Consulting, Port Townsend, Washington;

3. Toby Rossman, Ph.D., Professor of Environmental Medicine, New York University School of Medicine, Nelson Institute of Environmental Medicine, Tuxedo, New York.

These experts collectively have knowledge of arsenic'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

INTENTIONALLY

LEFT 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 ARSENIC? 1
1.2 WHAT HAPPENS TO ARSENIC WHEN IT ENTERS THE ENVIRONMENT? 3
1.3 HOW MIGHT I BE EXPOSED TO ARSENIC? 4
1.4 HOW CAN ARSENIC ENTER AND LEAVE MY BODY? 6
1.5 HOW CAN ARSENIC AFFECT MY HEALTH? 6
1.6 HOW CAN ARSENIC AFFECT CHILDREN? 8
1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO ARSENIC? 10
1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ARSENIC? 11
1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH? 12
1.10 WHERE CAN I GET MORE INFORMATION? 13

2. RELEVANCE TO PUBLIC HEALTH 15
2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ARSENIC IN THE UNITED STATES 15
2.2 SUMMARY OF HEALTH EFFECTS 16
2.3 MINIMAL RISK LEVELS 24

3. HEALTH EFFECTS 29
3.1 INTRODUCTION 29
3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE 29
3.2.1 Inhalation Exposure 32
3.2.1.1 Death 43
3.2.1.2 Systemic Effects 43
3.2.1.3 Immunological and Lymphoreticular Effects 51
3.2.1.4 Neurological Effects 51
3.2.1.5 Reproductive Effects 53
3.2.1.6 Developmental Effects 53
3.2.1.7 Cancer 55
3.2.2 Oral Exposure 60
3.2.2.1 Death 60
3.2.2.2 Systemic Effects 128
3.2.2.3 Immunological and Lymphoreticular Effects 141
3.2.2.4 Neurological Effects 141

3.2.2.5 Reproductive Effects 143
3.2.2.6 Developmental Effects 144
3.2.2.7 Cancer 147
3.2.3 Dermal Exposure 153
3.2.3.1 Death 153
3.2.3.2 Systemic Effects 155
3.2.3.3 Immunological and Lymphoreticular Effects 156
3.2.3.4 Neurological Effects 157
3.2.3.5 Reproductive Effects 157
3.2.3.6 Developmental Effects 157
3.2.3.7 Cancer 157
3.3 GENOTOXICITY 157
3.4 TOXICOKINETICS 169
3.4.1 Absorption 170
3.4.1.1 Inhalation Exposure 170
3.4.1.2 Oral Exposure 170
3.4.1.3 Dermal Exposure 173
3.4.2 Distribution 173
3.4.2.1 Inhalation Exposure 173
3.4.2.2 Oral Exposure 174
3.4.2.3 Dermal Exposure 175
3.4.2.4 Other Routes of Exposure 175
3.4.3 Metabolism 176
3.4.4 Elimination and Excretion 180
3.4.4.1 Inhalation Exposure 180
3.4.4.2 Oral Exposure 181
3.4.4.3 Dermal Exposure 181
3.4.4.4 Other Routes of Exposure 181
3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models 182
3.4.5.1 Summary of PBPK Models 183
3.4.5.2 Arsenic PBPK Model Comparison 185
3.4.5.3 Discussion of Models 185
3.5 MECHANISMS OF ACTION 197
3.5.1 Pharmacokinetic Mechanisms 197
3.5.2 Mechanisms of Toxicity 201
3.5.3 Animal-to-Human Extrapolations 203
3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS 204
3.7 CHILDREN'S SUSCEPTIBILITY 204
3.8 BIOMARKERS OF EXPOSURE AND EFFECT 209
3.8.1 Biomarkers Used to Identify or Quantify Exposure to Arsenic 210
3.8.2 Biomarkers Used to Characterize Effects Caused by Arsenic 213
3.9 INTERACTIONS WITH OTHER CHEMICALS 214
3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE 216
3.11 METHODS FOR REDUCING TOXIC EFFECTS 217
3.11.1 Reducing Peak Absorption Following Exposure 217
3.11.2 Reducing Body Burden 218
3.11.3 Interfering with the Mechanism of Action for Toxic Effects 219
3.12 ADEQUACY OF THE DATABASE 220
3.12.1 Existing Information on Health Effects of Arsenic 220
3.12.2 Identification of Data Needs 223
3.12.3 Ongoing Studies 233

4. CHEMICAL AND PHYSICAL INFORMATION 237
4.1 CHEMICAL IDENTITY 237
4.2 PHYSICAL AND CHEMICAL PROPERTIES 237

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL 249
5.1 PRODUCTION 249
5.2 IMPORT/EXPORT 254
5.3 USE 254
5.4 DISPOSAL 257

6. POTENTIAL FOR HUMAN EXPOSURE 259
6.1 OVERVIEW 259
6.2 RELEASES TO THE ENVIRONMENT 262
6.2.1 Air 262
6.2.2 Water 268
6.2.3 Soil 269
6.3 ENVIRONMENTAL FATE 270
6.3.1 Transport and Partitioning 270
6.3.2 Transformation and Degradation 276
6.3.2.1 Air 276
6.3.2.2 Water 276
6.3.2.3 Sediment and Soil 278
6.3.2.4 Other Media 279
6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT 280
6.4.1 Air 280
6.4.2 Water 282
6.4.3 Sediment and Soil 289
6.4.4 Other Environmental Media 293
6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE 301
6.6 EXPOSURES OF CHILDREN 314
6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES 319
6.8 ADEQUACY OF THE DATABASE 321
6.8.1 Identification of Data Needs 321
6.8.2 Ongoing Studies 324

7. ANALYTICAL METHODS 329
7.1 BIOLOGICAL MATERIALS 329
7.2 ENVIRONMENTAL SAMPLES 333
7.3 ADEQUACY OF THE DATABASE 334
7.3.1 Identification of Data Needs 338
7.3.2 Ongoing Studies 339

8. REGULATIONS AND ADVISORIES 341

9. REFERENCES 347

10. GLOSSARY 483

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 Inorganic Arsenic – Inhalation 37

3-2. Levels of Significant Exposure to Organic Arsenic – Inhalation 41

3-3. Levels of Significant Exposure to Inorganic Arsenic – Oral 100

3-4. Levels of Significant Exposure to Organic Arsenic – Oral 124

3-5. Inorganic Arsenic Biotransformation Pathway 177

3-6. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance 184

3-7. Parameters Used in the Mann PBPK Model for Animals 187

3-8. Parameters Used in the Mann PBPK Model for Humans 192

3-9. Parameters Used in the Yu PBPK Model for Animals 198

3-10. Existing Information on Health Effects of Inorganic Arsenic 221

3-11. Existing Information on Health Effects of Organic Arsenic 222

6-1. Frequency of NPL Sites with Arsenic Contamination 260

6-2. Counties in Which at Least 25% of Wells Exceed Different Arsenic Levels 284

THIS PAGE

INTENTIONALLY

LEFT BLANK

LIST OF TABLES

3-1. Levels of Significant Exposure to Inorganic Arsenic – Inhalation 33

3-2. Levels of Significant Exposure to Organic Arsenic - Inhalation 40

3-3. Levels of Significant Exposure to Inorganic Arsenic - Oral 61

3-4. Levels of Significant Exposure to Organic Arsenic - Oral 107

3-5. Levels of Significant Exposure to Inorganic Arsenic - Dermal 154

3-6. Genotoxicity of Inorganic Arsenic *In Vivo* 158

3-7. Genotoxicity of Inorganic Arsenic *In Vitro* 160

3-8. Genotoxicity of Organic Arsenic 167

3-9. Parameters Used in the Mann PBPK Model for Animals 188

3-10. Tissue Affinity Constants (K_{ij}) Obtained for the Mann PBPK Model for Animals by Fitting for Rabbits and Hamsters 189

3-11. Metabolic Rate Constants for the Mann PBPK Model for Animals Obtained by Fitting for Rabbits and Hamsters 190

3-12. Fitted Gastrointestinal Tract and Lung Absorption Half-time for the Hamster for the Mann PBPK Model 191

3-13. Physiological Data Used in the Mann PBPK Model for Humans 193

3-14. Tissue Affinity Constants (K_{ij}) Obtained by Fitting the Mann PBPK Animal Model for Use with Humans 194

3-15. Parameters Used in the Yu PBPK Model 199

3-16. Ongoing Studies on Health Effects of Arsenic, Federally Funded 234

4-1. Chemical Identity of Arsenic and Selected Inorganic Arsenic Compounds 238

4-2. Chemical Identity of Selected Organic Arsenic Compounds 240

4-3. Physical and Chemical Properties of Arsenic and Selected Inorganic Arsenic Compounds 243

4-4. Physical and Chemical Properties of Selected Organic Arsenic Compounds 245

5-1. Facilities that Produce, Process, or Use Arsenic 250

5-2. Facilities that Produce, Process, or Use Arsenic Compounds 252

5-3. Current U.S. Manufacturers of Selected Arsenic Compounds 255

6-1. Releases to the Environment from Facilities that Produce, Process, or Use Arsenic 264

6-2. Releases to the Environment from Facilities that Produce, Process, or Use Arsenic Compounds 266

6-3. Regional Occurrence of Arsenic in U.S. Water Sources and Finished Drinking Water 286

6-4. Levels of Arsenic in Fish and Shellfish—Recent Studies 294

6-5. Estimated Mean Daily Intake of Inorganic Arsenic 302

6-6. Mean Daily Dietary Intake of Arsenic for Selected U.S. Population Groups 303

6-7. Levels of Arsenic in Human Tissue and Urine—Recent Studies 307

6-8. Ongoing Studies on the Environmental Fate and Exposure of Humans to Arsenic 325

7-1. Analytical Methods for Determining Arsenic in Biological Samples 331

7-2. Analytical Methods for Determining Arsenic in Environmental Samples 335

7-3. Ongoing Studies on Analytical Methods for Arsenic in Environmental and Biological Samples 340

8-1. Regulations and Guidelines Applicable to Arsenic and Arsenic Compounds 342

1. PUBLIC HEALTH STATEMENT

This public health statement tells you about arsenic 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. Arsenic has been found in at least 784 of the 1,662 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 arsenic 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 arsenic, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS ARSENIC?

Arsenic is an element that is widely distributed in the Earth's crust. Elemental arsenic is ordinarily a steel grey metal-like material that occurs naturally. However, arsenic is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. Understanding the difference between

inorganic and organic arsenic is important because some of the organic forms are less harmful than the inorganic forms.

Most inorganic and organic arsenic compounds are white or colorless powders that do not evaporate. They have no smell, and most have no special taste. Thus, you usually cannot tell if arsenic is present in your food, water, or air.

Inorganic arsenic occurs naturally in soil and in many kinds of rock, especially in minerals and ores that contain copper or lead. When these ores are heated in smelters, most of the arsenic goes up the stack and enters the air as a fine dust. Smelters may collect this dust and take out the arsenic as a compound called arsenic trioxide (As_2O_3). However, arsenic is no longer produced in the United States; all of the arsenic used in the United States is imported.

Presently, about 90% of all arsenic produced is used as a preservative for wood to make it resistant to rotting and decay. The preservative is copper chromated arsenic (CCA) and the treated wood is referred to as "pressure-treated." In 2003, U.S. manufacturers of wood preservatives containing arsenic began a voluntary transition from CCA to other wood preservatives that do not contain arsenic in wood products for certain residential uses, such as play structures, picnic tables, decks, fencing, and boardwalks. This phase out was completed on December 31, 2003; however, wood treated prior to this date could still be used and existing structures made with CCA-treated wood would not be affected. CCA-treated wood products continue to be used in industrial applications. It is not known whether, or to what extent, CCA-treated wood products may contribute to exposure of people to arsenic.

In the past, inorganic arsenic compounds were predominantly used as pesticides, primarily on cotton fields and in orchards. Inorganic arsenic compounds can no longer be used in agriculture. However, organic arsenic compounds, namely cacodylic acid, disodium methylarsenate (DSMA), and monosodium methylarsenate (MSMA), are still used as pesticides, principally on cotton. Some organic arsenic compounds are used as additives in animal feed. Small quantities of arsenic metal are added to other metals to form metal mixtures or alloys with improved

properties. The greatest use of arsenic in alloys is in lead-acid batteries for automobiles. Another important use of arsenic compounds is in semiconductors and light-emitting diodes.

To learn more about the properties and uses of arsenic, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO ARSENIC WHEN IT ENTERS THE ENVIRONMENT?

Arsenic occurs naturally in soil and minerals and it therefore may enter the air, water, and land from wind-blown dust and may get into water from runoff and leaching. Volcanic eruptions are another source of arsenic. Arsenic is associated with ores mined for metals, such as copper and lead, and may enter the environment during the mining and smelting of these ores. Small amounts of arsenic also may be released into the atmosphere from coal-fired power plants and incinerators because coal and waste products often contain some arsenic.

Arsenic cannot be destroyed in the environment. It can only change its form, or become attached to or separated from particles. It may change its form by reacting with oxygen or other molecules present in air, water, or soil, or by the action of bacteria that live in soil or sediment. Arsenic released from power plants and other combustion processes is usually attached to very small particles. Arsenic contained in wind-borne soil is generally found in larger particles. These particles settle to the ground or are washed out of the air by rain. Arsenic that is attached to very small particles may stay in the air for many days and travel long distances. Many common arsenic compounds can dissolve in water. Thus, arsenic can get into lakes, rivers, or underground water by dissolving in rain or snow or through the discharge of industrial wastes. Some of the arsenic will stick to particles in the water or sediment on the bottom of lakes or rivers, and some will be carried along by the water. Ultimately, most arsenic ends up in the soil or sediment. Although some fish and shellfish take in arsenic, which may build up in tissues, most of this arsenic is in an organic form called arsenobetaine (commonly called "fish arsenic") that is much less harmful.

For more information on how arsenic behaves in the environment, see Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO ARSENIC?

Since arsenic is found naturally in the environment, you will be exposed to some arsenic by eating food, drinking water, or breathing air. Children may also be exposed to arsenic by eating dirt. You may also be exposed by skin contact with soil or water that contains arsenic. Analytical methods used by scientists to determine the levels of arsenic in the environment generally do not determine the specific form of arsenic present. Therefore, we do not always know the form of arsenic a person may be exposed to. Similarly, we often do not know what forms of arsenic are present at hazardous waste sites. Some forms of arsenic may be so tightly attached to particles or embedded in minerals that they are not taken up by plants and animals.

The concentration of arsenic in soil varies widely, generally ranging from about 1 to 40 parts of arsenic to a million parts of soil (ppm) with an average level of 3–4 ppm. However, soils in the vicinity of arsenic-rich geological deposits, some mining and smelting sites, or agricultural areas where arsenic pesticides had been applied in the past may contain much higher levels of arsenic. The concentration of arsenic in natural surface and groundwater is generally about 1 part in a billion parts of water (1 ppb), but may exceed 1,000 ppb in mining areas or where arsenic levels in soil are high. Groundwater is far more likely to contain high levels of arsenic than surface water. Surveys of U.S. drinking water indicate that about 80% of water supplies have less than 2 ppb of arsenic, but 2% of supplies exceed 20 ppb of arsenic. Levels of arsenic in food range from about 20 to 140 ppb. However, levels of inorganic arsenic, the form of most concern, are far lower. Levels of arsenic in the air generally range from less than 1 to about 2,000 nanograms (1 nanogram equals a billionth of a gram) of arsenic per cubic meter of air (less than 1–2,000 ng/m^3), depending on location, weather conditions, and the level of industrial activity in the area. However, urban areas generally have mean arsenic levels in air ranging from 20 to 30 ng/m^3.

You normally take in small amounts of arsenic in the air you breathe, the water you drink, and the food you eat. Of these, food is usually the largest source of arsenic. Seafood contains the greatest amounts of arsenic, but in fish and shellfish, this is mostly in an organic form of arsenic called arseonbetaine that is much less harmful. Some seaweeds may contain arsenic in inorganic

forms that may be more harmful. Children are likely to eat small amounts of dust or dirt each day, so this is another way they may be exposed to arsenic. The total amount of arsenic you take in from these sources is generally about 50 micrograms (1 microgram equals one-millionth of a gram) each day. The level of inorganic arsenic (the form of most concern) you take in from these sources is generally about 3.5 microgram/day.

In addition to the normal levels of arsenic in air, water, soil, and food, you could be exposed to higher levels in several ways, such as the following:

- Some areas of the United States contain unusually high natural levels of arsenic in rock, and this can lead to unusually high levels of arsenic in soil or water. If you live in an area like this, you could take in elevated amounts of arsenic in drinking water. Children may be taking in arsenic because of hand to mouth contact or eating dirt.

- Some hazardous waste sites contain large quantities of arsenic. If the material is not properly disposed of, it can get into surrounding water, air, or soil. If you live near such a site, you could be exposed to elevated levels of arsenic from these media.

- If you work in an occupation that involves arsenic production or use (for example, copper or lead smelting, wood treating, pesticide application), you could be exposed to elevated levels of arsenic during your work.

- If you saw or sand arsenic-treated wood, you could inhale some of the sawdust into your nose or throat. Similarly, if you burn arsenic-treated wood, you could inhale arsenic in the smoke.

- If you live in a formerly agricultural area where arsenic was used on crops, the soil could contain high levels of arsenic.

- In the past, several kinds of products used in the home (rat poison, ant poison, weed killer, some types of medicines) had arsenic in them. However, most of these uses of arsenic have ended, so you are not likely to be exposed from home products any longer.

You can find more information on how you may be exposed to arsenic in Chapter 6.

1.4 HOW CAN ARSENIC ENTER AND LEAVE MY BODY?

If you swallow arsenic in water, soil, or food, most of the arsenic may quickly enter into your body. The amount that enters your body will depend on how much you swallow and the kind of arsenic that you swallow. This is the most likely way for you to be exposed near a waste site. If you breathe air that contains arsenic dusts, many of the dust particles settle onto the lining of the lungs. Most of the arsenic in these particles is then taken up from the lungs into the body. You might be exposed in this way near waste sites where arsenic-contaminated soils are allowed to blow into the air, or if you work with arsenic-containing soil or products. If you get arsenic-contaminated soil or water on your skin, only a small amount will go through your skin into your body, so this is usually not of concern.

If you are exposed to arsenic, your liver changes some of this to a less harmful organic form. Both inorganic and organic forms leave your body in your urine. Most of the arsenic will be gone within several days, although some will remain in your body for several months or even longer.

You can find more information on how arsenic enters and leaves your body in Chapter 3.

1.5 HOW CAN ARSENIC AFFECT MY HEALTH?

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.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing may also help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

Inorganic arsenic has been recognized as a human poison since ancient times, and large oral doses (above 60,000 ppb in food or water) can result in death. If you swallow lower levels of inorganic arsenic (ranging from about 300 to 30,000 ppb in food or water), you may experience irritation of your stomach and intestines, with symptoms such as stomachache, nausea, vomiting, and diarrhea. Other effects you might experience from swallowing inorganic arsenic include decreased production of red and white blood cells, which may cause fatigue, abnormal heart rhythm, blood-vessel damage resulting in bruising, and impaired nerve function causing a "pins and needles" sensation in your hands and feet.

Perhaps the single-most characteristic effect of long-term oral exposure to inorganic arsenic is a pattern of skin changes. These include a darkening of the skin and the appearance of small "corns" or "warts" on the palms, soles, and torso, and are often associated with changes in the blood vessels of the skin. A small number of the corns may ultimately develop into skin cancer. Swallowing arsenic has also been reported to increase the risk of cancer in the liver, bladder, kidneys, prostate, and lungs. The Department of Health and Human Services (DHHS) has determined that inorganic arsenic is known to be a human carcinogen. The International Agency for Research on Cancer (IARC) has determined that inorganic arsenic is carcinogenic to humans. EPA also has classified inorganic arsenic as a known human carcinogen.

If you breathe high levels of inorganic arsenic, then you are likely to experience a sore throat and irritated lungs. You may also develop some of the skin effects mentioned above. The exposure level that produces these effects is uncertain, but it is probably above 100 micrograms of arsenic per cubic meter ($\mu g/m^3$) for a brief exposure. Longer exposure at lower concentrations can lead to skin effects, and also to circulatory and peripheral nervous disorders. There are some data suggesting that inhalation of inorganic arsenic may also interfere with normal fetal development, although this is not certain. An important concern is the ability of inhaled inorganic arsenic to increase the risk of lung cancer. This has been seen mostly in workers exposed to arsenic at smelters, mines, and chemical factories, but also in residents living near smelters and arsenical chemical factories. People who live near waste sites with arsenic may have an increased risk of lung cancer as well.

If you have direct skin contact with inorganic arsenic compounds, your skin may become irritated, with some redness and swelling. However, it does not appear that skin contact is likely to lead to any serious internal effects.

Despite all of the adverse health effects associated with inorganic arsenic exposure, there is some evidence that the small amounts of arsenic in the normal diet (10–50 ppb) may be beneficial to your health. For example, animals fed a diet with unusually low concentrations of arsenic did not gain weight normally. They also became pregnant less frequently than animals fed a diet containing a normal amount of arsenic. Further, the babies of these animals tended to be smaller than normal, and some died at an early age. However, no cases of arsenic deficiency in humans have ever been reported.

Almost no information is available on the effects of organic arsenic compounds in humans. Studies in animals show that most simple organic arsenic compounds (such as methyl and dimethyl compounds) are less toxic than the inorganic forms and that some complex organic arsenic compounds are virtually non-toxic. However, high doses can produce some of the same effects. Thus, if you are exposed to high doses of an organic arsenic compound, you might develop nerve injury, stomach irritation, or other effects, but this is not known for certain.

You can find more information on the health effects of inorganic and organic arsenic in Chapters 2 and 3.

1.6 HOW CAN ARSENIC AFFECT CHILDREN?

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

Children are exposed to arsenic in many of the same ways that adults are. Since arsenic is found in the soil, water, food, and air, children may take in arsenic in the air they breathe, the water they drink, and the food they eat. Since children tend to eat or drink less of a variety of foods

and beverages than do adults, ingestion of contaminated food or juice or infant formula made with arsenic-contaminated water may represent a significant source of exposure. In addition, since children often play in the dirt and put their hands in their mouths and sometimes intentionally eat dirt, ingestion of contaminated soil may be a more important source of arsenic exposure for children than for adults. In areas of the United States where natural levels of arsenic in the soil and water are high, or in areas in and around contaminated waste sites, exposure of children to arsenic through ingestion of soil and water may be significant. In addition, contact with adults who are wearing clothes contaminated with arsenic (e.g., with dust from copper- or lead-smelting factories, from wood-treating or pesticide application, or from arsenic-treated wood) could be a source of exposure. Because of the tendency of children to taste things that they find, accidental poisoning from ingestion of pesticides is also a possibility. Thus, although most of the exposure pathways for children are the same as those for adults, children may be at a higher risk of exposure because of normal hand-to-mouth activity.

Children who are exposed to arsenic may have many of the same effects as adults, including irritation of the stomach and intestines, blood vessel damage, skin changes, and reduced nerve function. Thus, all health effects observed in adults are of potential concern in children. There is also some evidence that suggests that long-term exposure to arsenic in children may result in lower IQ scores. We do not know if absorption of arsenic from the gut in children differs from adults. There is some information suggesting that children may be less efficient at converting inorganic arsenic to the less harmful organic forms. For this reason, children may be more susceptible to health effects from inorganic arsenic than adults.

There is some evidence that inhaled or ingested arsenic can injure pregnant women or their unborn babies, although the studies are not definitive. Studies in animals show that large doses of arsenic that cause illness in pregnant females can also cause low birth weight, fetal malformations, and even fetal death. Arsenic can cross the placenta and has been found in fetal tissues. Arsenic is found at low levels in breast milk.

You can find more information about how arsenic can affect children in Sections 3.7 and 6.6.

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

If your doctor finds that you have been exposed to substantial amounts of arsenic, ask whether your children might also have been exposed. Your doctor might need to ask your state health department to investigate.

If you use arsenic-treated wood in home projects, personal protection from exposure to arsenic-containing sawdust may be helpful in limiting exposure of family members. These measures may include dust masks, gloves, and protective clothing. Arsenic-treated wood should never be burned in open fires, or in stoves, residential boilers, or fire places, and should not be composted or used as mulch. If you live in an area with a high level of arsenic in the water or soil, substituting cleaner sources of water and limiting contact with soil (for example, through use of a dense groundcover or thick lawn) would reduce family exposure to arsenic. By paying careful attention to dust and dirt control in the home (air filters, frequent cleaning), you can reduce family exposure to contaminated dirt. Some children eat a lot of dirt. You should prevent your children from eating dirt. You should discourage your children from putting objects in their mouths. Make sure they wash their hands frequently and before eating. Discourage your children from putting their hands in their mouths or engaging in other hand-to-mouth activities. Since arsenic may be found in the home as a pesticide, household chemicals containing arsenic should be stored out of reach of young children to prevent accidental poisonings. Always store household chemicals in their original labeled containers; never store household chemicals in containers that children would find attractive to eat or drink from, such as old soda bottles. Keep your Poison Control Center's number by the phone.

It is sometimes possible to carry arsenic from work on your clothing, skin, hair, tools, or other objects removed from the workplace. This is particularly likely if you work in the fertilizer, pesticide, glass, or copper/lead smelting industries. You may contaminate your car, home, or other locations outside work where children might be exposed to arsenic. You should know about this possibility if you work with arsenic.

Your occupational health and safety officer at work can and should tell you whether chemicals you work with are dangerous and likely to be carried home on your clothes, body, or tools and whether you should be showering and changing clothes before you leave work, storing your street clothes in a separate area of the workplace, or laundering your work clothes at home separately from other clothes. Material safety data sheets (MSDS) for many chemicals used should be found at your place of work, as required by the Occupational Safety and Health Administration (OSHA) in the U.S. Department of Labor. MSDS information should include chemical names and hazardous ingredients, and important properties, such as fire and explosion data, potential health effects, how you get the chemical(s) in your body, how to properly handle the materials, and what to do in the case of emergencies. Your employer is legally responsible for providing a safe workplace and should freely answer your questions about hazardous chemicals. Your state OSHA-approved occupational safety and health program or OSHA can answer any further questions and help your employer identify and correct problems with hazardous substances. Your state OSHA-approved occupational safety and health program or OSHA will listen to your formal complaints about workplace health hazards and inspect your workplace when necessary. Employees have a right to seek safety and health on the job without fear of punishment.

You can find more information about how arsenic can affect children in Sections 3.7 and 6.6.

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

Several sensitive and specific tests can measure arsenic in your blood, urine, hair, or fingernails, and these tests are often helpful in determining if you have been exposed to above-average levels of arsenic in the past. These tests are not usually performed in a doctor's office. They require sending the sample to a testing laboratory.

Measurement of arsenic in your urine is the most reliable means of detecting arsenic exposures that you experienced within the last several days. Most tests measure the total amount of arsenic present in your urine. This can sometimes be misleading, because the nonharmful forms of

arsenic in fish and shellfish can give a high reading even if you have not been exposed to a toxic form of arsenic. For this reason, laboratories sometimes use a more complicated test to separate "fish arsenic" from other forms. Because most arsenic leaves your body within a few days, analysis of your urine cannot detect if you were exposed to arsenic in the past. Tests of your hair or fingernails can tell if you were exposed to high levels over the past 6–12 months, but these tests are not very useful in detecting low-level exposures. If high levels of arsenic are detected, this shows that you have been exposed, but unless more is known about when you were exposed and for how long, it is usually not possible to predict whether you will have any harmful health effects.

You can find more information on how arsenic can be measured in your hair, urine, nails, and other tissues in Chapters 3 and 7.

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

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

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

The federal government has taken several steps to protect humans from arsenic. First, EPA has set limits on the amount of arsenic that industrial sources can release into the environment. Second, EPA has restricted or canceled many of the uses of arsenic in pesticides and is considering further restrictions. Third, in January 2001, the EPA lowered the limit for arsenic in drinking water from 50 to 10 ppb. Finally, OSHA has established a permissible exposure limit (PEL), 8-hour time-weighted average, of 10 $\mu g/m^3$ for airborne arsenic in various workplaces that use inorganic arsenic.

You can find more information on regulations and guidelines that apply to arsenic in Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

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

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

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information

and technical assistance number at 1-888-42ATSDR (1-888-422-8737), by e-mail at atsdric@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

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 ARSENIC IN THE UNITED STATES

Arsenic is widely distributed in the Earth's crust, which contains about 3.4 ppm arsenic. In nature, arsenic is mostly found in minerals and only to a small extent in its elemental form. Arsenic is mainly obtained as a byproduct of the smelting of copper, lead, cobalt, and gold ores. Arsenic trioxide is the primary form in which arsenic is marketed and consumed. There has been no domestic production of arsenic since 1985. In 2003, the world's largest producer of arsenic compounds was China, followed by Chile and Peru.

In 2003, the U.S. was the world's largest consumer of arsenic. Production of wood preservatives, primarily copper chromated arsenic (CCA), $CrO_3 \cdot CuO \cdot As_2O_5$, accounted for more than 90% of domestic consumption of arsenic trioxide. In response to consumer concerns, U.S. manufacturers of arsenical wood preservative began a voluntary transition from CCA to other wood preservatives for certain residential wood products. This phase-out was completed on December 31, 2003; wood treated prior to this date could still be used and CCA-treated wood products continue to be used in industrial applications.

Other uses for arsenic compounds include the production of agricultural chemicals, as an alloying element in ammunition and solders, as an anti-friction additive to metals used for bearings, and to strengthen lead-acid storage battery grids. High-purity arsenic (99.9999%) is used by the electronics industry for gallium-arsenide semiconductors for telecommunications, solar cells, and space research. Various organic arsenicals are still used in the United States as herbicides and as antimicrobial additives for animal and poultry feed. However, the use of inorganic arsenic compounds in agriculture has virtually disappeared beginning around the 1960s. Arsenic trioxide and arsenic acid were used as a decolorizer and fining agent in the production of bottle glass and other glassware. Arsenic compounds also have a long history of use in medicine, and have shown a re-emergence of late with the recent introduction of arsenic trioxide treatment for acute promyelocytic leukemia.

The principal route of exposure to arsenic for the general population is likely to be the oral route, primarily in the food and in the drinking water. Dietary exposures to total arsenic were highly variable, with a mean of 50.6 µg/day (range of 1.01–1,081 µg/day) for females and 58.5 µg/day (range of 0.21–

1,276 µg/day) for males. The mean estimated average daily consumption of inorganic arsenic was 10.22 µg/day (range of 0.93–104.89 µg/day). Drinking water generally contains an average of 2 µg/L of arsenic, although 12% of water supplies from surface water sources in the North Central region of the country and 12% of supplies from groundwater sources in the Western region have levels exceeding 20 µg/L. Arsenic is also widely distributed in surface water, groundwater, and finished drinking water in the United States. Surveys of arsenic concentrations in rivers and lakes indicate that most values are below 10 µg/L, although individual samples may range up to 3,400 µg/L. Arsenic released to the land at hazardous waste sites is likely to be relatively immobile due to a high capacity for soil binding, particularly to iron and manganese oxides. Exposure to arsenic from other pathways is generally small, but may be significant for areas with high levels of arsenic contamination or in occupational settings. For a more complete discussion of possible exposures to arsenic, see Chapter 6 of the profile.

2.2 SUMMARY OF HEALTH EFFECTS

Arsenic is a potent toxicant that may exist in several valence states and in a number of inorganic and organic forms. Most cases of arsenic-induced toxicity in humans are due to exposure to inorganic arsenic, and there is an extensive database on the human health effects of the common arsenic oxides and oxyacids. Although there may be some differences in the potency of different chemical forms (e.g., arsenites tend to be somewhat more toxic than arsenates), these differences are usually minor. Humans may be exposed to a variety of organic arsenicals (mainly methyl and phenyl derivatives of arsenic acid) since these are widely used in agriculture. Although human health effects data are sparse, it is generally considered that organic arsenicals are substantially less toxic than the inorganic forms. However, available data (mainly from animal studies) make clear that adequate doses of the methyl and phenyl arsenates can produce adverse health effects that resemble those of the inorganic arsenicals; thus, the possibility of health risks from the organic arsenicals should not be disregarded.

Exposures of humans near hazardous waste sites could involve inhalation of arsenic dusts in air, ingestion of arsenic in water, food, or soil, or dermal contact with contaminated soil or water. By the inhalation route, the most sensitive effect of inorganic arsenic is an increased risk of lung cancer, although respiratory irritation, nausea, and skin effects may also occur. There are only a few quantitative data on noncancer effects in humans exposed to inorganic arsenic by the inhalation route. However, it appears that such effects are unlikely below a concentration of about 0.1–1.0 mg As/m^3. Animal data similarly identify effects on the respiratory system as the primary noncancer effect of inhaled inorganic arsenic compounds, although only a few studies are available. Only limited data on the effects of inhaled organic

arsenic compounds in humans or animals are available; these studies are generally limited to high-dose, short-term exposures, which result in frank effects.

Relatively little information is available on effects due to direct dermal contact with inorganic arsenicals, but several studies indicate the chief effect is local irritation and dermatitis, with little risk of other adverse effects.

The database for the oral toxicity of inorganic arsenic is extensive, containing a large number of studies of orally-exposed human populations. These studies have identified effects on virtually every organ or tissue evaluated, although some end points appear to be more sensitive than others. The available data from humans identify the skin as the most sensitive noncancer end point of long-term oral arsenic exposure. Typical dermal effects include hyperkeratinization of the skin (especially on the palms and soles), formation of multiple hyperkeratinized corns or warts, and hyperpigmentation of the skin with interspersed spots of hypopigmentation. Oral exposure data from studies in humans indicate that these lesions typically begin to manifest at exposure levels of about 0.002–0.02 mg As/kg/day. At these exposure levels, peripheral vascular effects are also commonly noted, including cyanosis, gangrene, and, in Taiwanese populations, the condition known as "Blackfoot Disease." Other reported cardiovascular effects of oral exposure to inorganic arsenic include increased incidences of high blood pressure and circulatory problems. Recently, the use of intravenous arsenic trioxide as therapy for acute promyelocytic leukemia has raised further concerns about the cardiovascular effects of arsenic, including alterations in cardiac QT interval and the development of torsades de pointes.

In addition to dermal and cardiovascular effects, oral exposure to inorganic arsenic may result in effects on other organ systems. Nausea, vomiting, and diarrhea are very common symptoms in humans following oral exposure to inorganic arsenicals, both after acute high-dose exposure and after repeated exposure to lower doses; these effects are likely due to a direct irritation of the gastrointestinal mucosa. Acute, high-dose exposure can lead to encephalopathy, with clinical signs such as confusion, hallucinations, impaired memory, and emotional lability, while long-term exposure to lower levels can lead to the development of peripheral neuropathy characterized by a numbness in the hands and feet that may progress to a painful "pins and needles" sensation. A recent study also reported decreases in intelligence scores of arsenic-exposed children.

Data on the effects of oral exposure to inorganic arsenic on reproductive end points in humans are not available. Animal data suggest that arsenic may cause changes to reproductive organs of both sexes,

including decreased organ weight and increased inflammation of reproductive tissues, although these changes may be secondary effects. However, these changes do not result in a significant impact on reproductive ability. Chronic exposure of humans to inorganic arsenic in the drinking water has been associated with excess incidence of miscarriages, stillbirths, preterm births, and infants with low birth weights, although dose-response data are not presently available for these effects. Animal studies of oral inorganic arsenic exposure have reported developmental effects, but generally only at concentrations that also resulted in maternal toxicity.

Arsenic is a known human carcinogen by both the inhalation and oral exposure routes. By the inhalation route, the primary tumor types are respiratory system cancers, although a few reports have noted increased incidence of tumors at other sites, including the liver, skin, and digestive tract. In humans exposed chronically by the oral route, skin tumors are the most common type of cancer. In addition to skin cancer, there are a number of case reports and epidemiological studies that indicate that ingestion of arsenic also increases the risk of internal tumors (mainly of bladder and lung, and to a lesser extent, liver, kidney, and prostate).

The Department of Health and Human Services (DHHS) has concluded that inorganic arsenic is known to be a human carcinogen. The International Agency for Research on Cancer (IARC) cites sufficient evidence of a relationship between exposure to arsenic and human cancer. The IARC classification of arsenic is Group 1. The EPA has determined that inorganic arsenic is a human carcinogen by the inhalation and oral routes, and has assigned it the cancer classification, Group A. EPA has calculated an oral cancer slope factor of 1.5 $(mg/kg/day)^{-1}$ and a drinking water unit risk of $5x10^{-5}$ $(\mu g/L)^{-1}$ for inorganic arsenic based on human dose-response data. The inhalation unit risk for cancer is 0.0043 $(\mu g/m^3)^{-1}$. EPA is currently revising the assessment for inorganic arsenic.

The following sections discuss significant effects resulting from exposure to inorganic arsenic in greater detail: dermal, cardiovascular, respiratory, gastrointestinal, neurological, and cancer. Additional information on these effects and on other effects is discussed in Section 3.2.

Dermal Effects. The most characteristic effect of long-term oral exposure to inorganic arsenic compounds is the development of skin lesions; these lesions are often used as diagnostic criteria for arsenicosis. The three lesions most often associated with chronic arsenicosis are hyperkeratinization of the skin (especially on the palms and soles), formation of multiple hyperkeratinized corns or warts, and hyperpigmentation of the skin with interspersed spots of hypopigmentation. Numerous studies of long-

term, low-level exposure to inorganic arsenic in humans have reported the presence of these lesions. In general, they begin to manifest at chronic exposure levels ranging from 0.002 to 0.02 mg As/kg/day. Chronic oral studies of lower exposure levels, ranging from 0.0004 to 0.01 mg As/kg/day, have generally not reported dermal effects. The mechanism(s) by which inorganic arsenic causes dermal effects is not well-understood. Elucidating the mechanism of dermal effects has been particularly difficult because the dermal effects common in humans have not been seen in studies in animals.

Dermal effects have also been reported following inhalation exposures to inorganic arsenic, although they are not as diagnostic as for oral exposure. Several studies of arsenic-exposed workers have reported the development of dermatitis; exposure levels required to produce this condition are not well-established. Altered dermal pigmentation and hyperkeratosis have also been reported in studies of humans exposed to inorganic arsenic by inhalation, although exposure levels have varied considerably. Direct dermal contact with inorganic arsenicals may cause irritation and contact dermatitis. Usually, the effects are mild (erythema and swelling), but may progress to papules, vesicles, or necrotic lesions in extreme cases; these conditions tend to heal without treatment if exposure ceases.

Following inhalation exposure to organic arsenic compounds, observed dermal effects are generally limited to irritation at high exposure levels. No studies of dermal effects of organic arsenic compounds were available.

Cardiovascular Effects. A large number of studies in humans have reported cardiovascular effects following oral exposure to inorganic arsenic compounds. The cardiac effects of arsenic exposure are numerous, and include altered myocardial depolarization (prolonged QT interval, nonspecific ST segment changes), cardiac arrhythmias, and ischemic heart disease. These effects have been seen after acute and long-term exposure to inorganic arsenic in the environment, as well as side effects from intravenous therapy with arsenic trioxide for acute promyelocytic leukemia. Exposure levels for environmental exposures have not been well characterized, but intravenous doses for arsenic trioxide therapy are generally on the order of 0.15 mg As/kg/day.

Chronic exposure to inorganic arsenic has also been shown to lead to effects on the vascular system. The most dramatic of these effects is "Blackfoot Disease," a disease characterized by a progressive loss of circulation in the hands and feet, leading ultimately to necrosis and gangrene. Blackfoot Disease is endemic in an area of Taiwan where average drinking water levels of arsenic range from 0.17 to 0.80 ppm, corresponding to doses of about 0.014–0.065 mg As/kg/day. Arsenic exposure in Taiwan has

also been associated with an increased incidence of cerebrovascular and microvascular diseases and ischemic heart disease. While Blackfoot Disease itself has not been reported outside of Taiwan, other vascular effects are common in areas with high arsenic exposures, and include such severe effects as increases in the incidences of Raynaud's disease and of cyanosis of fingers and toes as well as hypertension, thickening and vascular occlusion of blood vessels, and other unspecified cardiovascular conditions. However, while the majority of human studies have reported cardiovascular effects following exposure to inorganic arsenic, some have found no such effects.

Changes in cardiac rhythm and in some vascular end points have also been reported in animal studies of inorganic arsenicals, but generally only at higher exposure levels and not to the degree of severity seen in humans.

No studies of cardiovascular effects of organic arsenic compounds in humans were located. A few studies have reported cardiovascular effects in animals following exposure to organic arsenic compounds, but these effects have occurred only at very high exposure levels.

Respiratory Effects. While case reports and small cohort studies have routinely reported an increase in respiratory symptoms of humans exposed occupationally to inorganic arsenic, dose-response data for these symptoms are generally lacking. The only study that evaluated respiratory effects (changes in chest X-ray or respiratory performance) and reported an exposure estimate did not report significant changes at an exposure level of 0.613 mg As/m^3. Exposed workers often report irritation of the mucous membranes of the nose and throat, which may lead to laryngitis, bronchitis, or rhinitis. Increased mortality due to respiratory disease has been reported in some cohort mortality studies of arsenic-exposed workers, but no conclusive evidence of an association of these diseases with arsenic exposure has been presented. It is not known whether respiratory effects following inhaled inorganic arsenic compounds are due to a direct effect of arsenic on respiratory tissues, general effects of foreign material in the lungs, or an effect of arsenic on the pulmonary vasculature. Similar responses, including rales, labored breathing, and respiratory hyperplasia, have been noted in animal studies of inhaled or instilled inorganic arsenic compounds.

Respiratory effects have also been reported following oral exposure of humans to inorganic arsenic. Acute oral exposure to ≥8 mg As/kg may result in serious respiratory effects, including respiratory distress, hemorrhagic bronchitis, and pulmonary edema; however, it is not clear whether these are primary effects or are the result of damage to the pulmonary vascular system. In general, respiratory effects have

not been widely associated with repeated oral ingestion of low arsenic doses. However, some studies have reported minor respiratory symptoms, such as cough, sputum, rhinorrhea, and sore throat, in people with repeated oral exposure to 0.03–0.05 mg As/kg/day. More serious respiratory effects, such as bronchitis and sequelae (bronchiectasis, bronchopneumonia) have been observed in patients chronically exposed to arsenic and at autopsy in some chronic poisoning cases. There are few animal data reporting respiratory effects of oral exposure to inorganic arsenic, and those studies generally found effects only at very high dose levels.

Respiratory effects are not a sensitive end point following exposure to organic arsenicals by either the inhalation or oral exposure route.

Gastrointestinal Effects. Both short-term and chronic oral exposures to inorganic arsenicals have been reported to result in irritant effects on gastrointestinal tissues. Numerous studies of acute, high-dose exposure to inorganic arsenicals have reported nausea, vomiting, diarrhea, and abdominal pain, although specific dose levels associated with the onset of these symptoms have not been identified. Chronic oral exposure to 0.01 mg As/kg/day generally results in similar reported symptoms. For both acute and chronic exposures, the gastrointestinal effects generally diminish or resolve with cessation of exposure. Similar gastrointestinal effects have been reported after occupational exposures to inorganic arsenicals, although it is not known if these effects were due to absorption of arsenic from the respiratory tract or from mucociliary clearance resulting in eventual oral exposure.

The effects of organic arsenicals on the gastrointestinal tract have not been as thoroughly investigated. No reports were located of gastrointestinal complaints in humans exposed to organic arsenicals. Inhalation exposure of rats to high doses of dimethyl arsenic acid (DMA) can cause diarrhea, while oral exposure can result in diarrhea and histological damage to the stomach, small intestine, and large intestine. Oral exposure of rabbits to monomethylarsenic acid (MMA) has been shown to cause intestinal irritation and weakening of the intestinal wall. These data suggest that the organic arsenicals are capable of producing gastrointestinal effects similar to the inorganic arsenicals, but the data are too sparse to make quantitative comparisons.

Neurological Effects. A common effect following both oral and inhalation exposure to inorganic is the development of peripheral neuropathy. Following occupational exposure to inorganic arsenic in pesticide plants or smelters, exposed workers have shown increased incidence of neurological changes, including altered nerve conduction velocities. One study reported that these effects were seen after

28 years of exposure to 0.31 mg As/m^3; most other studies of the neurological effects of inhaled inorganic arsenicals in humans have not characterized the exposure concentration.

Following high-dose (>2 mg As/kg/day) acute oral exposures to inorganic arsenicals in humans, reported effects include headache, lethargy, mental confusion, hallucination, seizures, and coma. Following longer-term exposure to 0.03–0.1 mg As/kg/day, peripheral neuropathy, characterized initially by numbness of the hands and feet and a "pins and needles" sensation and progressing to muscle weakness, wrist-drop and/or ankle-drop, diminished sensitivity, and altered reflex action. Histological features of the neuropathy include a dying-back axonopathy and demylenation. Following removal from exposure, the neuropathy is only partially reversible and what recovery does occur is generally slow. Reports of neurological effects at lower arsenic levels (0.004–0.006 mg As/kg/day) have been inconsistent, with some human studies reporting fatigue, headache, depression, dizziness, insomnia, nightmare, and numbness while others reported no neurological effects. Neurological effects have also been reported in oral studies of arsenic toxicity in animals, although these were generally performed at higher doses (0.4–26.6 mg As/kg/day) than has been reported in exposed human populations. The mechanism(s) of arsenic-induced neurological changes has not been determined.

Information on the neurological effects of organic arsenicals is sparse, but the available studies suggest that high oral doses may result in neurological symptoms. A report of a 52-year-old woman who ingested high levels of organic arsenic in bird's nest soup reported numbness and tingling of the fingertips, toes, and circumoral region that resolved upon cessation of exposure. Oral animal studies with roxarsone and MMA have revealed treatment-related effects on neurological end points at doses ranging from 0.87 to 63 mg As/kg/day. By contrast, the limited data on inhalation exposure of humans to organic arsenicals have not reported significant neurological alterations; no animal studies of the neurotoxicity of inhaled organic arsenicals were located.

Cancer. There is clear evidence from studies in humans that exposure to inorganic arsenic by either the inhalation or oral routes increases the risk of cancer. Numerous studies of copper smelters or miners exposed to arsenic trioxide have reported an increased risk of lung cancer. Increased incidence of lung cancer has also been observed at chemical plants where exposure was primarily to arsenate. Other studies suggest that residents living near smelters or arsenical chemical plants may have increased risk of lung cancer, although the reported increases are small and are not clearly detectable in all cases. In general, studies reporting long-term exposure to 0.07 mg As/m^3 or greater have shown an increased incidence of lung cancer, while at lower exposure levels, the association has been less clear or not present.

2 RELEVANCE TO PUBLIC HEALTH

There is convincing evidence from a large number of epidemiological studies and case reports that ingestion of inorganic arsenic increases the risk of developing skin cancer. The most common tumors seen are squamous cell carcinomas, which may develop from the hyperkeratotic warts or corns commonly seen as a dermal effect of oral inorganic arsenic exposure. Early studies of populations within the United States did not suggest an increased risk of cancer from oral inorganic arsenic exposure, but more recent studies have suggested that while the risk to U.S. populations is less than for some other countries, the possibility of arsenic-induced skin cancers cannot be discounted. In most cases, exposure levels associated with the development of skin cancer have not been reported.

Recent studies have also identified other suspected targets of inorganic arsenic-induced carcinogenesis. There is increasing evidence that long-term exposure to arsenic can result in the development of bladder cancer, with transitional cell cancers being the most prevalent. While studies have noted statistical dose-response trends in arsenic-induced bladder cancers, reliable quantitative assessments of dose-response relationships have not been presented. Recent studies have also suggested that chronic oral exposure to arsenic may result in the development of respiratory tumors. Exposure levels in studies evaluating respiratory and bladder cancers have been comparable to those in studies evaluating skin tumors. Studies of U.S. populations have not consistently identified an increased risk of bladder or respiratory tumors following oral exposure to inorganic arsenic.

Animal studies of both inhalation and oral exposure to inorganic arsenicals have not resulted in increased incidence of cancer formation in adult animals. However, a recent study in mice reported that arsenic could function as a complete transplacental carcinogen, resulting in tumors in the offspring of exposed animals.

No studies on the carcinogenicity of organic arsenicals following inhalation exposure in humans or animals were located. No studies of the carcinogenic effects of organic arsenicals in humans exposed by the oral route were located. No increase in tumor formation was seen in dogs given 1.5 mg As/kg/day, rats given 2.9 mg As/kg/day, or mice given 3.8 mg As/kg/day as roxarsone for 2 years or in a lifetime carcinogenicity study in rats and mice exposed to up to 1.4 mg As/kg/day as roxarsone. Studies of mice and rats exposed orally to up to 47 mg As/kg/day for 104 weeks also showed no evidence of increased tumor formation. In contrast, dietary exposure of rats to DMA at levels of 0.14 mg As/kg/day or greater resulted in a significant increase in tumors of the urinary bladder. A recent study suggested that DMA primarily exerts its carcinogenic effects on spontaneous tumor development.

2.3 MINIMAL RISK LEVELS

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

Inhalation MRLs

No inhalation MRLs were derived for inorganic or organic arsenic. Adequate human studies evaluating dose-response relationships for noncancer end points were not located for inorganic arsenic, and animal data on the health effects of inorganic arsenic following inhalation exposure are limited to studies that did not evaluate a suitable range of health effects. In general, respiratory or immunological effects appeared to be the most common following inhalation exposure to inorganic arsenic in animals (Aranyi et al. 1985; Holson et al. 1999), while human data suggested that dermal or respiratory effects may be the most prevalent (Lagerkvist et al. 1986; Mohamed 1998; Perry et al. 1948). Lacking suitable studies upon which to base the MRLs, no inhalation MRLs were derived for inorganic arsenic. Few studies were located that examined the effects of organic arsenic compounds following inhalation exposure, none of which was suitable for use in derivation of inhalation MRLs for organic arsenic compounds due to the presence of serious effects or a lack of exposure characterization (Stevens et al. 1979; Watrous and McCaughey 1945).

Oral MRLs

- A provisional MRL of 0.005 mg/kg/day has been derived for acute-duration (14 days or less) oral exposure to inorganic arsenic.

Mizuta et al. (1956) summarized findings from 220 poisoning cases associated with an episode of arsenic contamination of soy sauce in Japan. The soy sauce was contaminated with approximately 0.1 mg As/mL, probably as calcium arsenate. Arsenic intake in the cases was estimated by the researchers to be 3 mg/day (0.05 mg/kg/day, assuming 55 kg average body weight for this Asian population). The duration of exposure was 2–3 weeks in most cases. The primary symptoms were edema of the face, and gastrointestinal and upper respiratory symptoms initially, followed by skin lesions and neuropathy in some patients. Other effects included mild anemia and leukopenia, mild degenerative liver lesions and hepatic dysfunction, abnormal electrocardiogram, and ocular lesions. For derivation of the provisional acute oral MRL, facial edema and gastrointestinal symptoms (nausea, vomiting, diarrhea), which were characteristic of the initial poisoning and then subsided, were considered to be the critical effects. The provisional MRL of 0.005 mg As/kg/day was calculated by applying an uncertainty factor of 10 (10 for use of a lowest-observed-adverse-effect level (LOAEL) and 1 for intrahuman variability) to the LOAEL of 0.05 mg As/kg/day (see Appendix A for MRL worksheets). The MRL is considered provisional because the gastrointestinal effects (nausea, vomiting, diarrhea, and occult blood in feces and gastric and duodenal juice) are serious and because serious neurological (hypesthesia in legs, abnormal patellar reflex) and cardiovascular (abnormal electrocardiogram) effects also occurred at the same dose. Although it is not customary to base an MRL on a serious LOAEL, public health concerns regarding arsenic suggested that a provisional value derived from these data would be useful for the general public.

- An MRL of 0.0003 mg/kg/day has been derived for chronic-duration (365 days or more) oral exposure to inorganic arsenic.

Tseng et al. (1968) and Tseng (1977) investigated the incidence of Blackfoot Disease and dermal lesions (hyperkeratosis and hyperpigmentation) in a large number of poor farmers (both male and female) exposed to high levels of arsenic in well water in Taiwan. A control group consisting of 17,000 people, including one group in which arsenic exposure was "undetermined" and which included those villages where arsenic-contaminated wells were no longer used or the level could not be classified, and a control population of 7,500 people who consumed water from wells almost free of arsenic (0.001–0.017 ppm) was also examined. The authors stated that the incidence of dermal lesions increased with dose, but individual doses were not provided. However, incidence data were provided based on stratification of the

exposed population into low (<300 µg/L), medium (300–600 µg/L), or high (>600 µg/L) exposure levels. Doses were calculated from group mean arsenic concentrations in well water, assuming the intake parameters described by Abernathy et al. (1989). Accordingly, the control, low-, medium-, and high-exposure levels correspond to doses of 0.0008, 0.014, 0.038, and 0.065 mg As/kg/day, respectively. The no-observed-adverse-effect level (NOAEL) identified by Tseng (1977) (0.0008 mg As/kg/day) was limited by the fact that the majority of the population was less than 20 years of age and the incidence of skin lesions increased as a function of age, and because the estimates of water intake and dietary arsenic intake are highly uncertain. Schoof et al. (1998) estimated that dietary intakes of arsenic from rice and yams may have been 15–211 µg/day (mean=61 µg/day), based on arsenic analyses of foods collected in Taiwan in 1993–1995. Use of the 50 µg/day estimate would result in an approximate doubling of the NOAEL (0.0016 mg/kg/day) (see Appendix A for MRL worksheets). The MRL was derived by applying an uncertainty factor of 3 (for intrahuman variability) to the NOAEL of 0.0008 mg/kg/day.

The MRL is supported by a large number of well-conducted epidemiological studies that identify reliable NOAELs and LOAELs for dermal effects. Southwick et al. (1981) identified a NOAEL of 0.006–0.007 mg As/kg/day for dermal lesions in several small populations in Utah. Harrington et al. (1978) identified a NOAEL of 0.003 mg As/kg/day for dermal effects in a small population in Alaska. Mazumder et al. (1988) identified a NOAEL of 0.009 mg As/kg/day and a LOAEL of 0.006 mg As/kg/day for pigmentation changes and hyperkeratosis in a small population in India. Haque et al. (2003) identified a LOAEL of 0.002 mg As/kg/day for hyperpigmentation and hyperkeratosis in a case-control study in India. Cebrián et al. (1983) identified a NOAEL of 0.0004 mg As/kg/day and a LOAEL of 0.022 mg As/kg/day in two regions in Mexico. Borgono and Greiber (1972) and Zaldívar (1974) identified a LOAEL of 0.02 mg As/kg/day for abnormal skin pigmentation in patients in Chile, and Borgono et al. (1980) identified a LOAEL of 0.01 mg As/kg/day for the same effect in school children in Chile. Valentine et al. (1985) reported a NOAEL of 0.02 mg As/kg/day for dermal effects in several small populations in California. Collectively, these studies indicate that the threshold dose for hyper-pigmentation and hyperkeratosis is approximately 0.002 mg As/kg/day. While many of these studies also identified effects on other end points at these exposure levels, including effects on gastrointestinal (Borgono and Greiber 1972; Cebrián et al. 1983; Guha Mazumder et al. 1988; Zaldívar 1974), cardiovascular (Tseng et al. 1995, 1996), hepatic (Hernandez-Zavala et al. 1998), and neurological end points (Guha Mazumder et al. 1988; Lianfang and Jianzhong 1994; Tsai et al. 2003), the overall database for dermal effects is considerably stronger than for effects on other end points.

A number of acute-duration studies of organic arsenic compounds are available, but these have focused primarily on serious or frank effects (Kaise et al. 1989; Kerr et al. 1963; Murai et al. 1993; NTP 1989b; Rogers et al. 1981) and have not consistently identified sensitive targets of organic arsenicals or exposure levels at which effects begin to occur. No intermediate- or chronic-duration oral studies of organic arsenicals in humans were located. Intermediate- and chronic-duration oral studies of roxarsone and DMA in rodents have been reported (Arnold et al. 1999; Cohen et al. 2001; NTP 1989b), but concerns regarding the high exposure levels used and possible species-related differences in sensitivity prevent the use of these studies for MRLs derivation. No oral MRLs were derived for organic arsenic compounds.

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 arsenic. 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.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

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

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.

Chemical Forms of Concern. Analysis of the toxic effects of arsenic is complicated by the fact that arsenic can exist in several different valence states and many different inorganic and organic compounds. Most cases of human toxicity from arsenic have been associated with exposure to inorganic arsenic, so these compounds are the main focus of this profile.

The most common inorganic arsenical in air is arsenic trioxide (As_2O_3), while a variety of inorganic arsenates (AsO_4^{-3}) or arsenites (AsO_2^-) occur in water, soil, or food. A number of studies have noted differences in the relative toxicity of these compounds, with trivalent arsenites tending to be somewhat more toxic than pentavalent arsenates (Byron et al. 1967; Gaines 1960; Maitani et al. 1987a; Sardana et al. 1981; Willhite 1981). However, these distinctions have not been emphasized in this profile, for several reasons: (1) in most cases, the differences in the relative potency are reasonably small (about 2–3-fold), often within the bounds of uncertainty regarding NOAEL or LOAEL levels; (2) different forms of arsenic may be interconverted, both in the environment (see Section 6.3) and the body (see Section 3.4);

and (3) in many cases of human exposure (especially those involving intake from water or soil, which are of greatest concern to residents near wastes sites), the precise chemical speciation is not known.

Gallium arsenide (GaAs) is another inorganic arsenic compound of potential human health concern, due to its widespread use in the microelectronics industry. Available toxicokinetic data suggest that although gallium arsenide is poorly soluble, it undergoes slow dissolution and oxidation to form gallium trioxide and arsenite (Webb et al. 1984, 1986). Therefore, the toxic effects of this compound are expected to be attributable to the arsenite that is liberated, plus the additional effects of the gallium species.

It is beyond the scope of this profile to provide detailed toxicity data on other less common inorganic arsenic compounds (e.g., As_2S_3), but these are expected to be of approximately equal or lesser toxicity than the oxycompounds, depending mainly on solubility (see Section 3.4).

Although organic arsenicals are usually viewed as being less toxic than the inorganics, several methyl and phenyl derivatives of arsenic that are widely used in agriculture are of possible human health concern. Chief among these are monomethylarsonic acid (MMA) and its salts, (monosodium methane arsonate [MSMA] and disodium methane arsonate [DSMA]), dimethyl arsinic acid (DMA, also known as cacodylic acid) and its sodium salt (sodium dimethyl arsinite, or sodium cacodylate), and roxarsone (3-nitro-4-hydroxyphenylarsonic acid). As with the inorganic compounds, there are toxicological differences between these various organic derivatives, but for the purposes of this profile, these differences have not been emphasized, because data are rarely adequate to permit rigorous quantitative comparisons between different chemicals, and most data are derived from studies in animals. As discussed below, animals do not appear to be good quantitative models for inorganic arsenic toxicity in humans, but it is not known if this also applies to toxicity of organic arsenicals.

Several organic arsenicals are found to accumulate in fish and shellfish. These derivatives (mainly arsenobetaine and arsenocholine, also referred to as "fish arsenic") have been studied by several researchers and have been found to be essentially nontoxic (Brown et al. 1990; Cannon et al. 1983; Charbonneau et al. 1978a; Kaise et al. 1985; Luten et al. 1982; Siewicki 1981; Tam et al. 1982; Yamauchi et al. 1986a). Thus, these compounds are not considered further here.

Arsine (AsH_3) and its methyl derivatives, although highly toxic, are also not considered in this profile, since these compounds are either gases or volatile liquids that are unlikely to be present at levels of concern at hazardous waste sites.

Use of Animal Data. An additional complexity to the analysis of arsenic toxicity is that most laboratory animals appear to be substantially less susceptible to arsenic than humans. For example, chronic oral exposure of humans to inorganic arsenic at doses of 0.05–0.1 mg/kg/day is frequently associated with neurological (Barton et al. 1992; Goddard et al. 1992; Guha Mazumder et al. 1988; Haupert et al. 1996; Hindmarsh et al. 1977; Huang et al. 1985; Sass et al. 1993; Silver and Wainman 1952; Szuler et al. 1979; Tay and Seah 1975; Valentine et al. 1981) or hematological signs of arsenic toxicity (Glazener et al. 1968; Guha Mazumder et al. 1988; Prasad and Rossi 1995; Sass et al. 1993; Tay and Seah 1975), but no characteristic neurological or hematological signs of arsenism were detected in monkeys, dogs, or rats chronically exposed to arsenate or arsenite at doses of 0.7–2.8 mg As/kg/day (Byron et al. 1967; EPA 1980f; Heywood and Sortwell 1979). This may be because the studies were not conducted for a sufficient length of time, or because too few animals were used. Moreover, while there is good evidence that arsenic is carcinogenic in humans by both oral and inhalation routes, evidence of arsenic-induced carcinogenicity in animals is mostly negative. For these reasons, quantitative dose-response data from animals are not judged to be reliable for determining levels of significant human exposure, and will be considered only briefly except when human data are lacking.

3.2.1 Inhalation Exposure

Most information on human inhalation exposure to arsenic derives from occupational settings such as smelters and chemical plants, where the predominant form of airborne arsenic is arsenic trioxide dust. One limitation to this type of study is that exposure data are usually difficult to obtain, especially from earlier time periods when exposure levels were higher than in recent years. This is further complicated by the fact that significant oral and dermal exposures are also likely to occur under these conditions and co-exposure to other metals and chemicals is also common. Thus, studies of this type are, like virtually all epidemiological studies, subject to some limitations and uncertainties. Table 3-1 and Figure 3-1 summarize studies that provide the most reliable quantitative data on health effects in humans, along with several studies in animals exposed to arsenic trioxide and other inorganic arsenic compounds by the inhalation route. Data for organic arsenicals are shown in Table 3-2 and Figure 3-2. All exposure data are expressed as milligrams of arsenic (as the element) per cubic meter of air (mg As/m^3). These studies and others that provide useful qualitative information on health effects of inorganic and organic arsenicals are discussed below.

DRAFT FOR PUBLIC COMMENT

Table 3-1 Levels of Significant Exposure to Inorganic Arsenic - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Immuno/ Lymphoret								
1	Mouse (CD-1)	3 hr		0.123 F	0.271 F (decr pulmonary bactericidal activity and incr susceptibility to streptococcal infection)		Aranyi et al. 1985 As(+3)	
2	Mouse (CD-1)	5 d 3 hr/d		0.259 F	0.519 F (decr pulmonary bactericidal activity and incr susceptibility to streptococcal infection)		Aranyi et al. 1985 As(+3)	
Developmental								
3	Mouse (CFLP)	Gd 9-12 4 hr/d		0.2	2.2 (10% decr avg fetal body wt)	21.6 (incr fetal deaths, skeletal malformations, and retarded growth)	Nagymajtenyi et al. 1985 As(+3)	
INTERMEDIATE EXPOSURE								
Death								
4	Rat (CD)	14 d pre- mating thru Gd 19 7 d/wk 6 hr/d				20 F (5/10 dams died)	Holson et al. 1999 As(+3)	
Systemic								
5	Rat (CD)	14 d pre- mating thru Gd 19 7 d/wk 6 hr/d	Resp	2 F	8 F (rales, dried red material around nose)		Holson et al. 1999 As(+3)	
			Bd Wt	2 F	8 F (decr body wt gain during gestation)			

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
6	Rat (CD)	14 d pre- mating thru Gd 19 7 d/wk 6 hr/d	Resp	0.9 F	8 F (rales)	20 F (labored breathing, gasping)	Holson et al. 1999 As(+3)	
			Gastro	8 F		20 F (gross gastrointestinal lesions)		
			Bd Wt	8 F		20 F (drastic decr body wt)		
Immuno/ Lymphoret								
7	Mouse (CD-1)	4 wk 5 d/wk 3 hr/d		0.126 F	0.245 F (decr pulmonary bactericidal activity)		Aranyi et al. 1985 As(+3)	
Reproductive								
8	Rat (CD)	14 d pre- mating thru Gd 19 7 d/wk 6 hr/d		8 F			Holson et al. 1999 As(+3)	
9	Rat (CD)	14 d pre- mating thru Gd 19 7 d/wk 6 hr/d		20 F			Holson et al. 1999 As(+3)	
Developmental								
10	Rat (CD)	14 d pre- mating thru Gd 19 7 d/wk 6 hr/d		8			Holson et al. 1999 As(+3)	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
11	Rat (CD)	14 d pre- mating thru Gd 19 7 d/wk 6 hr/d		8		20 (marked incr in post-implantation loss and marked decr in viable fetuses)	Holson et al. 1999 As(+3)	
CHRONIC EXPOSURE								
Systemic								
12	Human	23 yr (avg) (Occup)	Cardio			0.36 M (incr incidence of vasospasticity and clinical Raynaud's phenomenon)	Lagerkvist et al. 1986 As(+3)	
13	Human	0.5-50 yr (Occup)	Resp	0.613			Perry et al. 1948 As(+3)	
			Dermal		0.078 (mild pigmentation keratosis of skin)	0.613 (gross pigmentation with hyperkeratinization of exposed areas, wart formation)		
Neurological								
14	Human	28 yr (avg) (Occup)			0.31 M (decr nerve conduction velocity)		Lagerkvist and Zetterlund 1994 As(+3)	
Developmental								
15	Human	NS (Environ)		0.00006		0.0007 (incr risk of stillbirth)	Ihrig et al. 1998 As(+3)	
Cancer								
16	Human	1->30 yr (Occup)				0.213 M (CEL: lung cancer)	Enterline et al. 1987a As(+3)	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
17	Human	19.5 yr (avg) (Occup)				0.069 M (CEL: lung cancer)	Enterline et al. 1987b As(+3)	
18	Human	3 mo->30 yr (Occup)				0.2 M (CEL: lung cancer)	Jarup and Pershagen 1991 As(+3)	
19	Human	3 mo->30 yr (Occup)				0.05 M (CEL: lung cancer)	Jarup et al. 1989 As(+3)	
20	Human	1->30 yr (Occup)				0.38 M (CEL: lung cancer)	Lee-Feldstein 1986 As(+3)	
21	Human	>25 years (Occup)				0.29 M (CEL: lung cancer)	Lubin et al. 2000 As(+3)	
22	Human	14.8 yr (avg) (Occup)				0.3 M (CEL: lung cancer)	Welch et al. 1982 As(+3)	

aThe number corresponds to entries in Figure 3-1.

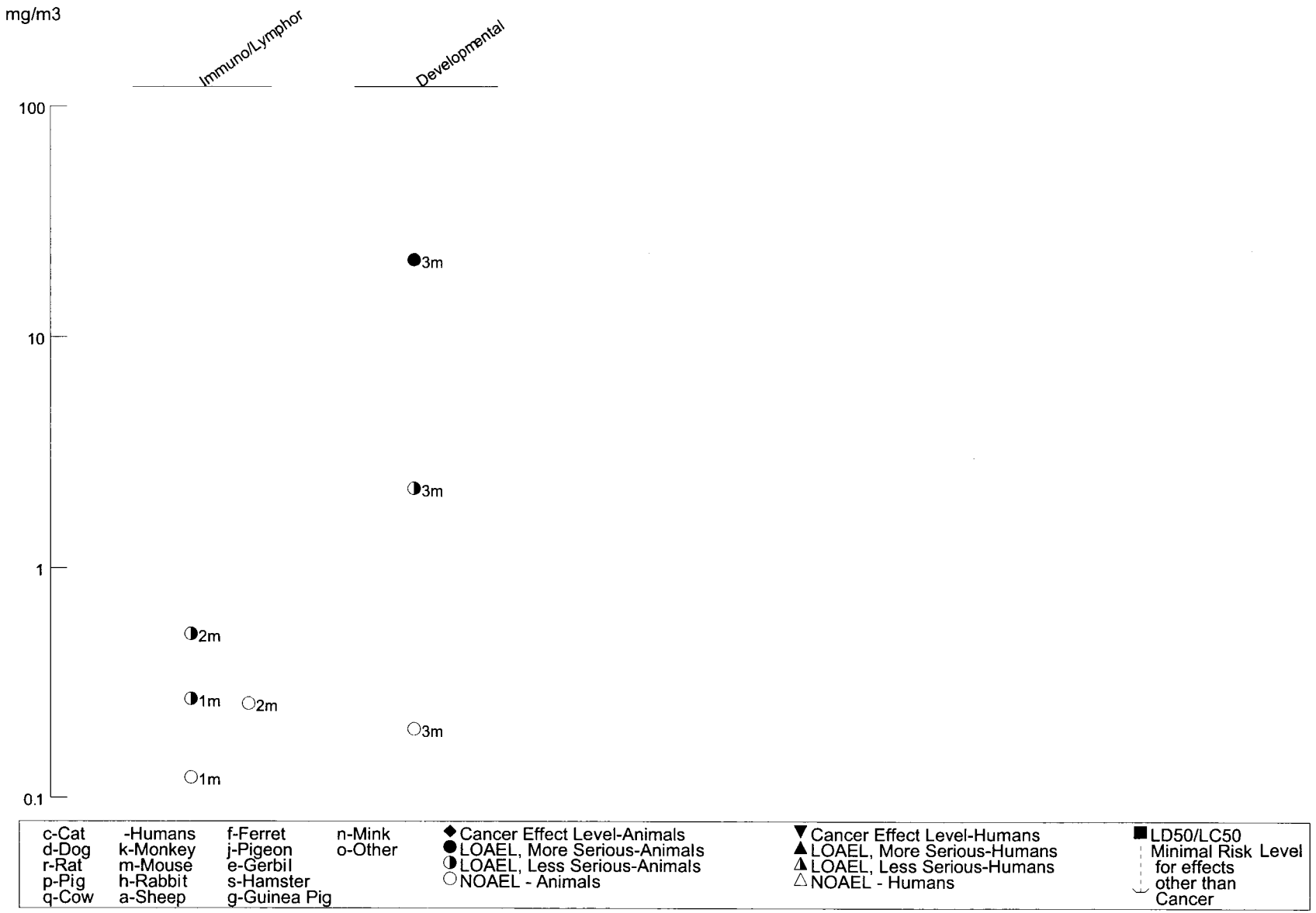
avg = average; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); decr = decreased; F = female; Gd = gestation day; hr = hour(s); incr = increased; LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s); wt = weight; yr = year(s)

DRAFT FOR PUBLIC COMMENT

DRAFT FOR PUBLIC COMMENT

Figure 3-1 Levels of Significant Exposure to Inorganic Arsenic - Inhalation

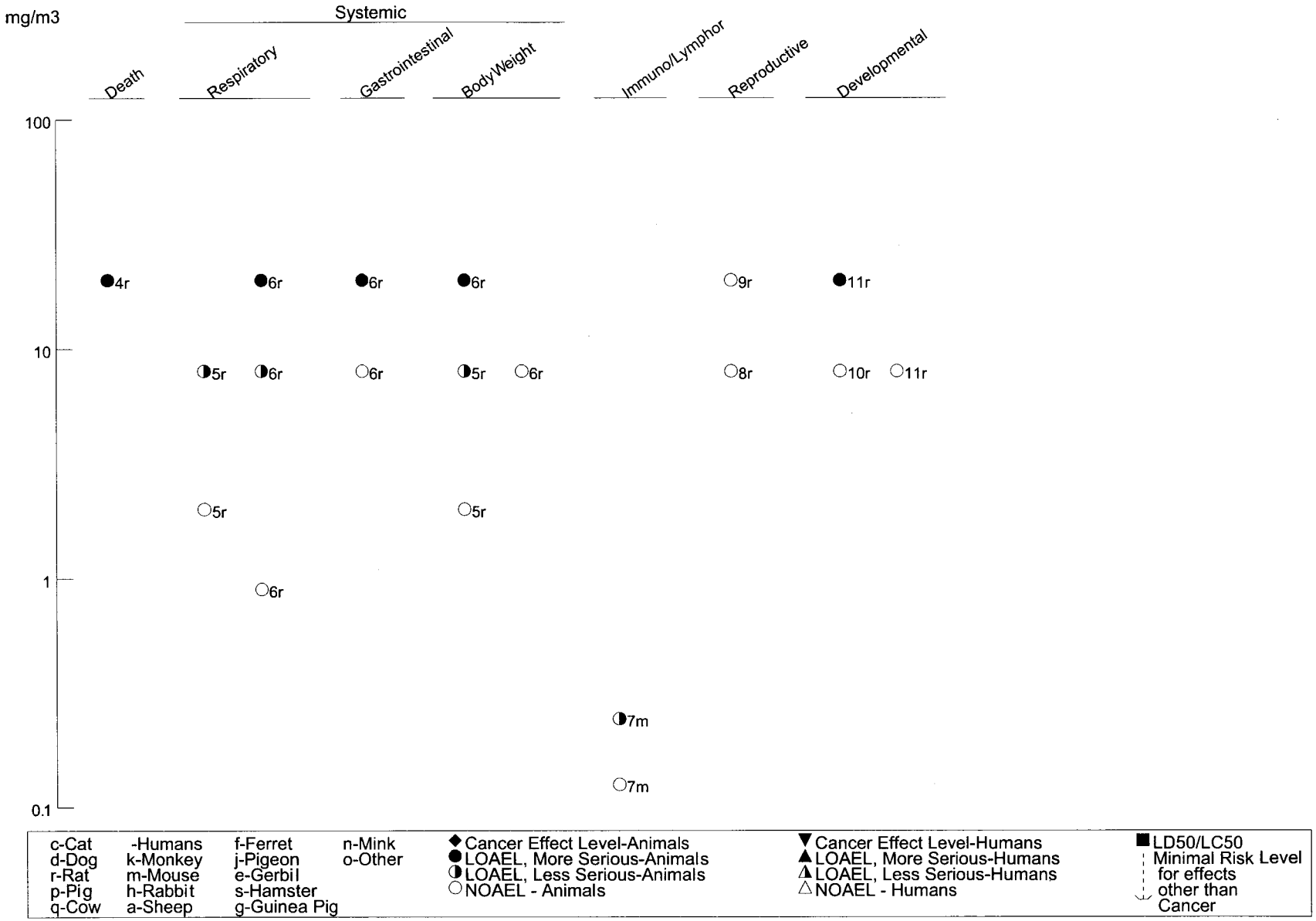
Acute (≤14 days)



DRAFT FOR PUBLIC COMMENT

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

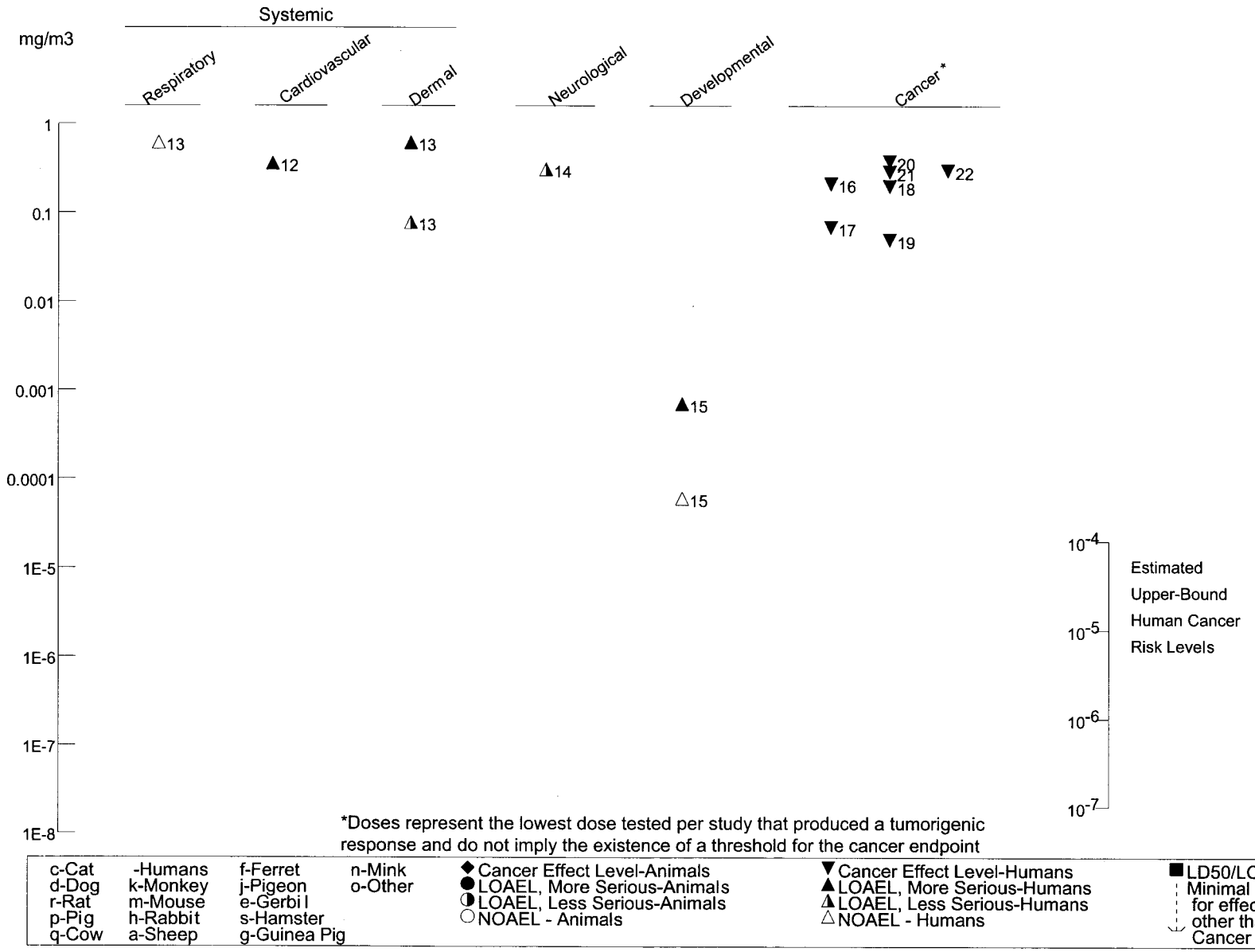
Intermediate (15-364 days)



DRAFT FOR PUBLIC COMMENT

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

Chronic (≥365 days)



DRAFT FOR PUBLIC COMMENT

Table 3-2 Levels of Significant Exposure to Organic Arsenic - Inhalation

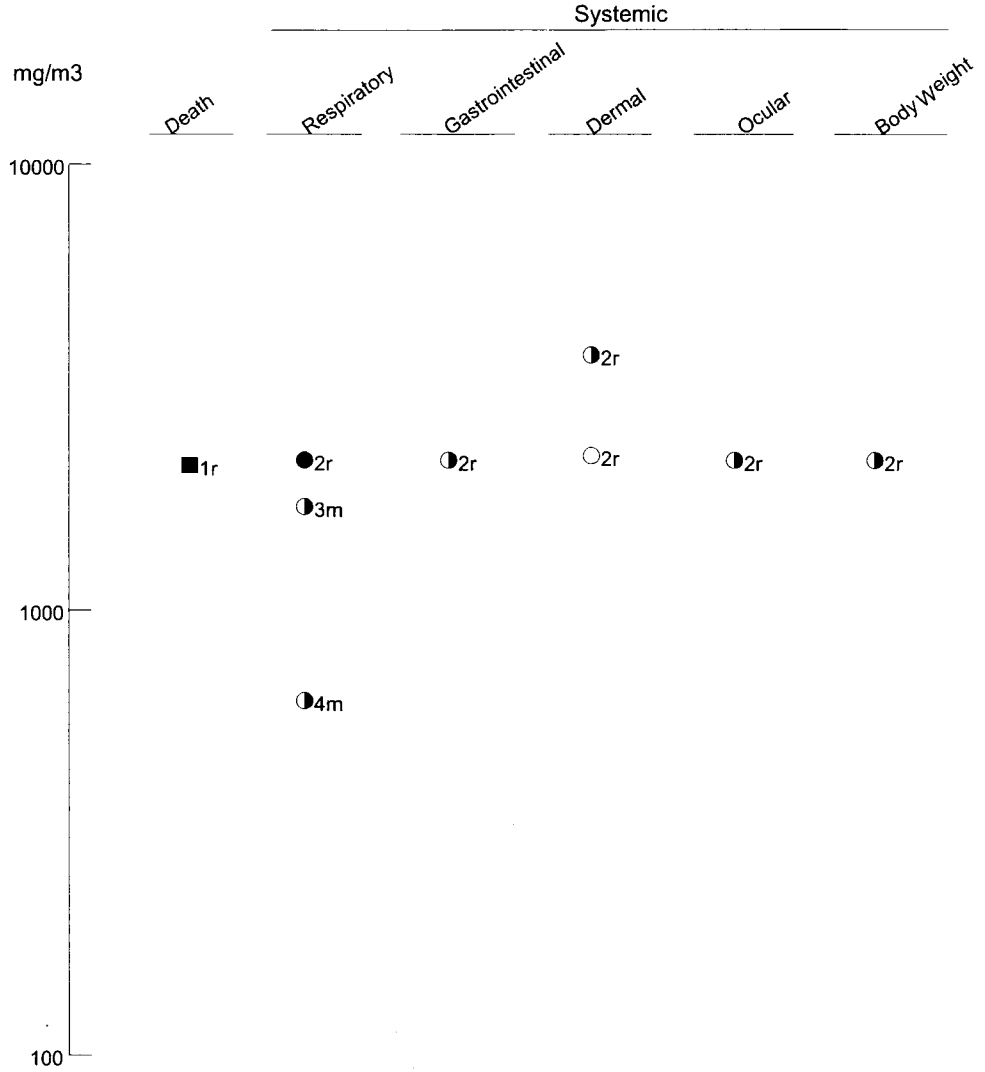
Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sherman)	2 hr				2117 F (LC50)	Stevens et al. 1979 DMA	
Systemic								
2	Rat (Sherman)	2 hr	Resp			2172 (respiratory distress)	Stevens et al. 1979 DMA	
			Gastro		2172 (diarrhea)			
			Dermal	2226	3746 F (erythematous lesions of ears and feet)			
			Ocular		2172 (eye encrustation)			
			Bd Wt		2172 (unspecified decr bd wt)			
3	Mouse (Swiss-Webster)	5 min	Resp		1710 M (RD50)		Stevens et al. 1979 DMA	
4	Mouse (Swiss-Webster)	5 min	Resp		627 M (RD50)		Stevens et al. 1979 MMA	
CHRONIC EXPOSURE								
Systemic								
5	Human	1.45-2.12 yr (group averages) (occup)	Hemato	0.13 M			Watrous and McCaughey 1945 AA	

aThe number corresponds to entries in Figure 3-2.

AA = arsanilic acid; Bd Wt = body weight; decr = decreased; DMA = dimethylarsenic acid; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; MMA = monomethylarsenic acid; NOAEL = no-observable-adverse-effect level; RD50 = concentration calculated to produce a 50% decrease in respiratory rate; Resp = respiratory; yr = year(s)

Figure 3-2 Levels of Significant Exposure to Organic Arsenic - Inhalation

Acute (≤14 days)



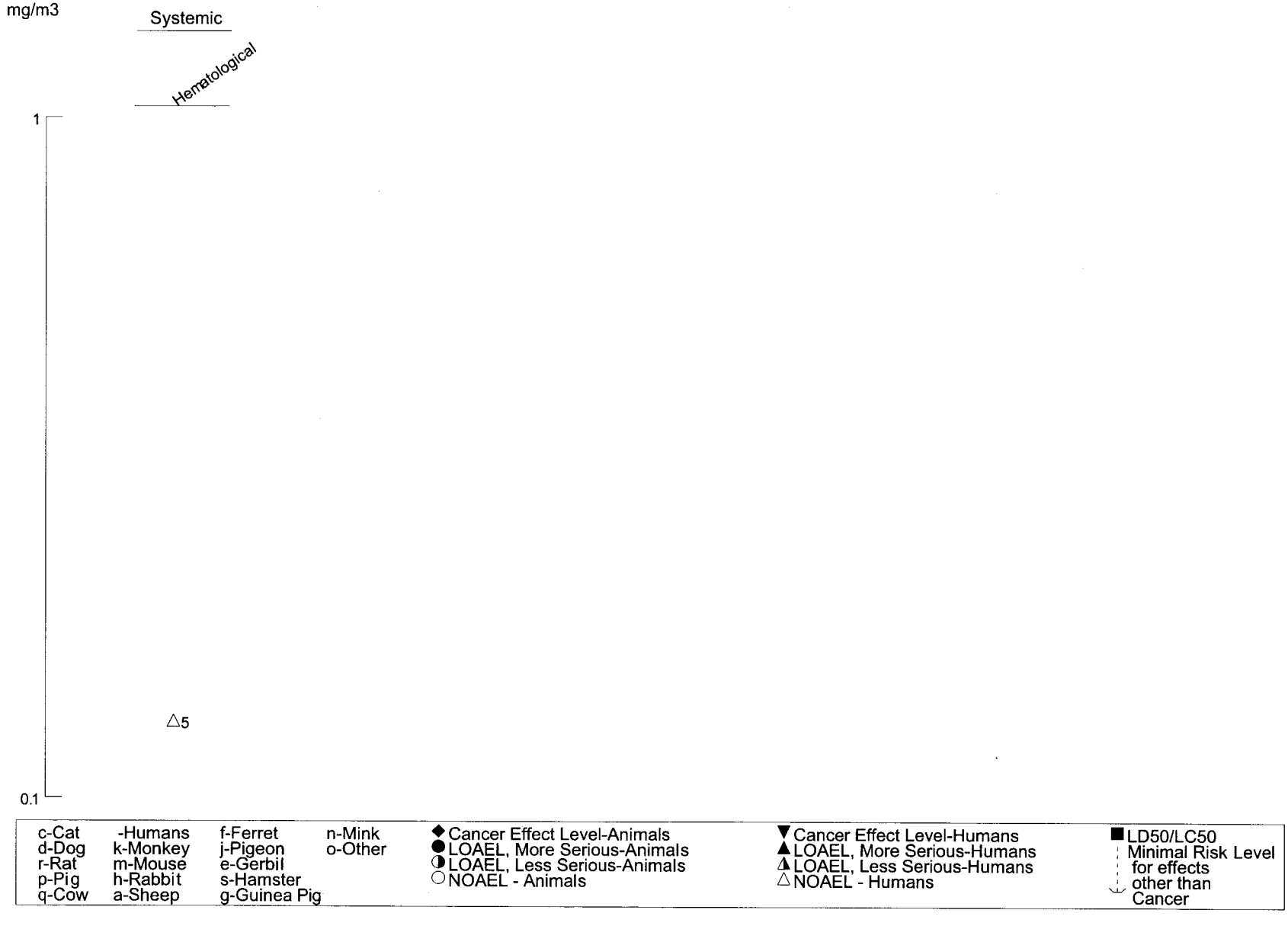
c-Cat	-Humans	f-Ferret	n-Mink	◆Cancer Effect Level-Animals	▼Cancer Effect Level-Humans	■LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	●LOAEL, More Serious-Animals	▲LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑LOAEL, Less Serious-Animals	◭LOAEL, Less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

DRAFT FOR PUBLIC COMMENT

DRAFT FOR PUBLIC COMMENT

Figure 3-2 Levels of Significant Exposure to Organic Arsenic - Inhalation (*Continued*)

Chronic (≥365 days)



3.2.1.1 Death

Inorganic Arsenicals. Although there are many studies of humans exposed to arsenic in air, no cases of lethality from short-term exposure were located. This suggests that death is not likely to be of concern following acute exposure, even at the very high exposure levels (1–100 mg As/m^3) found previously in the workplace (e.g., Enterline and Marsh 1982; Järup et al. 1989; Lee-Feldstein 1986). Delayed lethality from chronic exposure attributable to increased risk of cardiovascular disease or lung cancer is discussed below in Sections 3.2.1.2 and 3.2.1.7, respectively. The only report of a lethal effect of inhaled inorganic arsenic in animals was a developmental toxicology study in which four of nine pregnant rats died, and one rat was euthanized in extremis, between days 12 and 19 of gestation after 30–35 days of exposure to an aerosol of arsenic trioxide at an exposure concentration of 20 mg As/m^3 (Holson et al. 1999). These animals exhibited severe hyperemia and plasma discharge into the intestinal lumen at autopsy. In this same study, there was 100% mortality in groups of 10 pregnant rats after 1 day of exposure to concentrations ≥100 mg/m^3 (76 mg As/m^3).

Organic Arsenicals. No studies were located regarding death in humans after inhalation exposure to organic arsenicals. A 2-hour LC_{50} of 2,117 mg As/m^3 was calculated for DMA in female rats (Stevens et al. 1979). This LC_{50} is shown in Table 3-2 and Figure 3-2. Male rats and mice of both sexes were less susceptible, with only a few deaths after 2-hour exposures as high as 3,746 mg As/m^3 in rats and 3,474 mg As/m^3 in mice (Stevens et al. 1979). The cause of death was not specified, but was probably due to lung injury (see Section 3.2.1.2). No deaths were observed among rats and mice exposed to DSMA (the disodium salt of MMA) at concentrations up to 2,485 mg As/m^3 in rats and 2,811 mg As/m^3 in mice (Stevens et al. 1979). Chamber atmospheres at these high concentrations were so dense that it was difficult to see the animals clearly. These data indicate that there is no significant risk of acute lethality from concentrations of DMA or MMA that might be encountered in the environment or the workplace.

3.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects from inhalation exposure to inorganic arsenicals in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1, while the corresponding data for organic arsenicals are shown in Table 3-2 and Figure 3-2.

Respiratory Effects.

Inorganic Arsenicals. Workers exposed to arsenic dusts in air often experience irritation to the mucous membranes of the nose and throat. This may lead to laryngitis, bronchitis, or rhinitis (Dunlap 1921; Lundgren 1954; Morton and Caron 1989; Pinto and McGill 1953), and very high exposures (characteristic of workplace exposures in the past) can cause perforation of the nasal septum (Dunlap 1921; Pinto and McGill 1953; Sandstrom et al. 1989). Despite the known respiratory irritant effects of arsenic, there have been few systematic investigations of respiratory effects in humans exposed to arsenic. Perry et al. (1948) found no difference in chest X-rays or respiratory performance (vital capacity and exercise-tolerance tests) between unexposed and exposed workers in a cross-sectional study at a factory where sodium arsenite was prepared. The NOAEL of 0.613 mg As/m^3 for respiratory effects in this study is shown in Table 3-1 and plotted in Figure 3-1.

Increased mortality due to respiratory disease has been reported in some cohort mortality studies of arsenic-exposed workers, but no conclusive evidence of an association with arsenic has been produced. In studies of workers exposed to arsenic trioxide at the Anaconda copper smelter in Montana, mortality due to noncancer respiratory disease (e.g., emphysema) was significantly increased compared to the general population (Lee-Feldstein 1983; Lubin et al. 2000; Welch et al. 1982). However, the data were not adjusted for smoking (a well-known confounder for respiratory disease), and analysis of the data with respect to arsenic exposure level did not show a clear dose-response. Similarly, Enterline et al. (1995) found a significant excess of non-malignant respiratory disease mortality in workers at the ASARCO copper smelter in Tacoma, Washington, but only a slight negative relation to cumulative arsenic exposure. Xuan et al. (1993) found an increase in the relative risk of mortality from pneumoconiosis associated with arsenic exposure in a cohort of tin miners in China. However, this finding was based on a small number of observations (n=32), a clear exposure-response relationship with arsenic was not established, and the miners experienced confounding exposures to dust (a known risk factor for pneumoconiosis) and to radon. These studies were all considered to be inconclusive as to the relationship between inhaled inorganic arsenic and respiratory disease.

Respiratory symptoms were observed in a study of developmental effects in rats. Pregnant female rats exposed to arsenic trixode dust starting 14 days prior to mating and continuing through mating and gestation exhibited rales at 8 mg As/m^3 and labored breathing and gasping at 20 mg As/m^3, with no

symptoms at 2 mg As/m^3 (Holson et al. 1999). The lungs were examined by gross necropsy and no lesions were found. Intratracheal instillation of arsenic trioxide (13 mg As/kg) or gallium arsenide (1.5–52 mg As/kg) can cause marked irritation and hyperplasia in the lungs of rats and hamsters (Goering et al. 1988; Ohyama et al. 1988; Webb et al. 1986, 1987). Since this sort of response is produced by a number of respirable particulate materials, it is likely that the inflammatory response is not specifically due to the arsenic.

Organic Arsenicals. No studies were located regarding respiratory effects in humans exposed to organic arsenicals. Short-term exposure of rats and mice to high concentrations (≥2,172 mg As/m^3) of DMA caused respiratory distress, and necropsy of animals that died revealed bright red lungs with dark spots (Stevens et al. 1979). Respiratory distress was also observed in rats and mice exposed to high levels (≥2,485 mg As/m^3) of the disodium salt of MMA (Stevens et al. 1979), although none of the MMA-exposed animals died. Respiratory distress appears to be associated with inhalation of very high concentrations of organic arsenicals. In 5-minute whole-body plethysmography trials, DMA and the disodium salt of MMA had RD_{50} (concentration calculated to produce a 50% decrease in respiration rate) values of 1,710 and 627 mg As/m^3, respectively (Stevens et al. 1979). Based on these RD_{50} values, neither DMA nor MMA is considered to be a potent respiratory irritant. Reliable LOAELs for respiratory effects of organic arsenic are shown in Table 3-2 and Figure 3-2.

Cardiovascular Effects.

Inorganic Arsenicals. There is some evidence from epidemiological studies that inhaled inorganic arsenic can produce effects on the cardiovascular system. Cardiovascular effects following oral exposure to arsenic are well known (see Section 3.2.2.2). A cross-sectional study of workers exposed to an estimated time-weighted average of 0.36 mg As/m^3 (as arsenic trioxide) at the Ronnskar copper smelter in Sweden for an average of 23 years showed that smelter workers had significantly increased incidences of Raynaud's phenomenon (a peripheral vascular disease characterized by spasm of the digital arteries and numbness of the fingers) and showed increased vasospasticity (constriction of blood vessels) in response to cold when tested in the fingers (Lagerkvist et al. 1986). A follow-up study conducted 2–3 years later found that vasospasticity measurements in exposed workers had improved concurrent with a reduction in arsenic exposure levels, although symptoms of peripheral vascular effects (cold hands or feet, white fingers, numbness in fingers or feet) were still common (Lagerkvist et al. 1988). A cross-sectional study including 46 workers in Denmark with varying, unquantified occupational exposure to arsenic in different

occupations found that systolic blood pressure was significantly increased in the arsenic workers (median=125 mmHg) compared with controls (median=117 mmHg) (Jensen and Hansen 1998). Diastolic pressure was also increased in this study (77.9 vs. 74.7 mmHg), although the difference from controls was not statistically significant.

Cohort mortality studies of arsenic-exposed workers at the ASARCO copper smelter in Tacoma, Washington (Enterline et al. 1995), Anaconda copper smelter in Montana (Lee-Feldstein 1983; Welch et al. 1982), Ronnskar copper smelter in Sweden (Wall 1980), orchard workers in Washington state (Tollestrup et al. 1995), and tin miners in China (Qiao et al. 1997; Xuan et al. 1993) have all reported increased risk of mortality from cardiovascular disease, specifically ischemic heart disease and cerebrovascular disease, in the cohorts studied. However, none of these studies provided conclusive evidence that the observed increase in risk was due to arsenic exposure. The studies in the ASARCO and Anaconda copper smelter workers failed to find a clear dose-response relationship with arsenic (Enterline et al. 1995; Welch et al. 1982), while a follow-up study of the Ronnskar smelter workers not only found lack of a dose-response, but also that the risk of cardiovascular disease was no longer elevated in the cohort (Järup et al. 1989). The studies in orchard workers and tin miners were limited by confounding exposures to copper, lead, and radon, respectively (Qiao et al. 1997; Tollestrup et al. 1995). The risk of cardiovascular disease mortality in the tin miners not only showed no dose-response relationship with arsenic exposure, but was positively associated with radon exposure, suggesting that radon may have been responsible for the increased cardiovascular risk in this cohort (Xuan et al. 1993).

The LOAEL for Raynaud's phenomenon and vasospasticity identified by Lagerkvist et al. (1986) is shown in Table 3-1 and Figure 3-1. No studies were located regarding cardiovascular effects in animals after inhalation exposure to inorganic arsenic.

Organic Arsenicals. No studies were located regarding cardiovascular effects in humans or animals after inhalation exposure to organic arsenicals.

Gastrointestinal Effects.

Inorganic Arsenicals. Several case studies have reported nausea, vomiting, and diarrhea in workers with acute arsenic poisoning following occupational inhalation exposure (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988; Morton and Caron 1989; Pinto and McGill 1953). Although

gastrointestinal effects are not typically associated with arsenic poisoning by inhalation (Pinto and McGill 1953), such effects are a common feature of oral ingestion of high doses of arsenic (see Section 3.2.2.2), and it is possible that mucociliary transport of arsenic dust from the lungs to the gut could be responsible for the effects in these cases. Exposure levels were not reliably estimated for any of these cases.

The only report of gastrointestinal effects of inhaled inorganic arsenic in animals was a developmental toxicology study in which four of nine pregnant rats died, and one rat was euthanized *in extremis*, between days 12 and 19 of gestation after 30–35 days of exposure to an aerosol of arsenic trioxide at an exposure concentration of 20 mg As/m^3 (Holson et al. 1999). These animals exhibited severe hyperemia and plasma discharge into the intestinal lumen at autopsy. Exposure to 8 mg As/m^3 did not produce gross gastrointestinal lesions.

Organic Arsenicals. Data regarding gastrointestinal effects in people exposed to organic arsenic in the air are limited. The frequency of gastrointestinal complaints was no higher than controls in workers exposed to arsanilic acid (i.e., 4-aminophenyl arsonic acid) at mean concentrations up to 0.13 mg As/m^3 in a chemical factory (Watrous and McCaughey 1945). However, this sort of data might easily be biased by workers who chose not to complain about minor symptoms, so no conclusion can be reached. Rats and mice exposed to very high levels (above 2,000 mg As/m^3) of MMA (disodium salt) or DMA experienced diarrhea (Stevens et al. 1979). The LOAEL for this effect is shown in Table 3-2 and Figure 3-2. The diarrhea could be due to transport of inhaled particulate material from the lungs to the gastrointestinal system or to direct ingestion of the compound (e.g., from grooming of the fur).

Hematological Effects.

Inorganic Arsenicals. Although anemia is a common feature of arsenic poisoning following oral exposure in humans (see Section 3.2.2.2), case studies of workers with arsenic poisoning from occupational inhalation exposure reported no effects on red blood cell count (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988; Morton and Caron 1989). The reason for this apparent route specificity is not clear, but might simply be related to dose. No studies were located regarding hematological effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No effect on levels of hemoglobin, red cells, or white cells was detected in the blood of manufacturing workers (323 counts in 35 workers) exposed to airborne arsanilic acid dusts at a

mean concentration of 0.13 mg As/m^3 in the workplace (Watrous and McCaughey 1945). Controls were an unspecified number of unexposed manufacturing workers with 221 complete blood counts. The NOAEL from this study is shown in Table 3-2 and Figure 3-2. No studies were located regarding hematological effects in animals after inhalation exposure to organic arsenicals.

Musculoskeletal Effects.

Inorganic Arsenicals. Few data were located regarding musculoskeletal effects associated with inhalation exposure to inorganic arsenic, and none to suggest the existence of any such effects. Electromyographic examination of the calves and feet showed no differences between control and arsenic-exposed workers in a cross-sectional study of workers at the Ronnskar copper smelter in Sweden (Blom et al. 1985). No studies were located regarding musculoskeletal effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to organic arsenicals.

Hepatic Effects.

Inorganic Arsenicals. There is no evidence that inhaled inorganic arsenic produces effects on the liver, although few data are available. Case studies of workers with inhalation arsenic poisoning that included liver function tests did not find any evidence of hepatic dysfunction (Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988). No studies were located regarding hepatic effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located regarding hepatic effects in humans or animals after inhalation exposure to organic arsenicals.

Renal Effects.

Inorganic Arsenicals. The limited data available do not suggest any relationship between inhalation of inorganic arsenic and kidney effects. A cross-sectional study of renal function parameters in glass factory

workers exposed to arsenic (concentrations unknown) found no meaningful differences from controls in urinary levels of several proteins (albumin, retinol binding protein, β_2-microglobulin, brush-border antigen) used as markers of glomerular damage or tubular cell exfoliation (Foà et al. 1987). Routine clinical urinalysis was normal when included in case studies of workers with inhalation arsenic poisoning (Ide and Bullough 1988; Morton and Caron 1989). No studies were located regarding renal effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located regarding renal effects in humans or animals after inhalation exposure to organic arsenicals.

Dermal Effects.

Inorganic Arsenicals. Dermatitis has frequently been observed in industrial workers exposed to inorganic arsenic in the air, with the highest rates occurring in the workers with the greatest arsenic exposure (Cöl et al. 1999; Dunlap 1921; Holmqvist 1951; Lagerkvist et al. 1986; Pinto and McGill 1953). Limited quantitative information is available regarding the exposure levels that produce dermatitis, and the high likelihood of co-exposure by the dermal route makes dose-response analysis difficult. A cross-sectional study of workers at a factory where sodium arsenite was prepared found that workers with the highest arsenic exposure (mean air levels ranging from 0.384 to 1.034 mg As/m^3 and estimated to average 0.613 mg As/m^3) tended to be grossly pigmented with hyperkeratinization of exposed skin and to have multiple warts (Perry et al. 1948). In the same study, workers with lower arsenic exposure (estimated to average 0.078 mg As/m^3) were much less affected, but still had a higher incidence of pigmentation keratosis than controls. LOAEL values identified by Perry et al. (1948) and Mohamed (1998) are shown in Table 3-1 and Figure 3-1. NOAEL values for dermal irritation have not been identified. Dermal effects (hyperkeratoses, hyperpigmentation) are also very common in people exposed to inorganic arsenic by the oral route (see Section 3.2.2.2). No studies were located on dermal effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. Data regarding dermal effects in people exposed to organic arsenic in the air are limited. Complaints of keratosis were roughly 2-fold higher than unexposed controls in female packaging workers exposed to arsanilic acid at an average concentration of 0.05 mg As/m^3 and in male manufacturing workers exposed to an average concentration of 0.13 mg As/m^3 in a chemical factory (Watrous and McCaughey 1945). This observation is consistent with the arsenic database as a whole, but

limitations in study methodology (e.g., alternate sources of effects were not investigated, workers might choose not to report minor complaints to company officials) make the reliability of this observation uncertain. Female rats exposed to DMA at 3,746 mg As/m^3 developed erythematous lesions on the feet and ears (Stevens et al. 1979); these lesions did not develop in females exposed at lower concentrations (2,226 mg As/m^3) or males. The NOAEL and LOAEL values for dermal effects in female rats are shown in Table 3-2 and Figure 3-2. It seems likely that these effects were due to direct irritation from dermal contact with the dust.

Ocular Effects.

Inorganic Arsenicals. Chemical conjunctivitis, characterized by redness, swelling, and pain, has been observed in workers exposed to arsenic dusts in air, usually accompanied by facial dermatitis (Dunlap 1921; Pinto and McGill 1953). No information was located regarding air levels of arsenic that produce this effect. No studies were located on ocular effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located on ocular effects in humans after inhalation exposure to organic arsenicals. Rats and mice exposed to high concentrations of DMA (≥2,172 mg As/m^3) developed an encrustation around the eyes (Stevens et al. 1979). This LOAEL is shown in Table 3-2 and Figure 3-2. It seems likely that these effects were due to direct irritation from ocular contact with the dust.

Body Weight Effects.

Inorganic Arsenicals. No studies were located on body weight effects in humans after inhalation exposure to inorganic arsenicals. Female rats exposed to arsenic trioxide dust starting 14 days before mating and continuing through mating and gestation showed a marked decrease in body weight and food consumption at 20 mg As/m^3 (preliminary study) and a smaller decrease at 8 mg As/m^3 (definitive study), with no effect at 2 mg As/m^3 (Holson et al. 1999).

Organic Arsenicals. No studies were located on body weight effects in humans after inhalation exposure to organic arsenicals. Rats and mice exposed to high concentrations of DMA (≥2,172 mg As/m^3) for 2 hours had an unspecified decrease in body weight gain during the subsequent 14 days (Stevens et al. 1979). This LOAEL is shown in Table 3-2 and Figure 3-2.

3.2.1.3 Immunological and Lymphoreticular Effects

Inorganic Arsenicals. A single study was located regarding the immunological and lymphoreticular effects of inhaled inorganic arsenic in humans. Bencko et al. (1988) detected no abnormalities in serum levels of immunoglobins in workers exposed to arsenic in a coal-burning power plant. However, the levels of arsenic were not measured and may have been too low for this to be a meaningful result. The immune effects of inhaled arsenic in animals were studied by Aranyi et al. (1985). Female mice exposed to arsenic trioxide aerosol for 3 hours showed a concentration-related decrease in pulmonary bactericidal activity (presumably as a result of injury to alveolar macrophages) and a corresponding concentration-related increase in susceptibility to introduced respiratory bacterial pathogens. Similar results were found when the exposure was repeated over 1- and 4-week periods. The NOAEL and LOAEL values for this study are shown in Table 3-1 and Figure 3-1.

Intratracheal studies in animals offer some support for an immune effect of inhaled inorganic arsenic. Decreases in humoral response to antigens and in several complement proteins were noted in mice given an intratracheal dose of 5.7 mg As/kg as sodium arsenite (Sikorski et al. 1989), although these changes were not accompanied by any decrease in resistance to bacterial or tumor cell challenges. Animals given an intratracheal dose of GaAs (25 mg As/kg or higher) also displayed a variety of changes in numerous immunological end points (some increased, some decreased) (Burns and Munson 1993; Sikorski et al. 1989). Whether these effects were due to a direct effect on the immune system or were secondary to the inflammatory effect of GaAs on the lung (see Section 3.2.1.2, above) is uncertain.

Organic Arsenicals. No studies were located regarding immunological and lymphoreticular effects in humans or animals after inhalation exposure to organic arsenicals.

3.2.1.4 Neurological Effects

Inorganic Arsenicals. There is evidence from epidemiological studies that inhaled inorganic arsenic can produce neurological effects. A study by Gerr et al. (2000) reported an elevated incidence of peripheral neuropathy in subjects who lived near an arsenic-using pesticide plant (13/85=15.3%; odds ratio [OR]=5.1, p=0.004), relative to subjects who lived farther from the plant (4/118=3.4%). Concentrations of arsenic in soil and house dust were elevated (~30–300 μg As/g) for residences near the plant, according

to 1993–1995 monitoring data. Cross-sectional studies of copper smelter workers at the ASARCO smelter in Tacoma, Washington (Feldman et al. 1979) and the Ronnskar smelter in Sweden (Blom et al. 1985; Lagerkvist and Zetterlund 1994) have demonstrated peripheral neurological effects in workers associated with arsenic trioxide exposure. At the ASARCO smelter, the prevalence of clinically diagnosed peripheral neuropathy was markedly higher in arsenic-exposed workers (26/61=43%) than controls (4/33=12%), and although the difference in mean nerve conduction velocities (NCV) was not statistically significant, mean peroneal motor NCV was lower in arsenic-exposed workers than controls and all 12 cases of abnormally low NCV occurred in the arsenic group (Feldman et al. 1979). Similar results were observed at the Ronnskar smelter, where Blom et al. (1985) reported significantly increased prevalence of workers with abnormally low NCV in the exposed group, and lower, but not statistically significant, mean NCV in five peripheral nerves. A follow-up study on the Ronnskar workers 5 years later found that the prevalence of abnormally low NCV remained significantly increased in the exposed workers, but that the decrease in mean NCV was now also statistically significant in the tibial (motor) and sural (sensory) nerves (Lagerkvist and Zetterlund 1994). Blood lead was monitored in this study as a potential confounder, but levels were low and not considered likely by the researchers to have had any influence on the results. The follow-up Ronnskar study provided enough information to estimate that mean arsenic exposure was 0.31 mg As/m^3 and lasted an average of 28 years in the exposed group, and this LOAEL is shown in Table 3-1 and Figure 3-1.

The literature also contains several case studies of workers with inhalation arsenic poisoning who developed neurological symptoms. Although these studies do not provide reliable information on exposure levels or conclusive evidence that the observed effects were related to arsenic, the findings are suggestive. Symptoms in these cases included not only indicators of peripheral neuropathy (numbness, loss of reflexes, muscle weakness, tremors) (Ide and Bullough 1988; Morton and Caron 1989), but also frank encephalopathy (hallucinations, agitation, emotional lability, memory loss) (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Morton and Caron 1989). Both peripheral neuropathy and encephalopathy are associated with oral exposure to inorganic arsenic (see Section 3.2.2.4).

No studies were located regarding neurological effects in animals after inhalation exposure to inorganic arsenicals. Mice given a single intratracheal dose of 200 mg/kg of GaAs displayed a decrease in overall activity 6–8 hours later, but no additional neurological evaluations were conducted on these animals (Burns and Munson 1993).

Organic Arsenicals. Data regarding neurological effects in people exposed to organic arsenic in the air are limited to a single study. The frequency of central nervous system complaints was no higher than controls in workers at a chemical factory exposed to arsanilic acid at mean concentrations up to 0.13 mg As/m^3 (Watrous and McCaughey 1945). Although peripheral nerve complaints were higher in arsenic packaging workers (mean exposure=0.05 mg As/m^3) than in unexposed controls, this was not the case in manufacturing workers with higher arsenic exposure (mean=0.13 mg As/m^3). This suggests that the effects on the peripheral nerves in the exposed packaging workers were not due to arsenic. The reliability of these data is limited by shortcomings in the study methodology (e.g., the data might easily be biased by workers who chose not to complain about minor symptoms). No studies were located regarding neurological effects in animals after inhalation exposure to organic arsenicals.

3.2.1.5 Reproductive Effects

Inorganic Arsenicals. No studies were located regarding reproductive effects in humans after inhalation exposure to inorganic arsenicals. Reproductive performance was evaluated in female rats exposed to 0.08–20 mg As/m^3 (preliminary study) or 0.2–8 mg As/m^3 (definitive study) as As_2O_3 6 hours daily from 14 days prior to mating through gestation day 19 (Holson et al. 1999). No changes occurred in the precoital interval (time to mating), mating index (percentage of rats mated), or fertility index (percentage of matings resulting in pregnancy). The NOAEL values for this study are shown in Table 3-1 and Figure 3-1.

Organic Arsenicals. No studies were located regarding reproductive effects in humans or animals after inhalation exposure to organic arsenicals.

3.2.1.6 Developmental Effects

Inorganic Arsenicals. Developmental effects associated with occupational and environmental exposure to airborne arsenic have been investigated in a series of studies at the Ronnskar copper smelter in northern Sweden (Nordstrom et al. 1978a, 1978b, 1979a, 1979b). In comparison to a northern Swedish reference population, female employees of the smelter had a significantly increased incidence of spontaneous abortion (Nordstrom et al. 1979a), and their children had a significantly increased incidence of congenital malformations (Nordstrom et al. 1979b) and significantly decreased average birth weight (Nordstrom et al. 1978a). Increased incidence of spontaneous abortion and decreased average birth weight of children

were also found in populations living in close proximity to the smelter (Nordstrom et al. 1978a, 1978b, 1979b). While these data are suggestive of developmental effects associated with occupational and environmental exposure from the smelter, the reported effects are not large, the analyses include only limited consideration of potential confounders (e.g., smoking), and there are no data relating the apparent effects specifically to arsenic exposure.

More recently, Ihrig et al. (1998) conducted a case-control study of stillbirths in the vicinity of a Texas arsenic pesticide factory that included estimation of environmental arsenic exposures using atmospheric dispersion modeling and multiple regression analysis considering arsenic exposure, race/ethnicity, maternal age, median income, and parity as explanatory variables. There was a statistically significant increase in the risk of stillbirth in the highest exposure category (>100 ng As/m^3, midpoint=682 ng/m^3). Further analysis showed that this increase in risk was limited to people of Hispanic descent, who the researchers speculated may be an especially sensitive population due to a genetic impairment in folate metabolism. Interpretation of this study is limited by small numbers of cases and controls in the high exposure group, lack of data on smoking, potential confounding exposures to other chemicals from the factory, and failure to take into account previous years of deposition in the exposure estimates.

Arsenic has been shown to produce developmental effects by inhalation exposure in laboratory animals, although it is unclear whether or not the effects occur only at maternally toxic doses. Mice exposed to 22 mg As/m^3 (as As_2O_3) for 4 hours on days 9–12 of gestation had serious developmental effects (significant increases in the percentage of dead fetuses, skeletal malformations, and the number of fetuses with retarded growth), while those exposed to 2.2 mg As/m^3 had only a 10% decrease in average fetal body weight, and those exposed to 0.20 mg As/m^3 had no effects (Nagymajtenyi et al. 1985). The study was limited by failure to quantify malformations on a litter basis, discuss the nature and severity of the observed malformations, or report on the occurrence of maternal effects. No increases in fetal resorptions, fetal mortality, or malformations, and no decreases in fetal birth weight occurred when rats were exposed to 0.2–8 mg As/m^3 (as As_2O_3), 6 hours daily from 14 days prior to mating through gestation day 19 (Holson et al. 1999). At the 8 mg/m^3 exposure level, toxicity was observed in the dams, including rales, a dried red exudate at the nose, and lower gains in net body weight than controls. In a preliminary dose-range study, there was a marked significant increase in post-implantation loss (primarily early resorptions) and consequent marked significant decrease in viable fetuses per litter at 20 mg As/m^3, a concentration that also produced severe maternal effects including mortality (Holson et al. 1999).

The NOAEL and LOAEL values for increased risk of stillbirth in humans identified by Ihrig et al. (1998) and those for developmental effects in rodents found by Nagymajtenyi et al. (1985) and Holson et al. (1999) are shown in Table 3-1 and Figure 3-1.

Organic Arsenicals. No studies were located regarding developmental effects in humans or animals after inhalation exposure to organic arsenicals.

3.2.1.7 Cancer

Inorganic Arsenicals. There is convincing evidence from a large number of epidemiological studies that inhalation exposure to inorganic arsenic increases the risk of lung cancer. Most studies involved workers exposed primarily to arsenic trioxide dust in air at copper smelters (Axelson et al. 1978; Brown and Chu 1982, 1983a, 1983b; Enterline and Marsh 1982; Enterline et al. 1987a, 1987b, 1995; Ferreccio et al. 1996; Higgins et al. 1982; Järup and Pershagen 1991; Järup et al. 1989; Lee and Fraumeni 1969; Lee-Feldstein 1983, 1986; Lubin et al. 2000; Mazumdar et al. 1989; Pinto et al. 1977, 1978; Sandstrom et al. 1989; Viren and Silvers 1999; Wall 1980; Welch et al. 1982) and mines (Liu and Chen 1996; Qiao et al. 1997; Taylor et al. 1989; Xuan et al. 1993), but increased incidence of lung cancer has also been observed at chemical plants where exposure was primarily to arsenate (Bulbulyan et al. 1996; Mabuchi et al. 1979; Ott et al. 1974; Sobel et al. 1988). In addition, several studies suggest that residents living near smelters or arsenical chemical plants may also have increased risk of lung cancer (Brown et al. 1984; Cordier et al. 1983; Matanoski et al. 1981; Pershagen 1985), although the increases are small and are not clearly detectable in all cases (e.g., Frost et al. 1987). The strongest evidence that arsenic is responsible for the observed lung cancer comes from quantitative dose-response data relating specific arsenic exposure levels to lung cancer risk. These data are available for arsenic-exposed workers at the ASARCO copper smelter in Tacoma, Washington (Enterline and Marsh 1982; Enterline et al. 1987a, 1995; Mazumdar et al. 1989), the Anaconda copper smelter in Montana (Lee-Feldstein 1986; Welch et al. 1982), eight other U.S. copper smelters (Enterline et al. 1987b), and the Ronnskar copper smelter in Sweden (Järup and Pershagen 1991; Järup et al. 1989).

Enterline and Marsh (1982) reported a significant increase in respiratory cancer mortality (standard mortality ratio [SMR]=189.4) based on 104 observed respiratory cancer deaths and only 54.9 expected over the years 1941–1976 in a cohort of 2,802 male workers employed for ≥1 year between 1940 and 1964 at the ASARCO smelter. When the cohort was separated into low and high arsenic exposure groups, with mean estimated time-weighted average arsenic exposures of 0.054 and 0.157 mg As/m^3,

respectively (based on work history, historical urinary arsenic measurements, and an experimentally derived relationship between urinary and inhaled arsenic), respiratory cancer mortality was significantly increased in both groups in a concentration-related fashion (SMR=227.7 and 291.4 in the low and high groups, respectively). Enterline et al. (1987a) re-analyzed these data using improved exposure estimates that incorporated historical measurements of arsenic in the ambient air and personal breathing zone of workers. Respiratory cancer mortality was significantly increased in a concentration-related fashion in the low (SMR=213.0), medium (SMR=312.1), and high (SMR=340.9) arsenic exposure groups, which had mean estimated time-weighted average arsenic exposures of 0.213, 0.564, and 1.487 mg As/m^3, respectively. An alternative analysis of these data by Mazumdar et al. (1989) produced similar results. Enterline et al. (1995) extended the mortality follow-up from 1976 to 1986, but reported findings similar to the earlier study in a less thorough analysis. The CEL from Enterline et al. (1987a), the most complete analysis of the ASARCO cohort with the best exposure estimates, is presented in Table 3-1 and Figure 3-1.

Respiratory cancer mortality was significantly increased (SMR=285) based on 302 observed respiratory deaths between 1938 and 1977 in a cohort of 8,045 white male workers employed for at least 1 year between 1938 and 1956 at the Anaconda smelter (Lee-Feldstein 1986). When workers were categorized according to cumulative arsenic exposure and date of hire, lung cancer mortality was significantly increased in all groups hired between 1925 and 1947. Workers in the lowest cumulative exposure group (<10 mg-mo/m^3) were reported to have had <2 years of exposure at an average arsenic concentration of 0.38 mg/m^3. An alternative analysis of a subset of the Anaconda cohort (n=1,800, including all 277 employees with heavy arsenic exposure and 20% of the others) that included information on smoking and other occupational exposures was performed by Welch et al. (1982). This analysis showed that lung cancer mortality increased with increasing time-weighted average arsenic exposure, with a small nonsignificant increase in the low group (SMR=138) exposed to 0.05 mg/m^3 and significant increases in the medium (SMR=303), high (SMR=375), and very high (SMR=704) groups exposed to 0.3, 2.75, and 5.0 mg/m^3, respectively. Cohort members were more likely to be smokers than U.S. white males, but smoking did not differ among the arsenic exposure groups. Exposure-response analysis of smokers was similar to the analysis based on the full subcohort, while analysis of nonsmokers (limited by small group sizes) also showed a similar pattern, but with lower SMRs. In a followup analysis of the same cohort, Lubin et al. (2000) re-weighted the exposure concentrations based on duration and time of exposure and re-evaluated the effects of exposure. Relative risks for respiratory cancer increased with increasing duration in each arsenic exposure area (light, medium, and heavy) after adjustment for duration in the other two exposure areas. SMRs were significantly elevated following exposure to 0.58 mg/m^3 (medium;

SMR=3.01, 95% CI=2.0–4.6) or 11.3 mg/m^3 (high; SMR=3.68, 95% CI=2.1–6.4) for 10 or more years, and following exposure to 0.29 mg/m^3 (low; SMR=1.86, 95% CI=1.2–2.9) for 25 or more years. The CELs from the analyses of the Anaconda cohort are presented in Table 3-1 and Figure 3-1.

Enterline et al. (1987b) studied the mortality experience from 1949 to 1980 of a cohort of 6,078 white males who had worked for 3 years or more between 1946 and 1976 at one of eight U.S. copper smelters in Arizona, Utah, Tennessee, and Nevada. Lung cancer mortality was significantly increased only in the Utah smelter (SMR=226.7), which had the highest average arsenic exposure concentration (0.069 mg/m^3 vs. 0.007–0.013 mg/m^3 in the other smelters) and also contributed the largest number of cohort members (n=2,288 vs. 189–965 from the other smelters). A nested case-control study showed that arsenic exposure and cigarette smoking were significant risk factors for lung cancer in the smelter workers. Smoking was lower in the Utah smelter workers than in the other smelter workers, but still higher than in the referent Utah population, suggesting that the risk attributable to arsenic in this study population is somewhat lower than indicated by the SMR reported above. The CEL from this study is presented in Table 3-1 and Figure 3-1.

Järup et al. (1989) reported significantly increased lung cancer mortality (SMR=372, 95% confidence interval [CI]=304–450) based on 106 lung cancer deaths in a cohort of 3,916 male workers employed for ≥3 months between 1928 and 1967 at the Ronnskar smelter and followed for mortality through 1981. Workers were separated into low, medium, and high arsenic exposure groups with mean time-weighted average exposure estimates of 0.05, 0.2, and 0.4 mg/m^3, respectively. Lung cancer mortality was significantly increased in all three exposure groups in a concentration-related fashion (SMR=201, 353, and 480, respectively). A nested case-control analysis of 102 lung cancer cases and 190 controls from the cohort showed that lung cancer risk increased with increasing arsenic exposure in nonsmokers, light smokers, and heavy smokers (Järup and Pershagen 1991). The results demonstrated that arsenic is a risk factor for lung cancer in the smelter workers, but also suggested a greater-than-additive interaction between smoking and arsenic exposure. In this analysis, in contrast to the cohort study, lung cancer risk due to arsenic was increased only in the higher arsenic-exposure groups. Potential explanations for this difference between the cohort and case-control analyses include a higher proportion of smokers in the smelter workers than in the regional referent population in the cohort study, and limited power to detect increased risk in the case-control study due to small group sizes in the dose-response analysis. The CELs from both the cohort and case-control studies are presented in Table 3-1 and Figure 3-1.

Several researchers have examined the histological cell types of lung cancer (epidermoid carcinoma, small cell carcinoma, adenocarcinoma) in arsenic-exposed workers (e.g., Axelson et al. 1978; Newman et al. 1976; Pershagen et al. 1987; Qiao et al. 1997; Wicks et al. 1981). Although the incidence of the various cell types varied from population to population, all studies found an increase in several tumor types. This indicates that arsenic does not specifically increase the incidence of one particular type of lung cancer.

The studies of the ASARCO cohort (Enterline and Marsh 1982; Enterline et al. 1987a, 1995) noted a supralinear exposure-response relationship (i.e., steeper at lower doses) between arsenic exposure and lung cancer mortality. Hertz-Picciotto and Smith (1993) extended this observation to several other occupationally exposed cohorts with quantitative exposure information. The authors suggest that neither toxicokinetic mechanisms nor confounding from age, smoking, or other workplace carcinogens that differ by exposure level are likely explanations for the curvilinearity. Plausible explanations offered include: (1) synergism (with smoking), which varies in magnitude according to the level of arsenic exposure, (2) long-term survivorship at higher exposures among the healthier, less susceptible individuals, and (3) exposure estimate errors that were more prominent at higher-exposure levels as a result of past industrial hygiene sampling or worker protection practices.

Quantitative risk estimates for inhaled inorganic arsenic have been derived using the exposure-response data. EPA derived a unit risk estimate (the excess risk of lung cancer associated with lifetime exposure to 1 $\mu g/m^3$) of $4.3x10^{-3}$ per ($\mu g/m^3$) based on the dose-response relationships between arsenic exposure and excess lung cancer mortality in workers at the Anaconda smelter in Montana (Brown and Chu 1982, 1983a, 1983b; Higgins et al. 1982; Lee-Feldstein 1983) and the ASARCO smelter in Tacoma, Washington (Enterline and Marsh 1982; EPA 1984a; IRIS 2005). In some cases, calculations of exposure, as well as the procedures for generating quantitative risk estimates, are quite complex and the interested reader is referred to the EPA documents (EPA 1981c, 1984a, 1987e, 1996b; IRIS 2005) for a detailed description. Viren and Silvers (1994) re-evaluated the unit risk estimate using the same methods as EPA, but incorporating updated results from the ASARCO smelter (Enterline et al. 1987a; Mazumdar et al. 1989) and the findings from the Swedish smelter (Järup et al. 1989). Their analysis yielded a revised unit risk of $1.28x10^{-3}$ per ($\mu g/m^3$) that, when pooled with the earlier estimate from the Montana smelter cohort, yielded a composite unit risk of $1.43x10^{-3}$ per ($\mu g/m^3$). This unit risk estimate is a factor of 3 smaller than the EPA's current estimate of $4.3x10^{-3}$ per ($\mu g/m^3$). Figure 3-1 shows the air concentrations that correspond to excess lifetime cancer risks of 10^{-4} to 10^{-7} based on the EPA unit risk estimate.

There have been occasional reports of other types of cancer (i.e., non-respiratory cancer) potentially associated with inhalation exposure to inorganic arsenic, but there is no strong evidence for any of them. For example, Enterline et al. (1995) found significantly increased mortality due to cancer of the large intestine and bone cancer in the ASARCO cohort. However, neither cancer showed any relation to cumulative arsenic exposure, and the purported increase in bone cancer risk was based on a very small number of observations. Pesch et al. (2002) reported an increase in nonmelanoma skin cancers resulting from exposure from a Slovakian coal-burning power plant, but exposure levels associated with the lesions were not presented. Bulbulyan et al. (1996) reported an increase in risk of stomach cancer among workers exposed to the highest average arsenic concentrations at a Russian fertilizer plant, but this finding, which was based on a small number of observations and was only marginally statistically significant, was confounded by exposure to nitrogen oxides, which were more convincingly associated with stomach cancer in this study. Wingren and Axelson (1993) reported an association between arsenic exposure and stomach and colon cancer in Swedish glass workers, but this result was confounded by concomitant exposure to other metals. Lee-Feldstein (1983) observed a small, marginally significant increase in digestive tract cancer (SMR=125) in one study of the Anaconda cohort, but this was not found in other studies of this cohort (Lee and Fraumeni 1969; Lee-Feldstein 1986; Welch et al. 1982). Wulff et al. (1996) observed an apparent increase in the risk of childhood cancer (all types combined) in the population living within 20 km of the Ronnskar smelter, but the apparent increase was based on a small number of cases (13 observed vs. 6.7 expected) and was not statistically significant, and exposure to arsenic was confounded by exposure to lead, copper, cadmium, sulfur dioxide, and possibly other emissions such as nickel and selenium. Various case reports have implicated occupational arsenic exposure as a potential contributing factor in workers who developed sinonasal cancer (Battista et al. 1996), hepatic angiosarcoma (Tsai et al. 1998a), and skin cancer (Cöl et al. 1999; Tsuruta et al. 1998), but provide no proof that inhaled arsenic was involved in the etiology of the observed tumors. Wong et al. (1992) found no evidence that environmental exposure to airborne arsenic produced skin cancer in residents living near the Anaconda smelter or an open pit copper mine.

No studies were located regarding cancer in animals after inhalation exposure to inorganic arsenicals, although several intratracheal instillation studies in hamsters have provided evidence that both arsenite and arsenate can increase the incidence of lung adenomas and/or carcinomas (Ishinishi et al. 1983; Pershagen and Bjorklund 1985; Pershagen et al. 1984a; Yamamoto et al. 1987). These data support the conclusion that inhalation of arsenic may lead to lung cancer in humans.

Organic Arsenicals. No studies were located regarding cancer effects in humans or animals after inhalation exposure to organic arsenicals.

3.2.2 Oral Exposure

There are a large number of studies in humans and animals on the toxic effects of ingested arsenic. In humans, most cases of toxicity have resulted from accidental, suicidal, homicidal, or medicinal ingestion of arsenic-containing powders or solutions or by consumption of contaminated food or drinking water. In some cases, the chemical form is known (e.g., the most common arsenic medicinal was Fowler's solution, which contained 1% potassium arsenite or arsenic trioxide), but in many cases (e.g., exposures through drinking water), the chemical form is not known. In these cases, it is presumed that the most likely forms are either inorganic arsenate [As(+5)], inorganic arsenite [As(+3)], or a mixture. Table 3-3 and Figure 3-3 summarize a number of studies that provide reliable quantitative data on health effects in humans and animals exposed to inorganic arsenicals by the oral route. Similar data for organic arsenicals are listed in Table 3-4 and shown in Figure 3-4. All exposure data are expressed as milligrams of arsenic (as the element) per kilogram body weight per day (mg As/kg/day). These studies and others that provide useful qualitative information are summarized below.

3.2.2.1 Death

Inorganic Arsenicals. There are many case reports of death in humans due to ingestion of high doses of arsenic. In nearly all cases, the most immediate effects are vomiting, diarrhea, and gastrointestinal hemorrhage, and death may ensue from fluid loss and circulatory collapse (Levin-Scherz et al. 1987; Saady et al. 1989; Uede and Furukawa 2003). In other cases, death may be delayed and result from the multiple tissue injuries produced by arsenic (Campbell and Alvarez 1989). Some accounts of fatal arsenic poisoning describe both gastrointestinal effects soon after ingestion and extensive damage to multiple organ systems prior to death (Quatrehomme et al. 1992). A precise estimate of the ingested dose is usually not available in acute poisonings, so quantitative information on lethal dose in humans is sparse. The lethal doses ranged from 22 to 121 mg As/kg in four cases where known amounts were ingested as a single bolus (Civantos et al. 1995; Hantson et al. 1996; Levin-Scherz et al. 1987; Quatrehomme et al. 1992). Two people in a family of eight died from ingestion of water containing about 110 ppm of arsenic for a week (Armstrong et al. 1984). This corresponded to a dose of about 2 mg As/kg/day. Based on a review of clinical reports in the older literature, Holland (1904) estimated the minimum lethal dose to be

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Human	1 wk (W)				2 (death)	Armstrong et al. 1984	NS
2	Human	once (IN)				121 M (death)	Civantos et al. 1995	As(+5)
3	Human	once (IN)				108 M (death)	Hantson et al. 1996	As(+3)
4	Human	once (IN)				22 M (death)	Levin-Scherz et al. 1987	As(+3)
5	Human	once (IN)				93 M (death)	Quatrehomme et al. 1992	As(+3)
6	Rat (wild Norway)	once (G)				104 (LD50)	Dieke and Richter 1946	As(+3)
7	Rat (Sherman)	once (G)				112 F (LD50)	Gaines 1960	As(+5) calcium arsenate
8	Rat (Sherman)	once (G)				44 F (LD50)	Gaines 1960	As(+3)
9	Rat (Sherman)	once (G)				175 F (LD50)	Gaines 1960	As(+5) lead arsenate
10	Rat (Sprague-Dawley)	once (GW)				15 M (LD50)	Harrisson et al. 1958	As(+3)

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
11	Rat (Sprague-Dawley)	once (F)				145 M (LD50)	Harrisson et al. 1958 As(+3)	
12	Rat (CD)	once on Gd9 (GW)				23 F (7/25 dams died)	Stump et al. 1999 As(+3)	
13	Mouse (Swiss-Webster)	once (GW)				39 M (LD50)	Harrisson et al. 1958 As(+3)	
14	Mouse (C57H46)	once (GW)				26 M (LD50)	Harrisson et al. 1958 As(+3)	
15	Mouse (Dba2)	once (GW)				32 M (LD50)	Harrisson et al. 1958 As(+3)	
16	Mouse (C3H)	once (GW)				26 M (LD50)	Harrisson et al. 1958 As(+3)	
17	Mouse (ddY)	once (GW)				26 M (LD50)	Kaise et al. 1985 As(+3)	
18	Rabbit (New Zealand)	Gd 6-18 1x/d (GW)				1.49 F (7/20 dams died)	Nemec et al. 1998 As(+5)	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
19	Human	1 wk (W)	Gastro		0.2 (vomiting, diarrhea, abdominal pain)	2 M (diffuse inflammation of the GI tract)	Armstrong et al. 1984 NS	
			Hemato			0.2 (pancytopenia, leukopenia)		
			Hepatic			0.4 (hepatitis)		
			Renal			0.2 (nephropathy)		
			Ocular		0.2 (periorbital swelling)			
20	Human	once (IN)	Resp			121 M (respiratory distress, lung hemmorhage and edema)	Civantos et al. 1995 As(+5)	
			Cardio			121 M (hypotension, ventricular fibrillation, cardiac arrest)		
			Gastro			121 M (ulceration of upper gastrointestinal tract)		

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
21	Human	once (IN)	Cardio			19 F (tachycardia)	Cullen et al. 1995 As (+5)	
			Gastro			19 F (profuse vomiting and diarrhea)		
			Hemato	19 F				
			Hepatic	19 F				
			Renal	19 F				
22	Human	once (NS)	Resp			8 M (hemorrhagic bronchitis, pulmonary edema)	Fincher and Koerker 1987 As(+3)	
			Cardio			8 M (hypotension, tachycardia, massive cardiomegaly)		
			Gastro			8 M (gastrointestinal bleeding)		
			Hemato			8 M (hemolysis)		
			Musc/skel			8 M (marked atrophy of distal muscle groups)		
			Renal			8 M (acute renal failure)		
			Dermal		8 M (truncal macular rash)			
23	Human	once or twice (W)	Gastro		0.05 (occasional nausea, diarrhea, and abdominal cramps)		Franzblau and Lilis 1989 As(+3) As(+5)	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
24	Human	once (W)	Gastro			120 M (vomiting and diarrhea)	Goebel et al. 1990 NS	
			Renal			120 M (anuria)		
			Dermal		120 M (hyperkeratosis)			
25	Human	once (IN)	Gastro		2 F (vomiting)		Hantson et al. 1996 As(+3)	
			Hepatic		2 F (slight incr serum bilirubin)			
			Renal		2 F (altered renal function tests)			
26	Human	once (IN)	Gastro			13 M (frequent vomiting, diarrhea)	Kamijo et al. 1998 As(+3)	
			Hepatic			13 M (large incr serum bilirubin, ALT, AST, LDH)		
			Dermal		13 M (erythematous eruption)			
			Ocular		13 M (constricted vision)			

DRAFT FOR PUBLIC COMMENT

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
27	Human	once (IN)	Resp			22 M (tachypnea, respiratory failure)	Levin-Scherz et al. 1987 As(+3)	
			Cardio			22 M (cyanosis, hypotension, tachycardia, ventricular fibrillation)		
			Gastro			22 M (abdominal pain, nausea, diarrhea, massive vomiting, dysphagia, hemorrhage)		
			Hepatic			22 M (large incr serum AST and LDH)		
			Renal			22 M (large incr serum creatinine and BUN indicating acute renal failure)		
28	Human	once at wk 30 of pregnancy (IN)	Cardio			6 F (hypotension, rapid pulse)	Lugo et al. 1969 As(+3)	
			Gastro			6 F (abdominal pain, vomiting)		
			Hemato		6 F (high leukocyte count, low hematocrit)			
			Renal			6 F (acute renal failure)		

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
29	Human	2-3 wk (F)	Resp		0.05 (sore throat, rhinorrhea, cough, sputum)		Mizuta et al. 1956 As(+5)	
			Cardio			0.05 (abnormal electrocardiogram)		
			Gastro			0.05[b] (nausea, vomiting, diarrhea, occult blood in feces and gastric and duodenal juice)		
			Hemato		0.05 (mild anemia, leukopenia)			
			Musc/skel		0.05 (tender calf muscle)			
			Hepatic		0.05 (mild hepatomegaly, impaired liver function, degenerative lesions)			
			Renal	0.05				
			Dermal		0.05 (pigmentation, itching, desquamation, exanthema)			
			Ocular		0.05 (edema of eyelids, conjunctivitis, central scotoma, neuro-retinitis)			

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
30	Human	once (IN)	Resp	11 M		43 M (shortness of breath, decreased oxygen saturation)	Moore et al. 1994 As(+3)	
			Cardio	11 M		43 M (hypotension, asystolic cardiac arrest)		
			Gastro			11 M (profuse diarrhea and vomiting, severe abdominal pain)		
			Hemato	43 M				
			Renal		11 M (incr serum creatinine)	43 M (acute renal failure)		
31	Human	once (IN)	Resp			93 M (pulmonary edema)	Quatrehomme et al. 1992 As(+3)	
			Gastro			93 M (ulcero-necrotic hemorrhagic gastritis)		
			Hepatic			93 M (hepatomegaly, diffuse fatty degeneration)		
			Renal			93 M (glomerular congestion)		
			Dermal			93 M (dermoepidermic separation)		

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
32	Monkey (Rhesus)	13 d 1x/d (IN)	Gastro	3		6 (vomiting, unformed stool, "loss of condition")	Heywood and Sortwell 1979 As(+5)	
			Hepatic	3	6 (decr liver glycogen, vacuolation of hepatocytes)			
			Renal	3	6 (dilation of proximal tubules)			
33	Rat (Wistar-Barby)	4-14 d 5 d/wk 1x/d (G)	Cardio	2 F	11 F (decr vasoreactivity)		Bekemeier and Hirschelmann 1989 As(+3)	
			Gastro	2 F		11 F (diarrhea, bloody stools)		
34	Rat (Sprague-Dawley)	2x (GW)	Resp	14 F			Brown and Kitchin 1996 As(+3)	
			Hepatic		0.9 F (slight incr ornithine decarboxylase and heme oxygenase activity in liver)			
			Dermal	14 F				
35	Rat (Sprague-Dawley)	1x/d 15 d (G)	Bd Wt	10 M	20 M (20-25% decr body weight)		Rodriguez et al. 2001 As(+3)	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
36	Rat (CD)	once on Gd9 (GW)	Bd Wt	15 F	23 F (decr bd wt gain)		Stump et al. 1999 As(+3)	
37	Mouse (CD-1)	Gd 6-15 1x/d (GW)	Bd Wt	12 F	24 F (decr bd wt gain during gestation)		Nemec et al. 1998 As(+5)	
38	Mouse (B6C3F1)	1 or 4 d 1x/d (GW)	Hemato	3 M	6 M (decr polychromatic erythrocytes in bone marrow)		Tice et al. 1997 As(+3)	
39	Gn Pig	1x/d 8 d (G)	Cardio		3.8 M (prolongation of QT interval)		Chiang et al. 2002 As2O3	
40	Rabbit (New Zealand)	Gd 6-18 1x/d (GW)	Bd Wt	0.37 F	1.49 F (loss of body weight during treatment during gestation)		Nemec et al. 1998 As(+5)	
Neurological								
41	Human	1 wk (W)				2 (encephalopathy, peripheral neuropathy)	Armstrong et al. 1984 NS	
42	Human	once (IN)				121 M (confusion, brain edema)	Civantos et al. 1995 As(+5)	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
43	Human	once (IN)				19 F (lethargy)	Cullen et al. 1995 As (+5)	
44	Human	once (NS)				8 M (severe, persistent encephalopathy and peripheral neuropathy)	Fincher and Koerker 1987 As(+3)	
45	Human	once (W)				120 M (severe polyneuropathy)	Goebel et al. 1990 NS	
46	Human	once (IN)				216 M (peripheral neuropathy)	Hantson et al. 1996 As(+3)	
47	Human	once (IN)				13 M (peripheral neuropathy)	Kamijo et al. 1998 As(+3)	
48	Human	once (IN)				22 M (agitation, disorientation, paranoia, violent reactions)	Levin-Scherz et al. 1987 As(+3)	
49	Human	2-3 wk (F)				0.05 (hypesthesia in legs, abnormal patellar reflex)	Mizuta et al. 1956 As(+5)	
50	Human	once (IN)		43 M			Moore et al. 1994 As(+3)	

DRAFT FOR PUBLIC COMMENT

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
51	Human	once (IN)				93 M (encephalopathy)	Quatrehomme et al. 1992 As(+3)	
52	Monkey (Rhesus)	13 d 1x/d (IN)		3		6 (marked salivation, uncontrolled head shaking)	Heywood and Sortwell 1979 As(+5)	
53	Rat (Sprague-Dawley)	1x/d 15 d (G)		10 M	20 M (altered spontaneous locomotor activity)		Rodriguez et al. 2001 As(+3)	
54	Rabbit (New Zealand)	Gd 6-18 1x/d (GW)		0.37 F		1.49 F (prostration, ataxia)	Nemec et al. 1998 As(+5)	
Developmental								
55	Human	once at wk 30 of pregnancy (IN)				6 (severe pulmonary hemorrhage that may have contributed to death in premature neonate)	Lugo et al. 1969 As(+3)	
56	Rat (CD)	once on Gd9 (GW)		15		23 (incr post-implantation loss and decr viable fetuses)	Stump et al. 1999 As(+3)	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
57	Mouse (CD-1)	once during Gd 8-15 (GW)		11		23	(incr fetal mortality, exencephaly)	Baxley et al. 1981 As(+3)	
58	Mouse (CD-1)	once during Gd 7-15 (GW)				48	(incr fetal death, decr fetal wt, gross and skeletal malformations)	Hood et al. 1978 As(+5)	
59	Mouse (CD-1)	Gd 6-15 1x/d (GW)		12		24	(incr resorptions per litter, decr live fetuses per litter, decr mean fetal weight)	Nemec et al. 1998 As(+5)	
60	Hamster (Lak:LVG [SYR])	once during Gd 8-12 (GW)		11		14	(incr fetal mortality, decr fetal wt)	Hood and Harrison 1982 As(+3)	
61	Rabbit (New Zealand)	Gd 6-18 1x/d (GW)		0.37		1.49	(incr resorptions per litter, decr live fetuses per litter)	Nemec et al. 1998 As(+5)	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE								
Systemic								
62	Human	3 mo (W)	Gastro			0.1 (severe nausea, diarrhea, pain, cramps, vomiting, traces of blood in stool)	Franzblau and Lilis 1989 As(+3) As(+5)	
			Hemato			0.1 (anemia, leukopenia)		
			Hepatic			0.1 (large incr AST and ALT)		
			Dermal		0.1 (diffuse erythematous and scaly rash)			
			Ocular		0.1 (swelling and irritation of the eyes, impaired peripheral vision)			
63	Human	0.5-14 yr (W)	Dermal			0.05 (hyperpigmentation with keratosis, possibly pre-cancerous)	Huang et al. 1985 NS	

DRAFT FOR PUBLIC COMMENT

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
64	Human	4 mo (W)	Gastro			0.06 F (nausea, vomiting, diarrhea)	Wagner et al. 1979 NS	
			Hemato			0.06 F (anemia, leukopenia, erythroid hyperplasia of bone marrow)		
			Dermal			0.06 F (persistent extensive hyperkeratosis of palms and soles)		
			Bd Wt			0.06 F (40 lb weight loss)		
65	Rat (Wistar-Barby)	4 wk 5 d/wk 1x/d (GW)	Cardio		11 F (decr vasoreactivity)		Bekemeier and Hirschelmann 1989 As(+3)	
66	Rat (Sprague-Dawley)	6 wk (W)	Renal		4.7 M (incr relative kidney weight, impaired renal mitochondrial respiration, ultrastructural changes in proximal tubule)		Brown et al. 1976 As(+5)	
			Bd Wt	9.4 M	10.9 M (decr bd wt gain)			
67	Rat (Wistar)	1x/d 28 d (G)	Bd Wt	0.14 F			Chattopadhyay et al. 2001 As(+3)	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
68	Rat (CD)	6 wk (W)	Hepatic	3 M	6 M (ultrastructural changes in hepatocytes, impaired liver mitochondrial respiration)		Fowler et al. 1977 As(+5)	
			Bd Wt	6 M		12 M (final bd wt 28% lower than controls)		
69	Rat (CD)	14 d pre- mating thru Gd 19 1 x/d (GW)	Gastro	4 F		8 F (stomach adhesions, eroded luminal epithelium in the stomach)	Holson et al. 2000 As(+3)	
			Hepatic	2 F	4 F (incr liver wt)			
			Renal	4 F	8 F (incr kidney wt)			
			Bd Wt	4 F	8 F (decr body wt gain)			
70	Rat (NS)	16 wk (W)	Hemato		0.92 M (decr erythrocyte and leukocyte numbers)		Kannan et al. 2001 As(+3)	
			Hepatic	2.3 M				
71	Rat (Sprague-Dawley)	4 wk (W)	Hemato	0.12	0.3 (incr platelet aggregation)		Lee et al. 2002 As(+3)	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
72	Rat (NS)	1x/d 30 d (G)	Endocr		2.3 M (decr islet cells in pancreas, incr pancreatic SOD and catalase)		Mukherjee et al. 2003 As2O3	
73	Rat (Wistar)	1x/day 5 days/wk 12 wk (G)	Resp	19 M			Schulz et al. 2002 As(+3)	
			Renal	19 M				
			Bd Wt	9.5 M	19 M (~17% decr body weight gain)			
74	Mouse (C57BL)	6 wk (W)	Hepatic	5 M	10 M (ultrastructural changes in hepatocytes, impaired liver mitochondrial respiration)		Fowler and Woods 1979 As(+5)	
			Bd Wt	5 M	10 M (decr body wt gain)			
75	Mouse (C57BL/6 B6)	14 wk (W)	Hepatic	25 M			Kerkvliet et al. 1980 As(+5)	
			Renal	25 M				
76	Gn Pig (NS)	16 wk (W)	Hemato		0.69 M (decr erythrocyte number and leukocyte number, decr ALAD levels)		Kannan et al. 2001 As(+3)	
			Hepatic		0.69 M (incr ALAS activity)			

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
77	Dog (Beagle)	26 wk ad lib (F)	Hemato	1.9 F			Neiger and Osweiler 1989 As(+3)	
			Hepatic		0.8 F (mild incr serum ALT/AST)			
			Renal	1.9 F				
			Bd Wt	0.8 F	1.5 F (decr body wt gain)	1.9 F (25% decr in body wt)		
Immuno/ Lymphoret								
78	Mouse (C57BL/6 B6)	14 wk (W)		25 M			Kerkvliet et al. 1980 As(+5)	
Neurological								
79	Human	3 mo (W)				0.1 (paresthesia of hands and feet; confusion, disorientation and mental sluggishness)	Franzblau and Lilis 1989 As(+3) As(+5)	
80	Human	4 mo (W)				0.06 F (weakness, paresthesia)	Wagner et al. 1979 NS	
81	Rat (NS)	16 wk (W)		0.92 M	2.3 M (decr brain neurotransmitter levels)		Kannan et al. 2001 As(+3)	
82	Rat (Wistar)	1x/day 5 days/wk 12 wk (G)		19 M			Schulz et al. 2002 As(+3)	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
83	Gn Pig (NS)	16 wk (W)		0.69 M	1.7 M (changes in brain neurotransmitter levels)		Kannan et al. 2001 As(+3)	
Reproductive								
84	Rat (Wistar)	1x/d 28 d (G)			0.14 F (changes in uterine and ovarian weights, decr estradiol)		Chattopadhyay et al. 2001 As(+3)	
85	Rat (CD)	14 d pre- mating thru Gd 19 1 x/d (GW)		8 F			Holson et al. 2000 As(+3)	
86	Mouse (CD)	3 gen (W)				1 (decr litter size)	Schroeder and Mitchener 1971 As(+3)	
Developmental								
87	Rat (CD)	14 d pre- mating thru Gd 19 1 x/d (GW)		4	8 (decr fetal body wt, incr skeletal variations)		Holson et al. 2000 As(+3)	
88	Rat (Sprague-Dawley)	GD15 or postnatal day 1 through 4 months of age (W)			2.93 M (impaired performance in postnatal neurobehavioral tests)		Rodriguez et al. 2002 As(+3)	
89	Mouse (CD)	3 gen (W)				1 (decr litter size)	Schroeder and Mitchener 1971 As(+3)	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Death								
90	Human	2-7 yr children (W)				0.05 (death)	Zaldivar and Guillier 1977 NS	
91	Human	22 yr (W)				0.014 M (death)	Zaldivar et al. 1981 NS	cause of death was liver tumor
92	Monkey (Rhesus)	1 yr (IN)				3 (2/7 died)	Heywood and Sortwell 1979 As(+5)	
93	Rat (Wistar)	27 mo (F)				30 (incr mortality)	Kroes et al. 1974 As(+5) lead arsenate	
94	Mouse (CD)	2 yr (W)				1 (incr mortality, decr life span)	Schroeder and Balassa 1967 As(+3)	
95	Dog (Beagle)	2 yr (F)				2.4 (6/6 died)	Byron et al. 1967 As(+3)	
96	Dog (Beagle)	2 yr (F)				2.4 (1/6 died)	Byron et al. 1967 As(+5)	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
97	Human	NS (W)	Resp		0.032 (cough)		Ahmad et al. 1997 NS	
			Dermal			0.032 (melanosis, keratosis, hyperkeratosis, and depigmentation)		
			Ocular			0.032 (chronic conjunctivitis)		
98	Human	4 yr (IN)	Dermal			0.1 F (de-pigmentation with hyperkeratosis, possibly pre-cancerous)	Bickley and Papa 1989 As(+3)	
99	Human	NS (W)	Cardio			0.014 (gangrene of feet)	Biswas et al. 1998 NS	
			Dermal			0.014 (melanosis and keratosis of hand palms and foot soles)		
100	Human	12 yr (W)	Cardio			0.02 (Raynaud's disease, gangrene of toes)	Borgono and Greiber 1972 NS	
			Gastro		0.02 (diarrhea, abdominal pain)			
			Dermal			0.02 (abnormal pigmentation with hyperkaratosis, possibly pre-cancerous)		

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
101	Human	11-15 yr (W)	Dermal		0.01	(hypo- and hyperpigmentation)			Borgono et al. 1980	NS
102	Human	NS (W)	Gastro	0.0004	0.022	(gastrointestinal irritation, diarrhea, nausea)			Cebrian et al. 1983	As(+5)
			Dermal	0.0004			0.022	(pigmentation changes with hyperkeratosis, possibly pre-cancerous)		
103	Human	1-11 yr (W)	Hepatic		0.046	(hepatomegaly)			Chakraborty and Saha 1987	NS
			Dermal				0.046	(pigmentation changes with keratosis, possibly pre-cancerous)		
104	Human	NS (W)	Cardio				0.064	(Blackfoot Disease)	Chen et al. 1988b	NS
105	Human	>10 yr (W)	Cardio	0.0008			0.022	(incr risk of ischemic heart disease mortality)	Chen et al. 1996	NS
106	Human	NS (W)	Cardio				0.002	(incr prevalence of cerebrovascular disease and cerebral infarction)	Chiou et al. 1997	NS

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
107	Human	3-7 yr (W)	Cardio			0.05 (Blackfoot Disease)	Foy et al. 1992	
							NS	
			Dermal			0.05 (melanosis with hyperkeratosis, possibly pre-cancerous)		
108	Human	2-6 yr (IN)	Hepatic			0.08 M (cirrhosis, ascites)	Franklin et al. 1950	
							As(+3)	
			Dermal			0.08 M (pigmentation with hyperkeratosis, possibly pre-cancerous)		
109	Human	NS (W)	Hepatic	0.004		0.014 (hepatomegaly)	Guha Mazumder et al. 1988	
							NS	
			Dermal	0.004		0.014 (pigmentation changes with hyperkaratosis, possibly pre-cancerous)		
110	Human	1-20 yr (W)	Gastro		0.06 (abdominal pain)		Guha Mazumder et al. 1988	
							NS	
			Hemato		0.06 (anemia)			
			Hepatic			0.06 (hepatomegaly, fibrosis)		
			Dermal			0.06 (hyperpigmentation with hyperkeratosis, possibly pre-cancerous)		

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
111	Human	NS (W)	Dermal	0.0016			0.009	(hyperpigmentation with (keratosis, possibly pre-cancerous)	Guha Mazumder et al. 1998a NS	
112	Human	NS (W)	Dermal		0.0018	(hyperkeratosis, hyperpigmentation)			Haque et al. 2003 (NS)	
113	Human	10 yr (W)	Gastro	0.0046					Harrington et al. 1978 NS	
			Hemato	0.0046						
			Dermal	0.0046						
114	Human	NS (W)	Hepatic	0.0008	0.006	(incr serum alkaline phosphatase and bilirubin)			Hernandez-Zavala et al. 1998 NS	
115	Human	0.5-14 yr (W)	Dermal				0.05	(hyperpigmentation with keratosis, possibly pre-cancerous)	Huang et al. 1985 NS	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
116	Human	15 yr (IN)	Gastro			0.03 M (hematemesis, hemoperitoneum, melena)	Lander et al. 1975 As(+3)	
			Dermal			0.03 M (hyperkeratosis - possibly pre-cancerous)		
117	Human	NS (W)	Cardio	0.004		0.005 (cyanosis of extremities, palpitations/chest discomfort)	Lianfang and Jianzhong 1994 NS	
			Dermal	0.004		0.005 (keratosis, hyperpigmentation, depigmentation)		
118	Human	3-22 yr (IN)	Gastro			0.05 M (gastrointestinal hemorrhages)	Morris et al. 1974 As(+3)	
			Hepatic			0.05 M (vascular fibrosis, portal hypertension)		
			Dermal			0.05 M (hyperpigmentation with keratoses, possibly pre-cancerous)		
119	Human	15 yr (IN)	Hepatic			0.05 F (central fibrosis)	Piontek et al. 1989 As(+3)	
			Dermal			0.05 F (hyperkeratosis, possibly pre-cancerous)		

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
120	Human	NS (W)	Endocr			0.11 (diabetes mellitus)	Rahman et al. 1998 NS	
121	Human	28 mo (IN)	Cardio	0.06 F			Silver and Wainman 1952 As(+3)	
			Gastro		0.06 F (intermittent, progressively severe nausea, cramps, and diarrhea)			
			Hemato	0.06 F				
			Hepatic		0.06 F (hepatomegaly, fatty liver)			
			Renal	0.06 F				
			Dermal			0.06 F (melanosis with hyperkeratosis, possibly pre-cancerous)		
			Ocular		0.06 F (conjunctival injection, periocular edema)			
122	Human	> 5 yr (W)	Hemato	0.006[c] M 0.007 F			Southwick et al. 1981 NS	
			Dermal	0.0009[c] M 0.001 F				

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
123	Human	55 yr (IN)	Hepatic			0.03 M (portal fibrosis and hypertension, bleeding from esophageal varices)	Szuler et al. 1979 As(+3)	
			Dermal			0.03 M (hyperpigmentation with hyperkeratosis, possibly pre-cancerous)		
124	Human	45 yr (W)	Cardio			0.014 (Blackfoot Disease)	Tseng 1977 NS	
125	Human	NS (W)	Cardio			0.014 (Blackfoot Disease)	Tseng 1989 NS	
126	Human	> 45 yr (W)	Dermal	0.0008 M[d]	0.014 M (hyperkeratosis and hyperpigmentation)		Tseng et al. 1968 NS	
127	Human	> 30 yr (W)	Cardio		0.064 M (deficits in cutaneous microcirculation of the toes)		Tseng et al. 1995 As(+3)	
128	Human	52.6 yr (avg) (W)	Cardio	0.016		0.031 (peripheral vascular disease)	Tseng et al. 1996 NS	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
129	Human	16 mo (IN)	Resp	0.1 M			Wade and Frazer 1953 As(+3)	
			Cardio	0.1 M				
			Hemato	0.1 M				
			Hepatic		0.1 M (liver enlargment)			
			Dermal			0.1 M (hyperkeratosis, hyperpigmentation with hyperkeratosis, possibly pre-cancerous)		
130	Human	30-33 yr (W)	Dermal			0.015 M (hyperkeratosis of foot, possibly pre-cancerous)	Zaldivar 1974 NS	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
131	Human	12 yr (W)	Resp		0.015[c] M (bronchitis, bronchiectasis)		Zaldivar 1974 NS	
					0.018 F (bronchitis, bronchiectasis)			
			Cardio			0.015[c] M (Raynaud's disease, thrombosis)		
						0.018 F		
			Gastro		0.015[c] M (diarrhea)			
					0.018 F (diarrhea)			
			Dermal		0.015[c] M (scaling of skin, hyperkeratosis, leukoderma, melanoderma)			
					0.018 F			
			Bd Wt		0.015[c] M (unspecified decr body wt)			
					0.018 F (unspecified decr body wt)			
132	Human	NS (W)	Dermal			0.063 (hyperpigmentation with keratoses, possibly pre-cancerous)	Zaldivar 1977 NS	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
133	Human	2-7 yr children (W)	Resp			0.08 (inflammation of bronchi and larynx, bronchopneumonia)	Zaldivar and Guillier 1977 NS	
			Cardio			0.05 (vascular spasms, thrombosis, ischemia, hypotension, cardiac failure)		
			Gastro			0.05 (nause, vomiting, diarrhea, intestinal hemorrhage)		
			Hemato			0.05 (anemia)		
			Hepatic			0.08 (cirrhosis)		
			Renal		0.08 (cloudy swelling in kidneys)			
			Dermal			0.05 (hyperkeratosis of palms and soles, melanoderma, leukoderma)		
134	Human	1-39 yr (W)	Cardio			0.06 (arterial thickening, Raynaud's disease)	Zaldivar and Guillier 1977 NS	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
135	Rat (Osborne-Mendel)	2 yr (F)	Resp	20			Byron et al. 1967 As(+3)	
			Cardio	20				
			Gastro	20				
			Hemato	9	20 (slight transient decr in Hb and Hct values)			
			Hepatic	4		9 (enlarged bile duct, bile duct proliferation)		
			Renal	9	20 (pigmentation)			
			Bd Wt	2	4 (decr body wt gain)			
136	Rat (Osborne-Mendel)	2 yr (F)	Resp	30			Byron et al. 1967 As(+5)	
			Cardio	30				
			Gastro	30				
			Hemato	30				
			Hepatic	9	20 (enlarged bile duct)			
			Renal	9	20 (pigmentation, cysts)			
			Bd Wt		2 (decr body wt gain in females)			

DRAFT FOR PUBLIC COMMENT

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
137	Rat (Wistar)	27 mo (F)	Resp	7			Kroes et al. 1974 As(+5)	
			Cardio	7				
			Gastro	7				
			Hemato	7				
			Musc/skel	7				
			Hepatic	7				
			Renal	7				
			Endocr	7				
			Bd Wt		7 (decr body wt gain)			
138	Rat (Wistar)	27 mo (F)	Resp	30			Kroes et al. 1974 As(+5) lead arsenate	
			Cardio	30				
			Gastro	30				
			Hemato	7	30 (slight anemia)			
			Musc/skel	30				
			Hepatic	7		30 (enlarged bile duct with extensive dilation and inflammation)		
			Renal	30				
			Endocr	30				
			Bd Wt	7	30 (decr bd wt gain)			

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
139	Rat (Long-Evans)	3 yr (W)	Resp	0.6			Schroeder et al. 1968 As(+3)	
			Cardio	0.6				
			Hepatic	0.6				
			Renal	0.6				
			Dermal	0.6				
			Bd Wt	0.6				
140	Mouse (BALB/c)	15 mo (W)	Hepatic		0.7 M (incr liver weight, altered liver histopathology, decr hepatic enzymes in serum)		Santra et al. 2000 (NS)	
			Bd Wt		0.7 M (13-17% decr bd wt)			
141	Mouse (CD)	2 yr (W)	Bd Wt		1 (decr bd wt gain after the first 6 mo of the study)		Schroeder and Balassa 1967 As(+3)	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
142	Dog (Beagle)	2 yr (F)	Resp	2.4			Byron et al. 1967 As(+3)	
			Cardio	2.4				
			Gastro	1		2.4 (bleeding in the gut)		
			Hemato	1	2.4 (slight to moderate anemia)			
			Hepatic	1	2.4 (hemosiderin deposits in hepatic macrophages)			
			Renal	2.4				
			Bd Wt	1		2.4 (44-61% weight loss)		
143	Dog (Beagle)	2 yr (F)	Resp	2.4			Byron et al. 1967 As(+5)	
			Cardio	2.4				
			Gastro	2.4				
			Hemato	1	2.4 (mild anemia)			
			Hepatic	1	2.4 (pigmentation in hepatic macrophages)			
			Renal	2.4				
			Bd Wt	1		2.4 (marked decr weight gain)		
Neurological								
144	Human	3-7 yr (W)				0.11 F (wrist weakness)	Foy et al. 1992 NS	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
145	Human	1-20 yr (W)			0.06 (tingling of hands and feet)		Guha Mazumder et al. 1988	NS
146	Human	10 yr (W)		0.0046			Harrington et al. 1978	NS
147	Human	NS (W)		0.0014		0.04 (functional denervation)	Hindmarsh et al. 1977	NS
148	Human	NS (W)		0.004	0.005 (fatigue, headache, dizziness, insomnia, nighmare, numbness)		Lianfang and Jianzhong 1994	NS
149	Human	28 mo (IN)				0.06 F (paresthesia)	Silver and Wainman 1952	As(+3)
150	Human	> 5 yr (W)		0.006[c] M 0.007 F			Southwick et al. 1981	NS
151	Human	55 yr (IN)			0.03 M (absent ankle jerk reflex and vibration sense in legs)		Szuler et al. 1979	As(+3)

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
152	Human	NS (W)			0.0017 (decr performance in neurobehavioral tests)		Tsai et al. 2003 (NS)	
Developmental								
153	Human	NS (W)			0.008 F (incr frequencies for spontaneous abortion, stillbirth, and preterm birth rates)		Ahmad et al. 2001 (NS)	
Cancer								
154	Human	NS (W)				0.022 (CEL: skin cancer)	Cebrian et al. 1983 As(+5)	
155	Human	NS (W)				0.064 (CEL: bladder, lung and liver cancers)	Chen et al. 1986 NS	
156	Human	NS (W)				0.064 (CEL: malignant neoplasms of the bladder, skin, lung and liver)	Chen et al. 1988b NS	
157	Human	NS (W)				0.003 (CEL: bladder cancer)	Chiou et al. 2001 (NS)	
158	Human	2 wk-12 yr (IN)				3.67 (CEL: bladder cancer risk)	Cuzick et al.1992 As(+3)	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
159	Human	NS (W)				0.0011	(CEL: lung cancer)	Ferreccio et al. 1998 NS	
160	Human	NS (W)				0.0017	(CEL: lung cancers)	Ferreccio et al. 2000 (NS)	
161	Human	NS (W)				0.018	(CEL: lung cancer mortality)	Guo 2004 (NS)	
162	Human	NS (W)				0.018	(CEL: bladder cancer)	Guo and Tseng 2000 (NS)	
163	Human	NS (W)				0.052	(CEL: incr incidence of transitional cell carcinomas of the bladder, kidney, & ureters and all urethral cancer)	Guo et al. 1997 NS	
164	Human	NS (W)				0.0049[c] M	(CEL: squamous cell carcinoma of the skin)	Guo et al. 2001b (NS)	
						0.0094 F			

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
165	Human	>1 yr (W)				0.0075 (CEL: basal or squamous skin carcinoma)	Haupert et al. 1996 NS	
166	Human	16 yr (avg) (IN)				0.04 M (CEL: basal cell and squamous cell carcinomas of the skin, small cell and squamous cell carcinoma of the lung)	Luchtrath 1983 As(+5)	
167	Human	60 yr (W)				0.038 (CEL: intraepidermal carcinoma)	Tseng 1977 NS	
168	Human	> 45 yr (W)				0.014 (CEL: squamous cell carcinoma of the skin)	Tseng et al. 1968 NS	
169	Human	~5 yr (W)				0.033 (CEL: lung, urinary tract cancer)	Tsuda et al. 1995a As(+3)	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
170	Human	12 yr (W)				0.015 M (CEL: squamous cell carcinoma of the skin)	Zaldivar 1974 NS	
						0.018 F (CEL: squamous cell carcinoma of the skin)		
171	Human	22-34 yr (W)				0.014 M (CEL: basal cell and squamous cell carcinomas of the skin, hemangioendothelioma of the liver)	Zaldivar et al. 1981 NS	

aThe number corresponds to entries in Figure 3-3.

bUsed to derive provisional acute oral minimal risk level (MRL) of 0.005 mg/kg/day; dose divided by an uncertainty factor of 10 (for extrapolation from a LOAEL to a NOAEL).

cDifferences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

dUsed to derive chronic oral minimal risk level (MRL) of 0.0003 mg/kg/day; dose divided by an uncertainty factor of 3 (for human variability).

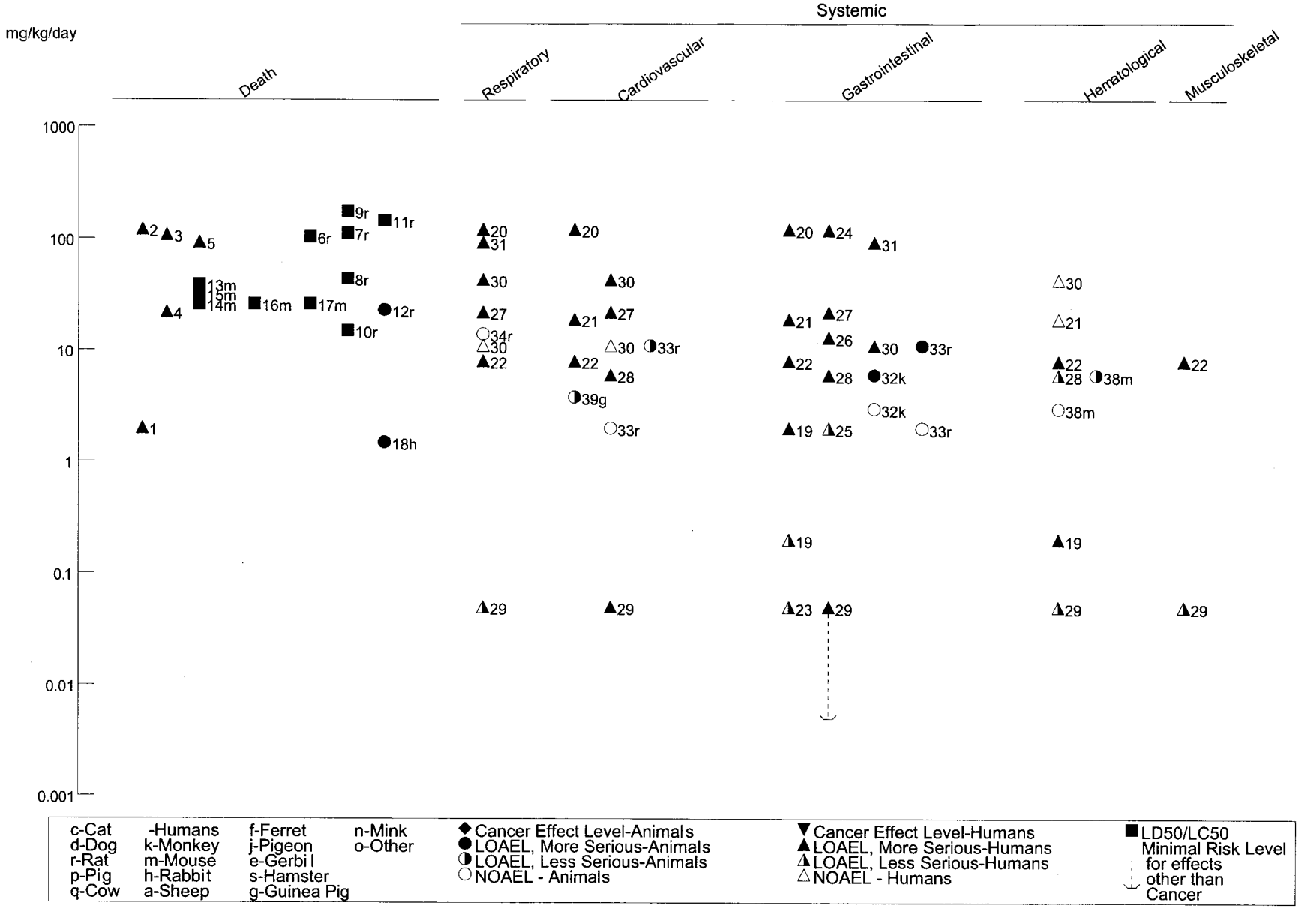
avg = average; ALAD = delta-aminolevulinic acid dehydratase; ALAS = delta-aminolevulinic acid synthetase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); decr = decreased; Endocr = endocrine; (F) = feed; F = female; Gastro = gastrointestinal; GI = gastrointestinal; (GW) = gavage in water; gen = generation; Gd = gestation day; Gn pig = guinea pig; Hb = hemoglobin; Hct = hematocrit; Hemato = hematological; hr = hour(s); IN = ingestion; incr = increased; LD50 = lethal dose, 50% kill; LDH = lactate dehydrogenase; LOAEL = lowest-observable-adverse-effect level; M = male; Metab = metabolic; mo = month(s); NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; SOD = superoxide dismutase; (W) = water; wk = week(s); yr = year(s)

DRAFT FOR PUBLIC COMMENT

DRAFT FOR PUBLIC COMMENT

Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

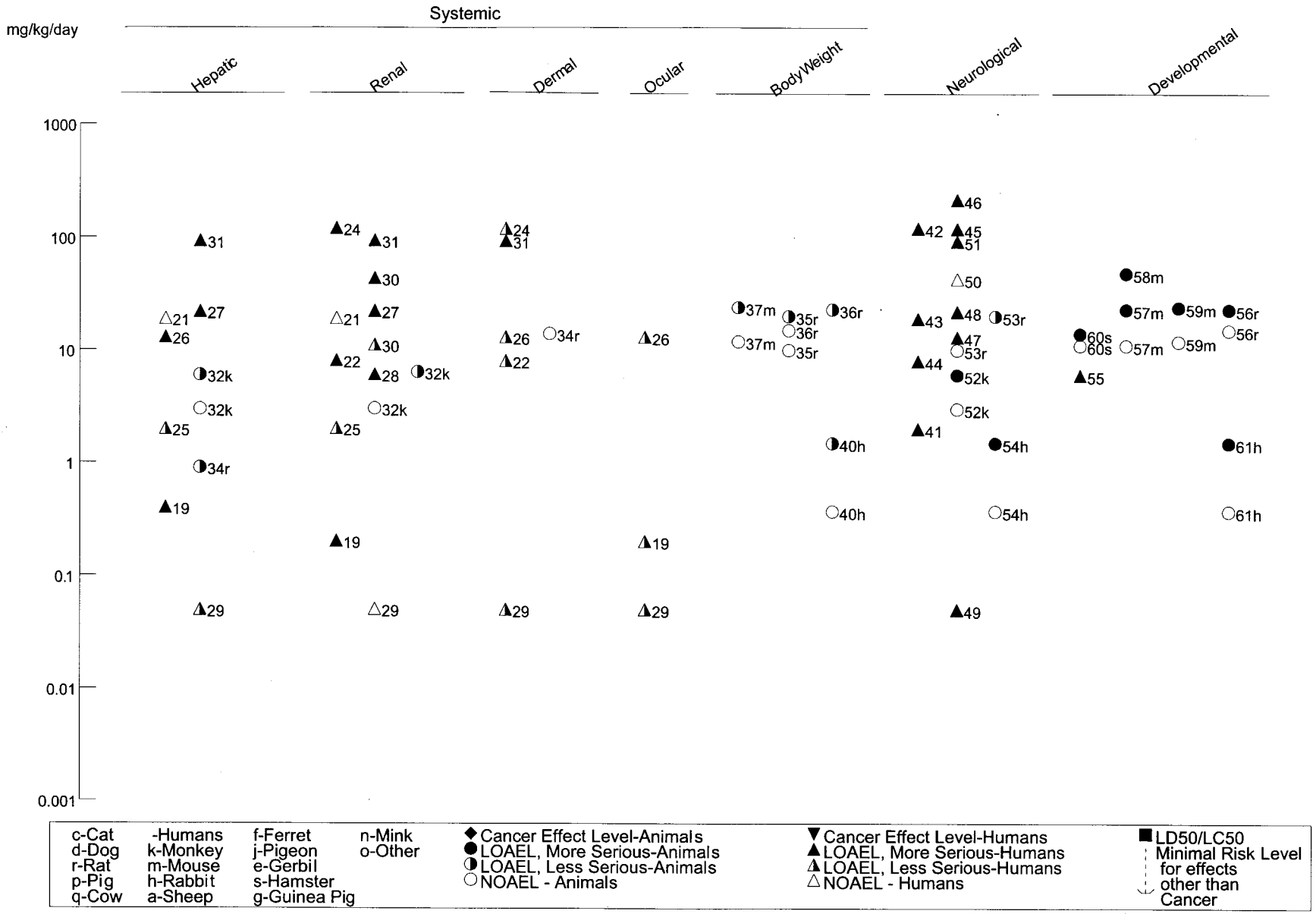
Acute (≤14 days)



DRAFT FOR PUBLIC COMMENT

Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (*Continued*)

Acute (≤14 days)



DRAFT FOR PUBLIC COMMENT

Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (*Continued*)

Intermediate (15-364 days)

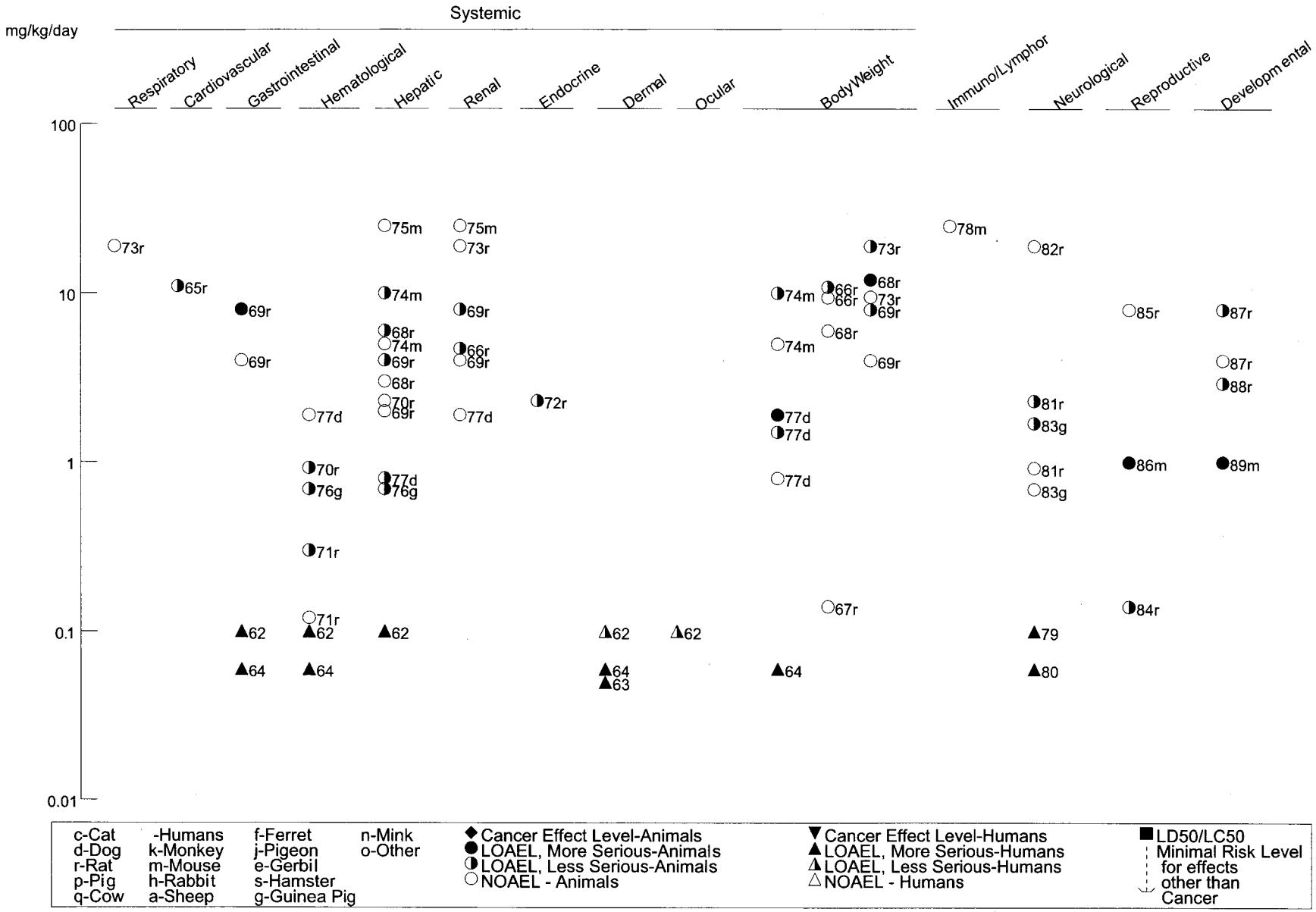
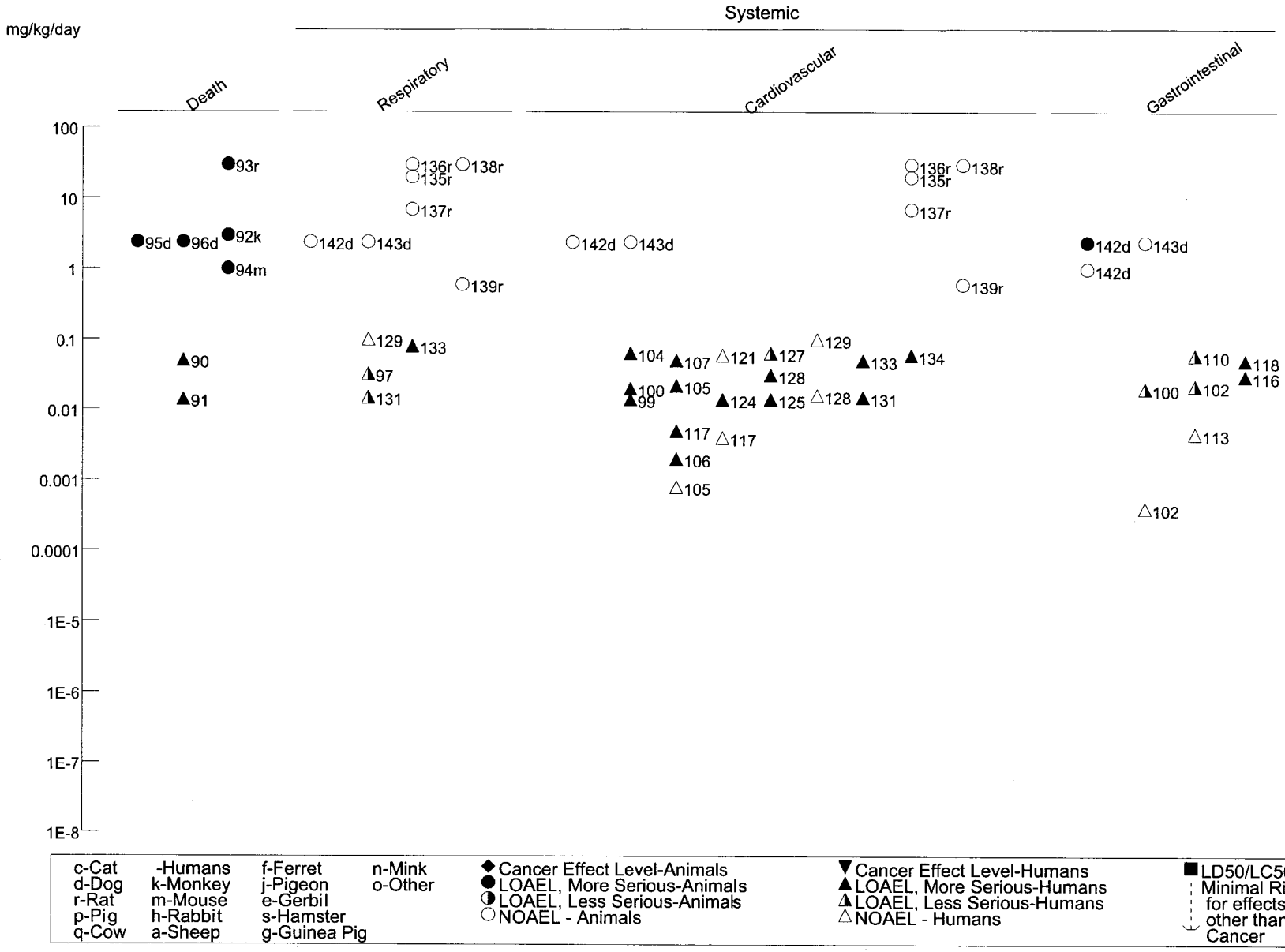


Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (*Continued*)

Chronic (≥365 days)



DRAFT FOR PUBLIC COMMENT

DRAFT FOR PUBLIC COMMENT

Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (*Continued*)

Chronic (≥365 days)

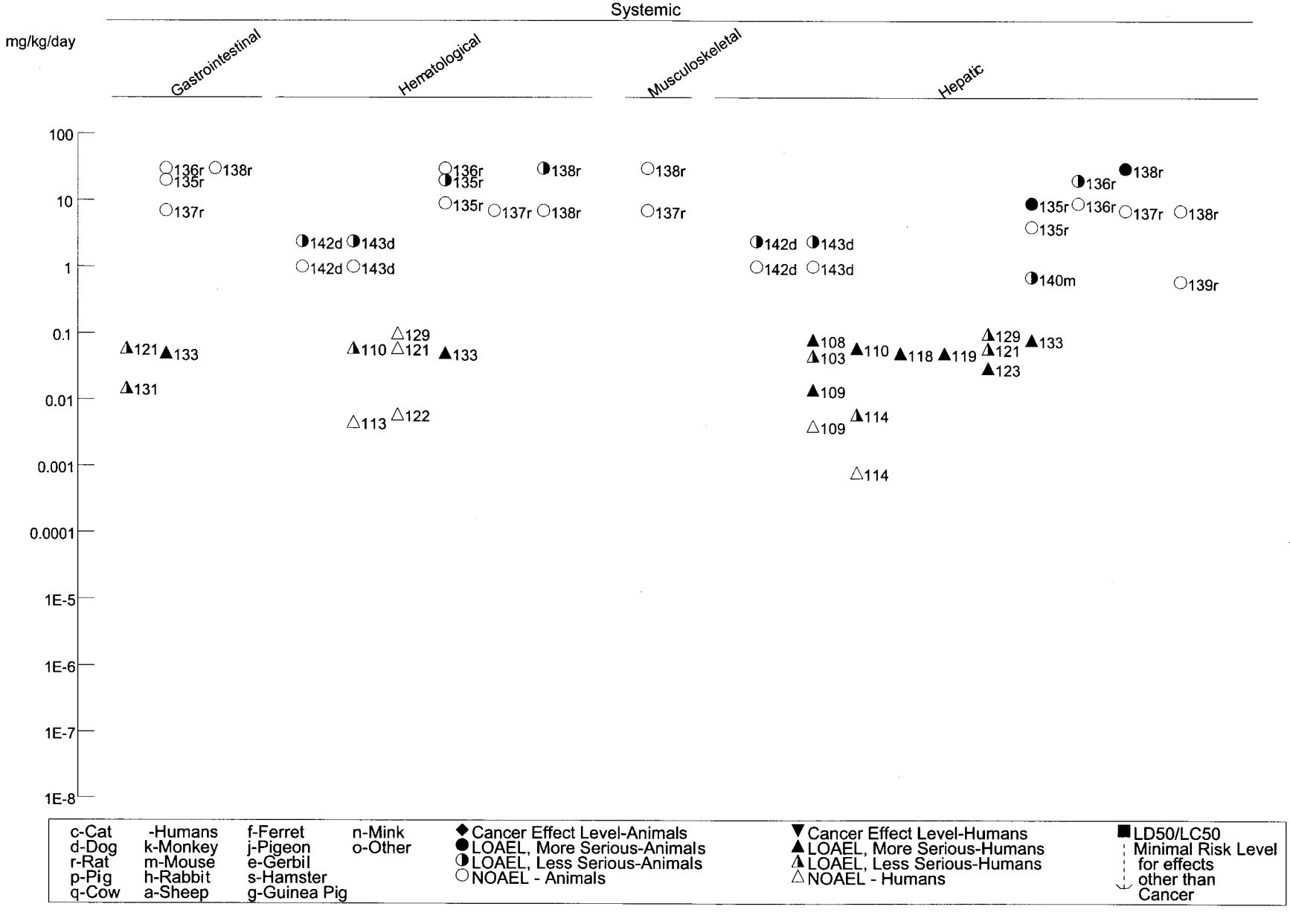
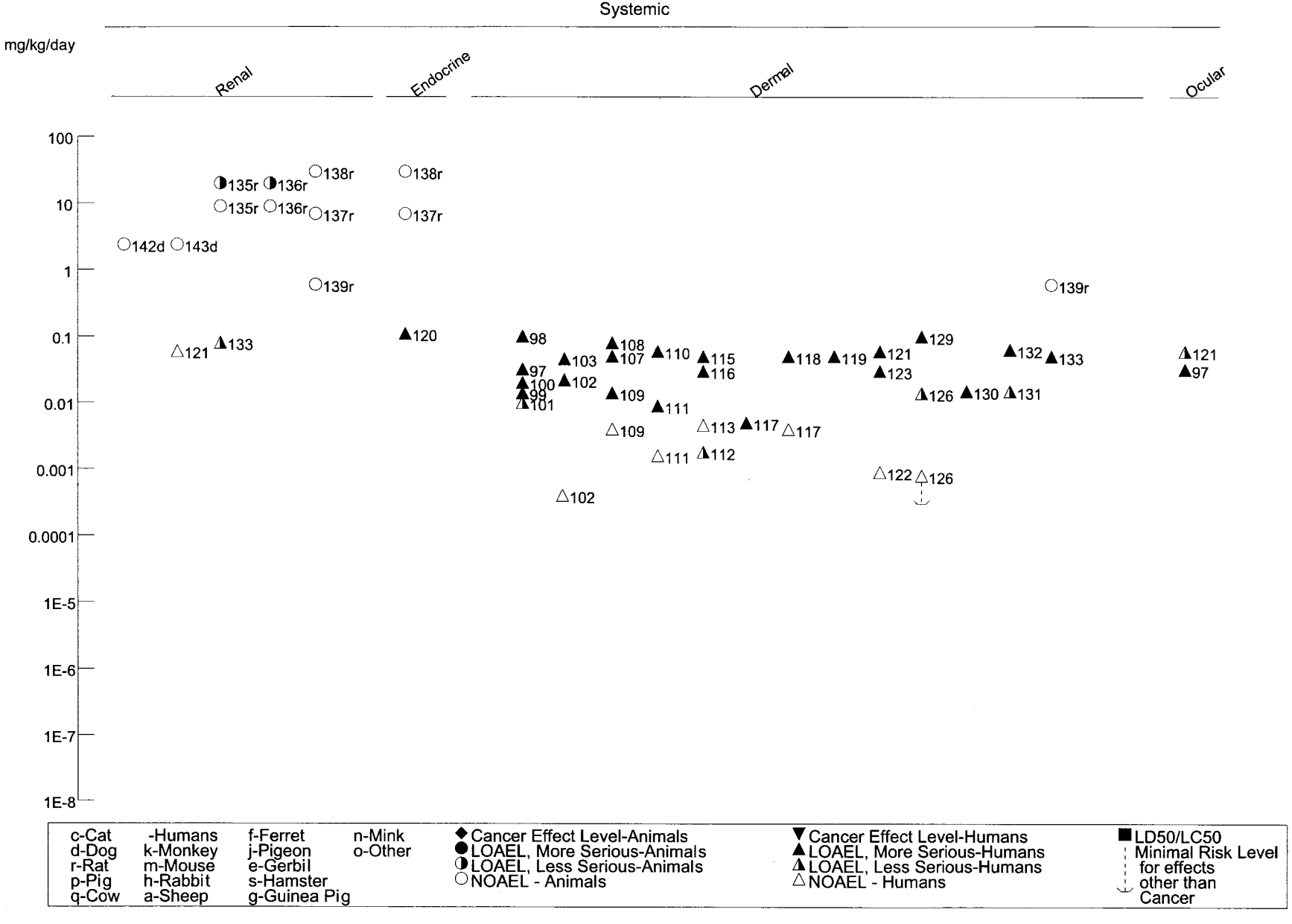


Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (*Continued*)

Chronic (≥365 days)

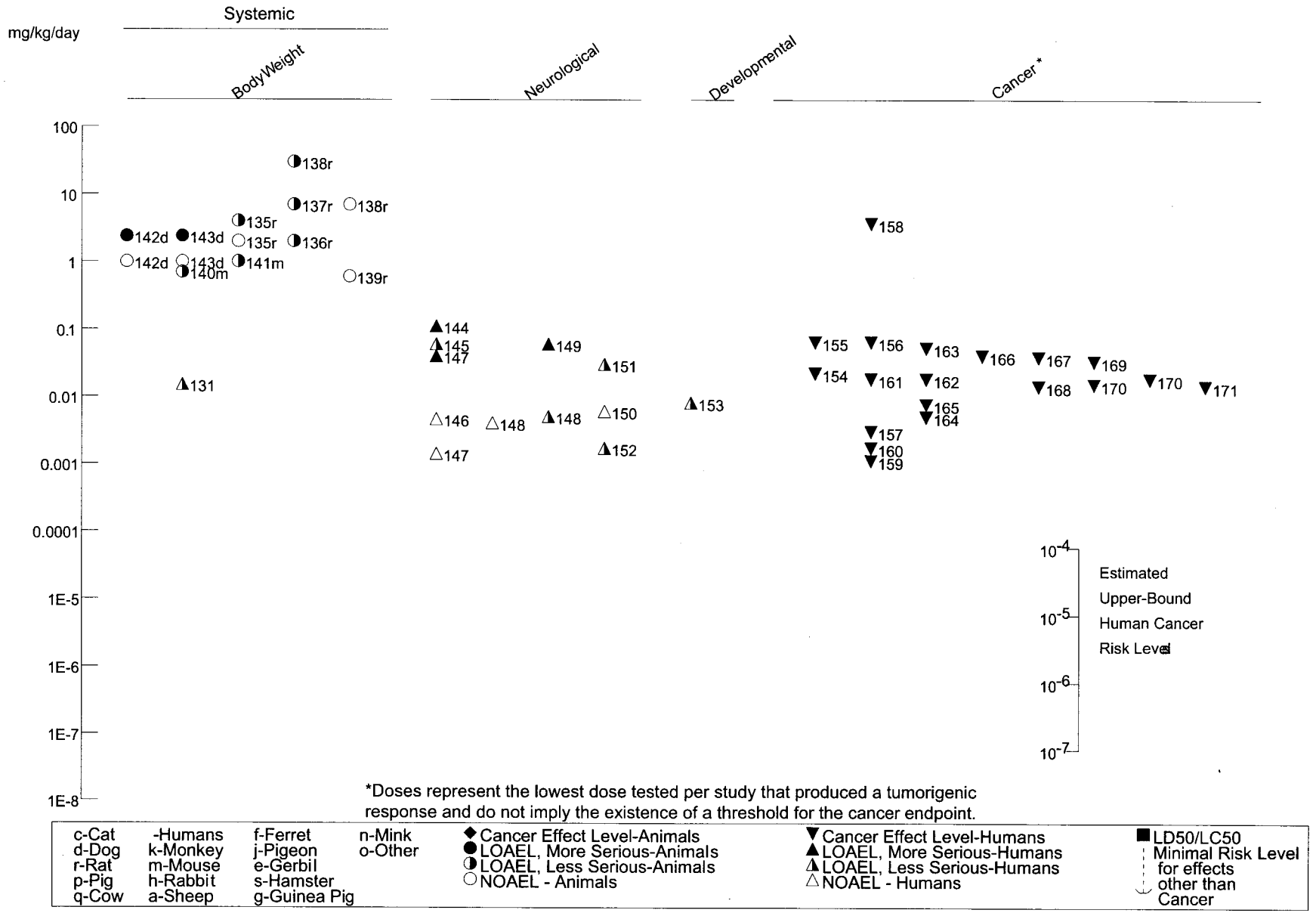


DRAFT FOR PUBLIC COMMENT

DRAFT FOR PUBLIC COMMENT

Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (*Continued*)

Chronic (≥365 days)



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

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

DRAFT FOR PUBLIC COMMENT

Table 3-4 Levels of Significant Exposure to Organic Arsenic - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Holtzman)	once (GW)				44 (LD50)	Kerr et al. 1963 ROX	
2	Rat (Fischer- 344)	9d 1x/d (G)				61 (1/3 died)	Murai et al. 1993 DMA	
3	Rat (Fischer- 344)	once (GO)				42.7 M (5/5 died) 21.4 F (2/5 died; LD50=23.1 mg As/kg)	NTP 1989b ROX	
4	Rat (Fischer- 344)	14 d (F)				36.46 M (3/5 died) 41.02 F (5/5 died)	NTP 1989b ROX	
5	Rat (CD)	10 d Gd 7-16 1x/d (GW)				21.7 F (4% mortality)	Rogers et al. 1981 DMA	
6	Mouse (ddY	once (GW)				652 M (LD50)	Kise et al. 1989 DMA	
7	Mouse (ddY	once (GW)				963 M (LD50)	Kise et al. 1989 MMA	
8	Mouse (B6C3F1)	once (GO)				85.4 M (5/5 died) 69.5 F (LD50)	NTP 1989b ROX	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
9	Mouse (B6C3F1)	14 d (F)				48.4 (2/5 males died; 5/5 females died)	NTP 1989b ROX	
10	Mouse (CD-1)	10 d Gd 7-16 1x/d (GW)				217 F (3% mortality)	Rogers et al. 1981 DMA	
11	Dog (Mongrel)	once (C)				14.2 (LD50)	Carr et al. 1963 ROX	
12	Rabbit (New Zealand)	once (GW)				47 M (LD50)	Jaghabir et al. 1988 MMA	
Systemic								
13	Human	once (IN)	Cardio		77.1 M (sinus tachycardia)		Lee et al. 1995 DMA	
			Gastro		77.1 M (vomiting, abdominal pain, hyperactive bowel, watery garlic-smelling stools)			
			Hemato	77.1 M				
			Hepatic	77.1 M				

DRAFT FOR PUBLIC COMMENT

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
14	Human	once (IN)	Resp	793 M			Shum et al. 1995 MSMA	
			Cardio	793 M				
			Gastro		793 M (vomiting)			
			Hepatic	793 M				
			Renal	793 M				
15	Rat (Fischer- 344)	2 wk (F)	Renal		6 F (altered bladder cell surface characteristics)		Cohen et al. 2001 DMA	
			Bd Wt	6 F				
16	Rat (Fischer- 344)	14 d (F)	Hemato	18.23[b] M	36.46[b] M (cyanosis of the eye)		NTP 1989b ROX	
				20.51 F	41.02 F (cyanosis of the eye)			
			Bd Wt	4.56[b] M	9.11 M (22% reduced body weight)			
				41.02 F				
17	Rat (CD)	10 d Gd 7-16 1x/d (GW)	Bd Wt			21.7 F (27% decr maternal weight gain)	Rogers et al. 1981 DMA	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
18	Mouse (ddY)	once (GW)	Resp			489 M (respiratory arrest)	Kise et al. 1989 DMA	
			Gastro		954 M (diarrhea, slight congestion of the intestion)			
19	Mouse (ddY)	once (GW)	Resp			963 M (respiratory arrest)	Kise et al. 1989 MMA	
			Gastro		1177 M (diarrhea, slight congestion of the small intestine)			
20	Mouse (B6C3F1)	14 d (F)	Hemato	5.8	12.1 (pale skin)		NTP 1989b ROX	
			Bd Wt	48.4				
21	Mouse (CD-1)	10 d Gd 7-16 1x/d (GW)	Bd Wt			109 F (26% decr maternal weight gain)	Rogers et al. 1981 DMA	

DRAFT FOR PUBLIC COMMENT

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
22	Dog (Mongrel)	once (C)	Resp			14.2 (localized hemorrhage in lung)	Orr et al. 1963 ROX	
			Gastro			14.2 (vomiting; hemorrhages in the pyloric portion of the stomach, colon and cecum)		
			Hepatic			14.2 (generalized icterus)		
			Renal			14.2 (hematuria, congested kidney)		
			Other		14.2 (bloody mucus in feces)			
23	Rabbit (New Zealand)	once (GW)	Gastro		28 M (constipation, diarrhea)		Jaghabir et al. 1988 MMA	
			Renal		28 M (oliguria)			
Neurological								
24	Rat (Fischer- 344)	14 d (F)		5.13 4.56[b]	9.11[b] M (slight inactivity) 10.25 F		NTP 1989b ROX	
25	Mouse (ddY)	once (GW)				954 M (increased startle reflex; ataxia)	Kise et al. 1989 DMA	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
26	Mouse (B6C3F1)	14 d (F)		5.8	12.1 (slight inactivity; ruffled fur)		NTP 1989b ROX	
27	Rabbit (New Zealand)	once (GW)			28 M (weakness, loss of appetite)		Jaghabir et al. 1988 MMA	
Developmental								
28	Rat (CD)	10 d Gd 7-16 1x/d (GW)		8.1		16.3 (malformed palates in 15%)	Rogers et al. 1981 DMA	
29	Mouse (CD-1)	10 d Gd 7-16 1x/d (GW)		109		217 (18% decr in fetal weight, delayed ossification, cleft palate in 12/28; irregular palatine rugae in 4.8%)	Rogers et al. 1981 DMA	
INTERMEDIATE EXPOSURE								
Death								
30	Rat (Holtzman)	13 wk (F)				5.7 (10/12 died)	Kirr et al. 1963 ROX	
31	Rat (Fischer- 344)	4 wk 5 d/wk 1x/d (G)				31 (50% survival in males; 20% survival in females)	Murai et al. 1993 DMA	
32	Rat (Fischer- 344)	13 wk ad lib (F)				18.23 M (3/10 died) 20.51 F (2/10 died)	NTP 1989b ROX	

DRAFT FOR PUBLIC COMMENT

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
33	Rat (Fischer- 344)	8 wk (W)				16 (10/10 died)	Wanibuchi et al. 1996 DMA	
34	Mouse (B6C3F1)	13 wk ad lib (F)				13.4 (1/10 males died; 1/10 females died)	NTP 1989b ROX	
35	Pig	28 d (F)				5.7 (death in 2/18)	Edmonds and Baker 1986 ROX	
Systemic								
36	Rat (Fischer- 344)	10 wk (F)	Renal	0.61 F	5.4 M (incr bladder weight, urinary pH, urinary volume, and urinary calcium)		Arnold et al. 1999 DMA	
					2.5 F[b] (incr bladder weight, altered urinary chemistry)			
			Bd Wt	5.4 M				
37	Rat (Fischer- 344)	10 wk (F)	Renal		6 F (incr bladder and kidney weights, hyperplasia and necrosis of bladder epithelium)		Cohen et al. 2001 DMA	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
38	Rat (Fischer- 344)	4 wk 5 d/wk 1x/d (G)	Renal			31 (papillary necrosis and hyperplasia; cortical degeneration and necrosis)	Murai et al. 1993 DMA	
			Bd Wt		31 (decr body weight)			
39	Rat (Fischer- 344)	31 or 90 d ad lib (F)	Hemato	9.11[b] M 10.25 F			NTP 1989b ROX	
			Hepatic	9.11 M 2.56[b] F	10.25 F (decr relative liver weight)			
			Renal	2.28[b] M 10.25 F	9.11 M (incr relative kidney weight; mild tubular degeneration)			

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
40	Rat (Fischer- 344)	13 wk ad lib (F)	Resp	18.33[b] M 20.51 F			NTP 1989b ROX	
			Cardio	18.33[b] M 20.51 F				
			Gastro	18.33[b] M 20.51 F				
			Hemato	9.11[b] M 10.25 F	18.23[b] M (pale skin) 20.51 F (pale skin)			
			Musc/skel	18.33[b] M 20.51 F				
			Hepatic	1.14[b] M 10.25 F	2.28[b] M (incr relative liver wt.) 20.51 F (incr relative liver wt.)			
			Renal		9.11[b] M (interstitial inflammation, focal regenerative hyperplasia of tubular cell epithelium and mineralization) 10.25 F	18.23[b] M (tubular necrosis) 20.51 F		
			Endocr	18.33[b] M 20.51 F				
			Dermal	18.33[b] M 20.51 F				
			Bd Wt	2.28[b] M 5.13 F	4.56[b] M (14% decr bd wt) 10.25 F (11% decr bd wt)	9.11[b] M (26% decr bd wt) 20.51 F (33% decr bd wt)		

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
41	Rat (Sprague-Dawley)	42 d (F)	Hemato	1.99 M			Siewicki 1981 DMA	
			Hepatic	1.99 M				
			Renal	1.99 M				
			Bd Wt	1.99 M				
42	Mouse (B6C3F1)	13 wk ad lib (F)	Resp			38.7 (interstitial pneumonia)	NTP 1989b ROX	
			Cardio	38.7				
			Gastro	38.7				
			Musc/skel	38.7				
			Hepatic	38.7				
			Renal	38.7				
			Endocr	38.7				
			Dermal	38.7				
			Bd Wt		38.7 (18% decr bd wt in males; 11% decr bd wt in females)			
43	Mouse (B6C3F1)	29 or 91 d ad lib (F)	Hemato	13.4			NTP 1989b ROX	
			Hepatic	13.4				
			Renal	13.4				

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
44	Mouse (Swiss)	10 wk 1x/2d (GW)	Hemato	55			Prukop and Savage 1986 MMA	
45	Rabbit (New Zealand)	40 d 1x/d (GW)	Gastro		2.3 M (intestinal hyperemia)		Jaghabir et al. 1989 MMA	
			Hepatic		2.3 M (hepatocellular degeneration in 4/4)			
			Renal		2.3 M (interstitial nephritis in 2/4)			
Neurological								
46	Rat (Fischer- 344)	13 wk ad lib (F)		9.11[b] M 10.25 F		18.23[b] M (trembling, ataxia, hyperexcitability, slight inactivity, ruffled fur) 20.51 F	NTP 1989b ROX	
47	Pig	28 d (F)		1.43		2.85 (muscle tremors)	Edmonds and Baker 1986 ROX	
48	Pig	30 d (F)				0.87 (myelin degeneration)	Kennedy et al. 1986 ROX	
49	Pig (Landrace)	30 d ad lib (F)				1.07 (seizures in 100%)	Rice et al. 1985 ROX	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
50	Mouse (Swiss)	19 d 3 d/wk (GW)		5 M		55 M (reduced fertility)	Prukop and Savage 1986 MMA	
Cancer								
51	Mouse A/J	50 wk ad lib (W)				5.5 M (CEL: lung tumors)	Hayashi et al. 1998 DMA	
CHRONIC EXPOSURE								
Death								
52	Rat (Fischer- 344)	104 wk (F)				34.8 M (incr mortality)	Arnold et al. 2003 MMA	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
53	Rat (Fischer- 344) (F)	104 wk	Cardio	1.8 F	16.3 F (incr absolute and relative heart weight)		Arnold et al. 2003 MMA	
			Gastro		1.4[b] M (diarrhea)			
					1.8 F (diarrhea)			
			Hemato	34.8[b] M				
				47.3 F				
			Hepatic	12.3[b] M	34.8[b] M (incr absolute liver weight)			
				16.3 F				
					47.3 F (histiocytic proliferation of the liver)			
			Renal	1.4[b] M	12.6[b] M (incr absolute kidney weight)			
				1.8 F				
					16.3 F (incr relative kidney weight)			
			Endocr	1.4[b] M	12.3[b] M (decr absolute thyroid weight)			
				1.8 F				
					16.3 F (decr absolute thyroid weight)			
			Bd Wt	1.4[b] M	12.3[b] M (decr body weight)			
				1.8 F	16.3 F (decr body weight)			

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
54	Rat (Fischer- 344)	103 wk ad lib (F)	Resp	2.29[b] M 2.56 F			NTP 1989b ROX	
			Cardio	2.29[b] M 2.56 F				
			Gastro	2.29[b] M 2.56 F				
			Musc/skel	2.29[b] M 2.56 F				
			Hepatic	2.29[b] M 2.56 F				
			Renal	2.29[b] M 2.56 F				
			Endocr	2.29[b] M 2.56 F				
			Dermal	2.29[b] M 2.56 F				
			Ocular	2.29[b] M 2.56 F				
			Bd Wt	2.29[b] M 2.56 F				
			Other	2.29[b] M 2.56 F				

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
55	Mouse (B6C3F1)	104 wk (F)	Cardio	32.2[b] M 48.5 F			Arnold et al. 2003 MMA	
			Gastro	12[b] M 15 F		32.2[b] M (loose and mucoid feces, metaplasia of the cecum and colon) 48.5 F (loose and mucoid feces, metaplasia of the cecum and colon)		
			Renal	12[b] M 15 F	32.2[b] M 48.5 F (incr incidence of nephrocalcinosis)			
			Bd Wt	12[b] M 15 F	32.2[b] M 48.5 F			

DRAFT FOR PUBLIC COMMENT

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
56	Mouse (Fischer- 344)	103 wk ad lib (F)	Resp	9.7			NTP 1989b ROX	
			Cardio	9.7				
			Gastro	9.7				
			Musc/skel	9.7				
			Hepatic	9.7				
			Renal	9.7				
			Endocr	9.7				
			Dermal	9.7				
			Ocular	9.7				
			Bd Wt	9.7 M	4.8 F (6-11% decr. bd wt.)			
Neurological								
57	Rat (Fischer- 344)	104 wk (F)		1.4 M[b] 1.8 F	12.3 M[b] (decr absolute brain weight) 16.3 F (decr absolute brain weight)		Arnold et al. 2003 MMA	
Cancer								
58	Rat (Fischer- 344)	104 wk (W)				0.14 M (CEL: urinary bladder tumors)	Wei et al. 1999 DMA	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
59	Mouse knockout	Continuous 18 mo (W)				6.4 M (CEL)	Salim et al. 2003 DMA	

aThe number corresponds to entries in Figure 3-4.

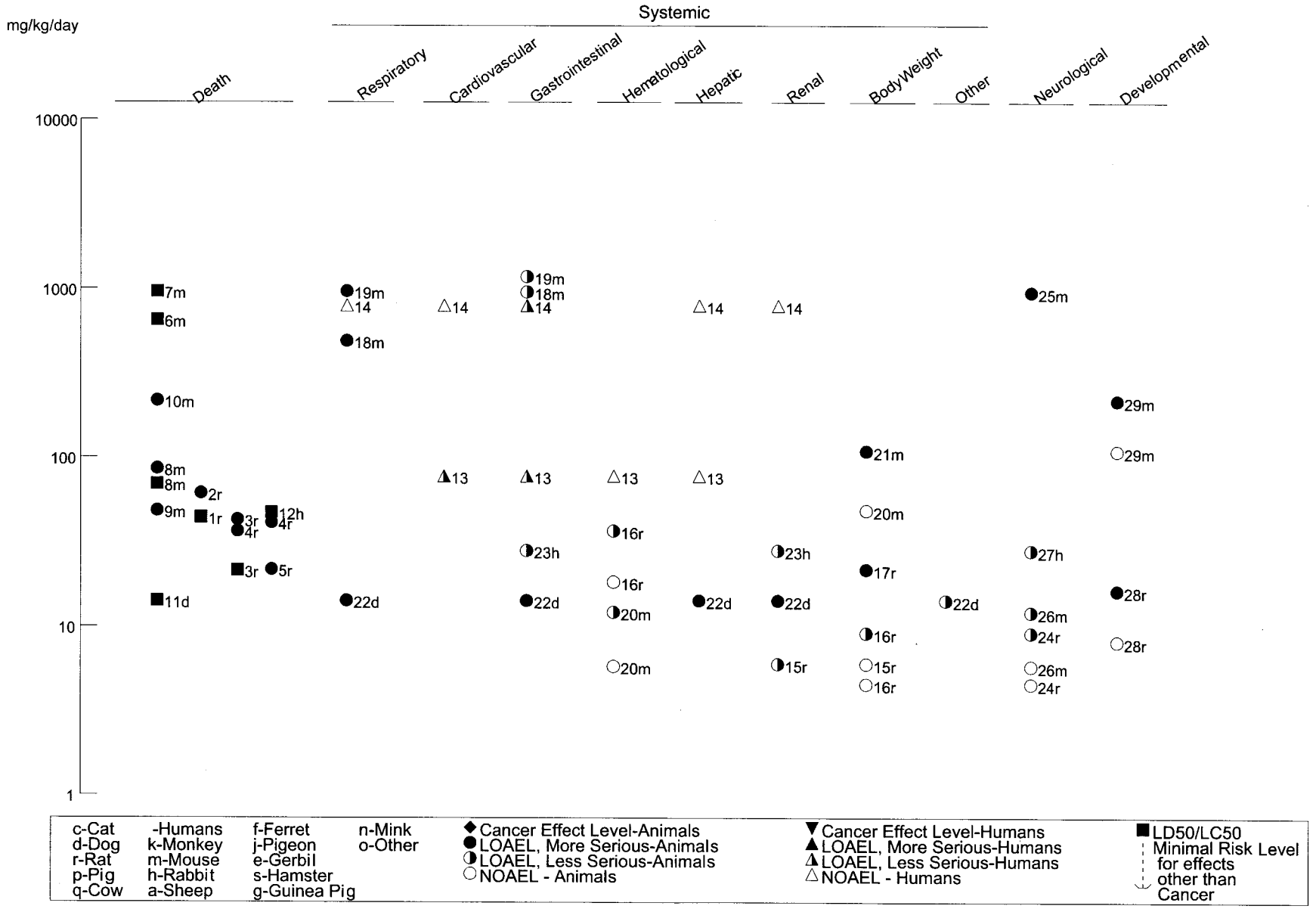
b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-4. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

ad lib = ad libitum; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); decr = decreased; DMA = dimethyl arsenic acid or cacodylic acid; Endocr = endocrine; (F) = feed; F = female; Gastro = gastrointestinal; (GO) = gavage in oil; (GW) = gavage in water; Gd = gestation day; Hemato = hematological; IN = ingestion; incr = increased; LD50 = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; MMA = monomethylarsonic acid; mo = month(s); MSMA = monosodium methane arsonate; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; Resp = respiratory; ROX= roxarsone; wk = week(s); x = time(s)

DRAFT FOR PUBLIC COMMENT

Figure 3-4 Levels of Significant Exposure to Organic Arsenic - Oral

Acute (≤14 days)

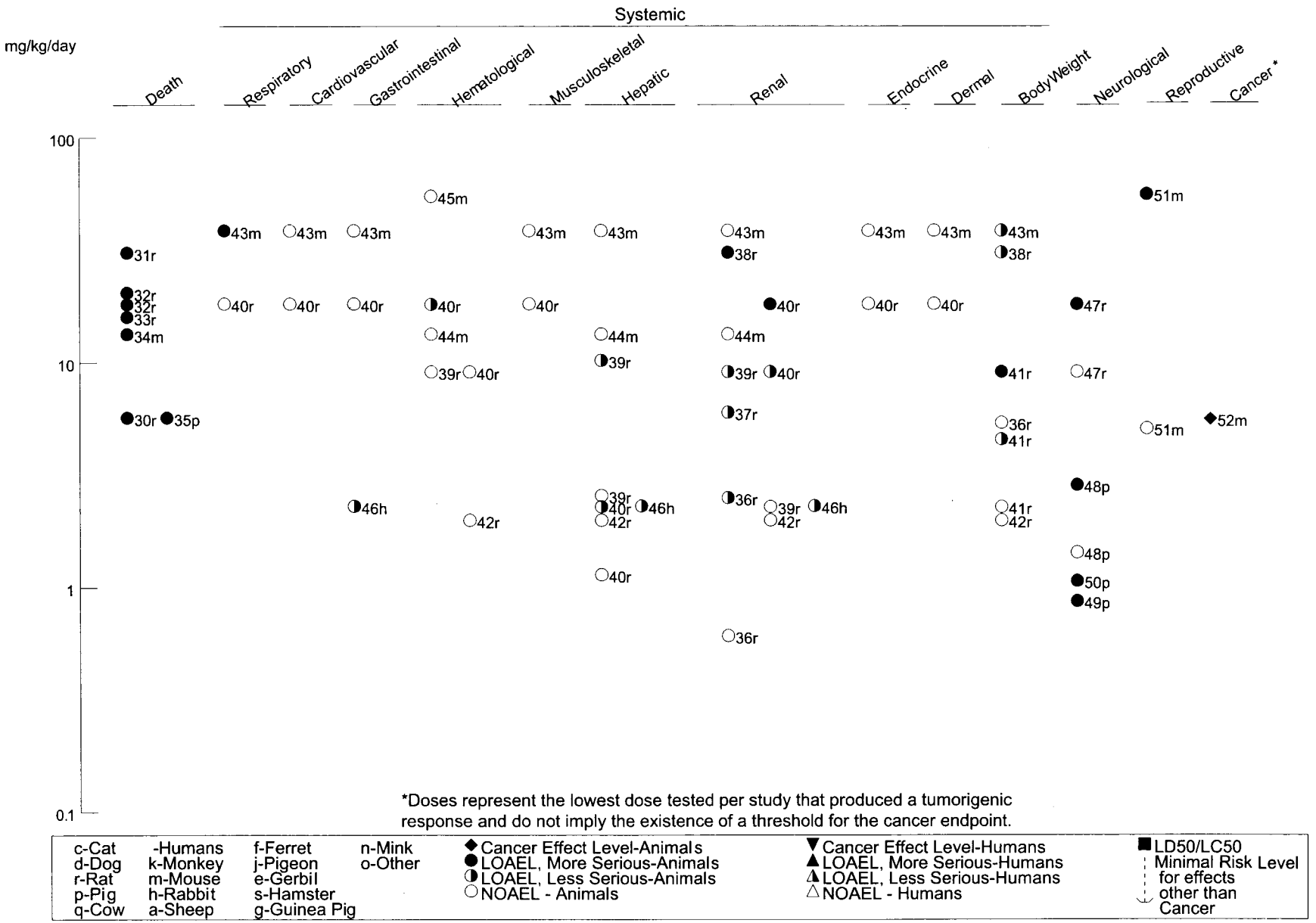


DRAFT FOR PUBLIC COMMENT

DRAFT FOR PUBLIC COMMENT

Figure 3-4 Levels of Significant Exposure to Organic Arsenic - Oral (*Continued*)

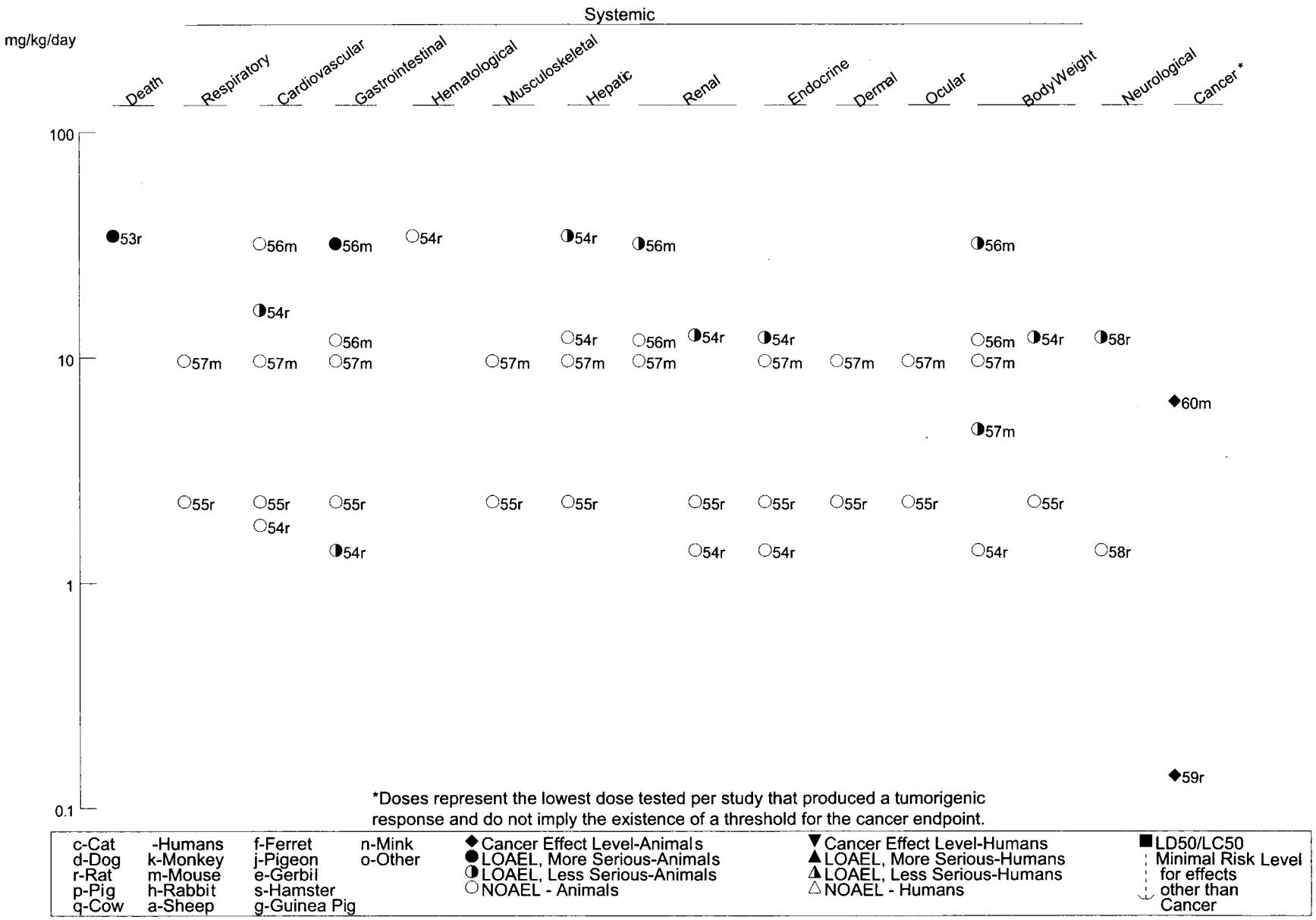
Intermediate (15-364 days)



DRAFT FOR PUBLIC COMMENT

Figure 3-4 Levels of Significant Exposure to Organic Arsenic - Oral (*Continued*)

Chronic (≥365 days)



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

c-Cat	-Humans	f-Ferret	n-Mink
d-Dog	k-Monkey	j-Pigeon	o-Other
r-Rat	m-Mouse	e-Gerbil	
p-Pig	h-Rabbit	s-Hamster	
q-Cow	a-Sheep	g-Guinea Pig	

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◮ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

about 130 mg (also about 2 mg/kg). A similar estimate of 70–180 mg (about 1–3 mg/kg) was provided by Vallee et al. (1960). Death due to chronic arsenic exposure has been reported at lower concentrations. Five children between the ages of 2 and 7 years died from late sequelae of chronic arsenic poisoning after drinking contaminated water throughout their lives at estimated average doses of 0.05–0.1 mg As/kg/day (Zaldívar and Guillier 1977). A 22-year-old man with chronic arsenical dermatosis died from arsenic-related effects after lifetime exposure to an estimated average dose of 0.014 mg As/kg/day in the drinking water (Zaldívar et al. 1981). Systematic studies of lethality from chronic exposure attributable to increased risk of cardiovascular disease or cancer are discussed below in Sections 3.2.2.2 and 3.2.2.7, respectively.

Lethality studies in animals are consistent with the limited data in humans. Available LD_{50} values for arsenate and arsenite in rats and mice range from 15 to 175 mg As/kg (Dieke and Richter 1946; Gaines 1960; Harrisson et al. 1958; Kaise et al. 1985). The variability can be attributed to differences based on species, strain, specific route of exposure (feed vs. gavage), specific compound tested, and testing laboratory. Most deaths occurred within 1 day of exposure, but details regarding cause of death were not generally reported. Seven of 25 pregnant rats given a single gavage dose of 23 mg As/kg as arsenic trioxide on day 9 of gestation died soon after dosing, while no deaths occurred at doses of 4–15 mg As/kg (Stump et al. 1999). Data on lethality from repeated exposure studies in animals are relatively sparse. Seven of 20 pregnant rabbits died from repeated gavage doses of 1.5 mg As/kg/day as arsenic acid during gestation, while none died at 0.1–0.4 mg As/kg/day (Nemec et al. 1998). Chronic studies observed treatment-related mortality in monkeys exposed to 3 mg As/kg/day as arsenate (Heywood and Sortwell 1979), dogs exposed to 2.4 mg As/kg/day as arsenite or arsenate (Byron et al. 1967), mice exposed to 1 mg As/kg/day as arsenite (Schroeder and Balassa 1967), and rats exposed to 30 mg As/kg/day as lead arsenate (Kroes et al. 1974).

Reliable LOAEL and LD_{50} values for lethality from oral exposure to inorganic arsenicals in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

Organic Arsenicals. No studies were located regarding death in humans after oral exposure to organic arsenicals, but the acute lethality of MMA, DMA, and roxarsone have been investigated in several animal studies. As shown in Table 3-4 and Figure 3-4, most acute lethal values range from about 15 to 70 mg As/kg (Jaghabir et al. 1988; Kerr et al. 1963; NTP 1989b; Rogers et al. 1981), although one study (Kaise et al. 1989) reported somewhat higher values (650–970 mg As/kg) for MMA and DMA in mice. The cause of death was not investigated in any of these studies. Intermediate-duration exposure to roxarsone

caused death in pigs and rats at exposure levels of 5.7–21.5 mg As/kg/day (Edmonds and Baker 1986; Kerr et al. 1963; NTP 1989b). No increase in mortality was seen after chronic exposure of rats (2.3–2.6 mg/kg/day) or mice (9.7 mg/kg/day) to roxarsone (NTP 1989b).

3.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects from oral exposure in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3. Similar data for oral exposure to organic arsenicals are shown in Table 3-4 and plotted in Figure 3-4.

Respiratory Effects.

Inorganic Arsenicals. Serious respiratory effects, including respiratory distress, hemorrhagic bronchitis, and pulmonary edema, have been reported in some cases of acute oral arsenic poisoning at doses of 8 mg As/kg and above (e.g., Civantos et al. 1995; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Moore et al. 1994; Quatrehomme et al. 1992). These effects may be secondary to injury to the pulmonary vasculature (see Cardiovascular Effects, below). In addition, bronchitis and sequelae (bronchiectasis, bronchopneumonia) have been observed in patients and at autopsy in some chronic poisoning cases (Milton and Rahman 2002; Rosenberg 1974; Tsai et al. 1999; Zaldívar 1974; Zaldívar and Guillier 1977). Bronchopneumonia secondary to arsenic-induced bronchitis was considered to be the cause of death in one young child who died after several years of exposure to an average dose of 0.08 mg As/kg/day (Zaldívar and Guillier 1977). Signs of obstructive or combined obstructive/restrictive lung disease were observed in some patients exposed chronically to 0.001–0.09 mg As/kg/day (Guha Mazumder et al. 1998c). In general, however, respiratory effects have not been widely associated with repeated oral ingestion of low arsenic doses. Nevertheless, a few studies have reported minor respiratory symptoms, such as cough, sputum, rhinorrhea, and sore throat, in people with repeated oral exposure to 0.03–0.05 mg As/kg/day (Ahmad et al. 1997; Mizuta et al. 1956).

There are few data regarding respiratory effects in animals following acute oral exposure to inorganic arsenic. An infant Rhesus monkey that died after 7 days of oral exposure to a complex arsenate salt at a dose of 3 mg As/kg/day exhibited bronchopneumonia with extensive pulmonary hemorrhage, edema, and necrosis (Heywood and Sortwell 1979). Two other monkeys in this treatment group survived a 1-year exposure period and had no gross or microscopic pulmonary lesions at sacrifice. Increased relative lung

weights were seen in rats exposed to 6.66 mg As/kg/day as sodium arsenite 5 days/week for 12 weeks (Schulz et al. 2002). Chronic oral studies in dogs and rats treated with arsenate or arsenite failed to find respiratory lesions (Byron et al. 1967; Kroes et al. 1974; Schroeder et al. 1968).

One study utilizing gallium arsenide included limited investigation of respiratory function. Respiration rate was significantly decreased in rats following ingestion of a single dose of gallium arsenide at 1,040 mg As/kg, but was unaffected at a dose of 520 mg As/kg (Flora et al. 1997a). Respiration rate was measured 1, 7, and 15 days after dosing, but the decrease was most noticeable after 15 days.

Organic Arsenicals. No respiratory effects were noted after acute human ingestion of 793 mg/kg arsenic (as monosodium methanearsenate) (Shum et al. 1995). Mice exhibited respiratory arrest after a single oral dose of 489 mg/kg DMA or 963 mg/kg MMA (Kaise et al. 1989), and lung ornithine decarboxylase activity was reduced after ingestion of one or two doses of 720 mg DMA/kg (Ahmad et al. 1999). Localized lung hemorrhage was observed in dogs after a single oral dose of 14.2 mg/kg roxarsone in a capsule (Kerr et al. 1963). No respiratory effects were seen after intermediate or chronic exposure of rats (18–20 or 2–3 mg/kg/day, respectively) or mice (39 or 10 mg/kg/day, respectively) to roxarsone (NTP 1989b).

Cardiovascular Effects.

Inorganic Arsenicals. A number of studies in humans indicate that arsenic ingestion may lead to serious effects on the cardiovascular system. Characteristic effects on the heart from both acute and long-term exposure include altered myocardial depolarization (prolonged QT interval, nonspecific ST segment changes) and cardiac arrhythmias (Cullen et al. 1995; Glazener et al. 1968; Goldsmith and From 1986; Heyman et al. 1956; Little et al. 1990; Mizuta et al. 1956; Moore et al. 1994). Hypertrophy of the ventricular wall was observed at autopsy after acute exposure to 93 mg of arsenic (Quatrehomme et al. 1992). Long-term, low-level exposures may also lead to damage to the vascular system. The most dramatic example of this is "Blackfoot Disease," a condition that is endemic in an area of Taiwan where average drinking water levels of arsenic range from 0.17 to 0.80 ppm (Tseng 1977), corresponding to doses of about 0.014–0.065 mg As/kg/day (Abernathy et al. 1989). The disease is characterized by a progressive loss of circulation in the hands and feet, leading ultimately to necrosis and gangrene (Chen et al. 1988b; Ch'i and Blackwell 1968; Tseng 1977, 1989; Tseng et al. 1968, 1995, 1996). Several researchers have presented evidence that other factors besides arsenic (e.g., other water contaminants,

dietary deficits) may play a role in the etiology of this disease (Ko 1986; Lu et al. 1990; Yu et al. 1984). While this may be true, the clear association between the occurrence of Blackfoot Disease and the intake of elevated arsenic levels indicates that arsenic is at least a contributing factor. Arsenic exposure in Taiwan has also been associated with an increased incidence of cerebrovascular and microvascular diseases (Chiou et al. 1997; Wang et al. 2003) and ischemic heart disease (Chang et al. 2004; Chen et al. 1996; Hsueh et al. 1998b; Tsai et al. 1999; Tseng et al. 2003). Moreover, effects of arsenic on the vascular system have also been reported in a number of other populations. For example, increased arsenic exposure has been associated with an increase in hypertension in Bangladesh (Rahman et al. 1999a). Studies in Chile indicate that ingestion of 0.6–0.8 ppm arsenic in drinking water (corresponding to doses of 0.02–0.06 mg As/kg/day, depending on age) increases the incidence of Raynaud's disease and of cyanosis of fingers and toes (Borgono and Greiber 1972; Zaldívar 1974, 1977; Zaldívar and Guillier 1977). Autopsy of five children from this region who died of apparent arsenic toxicity showed a marked thickening of small and medium sized arteries in tissues throughout the body, especially the heart (Rosenberg 1974). In addition, cardiac failure, arterial hypotension, myocardial necrosis, and thrombosis have been observed in children who died from chronic arsenic ingestion (Zaldívar 1974), as well as adults chronically exposed to arsenic (Dueñas et al. 1998). Likewise, thickening and vascular occlusion of blood vessels were noted in German vintners exposed to arsenical pesticides in wine and in adults who drank arsenic-contaminated drinking water (Roth 1957; Zaldívar and Guillier 1977). A survey of Wisconsin residents using private wells for their drinking water found that residents exposed for at least 20 years to water concentrations of >10 µg As/L had increased incidences of cardiac bypass surgery, high blood pressure, and circulatory problems as compared with residents exposed to lower arsenic concentrations (Zierold et al. 2004). Similarly, Lewis et al. (1999) reported increased mortality from hypertensive heart disease in both men and women among a cohort exposed to arsenic in their drinking water in Utah, as compared with the general population of Utah.

Similar alterations in vascular reactivity have been noted in rats given repeated oral doses of arsenic trioxide (11 mg As/kg/day) for several weeks (Bekemeier and Hirschelmann 1989), although no histological effects could be detected in the hearts of rats or dogs exposed to up to 30 mg As/kg/day as arsenate or arsenite for 2 years (Byron et al. 1967; Kroes et al. 1974; Schroeder et al. 1968). Acute exposure of rats to gallium arsenide at a dose of 1,040 mg As/kg resulted in an increase in blood pressure and heart rate, while 520 mg As/kg had no effect (Flora et al. 1997a). Guinea pigs exposed to arsenic trioxide for 1 day (0, 7.6, 22.7, or 37.9 mg As/kg) or 8 days (0 or 3.8 mg As/kg/day) showed prolongation of the cardiac QT interval and action potential duration (Chiang et al. 2002).

Organic Arsenicals. No adverse cardiovascular effects were noted after acute human ingestion of 793 mg/kg arsenic (as monosodium methanearsenate) (Shum et al. 1995). However, sinus tachycardia was noted after acute ingestion of 77 mg/kg arsenic (as dimethyl arsenic acid and dimethyl arsenate) (Lee et al. 1995). No cardiovascular effects were seen after intermediate or chronic exposure of rats (18–20 or 2–3 mg/kg/day, respectively) or mice (39 or 10 mg/kg/day, respectively) to roxarsone (NTP 1989b).

Gastrointestinal Effects.

Inorganic Arsenicals. Clinical signs of gastrointestinal irritation, including nausea, vomiting, diarrhea, and abdominal pain, are observed in essentially all cases of short-term high-dose exposures to inorganic arsenic (e.g., Armstrong et al. 1984; Bartolome et al. 1999; Campbell and Alvarez 1989; Chakraborti et al. 2003a; Cullen et al. 1995; Fincher and Koerker 1987; Goebel et al. 1990; Kingston et al. 1993; Levin-Scherz et al. 1987; Lugo et al. 1969; Moore et al. 1994; Muzi et al. 2001; Uede and Furukawa 2003; Vantroyen et al. 2004). Similar signs are also frequently observed in groups or individuals with longer-term, lower-dose exposures (e.g., Borgono and Greiber 1972; Cebrián et al. 1983; Franzblau and Lilis 1989; Guha Mazumder et al. 1988, 1998a; Haupert et al. 1996; Holland 1904; Huang et al. 1985; Mizuta et al. 1956; Nagai et al. 1956b; Silver and Wainman 1952; Wagner et al. 1979; Zaldívar 1974), but effects are usually not detectable at exposure levels below about 0.01 mg As/kg/day (Harrington et al. 1978; Valentine et al. 1985). These symptoms generally decline within a short time after exposure ceases. Gastrointestinal irritation symptoms form the basis (in part) for the provisional acute oral MRL of 0.005 mg/kg/day for inorganic arsenic, as described in footnote b in Table 3-3. More severe symptoms (hematemesis, hemoperitoneum, gastrointestinal hemorrhage, and necrosis) have been reported in some cases with acute exposure to 8 mg As/kg or more (Civantos et al. 1995; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Quatrehomme et al. 1992), and also in some people with long-term ingestion of 0.03–0.05 mg As/kg/day as a medicinal preparation (Lander et al. 1975; Morris et al. 1974).

Clinical signs of gastrointestinal irritation were observed in monkeys and rats given repeated oral doses of arsenic (6 and 11 mg As/kg/day, respectively) for 2 weeks (Bekemeier and Hirschelmann 1989; Heywood and Sortwell 1979). Hemorrhagic gastrointestinal lesions have also been reported in animal studies. A monkey that died after repeated oral treatment with 6 mg As/kg/day for approximately 1 month was found to have acute inflammation and hemorrhage of the small intestine upon necropsy (Heywood and Sortwell 1979). This lesion was not found in other monkeys that died in this study, or in the survivors. Two pregnant mice that died after repeated gavage treatment with 24 mg As/kg/day as arsenic acid had

hemorrhagic lesions in the stomach (Nemec et al. 1998). Gross gastrointestinal lesions (stomach adhesions, eroded luminal epithelium in the stomach) were seen frequently in rats treated by gavage with 8 mg As/kg/day as arsenic trioxide starting before mating and continuing through the end of gestation (Holson et al. 2000). The lesions were not found in rats treated with 4 mg As/kg/day in this study. No histological evidence of gastrointestinal injury was detected in rats exposed to arsenate or arsenite in the feed for 2 years at doses up to 30 mg As/kg/day, but dogs fed a diet containing 2.4 mg As/kg/day as arsenite for 2 years had some bleeding in the gut (Byron et al. 1967; Kroes et al. 1974).

Organic Arsenicals. Vomiting was noted after ingestion of 793 mg/kg arsenic (as monosodium methanearsenate) in a suicide attempt (Shum et al. 1995). Ingestion of 77 mg/kg arsenic (as dimethyl arsenic acid and dimethyl arsenate) induced vomiting, abdominal pain, hyperactive bowel, and diarrhea (Lee et al. 1995).

Male and female rats exposed to 50, 400, or 1300 ppm (reduced to 1,000 ppm during week 53, and to 800 ppm during week 60, due to mortality) of monomethylarsenate (approximate daily doses of 0, 1.4, 12.3, or 34.8 mg As/kg/day for males and 0, 1.8, 16.3, or 47.3 mg As/kg/day for females) in the diet for 104 weeks had diarrhea that increased in frequency and severity with increasing dose (Arnold et al. 2003). Histological lesions, including ulcerations, of the large and small intestines and thickening of the stomach wall occurred sporadically at the mid-dose and primarily at the high-dose, with significant positive trends. Peritonitis also occurred commonly with a significant positive trend. In mice exposed in the diet to 0, 10, 50, 200, or 400 ppm monomethylarsenate for 104 weeks (approximate daily doses of 0, 0.6, 2.9, 12.0, or 32.2 mg As/kg/day for males and 0, 0.7, 3.4, 15.0, or 48.5 mg As/kg/day for females), the large intestine was also the primary target organ, with a significant trend toward lesions (metaplasia) of the cecum, colon, and rectum (Arnold et al. 2003). This study, however, did not report the incidences or statistical significance of these lesions compared with controls for individual treatment groups of rats or mice. Diarrhea and slight congestion of the intestines was observed in mice after a single dose of 954 mg/kg arsenic (as dimethylarsinic acid) or 1,177 mg/kg arsenic as MMA (Kaise et al. 1989). Vomiting and gastrointestinal hemorrhage were observed in dogs after a single capsulized dose of 14 mg arsenic as roxarsone (Kerr et al. 1963), although slightly higher doses administered for 13 weeks to rats and mice had no effect (NTP 1989b). One study in rabbits indicates that the intestinal wall may be irritated and weakened by repeated intake of MMA (Jaghabir et al. 1989), but this one observation is not enough to support a firm conclusion. No gastrointestinal effects were seen after chronic exposure of rats (2–3 mg/kg/day) or mice (10 mg/kg/day) to roxarsone (NTP 1989b).

Hematological Effects.

Inorganic Arsenicals. Anemia and leukopenia are common effects of arsenic poisoning in humans, and have been reported following acute (Armstrong et al. 1984; Goldsmith and From 1986; Mizuta et al. 1956; Muzi et al. 2001; Westhoff et al. 1975), intermediate (Franzblau and Lilis 1989; Heyman et al. 1956; Nagai et al. 1956b; Wagner et al. 1979), and chronic oral exposures (Chakraborti et al. 2003a; Glazener et al. 1968; Guha Mazumder et al. 1988; Kyle and Pease 1965; Tay and Seah 1975) at doses of 0.05 mg As/kg/day or more. These effects may be due to both a direct cytotoxic or hemolytic effect on the blood cells (Armstrong et al. 1984; Fincher and Koerker 1987; Goldsmith and From 1986; Kyle and Pease 1965; Lerman et al. 1980) and a suppression of erythropoiesis (Kyle and Pease 1965; Lerman et al. 1980). However, hematological effects are not observed in all cases of arsenic exposure (Harrington et al. 1978; Huang et al. 1985; Silver and Wainman 1952; Southwick et al. 1981) or even all acute poisoning cases (Cullen et al. 1995; Moore et al. 1994).

In an acute animal study, Tice et al. (1997) found that there was a decrease in polychromatic erythrocytes in the bone marrow of mice treated with 6 mg As/kg/day for 1 or 4 days. There was no effect at 3 mg As/kg/day. Long-term studies found mild anemia in dogs fed arsenite or arsenate for 2 years at 2.4 mg As/kg/day, but no hematological effect in dogs fed 1 mg As/kg/day for 2 years or 1.9 mg As/kg/day for 26 weeks (Byron et al. 1967; Neiger and Osweiler 1989). Chronic rat studies found little or no evidence of anemia at doses up to 30 mg As/kg/day, even with co-exposure to lead (Byron et al. 1967; Kroes et al. 1974). No hematological effects were found in monkeys exposed to arsenic doses of 3–6 mg As/kg/day for 1 year (Heywood and Sortwell 1979).

Rats exposed to arsenate for 6 weeks had decreased activities of several enzymes involved in heme synthesis, but data were not provided on whether this resulted in anemia (Woods and Fowler 1977, 1978). Exposure of rats to ≥5 ppm of arsenic (0.30 mg As/kg/day as sodium arsenite) in the drinking water for 4 weeks resulted in increased platelet aggregation, while 10 or 25 ppm (0.60 or 1.5 mg As/kg/day) and was associated with increased P-selectin-positive cells and decreased occlusion time (Lee et al. 2002), representing a change in platelet function. Similarly, exposure of rats or guinea pigs to 10 or 25 ppm of arsenic as arsenite (approximate doses of 0, 0.92, or 2.3 mg As/kg/day for rats and 0, 0.69, or 1.7 mg As/kg/day for guinea pigs) in the drinking water for 16 weeks (Kannan et al. 2001) resulted in decreases in erythrocyte and leukocyte numbers (rats and guinea pigs), increased blood mean corpuscular volume and corpuscular hemoglobin mass (guinea pigs only), and decreased mean corpuscular hemoglobin

concentration (rats only). Gallium arsenide also disrupts heme synthesis in rats, although the evidence suggests that this effect is due primarily to the gallium moiety (Flora et al. 1997a).

Organic Arsenicals. No adverse hematological effects were noted in a man who ingested 77 mg/kg As (as dimethyl arsenic acid and dimethyl arsenate) (Lee et al. 1995). Several studies in rats and mice have not detected any significant hematological effects from repeated exposure (2–104 weeks) to MMA (Arnold et al. 2003; Prukop and Savage 1986), DMA (Siewicki 1981), or roxarsone (NTP 1989b) at doses of 5–55 mg As/kg/day. These data suggest that oral exposure to organic arsenicals is unlikely to cause hematological effects, but this is not certain.

Musculoskeletal Effects.

Inorganic Arsenicals. No studies were located regarding musculoskeletal effects in humans or animals after oral exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located regarding musculoskeletal effects in humans after oral exposure to organic arsenicals. No musculoskeletal effects were seen after intermediate or chronic exposure of rats (18–20 or 2–3 mg/kg/day, respectively) or mice (39 or 10 mg/kg/day, respectively) to roxarsone (NTP 1989b).

Hepatic Effects.

Inorganic Arsenicals. A number of studies in humans exposed to inorganic arsenic by the oral route have noted signs or symptoms of hepatic injury. Clinical examination often reveals that the liver is swollen and tender (Chakraborty and Saha 1987; Franklin et al. 1950; Guha Mazumder et al. 1988, 1998a; Liu et al. 2002a; Mizuta et al. 1956; Silver and Wainman 1952; Wade and Frazer 1953; Zaldívar 1974), and analysis of blood sometimes shows elevated levels of hepatic enzymes (Armstrong et al. 1984; Franzblau and Lilis 1989; Hernandez-Zavala et al. 1998). These effects are most often observed after repeated exposure to doses of 0.01–0.1 mg As/kg/day (Chakraborty and Saha 1987; Franklin et al. 1950; Franzblau and Lilis 1989; Guha Mazumder et al. 1988; Mizuta et al.1956; Silver and Wainman 1952; Wade and Frazer 1953), although doses as low as 0.006 mg As/kg/day have been reported to have an effect following chronic exposure (Hernandez-Zavala et al. 1998). Hepatic effects have also been reported in acute bolus poisoning cases at doses of 2 mg As/kg/day or more (Hantson et al. 1996; Kamijo

et al. 1998; Levin-Scherz et al. 1987; Quatrehomme et al. 1992; Vantroyen et al. 2004), although acute exposure to 19 mg As/kg did not cause hepatic effects in an infant (Cullen et al. 1995). Histological examination of the livers of persons chronically exposed to similar doses has revealed a consistent finding of portal tract fibrosis (Guha Mazumder et al. 1988; Morris et al. 1974; Piontek et al. 1989; Szuler et al. 1979), leading in some cases to portal hypertension and bleeding from esophageal varices (Szuler et al. 1979); cirrhosis has also been reported at an increased frequency in arsenic-exposed individuals (Tsai et al. 1999). Several researchers consider that these hepatic effects are secondary to damage to the hepatic blood vessels (Morris et al. 1974; Rosenberg 1974), but this is not directly established.

Acute exposure of monkeys to 6 mg As/kg/day resulted in vacuolization of the hepatocytes (Heywood and Sortwell 1979). Studies in dogs or mice have not detected clinically significant hepatic injury following exposure to either arsenite or arsenate (Byron et al. 1967; Fowler and Woods 1979; Kerkvliet et al. 1980; Neiger and Osweiler 1989; Schroeder and Balassa 1967), although enlargement of the common bile duct was noted in rats fed either arsenate or arsenite in the diet for 2 years (Byron et al. 1967; Kroes et al. 1974) and lipid vacuolation and fibrosis were seen in the livers of rats exposed to 12 mg As/kg/day as arsenate in the drinking water for 6 weeks (Fowler et al. 1977). Similarly, fatty changes and inflammatory cell infiltration were seen in the livers of both normal and metallothionein-null mice exposed to 5.6 mg arsenic/kg/day in the drinking water for 48 weeks (Liu et al. 2000a). Increases in liver zinc and copper concentrations were noted in rats receiving a single oral dose of 10 mg As/kg as sodium arsenite (Flora and Tripathi 1998) and hepatic levels of malondialdehyde were increased and glutathione levels were decreased in livers of rats receiving 200 mg As/kg as GaAs (Flora et al. 1998). Elevated levels of serum aspartate aminotransferase (AST) were observed in rats administered a single oral dose of 100 mg As/kg as GaAs (Flora et al. 1998). Exposure of guinea pigs to 0.69 or 1.7 mg As/kg/day in the drinking water for 16 weeks, but not in rats exposed to 0.92 or 2.3 mg As/kg/day, resulted in increases in delta-aminolevulinic acid synthetase (ALAS) levels (Kannan et al. 2001). Exposure of BALB/C mice to 0.7 mg arsenic/kg/day in the drinking water for 15 months resulted in increased liver weights, changes in liver enzymes (glutathione S-transferase, glutathione reductase, catalase, glucose-6-phosphate dehydrogenase, glutathione peroxidase), fatty liver, and fibrosis (Santra et al. 2000).

Organic Arsenicals. No adverse hepatic effects were noted after ingestion of 793 mg As/kg (as monosodium methanearsenate) or 77 mg As/kg (as dimethyl arsenic acid and dimethyl arsenate) in a suicide attempt (Lee et al. 1995; Shum et al. 1995). No other studies of the hepatic effects of organic arsenicals in humans were located.

Generalized icterus was reported in dogs after acute exposure to roxarsone (Kerr et al. 1963). Some small fluctuations in liver weight have been noted in rats and mice after intermediate oral exposure to roxarsone, but the toxicological significance of this is not clear and is not observed after chronic exposure of rats and mice to lower doses (NTP 1989b). Histological examination of liver from rabbits given repeated oral doses of MMA showed diffuse inflammation and hepatocellular degeneration (Jaghabir et al. 1989), but the lesions were not severe. Male rats exposed to a time-weighted average (TWA) dose of 34.8 mg As/kg/day as MMA for 104 weeks showed a decrease in absolute liver weight, while females exposed to 47.3 mg As/kg/day as MMA showed histiocytic proliferation of the liver (Arnold et al. 2003). Shen et al. (2003a) reported increases in hepatic adenomas and GST-P-positive foci in the livers of rats exposed to average concentrations of 2.1 or 8.4 mg MMA(V)/kg/day in the diet for 104 weeks. No effects were observed in rats exposed to DMA (Siewicki 1981), but mice exposed to one or two oral doses of 720 mg DMA/kg had decreased liver glutathione and cytochrome P-450 content and serum ornithine decarboxylase activity (Ahmad et al. 1999). These data suggest that organic arsenicals may cause mild injury to the liver, but the data are too limited to draw firm conclusions.

Renal Effects.

Inorganic Arsenicals. Most case studies of acute and chronic arsenic toxicity do not report clinical signs of significant renal injury, even when other systems are severely impaired (e.g., Cullen et al. 1995; Franzblau and Lilis 1989; Jenkins 1966; Kersjes et al. 1987; Mizuta et al. 1956; Silver and Wainman 1952). In some cases, elevated serum levels of creatinine or bilirubin have been noted (Armstrong et al. 1984; Levin-Scherz et al. 1987; Moore et al. 1994), and mild proteinuria may occur (Armstrong et al. 1984; Glazener et al. 1968; Tay and Seah 1975). Acute renal failure in some bolus poisoning episodes (e.g., Fincher and Koerker 1987; Goebel et al. 1990; Levin-Scherz et al. 1987; Lugo et al. 1969; Moore et al. 1994) is probably a result of fluid imbalances or vascular injury (Rosenberg 1974; Zaldívar 1974). Glomerular congestion has been observed after an acute exposure to high doses (Quatrehomme et al. 1992).

Studies in animals also indicate that the kidney is not a major target organ for inorganic arsenic (Byron et al. 1967; Schroeder and Balassa 1967; Woods and Southern 1989), although some effects have been reported at high exposure levels. Mild histological changes in the renal tubules of monkeys exposed to arsenate for 2 weeks were noted by Heywood and Sortwell (1979), and some mild alterations in renal mitochondria in rats exposed to arsenate for 6 weeks were noted by Brown et al. (1976). Mild proteinuria

(Flora et al. 1998) and an increase in kidney zinc concentration (Flora and Tripathi 1998) have also been noted in rats exposed orally to a single dose of 100 mg As/kg as GaAs or 10 mg As/kg as sodium arsenite, respectively. These data suggest that the kidney is relatively less sensitive to arsenic than most other organ systems, and renal effects are unlikely to be of concern except secondary to fluid imbalances or cardiovascular injury.

Organic Arsenicals. No adverse renal effects were noted after ingestion of 793 mg/kg arsenic (as monosodium methanearsenate) in a suicide attempt (Shum et al. 1995). Exposure of male rats to ≥12.3 mg As/kg/day as MMA in the diet for 104 weeks resulted in significant increases in absolute and relative kidney weights (Arnold et al. 2003). A trend was seen toward an increased incidence of papillary necrosis, basophilic tubules and hydronephrosis, and pyelonephritis, but statistical significance and incidence data were not reported for these end points, and the authors suggested that they may have been secondary to inflammation of the ureter resulting from ulceration of the intestinal tract and the resulting peritonitis. Significant positive trends for progressive glomerulonephropathy and nephrocalcinosis were reported in male and female mice, but again, statistical significance and incidence data were not reported (Arnold et al. 2003). Exposure of rats to 8.4 mg As/kg/day, but not 2.1 mg/kg/day, as MMA(V) for 104 weeks resulted in hyperplasia of the urinary bladder (Shen et al. 2003a). Oliguria was noted after acute exposure and interstitial nephritis and tubular nephrosis have been noted in rabbits given repeated oral doses of MMA (Jaghabir et al. 1989). Hematuria and congested kidneys have been observed in dogs after acute exposure, and tubular degeneration and necrosis have been noted in rats (but not mice) given repeated oral doses of roxarsone (up to 20 mg/kg/day As) (Abdo et al. 1989; Kerr et al. 1963; NTP 1989b). However, no renal injury was observed in rats and mice chronically exposed to roxarsone at lower doses (2–10 mg/kg/day As) (NTP 1989b). Exposure of female rats to 40 or 100 ppm (2.5 or 6.1 mg As/kg/day) of DMA in the diet for 10 weeks resulted in increases in the occurrence of hyperplasia and necrosis of the bladder epithelium and renal calcification (Arnold et al. 1999), while exposure of male rats to 100 ppm (~5.4–6.0 mg As/kg/day) of DMA had similar effects (Arnold et al. 1999; Cohen et al. 2001). These data suggest that exposure to organic arsenicals can lead to significant renal injury.

Endocrine Effects.

Inorganic Arsenicals. Very little has been written about the effects of oral exposure to arsenic on endocrine glands. In a report of the autopsies of five children who died in Chile after chronic exposure to arsenic in the drinking water, arterial thickening in the pancreas was noted (Rosenberg 1974). An

association has been demonstrated between exposure to arsenic in drinking water and an increased incidence of diabetes mellitus (Rahman et al. 1998; Tsai et al. 1999; Tseng et al. 2000; Wang et al. 2003), although dose-response relationships are not available.

Exposure of rats to 2.3 mg As/kg/day as arsenic trioxide for 30 days resulted in reductions in the number of islet cells in the pancreas, as well as significant reductions in pancreatic superoxide dismutase (SOD) and catalase enzyme levels and increases in the production of nitric oxide and malondialdehyde (Mukherjee et al. 2004).

Organic Arsenicals. No studies of effects of organic arsenic compounds on human endocrine glands were found. No adverse effects were seen in the adrenal or pituitary glands, thyroid, or pancreas after intermediate or chronic exposure of rats (18–20 or 2–3 mg/kg/day, respectively) or mice (39 or 10 mg/kg/day, respectively) to roxarsone (NTP 1989b). Chronic (104 weeks) exposure of female rats, but not male rats, to 16.3 mg As/kg/day as MMA resulted in significantly decreased thyroid weight (Arnold et al. 2003).

Dermal Effects.

Inorganic Arsenicals. One of the most common and characteristic effects of arsenic ingestion is a pattern of skin changes that include generalized hyperkeratosis and formation of hyperkeratotic warts or corns on the palms and soles, along with areas of hyperpigmentation interspersed with small areas of hypopigmentation on the face, neck, and back. These and other dermal effects have been noted in a large majority of human studies involving repeated oral exposure (e.g., Ahmad et al. 1997, 1999; Ahsan et al. 2000; Bickley and Papa 1989; Borgono and Greiber 1972; Borgono et al. 1980; Cebrián et al. 1983; Chakraborti et al. 2003a, 2003b; Chakraborty and Saha 1987; Foy et al. 1992; Franklin et al. 1950; Franzblau and Lilis 1989; Guha Mazumder et al. 1988, 1998a, 1998b, 1998c; Guo et al. 2001a; Haupert et al. 1996; Huang et al. 1985; Lander et al. 1975; Liu et al. 2002a; Lüchtrath 1983; Milton et al. 2004; Mizuta et al. 1956; Morris et al. 1974; Nagai et al. 1956b; Piontek et al. 1989; Rosenberg 1974; Saha and Poddar 1986; Silver and Wainman 1952; Szuler et al. 1979; Tay and Seah 1975; Tseng et al. 1968; Wade and Frazer 1953; Wagner et al. 1979; Wong et al. 1998a, 1998b; Zaldívar 1974, 1977). In cases of low-level chronic exposure (usually from water), these skin lesions appear to be the most sensitive indication of effect, so this end point is considered to be the most appropriate basis for establishing a chronic oral MRL. This is supported by the finding that other effects (hepatic injury, vascular disease, neurological

effects) also appear to have similar thresholds. As shown in Table 3-3 and Figure 3-3, numerous studies in humans have reported dermal effects at chronic dose levels ranging from about 0.002 to 0.1 mg As/kg/day (Bickley and Papa 1989; Borgono and Greiber 1972; Borgono et al. 1980; Cebrián et al. 1983; Chakraborty and Saha 1987; Foy et al. 1992; Franklin et al. 1950; Guha Mazumder et al. 1988; Haque et al. 2003; Huang et al. 1985; Lüchtrath 1983; Piontek et al. 1989; Silver and Wainman 1952; Tseng et al. 1968; Zaldívar 1974, 1977). Several epidemiological studies of moderately sized populations (20–200 people) exposed to arsenic through drinking water have detected no dermal or other effects at average chronic doses of 0.0004–0.01 mg As/kg/day (Cebrián et al. 1983; Guha Mazumder et al. 1988; Harrington et al. 1978; Southwick et al. 1981; Valentine et al. 1985), and one very large study (based on 17,000 people) detected no effects in any person at an average total daily intake (from water plus food) of 0.0008 mg As/kg/day (Tseng et al. 1968). This value has been used to calculate a chronic oral MRL for inorganic arsenic of 0.0003 mg/kg/day, as described in footnote c in Table 3-3.

Another prominent dermal effect associated with chronic ingestion of inorganic arsenic is skin cancer. As discussed in greater detail in Section 3.2.2.7 (below), some of these skin cancers may evolve from the hyperkeratotic corns or warts, while the areas of altered pigmentation are not considered to be precancerous (EPA 1988d).

Dermal lesions similar to those observed in humans have not been noted in oral exposure studies in monkeys (Heywood and Sortwell 1979), dogs (Byron et al. 1967), or rodents (Schroeder et al. 1968). However, a hyperplastic response to oral arsenic exposure was recently reported in arsenic-exposed mice (Rossman et al. 2004).

Organic Arsenicals. No studies were located regarding dermal effects in humans or animals after oral exposure to organic arsenicals.

Ocular Effects.

Inorganic Arsenicals. Periorbital swelling was reported in people drinking contaminated well water at an approximate dose of 0.2 mg As/kg for 1 week (Armstrong et al. 1984). Facial edema, generally involving the eyelids, was a prominent feature of arsenic poisoning among 220 cases associated with an episode of arsenic contamination of soy sauce in Japan (Mizuta et al. 1956). Exposure was to an estimated dose of 0.05 mg/kg/day and lasted for up to 2–3 weeks. The edema developed soon after the initial exposure and

then subsided. This effect forms the basis (in part) for the provisional acute oral MRL of 0.005 mg/kg/day for inorganic arsenic, as described in footnote b in Table 3-3. Nemec et al. (1998) noted the appearance of dried red material around the eyes of mice receiving daily oral doses of 24 mg As/kg as arsenic acid for 10 days during gestation.

Organic Arsenicals. No studies were located regarding ocular effects in humans or animals after oral exposure to organic arsenicals.

Body Weight Effects.

Inorganic Arsenicals. A 41-year old woman exposed to arsenic in the drinking water for 4 months at an approximate dose of 0.06 mg As/kg/day reported losing 40 pounds (18 kg) of body weight before seeking treatment (Wagner et al. 1979). Weight loss was also among the effects observed in a series of 475 chronic arsenism patients hospitalized in Antofagasto, Chile after receiving approximate doses of 0.02 mg As/kg/day in the drinking water for an unspecified number of years (Zaldívar 1974).

Reductions in body weight gain are commonly seen in animal studies of ingested arsenic. In pregnant rats, body weight gain was reduced by gavage treatment with 23 mg As/kg/day as arsenic trioxide on day 9 of gestation (NOAEL=15 mg As/kg/day, Stump et al. 1999), and by repeated gavage treatment with 8 mg As/kg/day as arsenic trioxide from 2 weeks prior to mating through gestation (NOAEL=4 mg As/kg/day, Holson et al. 2000). Exposure of rats by gavage to 26.6 mg As/kg/day as sodium arsenite, but not 13.3 mg As/kg/day or lower, 5 days/week for 4 weeks resulted in a significant decrease in body weight (Schulz et al. 2002). In 6-week rat studies, body weight gain was decreased at 11–12 mg As/kg/day, but not at 6–9 mg As/kg/day (Brown et al. 1976; Fowler et al. 1977). In chronic rat studies of arsenate and arsenite, body growth decreases were found at doses as low as 2 mg As/kg/day in feeding studies (Byron et al. 1967; Kroes et al. 1974), while rats exposed to lower levels of sodium arsenite in the drinking water (0.6 mg As/kg/day) throughout their lifetimes grew normally (Schroeder et al. 1968). Rats given a single oral dose of 100 mg As/kg as GaAs exhibited a 15% reduction in body weight compared to controls 7 days after exposure (Flora et al. 1998). Body weight gain was decreased in mice at 24 mg As/kg/day in a gestation exposure study (Nemec et al. 1998), 10 mg As/kg/day in a 6-week study (Fowler and Woods 1979), and 1 mg As/kg/day in a 2-year study (Schroeder and Balassa 1967). Growth was unaffected in mice that received 12 mg As/kg/day in the gestation exposure study (Nemec et al. 1998), 5 mg As/kg/day in the 6-week study (Fowler and Woods 1979), or 0.7–0.8 mg As/kg/day in 1–3 month

arsenate drinking water studies (Healy et al. 1998). Dogs chronically treated with 2.4 mg As/kg/day as sodium arsenite lost 44–61% of their starting body weight and died, while lower doses had no effect on growth (Byron et al. 1967). Weight depression was also reported in dogs chronically treated with 2.4 mg As/kg/day as sodium arsenate (Byron et al. 1967). Feed consumption and body weight gain were significantly reduced in a dose-related manner in dogs fed 1.5 or 1.9 mg As/kg/day as sodium arsenite in the diet (Neiger and Osweiler 1989). Dogs in the high-dose group lost 25% of their body weight over the 17-week study period. Pair-fed controls lost weight at the same rate as high-dose dogs, showing that the effect on body weight was due to reduced feed consumption, rather than a direct effect of arsenic.

Organic Arsenicals. No studies were located regarding body weight effects in humans after oral exposure to organic arsenicals. In animal studies of organic arsenicals, decreases in body weight gain were observed in rats and mice after acute, intermediate, and chronic duration exposure to DMA and roxarsone (Murai et al. 1993; NTP 1989b; Rogers et al. 1981; Siewicki 1981). The lowest dose to produce a decrease in growth was approximately 4 mg As/kg/day (NTP 1989b).

3.2.2.3 Immunological and Lymphoreticular Effects

Inorganic Arsenicals. No studies were located regarding immunological and lymphoreticular effects in humans after oral exposure to inorganic arsenicals. No evidence of immunosuppression was detected in mice exposed to arsenate at levels up to 100 ppm (20 mg As/kg/day) in drinking water (Kerkvliet et al. 1980). This NOAEL is shown in Table 3-3 and Figure 3-3. Gallium arsenide at doses of 52–260 mg As/kg/day produced significant, dose-related decreases in relative spleen weight, spleen cellularity, humoral immune response (antibody forming cell response to sheep RBC), and delayed type hypersensitivity in rats (Flora et al. 1998). However, it is not clear to what extent these effects are due to the arsenic moiety.

Organic Arsenicals. No studies were located regarding immunological and lymphoreticular effects in humans or animals after oral exposure to organic arsenicals.

3.2.2.4 Neurological Effects

Inorganic Arsenicals. A large number of epidemiological studies and case reports indicate that ingestion of inorganic arsenic can cause injury to the nervous system. Acute, high-dose exposures (2 mg As/kg/day

or above) often lead to encephalopathy, with signs and symptoms such as headache, lethargy, mental confusion, hallucination, seizures, and coma (Armstrong et al. 1984; Bartolome et al. 1999; Civantos et al. 1995; Cullen et al. 1995; Danan et al. 1984; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Quatrehomme et al. 1992; Uede and Furukawa 2003; Vantroyen et al. 2004). Repeated exposures to lower levels (0.03–0.1 mg As/kg/day) are typically characterized by a symmetrical peripheral neuropathy (Chakraborti et al. 2003a, 2003b; Foy et al. 1992; Franzblau and Lilis 1989; Guha Mazumder et al. 1988; Hindmarsh et al. 1977; Huang et al. 1985; Lewis et al. 1999; Mizuta et al. 1956; Muzi et al. 2001; Silver and Wainman 1952; Szuler et al. 1979; Wagner et al. 1979). This neuropathy usually begins as a numbness in the hands and feet, but later may develop into a painful "pins and needles" sensation. Both sensory and motor nerves are affected, and muscle weakness often develops, sometimes leading to wrist-drop or ankle-drop (Chhuttani et al. 1967; Heyman et al. 1956). Diminished sensitivity to stimulation and abnormal patellar reflexes have also been reported (Mizuta et al. 1956). Histological examination of nerves from affected individuals reveals a dying-back axonopathy with demyelination (Goebel et al. 1990; Hindmarsh and McCurdy 1986). Some recovery may occur following cessation of exposure, but this is a slow process and recovery is usually incomplete (Fincher and Koerker 1987; LeQuesne and McLeod 1977; Murphy et al. 1981). Peripheral neuropathy is also sometimes seen following acute high-dose exposures, with or without the previously described encephalopathy (Armstrong et al. 1984; Fincher and Koerker 1987; Goebel et al. 1990; Hantson et al. 1996; Kamijo et al. 1998). Neurological effects were not generally found in populations chronically exposed to doses of 0.006 mg As/kg/day or less (Harrington et al. 1978; Hindmarsh et al. 1977; Southwick et al. 1981), although fatigue, headache, dizziness, insomnia, nightmare, and numbness of the extremities were among the symptoms reported at 0.005, but not 0.004 mg As/kg/day in a study of 31,141 inhabitants of 77 villages in Xinjiang, China (Lianfang and Jianzhong 1994), and depression was reported in some Wisconsin residents exposed to 2–10 µg As/L in the drinking water for 20 years or longer (Zierold et al. 2004). Exposure to arsenic may also have detrimental effects on the IQ of exposed children (Calderon et al. 2001, 2004; Tsai et al. 2003; Wasserman et al. 2004) (see Section 3.7 for details).

Neurological effects have also been observed in animal studies. Rodriguez et al. (2001) evaluated neurobehavioral changes in male Sprague-Dawley rats exposed to 0, 5, 10, or 20 mg As/kg/day as sodium arsenite by gavage for 2 or 4 weeks; significant effects were seen in spontaneous locomotor activity and the food pellet manipulation test in the high-dose animals, while no effects were seen in the low- or mid-dose rats. Decreased performance in open field tests were also seen in rats exposed to 26.6 mg As/kg/day, but not to 13.3 mg/kg/day or less, as sodium arsenite for 4 weeks (Schulz et al. 2002); curiously, the behavioral changes were no longer present at 8 and 12 weeks of exposure, which may

suggest an adaptive response. Heywood and Sortwell (1979) reported salivation and uncontrolled head shaking in two monkeys given several doses of 6 mg As/kg/day as arsenate, while no such effects were noted in monkeys given 3 mg As/kg/day for 2 weeks. Nemec et al. (1998) observed ataxia and prostration in pregnant female rabbits treated with 1.5 mg As/kg/day repeatedly during gestation, but not in rabbits treated with 0.4 mg As/kg/day. Some changes in levels of neurotransmitters (dopamine, norepinephrine, and 5-hydroxytryptamine) were seen in rats exposed to 2.3 mg As/kg/day as sodium arsenite and guinea pigs exposed to 1.7 mg As/kg/day as sodium arsenite in the drinking water for 16 weeks (Kannan et al. 2001) or in rats exposed to 0.14 mg As/kg/day as sodium arsenite by gavage for 28 days (Chattopadhyay et al. 2001), but the functional significance of these changes is not clear.

The highest NOAEL values and all reliable LOAEL values for neurological effects from inorganic arsenic in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

Organic Arsenicals. One case report of the ingestion of organic arsenic was located. A 52-year-old Vietnamese woman ingested an unspecified amount of organic arsenic in the form of bird's nest soup, resulting in numbness and tingling of the fingertips, toes, and circumoral region. Discontinuation of exposure resulted in the disappearance of symptoms (Luong and Nguyen 1999). Several studies in pigs indicate that repeated oral doses of roxarsone (0.87–5.8 mg As/kg/day for 1 month) can cause significant neurotoxicity (Edmonds and Baker 1986; Rice et al. 1985). The main signs were muscle tremors, partial paralysis, and seizures. Histological examinations of the spinal cord revealed a time-dependent degeneration of myelin and axons (Kennedy et al. 1986). Such prominent signs of neurological effects were not detected in rats or mice exposed to roxarsone, although evidence of neurological effects (hyperexcitability, ataxia, trembling) was noted in rats at the highest dose (11.4 mg As/kg/day) (NTP 1989b). Increased relative brain weights were seen in male rats exposed to 60.3 mg As/kg/day as MMA and in female rats exposed to ≥16.3 mg As/kg/day as MMA (Arnold et al. 2003); no neurological clinical signs were reported. These data (shown in Table 3-4 and Figure 3-4) suggest that organic arsenicals (at least the phenyl arsenates) are neurotoxic at high doses.

3.2.2.5 Reproductive Effects

Inorganic Arsenicals. Lugo et al. (1969) reported a case of a 17-year-old mother who ingested inorganic arsenic (Cowley's Rat and Mouse Poison) at week 30 of pregnancy. Twenty-four hours after ingestion, she was admitted for treatment of acute renal failure 24 hours after she ingested approximately 30 mL of arsenic trioxide (0.39 mg As/kg). She went into labor and delivered a live female infant weighing

2 pounds, 7 ounces with a 1-minute Apgar score of 4. The infant's clinical condition deteriorated and she died at 11 hours of age.

Reproductive performance was not affected in female rats that received gavage doses of 8 mg As/kg/day (as As_2O_3) from 14 days prior to mating through gestation day 19 (Holson et al. 2000). Reproductive indices that were evaluated included the precoital interval (time to mating), mating index (percentage of rats mated), and fertility index (percentage of matings resulting in pregnancy). In a 3-generation study in mice given sodium arsenite in drinking water at an average dose of 1 mg As/kg/day, there was a significant increase in the incidence of small litters and a trend toward a decreased number of pups per litter in all three generations of the treated group (Schroeder and Mitchner 1971). This finding is consistent with the results of developmental toxicity studies reported in Section 3.2.2.6. Female rats exposed to 0.24 mg As/kg/day (as arsenite) for 28 days showed changes in several reproductive system end points, including decreases in wet weights of the ovary and uterus, inhibition of steroidogenic enzymes, decreased ovarian and uterine peroxidase activites, and decreased estradiol levels relative to controls (Chattopadhyay et al. 2001). NOAEL and LOAEL values from these studies are show in Table 3-3 and Figure 3-3.

Organic Arsenicals. No studies were located regarding reproductive effects in humans after oral exposure to organic arsenicals. Male and female mice dosed with MMA (55 mg As/kg/day) prior to mating and during pregnancy produced fewer litters than normal, an effect that was attributable mainly to decreased fertility of the males (Prukop and Savage 1986). This observation (shown in Figure 3-4 and summarized in Table 3-4) suggests that spermatogenesis or sperm function might be impaired by organic arsenicals, but this was not studied directly. This suggestion is supported by the observation that chronic exposure to MMA in rats resulted in inflammation of the ureter, prostate, testes, epididymis, and seminal vesicles (Arnold et al. 2003), although the study authors suggested that inflammation may have been secondary to intestinal ulceration and peritonitis rather than a direct effect.

3.2.2.6 Developmental Effects

Inorganic Arsenicals. Whether ingestion of inorganic arsenic may cause developmental effects in humans has not been extensively investigated. Lugo et al. (1969) reported a case of a mother who ingested inorganic arsenic (Cowley's Rat and Mouse Poison) at 30 weeks of gestation. Twenty-four hours after ingestion, she went into labor and delivered a live female infant weighing 2 pounds, 7 ounces with a 1-minute Apgar score of 4. The infant's clinical condition deteriorated with frequent episodes of apnea

and bradycardia; subsequent venous blood gas determinations documented hypoxia, hypercapnea, and acidosis. The infant died at 11 hours of age. Autopsy performed 8 hours after death showed organ immaturity, generalized petechial hemorrhages, and hyaline membrane disease. Severe intra-alveolar pulmonary hemorrhage was remarkable. High arsenic levels were found in the infant's liver, kidney, and brain, demonstrating easy passage of inorganic arsenic across the placenta. The authors considered most of the findings in the neonate to be attributable to immaturity, but suggested that arsenic may have played a role in the severe intra-alveolar hemorrhaging that contributed to death.

Chronic exposure of women to arsenic in the drinking water has been associated with excess incidence of miscarriages, stillbirths, preterm births, and infants with low birth weights in Bangladesh, India, and Taiwan (Ahmad et al. 2001; Chakraborti et al. 2003b, 2004; Yang et al. 2003), although dose-response data are not presently available for these effects. Similar associations have been made between late fetal mortality, neonatal mortality, and postneonatal mortality and exposure to high levels of arsenic in the drinking water, based on comparisons between subjects in low- and high-arsenic areas of Chile (Hopenhayn-Rich et al. 2000).

No overall association between arsenic in drinking water and congenital heart defects was detected in a case-control study in Boston (Zierler et al. 1988), although an association with one specific lesion (coarctation of the aorta) was noted (OR=3.4, 95% CI=1.3–8.9). Due to the small study size (a total of 270 cases with any congenital heart disease and 665 controls), this association could be due to random variation. In a similar case-control study, a marginal association (not statistically significant) was noted between detectable levels of arsenic in drinking water and the occurrence of spontaneous abortion (Aschengrau et al. 1989). Marginal positive associations were also noted for mercury, potassium, silica, and water hardness in this study, while a decreased incidence of abortion was associated with sulfate, nitrate, and alkalinity. This pattern of divergent associations for multiple contaminants suggests that at least some of the apparent associations may be random, or may be due to covariation with other risk factors. Thus, neither of these studies provides convincing evidence that ingestion of arsenic, at least at the levels usually encountered in drinking water, causes developmental toxicity in humans.

Studies in animals, however, suggest that ingested inorganic arsenic may produce developmental effects at high doses that also produce overt maternal toxicity. Rats treated with a single gavage dose of 23 mg As/kg as arsenic trioxide on day 9 of gestation had a significant increase in post-implantation loss and a decrease in viable fetuses per litter, while those treated with 15 mg As/kg showed no effects (Stump et al. 1999). Rats treated by daily gavage with 8 mg As/kg/day starting 14 days before mating and continuing

through gestation had significantly reduced fetal body weights and significantly increased incidences of several skeletal variations (unossified sternebrae #5 or #6, slight or moderate sternebrae malalignment, 7th cervical ribs) that the researchers considered to be consequences of developmental growth retardation (Holson et al. 2000). No developmental effects were found at 4 mg As/kg/day in this study. Exposure of rats to 2.93–4.20 mg As/kg/day throughout gestation and for 4 months postnatally resulted in alterations in neurobehavioral parameters in the offspring, including increased spontaneous locomotor activity and number of errors in a delayed alternation task; maternal behavior was not affected (Rodriguez et al. 2002). Studies in mice found increased fetal mortality, decreased fetal body weight, a low incidence of gross malformations (primarily exencephaly), and an increase in skeletal malformations in mice given single gavage doses of 23–48 mg As/kg during gestation (Baxley et al. 1981; Hood et al. 1978), with no effects at 11 mg As/kg. Similarly, in mice treated with 24 mg As/kg/day as arsenic acid on days 6–15 of gestation, there was a significant increase in the number of resorptions per litter (42% vs. 4% in controls) and significant decreases in the number of live pups per litter (6.6 vs. 12.3 in controls) and mean fetal weight (1.0 g vs. 1.3 g in controls), while no developmental effects were found at 12 mg As/kg/day (Nemec et al. 1998). Hamsters treated with a single gavage dose of 14 mg As/kg during gestation also had increased fetal mortality and decreased fetal body weight (Hood and Harrison 1982), with no effect at 11 mg As/kg. However, the most sensitive species was the rabbit, which had increased resorptions and decreased viable fetuses per litter at 1.5 mg As/kg/day and a developmental NOAEL of 0.4 mg As/kg/day, following repeated gavage dosing with arsenic acid during gestation (Nemec et al. 1998). In each of these studies (except Hood et al. 1978, which failed to report maternal effects), overt maternal toxicity, including death in some cases, was found at the same or lower doses as the developmental effects (Baxley et al. 1981; Holson et al. 2000; Hood and Harrison 1982; Nemec et al. 1998; Stump et al. 1999).

It is noteworthy that the effect in the 3-generation reproduction study in mice by Schroeder and Mitchner (1971), decreased pups per litter (all generations), is consistent with the findings of many of these shorter-term studies (Baxley et al. 1981; Hood and Harrison 1982; Hood et al. 1978; Nemec et al. 1998; Stump et al. 1999). The dose in this long-term study was 1 mg As/kg/day; in a 2-year study by these researchers, this dose produced effects such as decreased body weight gain and increased mortality (Schroeder and Balassa 1967).

A series of recent studies has presented evidence that inorganic arsenic may be a transplacental carcinogen in animals. Waalkes et al. (2003a, 2004a, 2004b, 2004c) exposed timed-pregnant AJ mice to 0, 42.5, or 85 ppm of sodium arsenite in the drinking water from gestation day 8 through 18 and observed

the offspring for 90 weeks following birth; the study authors estimated daily doses at 9.55 and 19.3 mg As/kg/day. A dose-related increase was reported in the incidence of hepatocellular carcinomas and adrenal tumors in the male offspring from both treatment levels, while male offspring from high-dose animals showed an increase in total number of tumors. In female offspring, an increase in uterine hyperplasia was seen in the offspring of both treated groups while the offspring of high-dose animals showed increased incidence of lung carcinomas. For both exposed groups, regardless of gender, the offspring showed a significant increase in the number of malignant tumors (Waalkes et al. 2003a).

These studies (shown in Table 3-3 and Figure 3-3) indicate that the fetus may be affected by ingested arsenic, but suggest that the fetus is not more susceptible to arsenic than the mother.

Organic Arsenicals. No studies were located regarding developmental effects in humans after oral exposure to organic arsenicals. However, effects on fetal development (malformed palate, reduced fetal weight, delayed ossification, increased fetal mortality) have been observed in rats and mice given repeated oral doses of DMA during gestation (Rogers et al. 1981). These findings (summarized in Table 3-4 and shown Figure 3-4) suggest that high doses of organic arsenicals may have significant developmental toxicity, but the data are too limited to draw broad conclusions.

3.2.2.7 Cancer

Inorganic Arsenicals. There is convincing evidence from a large number of epidemiological studies and case reports that ingestion of inorganic arsenic increases the risk of developing skin cancer (Alain et al. 1993; Beane Freeman et al. 2004; Bickley and Papa 1989; Cebrián et al. 1983; Chen et al. 2003a; Guo et al. 2001a; Haupert et al. 1996; Hsueh et al. 1995; Lewis et al. 1999; Lüchtrath 1983; Mitra et al. 2004; Morris et al. 1974; Piontek et al. 1989; Sommers and McManus 1953; Tay and Seah 1975; Tsai et al. 1998a, 1999; Tseng 1977; Tseng et al. 1968; Zaldívar 1974; Zaldívar et al. 1981). Lesions commonly observed are multiple squamous cell carcinomas, which appear to develop from some of the hyperkeratotic warts or corns described in Section 3.2.2.2. In addition, multiple basal cell carcinomas may occur, typically arising from cells not associated with hyperkeratinization. In most cases, skin cancer develops only after prolonged exposure, but one study has reported skin cancer in people exposed for less than 1 year (Reymann et al. 1978). Although both types of skin cancer can be removed surgically, they may develop into painful lesions that may be fatal if left untreated (Shannon and Strayer 1989).

A number of studies that identify CELs in exposed humans are summarized in Table 3-3 and shown in Figure 3-3. The EPA reviewed the studies that provided dose-response data on the risk of skin cancer (EPA 1988d) and concluded that the most useful study for the purposes of quantitative risk assessment was the ecologic epidemiology study by Tseng et al. (1968). In this study, the incidence of skin cancer was measured as a function of exposure level in over 40,000 people residing in 37 villages in Taiwan, and compared to a control group of over 7,500 people. Beyond the very large sample size, other strengths of this study include excellent case ascertainment (physical examination), inclusion of both males and females, and lifetime exposure duration. Weaknesses and uncertainties include poor nutritional status of the exposed populations, their genetic susceptibility, their exposure to inorganic arsenic from nonwater sources, and the applicability of extrapolating data from Taiwanese to the U.S. population because of different background rates of cancer, possibly genetically determined, and differences in diet other than arsenic (e.g., low protein and fat and high carbohydrate) (EPA 1988d). Because of a lack of information on the amount of individual exposure, subjects were classified into three exposure groups (i.e., high, medium, and low). Based upon pooled data for skin cancer incdence and average well concentrations for each village in the Tseng et al. (1968) study, the EPA calculated a unit risk (the upper-bound excess cancer risk from lifetime exposure to water containing 1 μg As/L) of $5x10^{-5}$ (IRIS 2005). The average daily doses (expressed as mg As/kg/day) that correspond to excess cancer risks of $1x10^{-4}$–$1x10^{-7}$ are shown in Figure 3-3.

The use of a cancer risk estimate derived from the Tseng et al. (1968) study for a U.S. population has been the source of intense debate. A number of concerns have been raised including the adequacy of the model used by EPA and the accuracy and reliability of the exposure data (Brown et al. 1997a, 1997b); a number of host and environmental factors among the Taiwanese not applicable elsewhere (Carlson-Lynch et al. 1994); a possible threshold for arsenic carcinogenicity and nonlinearities in the dose-response curve (Abernathy et al. 1996; Slayton et al. 1996); differences in health and nutrition between Taiwan and the United States that might increase cancer risk in Taiwan (Beck et al. 1995); the possibility that arsenic is an essential nutrient at lower doses (EPA 1988d; NAP 2001; NRC 1999, 2001); and the possibility of significant exposure to arsenic from sources other than the well water (Chappell et al. 1997). These factors, many of which were recognized by EPA (1988d). A more recent report by NRC (2001) suggested that the risks of arsenic-induced lung and bladder cancers may be greater than those calculated by the EPA (based on skin cancer risk at the time of the assessment, all contribute to uncertainty in the risk assessment).

Several early epidemiological studies performed in the United States did not report an increased frequency of skin cancer in small populations consuming water containing arsenic at levels of around 0.1–0.2 ppm (Goldsmith et al. 1972; Harrington et al. 1978; Morton et al. 1976; Southwick et al. 1981). These early data suggested that arsenic-associated skin cancer is not a common problem in this country, but these studies lacked sufficient statistical power to detect small increases in skin cancer incidence that might have occurred at these low doses (EPA 1983g). More recent studies in exposed U.S. populations from Utah (Lewis et al. 1999) and Iowa (Beane Freeman et al. 2004) have suggested that arsenic-exposed individuals within the United States may have increased incidence or risk of mortality from some skin cancers, melanoma in particular; however, exposure data from these studies are generally insufficient for dose-response analysis. Another recent study found a suggestion of an arsenic-induced effect on the development of skin cancer, but the association did not achieve statistical significance (Karagas et al. 2001). Therefore, the risk of arsenic-induced skin cancers in U.S. populations, while likely less than in some other evaluated populations, cannot be presently discounted.

In addition to the risk of skin cancer, there is mounting evidence that ingestion of arsenic may increase the risks of internal cancers as well. Many case studies have noted the occurrence of internal tumors of the liver and other tissues in patients with arsenic-induced skin cancer (Falk et al. 1981b; Kasper et al. 1984; Koh et al. 1989; Lander et al. 1975; Regelson et al. 1968; Sommers and McManus 1953; Tay and Seah 1975; Zaldívar et al. 1981). These studies are supported by large-scale epidemiological studies, where associations and/or dose response trends have been detected for tumors of the bladder, kidney, liver, lung, and prostate (Chen and Wang 1990; Chen et al. 1985, 1986, 1988a, 1988b, 1992; Chiou et al. 1995; Cuzick et al. 1992; Ferreccio et al. 1998; Guo et al. 1997; Hopenhayn-Rich et al. 1998; Kurttio et al. 1999; Lewis et al. 1999; Moore et al. 2002a; Rivara et al. 1997; Smith et al. 1998a; Tsuda et al. 1995a; Wu et al. 1989). The EPA has not yet calculated a unit risk value or slope factor for arsenic-induced internal tumors.

There is increasingly convincing evidence that long-term exposure to arsenic can result in the development of bladder cancer (Bates et al. 2004; Chen et al. 1992, 2003a; Chiou et al. 1995, 2001; Cuzick et al. 1992; Guo et al. 2001b; Karagas et al. 2004; Lamm et al. 2004; Michaud et al. 2004; Steinmaus et al. 2003), with transitional cell cancers being the most prevalent. Chiou et al. (1995) reported a dose-response relationship between long-term arsenic exposure from drinking artesian well water and the incidence of lung cancer, bladder cancer, and cancers of all sites combined (after adjustment for age, sex, and cigarette smoking) in four townships in Taiwan exposed to inorganic arsenic in drinking water (0–1.14 mg/L). In a later followup study of the same cohort, the increase in bladder

cancer was found to be statistically significant only in subjects exposed for 40 years or longer (Chiou et al. 2001). Cuzick et al. (1992) evaluated a cohort treated with Fowler's solution (potassium arsenite) in Lancashire, England, during the period 1945–1969 and followed through 1991; the cohort of 478 patients showed a significant excess of bladder cancer, but no excess for other causes of death. Of a subcohort of 142 patients examined for signs of arsenicism around 1970 (Cuzick et al. 1992), all 11 subsequent cancer deaths occurred in those with signs of arsenicism ($p=0.0009$). Hopenhayn-Rich et al. (1996a) investigated bladder cancer mortality for the years 1986–1991 in the 26 counties of Cordoba, Argentina, and reported that bladder cancer SMRs were consistently higher in counties with documented arsenic exposure; a later case-control study by the same authors (Bates et al. 2004) did not report statistically significant increases in bladder cancers resulting from arsenic exposure, except in individuals exposed for 50 years or longer. Guo et al. (2001a) reported significantly increased rate differences for bladder cancer in men and women in Taiwan exposed to 0.64 mg arsenic/L in the drinking water, but not at lower exposure levels. The arsenic-induced bladder tumors do not appear to be histologically different than similar bladder tumor types of non-arsenic origin (Chow et al. 1997), although they tended to be more pronounced. In contrast, Michaud et al. (2004) reported no correlation between arsenic levels in toenails and the incidence of bladder cancers in Finnish workers. Among evaluated U.S. cohorts, there has generally been no association between arsenic exposure (~60–100 µg As/L) and the incidence of mortality from bladder cancers (Lamm et al. 2004; Steinmaus et al. 2003), although it is possible that smoking may render individuals more susceptible to arsenic-induced bladder tumors (Karagas et al. 2004; Steinmaus et al. 2003).

Recent studies have also suggested that chronic oral exposure to arsenic may result in the development of respiratory tumors (Ferreccio et al. 2000; Guo 2004; Nakadaira et al. 2002; Viren and Silvers 1999). A study of arsenic-exposed individuals in northern Chile reported significantly increased odds ratios for lung cancer among subjects with ≥30 µg As/L of drinking water (Ferreccio et al. 2000), although when adjusted for socioeconomic status, smoking, and other factors, the increase was only significant at 60 µg As/L or greater. Guo (2004) reported significantly increased rates differences (RD) for lung cancer for Taiwanese men and women exposed to 0.64 mg As/L or greater, with those subjects >50 years of age being particularly at risk. Nakadaira et al. (2002) suggested that even comparatively short exposure durations (≤5 years) may be sufficient for the development of arsenic-induced lung cancer.

Studies in U.S. populations exposed to arsenic in drinking water (Morton et al. 1976; Southwick et al. 1981; Valentine et al. 1992) have not yielded the cancer incidences and health effects noted in Taiwan, Mexico, and Chile. Whether this difference is due to a smaller population of subjects compared to

Taiwan, to overall lower doses in exposed U.S. populations, or to differences in nutritional or socioeconomic conditions has not been resolved. It should be noted that exposed populations in Mexico and Chile are also smaller than those in Taiwan.

Most studies of animals exposed to arsenate or arsenite by the oral route have not detected any clear evidence for an increased incidence of skin cancer or other cancers (Byron et al. 1967; Kroes et al. 1974; Schroeder et al. 1968). Arsenic has sometimes been called a "paradoxical" human carcinogen because of this lack of animal data (Jager and Ostrosky-Wegman 1997). The basis for the lack of tumorigenicity in animals is not known, but could be related to species-specific differences in arsenic distribution, and induction of cell proliferation (Byrd et al. 1996) (see Section 3.5). As discussed in Section 3.5 below, the carcinogenic effects of arsenic may partially result from its function as a cocarcinogen, which would not manifest in most animal carcinogenicity studies.

A series of recent animal studies has presented evidence that inorganic arsenic may be a transplacental carcinogen in animals. Waalkes et al. (2003a, 2004a, 2004b, 2004c) exposed timed-pregnant mice to 0, 42.5, or 85 ppm of sodium arsenite in the drinking water from gestation day 8 through 18 and observed the offspring for 90 weeks following birth; the study authors estimated daily doses at 9.55 and 19.3 mg As/kg/day. A dose-related increase was reported in the incidence of hepatocellular carcinomas and adrenal tumors in the male offspring from both treatment levels, while male offspring from high-dose animals showed an increase in total number of tumors. In female offspring, an increase in uterine hyperplasia was seen in the offspring of both treated groups, while the offspring of high-dose animals showed increased incidence of lung carcinomas. For both exposed groups, regardless of gender, the offspring showed a significant increase in the number of malignant tumors (Waalkes et al. 2003a).

One mouse study using transgenic mice (which carry the v-Ha-ras oncogene) administered 48 mg As/kg/day as sodium arsenite in drinking water for 4 weeks followed by dermal application of 12-O-tetradecanoylphorbol-13-acetage (TPA) to shaved back skin twice a day for 2 weeks showed an increase in the incidence of skin papillomas when compared to transgenic mice receiving only TPA treatment, only arsenic, or to wild-type mice receiving both TPA and arsenic (Germolec et al. 1998); arsenic treatment alone did not result in increased papilloma incidence. Increases in mRNA transcripts for the growth factors transforming growth factor-α (TGF-α) and granulocyte/ macrophage-colony stimulating factor (GM-CSF) were detected in the epidermis of the arsenic-treated mice.

A few studies in mice have noted that arsenic ingestion may actually decrease the incidence of some tumor types. For example, arsenic exposure caused decreased incidence of urethane-induced pulmonary tumors (Blakley 1987), spontaneous mammary tumors (Schrauzer and Ishmael 1974; Schrauzer et al. 1976), and tumors resulting from injection of mouse sarcoma cells (Kerkvliet et al. 1980). However, arsenic also increased the growth rate of the tumors that did occur, resulting in a net decrease in survival time in tumor-bearing animals (Kerkvliet et al. 1980; Schrauzer and Ishmael 1974). These observations suggest that arsenic may affect different types of neoplastic cells differently, perhaps acting mainly as a tumor promoter (Schrauzer and Ishmael 1974; Shirachi et al. 1983), although some studies have suggested that arsenic's actions are not consistent with tumor promotion (Baroni et al. 1963; Boutwell 1963). However, these data do not suggest that arsenic should be viewed as having any net therapeutic "anti-cancer" effect.

Organic Arsenicals. No studies were located regarding cancer in humans after oral exposure to organic arsenicals. In an early 2-year study of roxarsone toxicity in animals, no increase in tumor frequency was detected in dogs given 1.5 mg As/kg/day, rats given 2.9 mg As/kg/day, or mice given 3.8 mg As/kg/day (Prier et al. 1963). More recently, lifetime studies of roxarsone at doses up to 1.4 mg As/kg/day yielded no evidence of carcinogenicity in male or female mice or female rats, but a slight increase in pancreatic tumors was noted in male rats (NTP 1989b). This was considered to constitute equivocal evidence of carcinogenicity.

Recently, two groups have conducted lifetime carcinogenicity studies with MMA. Arnold et al. (2003) exposed male and female F344 rats to 0, 50, 400, or 1,300 ppm MMA and male and female B6C3F1 mice to 0, 10, 50, 200, or 400 ppm MMA in the diet for 104 weeks. Due to mortality, the highest dose for rats was lowered twice, finishing the study at 800 ppm; average daily doses were approximately 0, 1.4, 12.3, or 34.8 mg As/kg/day for male rats, 0, 1.8, 16.3, or 47.3 mg As/kg/day for female rats, 0, 0.6, 2.9, 12.0, or 32.2 mg As/kg/day for male mice, and 0, 0.7, 3.4, 15.0, or 48.5 mg As/kg/day for female mice. No treatment-related neoplastic changes were seen in either sex of either species. A similar lack of carcinogenicity of MMA was reported by Shen et al. (2003a), who exposed male F344 rats to 0, 50, or 200 ppm of MMA(V) in the drinking water for 104 weeks.

Wei et al. (1999, 2002) exposed male F344 rats to 0, 12.5, 50, or 200 ppm of DMA in the diet for 104 weeks; average daily doses were approximately 0, 0.03, 0.14, or 0.53 mg As/kg/day. Increases in the number of animals with tumors of the bladder were seen in the 50 and 200 ppm groups. No increases in tumor incidence were seen in organs other than the bladder. Hayashi et al. (1998) reported that mice

exposed to 400 ppm of DMA for 50 weeks, but not those exposed to 50 or 200 ppm, showed an increased incidence of papillary adenomas and an elevated number of average lung tumors per mouse.

The incidence of basophilic foci (believed to be a precancerous lesion) in the liver of rats initiated with diethylnitrosamine was increased by subsequent 6-month drinking water exposure to 6.1 mg As/kg/day as DMA, suggesting that this compound could act as a cancer promoter (Johansen et al. 1984). Additional evidence for the possible role of DMA as a promoter comes from Yamamoto et al. (1995), who reported that 8 or 34 mg As/kg/day as DMA in the drinking water for 24 weeks significantly enhanced the tumor induction in the urinary bladder, kidney, liver, and thyroid gland in male F344 rats treated with a series of initiators. Wanibuchi et al. (1996) reported that treatment of F344 rats for 32 weeks with up to 100 ppm of DMA in the drinking water (~8.4 mg As/kg/day) did not result in increased incidences of urinary bladder papillomas or carcinomas, but that incidence of these tumors was elevated if the animals were first pretreated with an initiating compound (BBN). A later study by Li et al. (1998b) reported that NBR rats (which do not synthesize $\alpha_{2\mu}$-globulin) exposed to an initiator for 4 weeks followed by DMA for 32 weeks, similar to the Wanibuchi et al. (1996) study, showed a statistically significant increase in simple hyperplasia and papillary or nodular hyperplasia of the bladder. A recent study by Salim et al. (2003) suggested that DMA primarily exerts its carcinogenic effects on spontaneous tumor development. Thus, some evidence exists suggesting that organic arsenicals might possess weak carcinogenic potential and may promote carcinogenicity, but the evidence is not conclusive.

3.2.3 Dermal Exposure

Adverse effects from dermal exposure to inorganic or organic arsenicals have not been extensively investigated. Table 3-5 summarizes studies in animals and humans that provide quantitative data on dermal exposure-effect relationships for inorganic arsenicals. No quantitative data on dermal exposure to organic arsenicals were located. Available quantitative and qualitative data are discussed in greater detail below.

3.2.3.1 Death

Inorganic Arsenicals. No studies were located regarding death in humans after dermal exposure to inorganic arsenicals. In rats, no deaths resulted from dermal exposure to arsenate or arsenite at doses up

Table 3-5 Levels of Significant Exposure to Inorganic Arsenic - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
ACUTE EXPOSURE							
Immuno/ Lymphoret							
Gn pig (Hartley)	once		50 mg/L			Wahlberg and Boman 1986 As(3)	
Gn pig (Hartley)	once		4000 mg/L			Wahlberg and Boman 1986 As(5)	
INTERMEDIATE EXPOSURE							
Systemic							
Mouse (Rockland)	30 wk 11x/wk	Dermal		6 F mg/kg/day	(gross hyperplasia, ulceration)	Boutwell 1963 As(3)	

F = female; Gn pig = guinea pig; wk = week(s); x = time(s)

DRAFT FOR PUBLIC COMMENT

to 1,000 mg As/kg (Gaines 1960). These data indicate that dermal exposure to inorganic arsenic compounds is very unlikely to result in death.

Organic Arsenicals. No studies were located regarding death in humans or animals after dermal exposure to organic arsenicals.

3.2.3.2 Systemic Effects

No studies were located that have associated respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, or body weight effects in humans or animals with dermal exposure to inorganic or organic arsenicals.

Dermal Effects.

Inorganic Arsenicals. Several studies of humans exposed to arsenic dusts in the workplace have reported that inorganic arsenic (usually arsenic trioxide) can cause contact dermatitis (Holmqvist 1951; Pinto and McGill 1953). Typical responses included erythema and swelling, with papules and vesicles in more severe cases (Holmqvist 1951). The dermal contact rates that cause these effects in humans have not been quantified, but a similar direct irritation of the skin has been noted in mice exposed to 4 mg As/kg/day as potassium arsenite for 30 weeks (Boutwell 1963). In contrast, no significant dermal irritation was noted in guinea pigs exposed to aqueous solutions containing 4,000 mg As/L as arsenate or 580 mg As/L as arsenite (Wahlberg and Boman 1986). These studies indicate that direct contact may be of concern at high exposure levels, but do not suggest that lower levels are likely to cause significant irritation.

Studies on possible dermal sensitization by inorganic arsenicals are discussed in Section 3.2.3.3 below.

Organic Arsenicals. Application of MMA to the skin of rabbits was reported to result in mild dermal irritation (Jaghabir et al. 1988), but too few details on dose, duration, or degree of irritation were provided to draw firm conclusions regarding the dermal irritancy of organic arsenicals.

Ocular Effects.

Inorganic Arsenicals. No studies were located regarding ocular effects in humans or animals after dermal exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located regarding ocular effects in humans or animals after dermal exposure to organic arsenicals.

3.2.3.3 Immunological and Lymphoreticular Effects

Inorganic Arsenicals. Examination of workers exposed to arsenic trioxide dusts in a copper smelter led Holmqvist (1951) to suspect that repeated dermal contact could lead to dermal sensitization. In support of this, Holmqvist (1951) found a positive patch test in 80% of the exposed workers compared to 30% in a control population. These data do suggest that workers may be sensitized to arsenic, but the high response rate in controls seems unusual. A much lower response rate (0.5%) was noted in a more recent patch test study of dermal sensitization (Wahlberg and Boman 1986), and the few positive responses seemed to be due to a cross-reactivity with nickel. Mohamed (1998) evaluated 11 male workers at a tin smelting factory where arsenic trioxide levels ranged from 5.2 to 14.4 mg/m^3. The workers experienced symptoms of generalized itch, dry and hyperpigmented skin, folliculitis, and superficial ulcerations. The authors concluded that arsenic-containing dust collected on the sweat on the workers' skin, causing contact dermatitis. Studies in guinea pigs did not yield evidence of a sensitization reaction to inorganic arsenic (Wahlberg and Boman 1986).

Organic Arsenicals. Support for sensitization to DMA is provided in a case report of a 26-year-old woman who was occupationally exposed to DMA and experienced eczema on her face (Bourrain et al. 1998). Patch testing confirmed an allergic reaction to DMA, and avoidance of DMA resulted in disappearance of the symptoms. No studies were located regarding immunological or lymphoreticular effects in animals after dermal exposure to organic arsenicals.

No studies were located that have associated any of the following effects in humans or animals with dermal exposure to inorganic or organic arsenicals:

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

Inorganic Arsenicals. No studies were found that have associated cancer in humans with dermal exposure to arsenic. Application of arsenic acid to the skin of mice pretreated with dimethylbenz-anthracene did not result in any skin tumors (Kurokawa et al. 1989), suggesting that arsenic does not act as a promoter in this test system.

Organic Arsenicals. No studies were located regarding cancer in humans or animals after dermal exposure to organic arsenicals.

3.3 GENOTOXICITY

There have been a large number of studies of the genotoxic effects of arsenic. Tables 3-6 and 3-7 summarize a number of reports on the *in vivo* and *in vitro* genotoxicity of inorganic arsenicals, respectively. The results are mixed, but in general, it appears that the inorganic arsenicals are either inactive or weak mutagens (Jacobson-Kram and Montalbano 1985), but are able to produce chromosomal effects (aberrations, sister chromatid exchange) in most systems. Studies of humans have detected a higher-than-average incidence of chromosomal aberrations in peripheral lymphocytes, both after inhalation exposure (Beckman et al. 1977; Nordenson et al. 1978) and oral exposure (Burgdorf et al. 1977; Nordenson et al. 1979). These studies must be interpreted with caution, since in most cases there were only a small number of subjects and a number of other chemical exposures were possible (EPA 1984a). However, the *in vivo* findings are strongly supported by *in vitro* studies using eukaryotic cells (e.g., Lee et al. 1985; Nakamuro and Sayato 1981; Zanzoni and Jung 1980) (see Table 3-7).

Inorganic Arsenicals. Human and animal data are available indicating that inhaled inorganic arsenic is clastogenic. Workers exposed to unspecified concentrations of arsenic trioxide at the Ronnskar copper smelter in Sweden were found to have a significant increase in the frequency of chromosomal aberrations in peripheral lymphocytes (Beckman et al. 1977; Nordenson et al. 1978). This result is supported by an animal study that found increased chromosomal aberrations in the livers of fetuses from pregnant mice

Table 3-6. Genotoxicity of Inorganic Arsenic *In Vivo*

Species		Exposure		Species		Endpoint		Results	
Non-mammalian									
As^{3}	As^{5}	Injection		*Drosophila melanogaster*		Sex-linked recessive lethal mutation		+	Reference
As^{3}	As^{5}	Ingestion		*D. melanogaster*		Sex-linked recessive lethal mutation		+	Reference
As^{5}		Larvae		*D. melanogaster*		Mitotic recombination +	Reference		
Mammalian									
As^{3}		Intravenous	Micronucleus					–	Reference
As^{3}		Intravenous	Micronucleus					+	Reference
As^{3}		Oral	Micronucleus					–	Reference
Not Specified	Oral		Micronucleus					–	Reference
Not Specified	Oral		Unscheduled DNA synthesis		+	Reference			
As^{3}		Oral	Sister chromatid exchange					–	Reference
As^{3}		Oral	Sister chromatid exchange					+	Reference
Not Specified	Oral		Sister chromatid exchange					+	Reference
Not Specified	Oral		Sister chromatid exchange					+	Reference
Not Specified	Oral		Sister chromatid exchange					+	Reference
As^{3}		Oral	Sister chromatid exchange					–	Reference
Not Specified	Oral		Sister chromatid exchange					–	Reference
Not Specified	Oral		Micronucleus			Mitotic index		+	Reference
As^{3}		Oral	Chromosomal aberration			Mitosis		+	Reference
As^{3}		Oral	Chromosomal aberration			Mitosis		+	Reference
Not Specified	Oral		Micronucleus			Mitosis		+	Reference
Not Specified	Oral		Micronucleus					+	Reference
Not Specified	Oral		Micronucleus					+	Reference

Table 3-6. Genotoxicity of Inorganic Arsenic *In Vivo*

Species	Exposure	Species	End point	Result	Reference
Rodent cell culture	Oral	Mouse	Micronucleus formation	+	Beckett et al. 1993
Rodent cell culture	Oral	Mouse	Micronucleus formation	+	Beckett et al. 1993
As^{5+}	Oral	Rat	Chromosome aberrations	+	Deknudt et al. 1989
As^{3+}	Intravenous	Mouse	Chromosome aberrations	+	Nagas et al. 1984
As^{3+}	Oral	Mouse	Chromosome aberrations	+	Deknudt et al. 1989
As^{3+}	Oral	Mouse	Chromosome aberrations	+	Poddar et al. 1992
As^{3+}	Oral	Mouse	Chromosome aberrations	–	Poddar et al. 1989
As^{3+}	Oral	Mouse	Chromosome aberrations	–	Poddar et al. 1989
As^{3+}	Oral	Mouse	Micronucleus formation + Chromosome aberrations + Mitotic index		Deknudt et al. 1992
As^{3+}	Intraperitoneal	Mouse	Chromosome aberrations	–	Poddar et al. 1989
As^{3+}	Intraperitoneal	Mouse	Micronucleus formation	+	Deknudt et al. 1989
As^{3+}	Intraperitoneal	Mouse	Sperm abnormalities	–	Poddar et al. 1989
As^{3+}	Intraperitoneal	Mouse	Sperm abnormalities	–	Deknudt et al. 1989
As^{3+}	Intraperitoneal	Mouse	Dominant lethal assay	–	Deknudt et al. 1989

DNA =

Table 3-7. Genotoxicity of Inorganic Arsenic *In Vitro*

				Rs			
P							
As[3]	*Escherichia coli*	R	N	+	N		
As[3]	*E. coli* P		N	–	L		
As[3]	*E. coli*	R	N	–	R		
As[3]	*Salmonella typhimurium*		N	–	L		
As[3]	*Photobacterium fischeri*		N	–	U	B	
As[5]	*S. typhimurium*		N	–	L		
As[5]	*P. fischeri*		N	+	U	B	
E							
	F						
As[3]; As[5]	*Saccharomyces cerevisiae*		N	–	S		
	M						
As[3]		DNA	N	+	O		
As[3]		DNA		+	+		
As[3]		DNA		+			
As[3]		DNA	N	+			
	(MRC						
As[3]			N	+	L		
As[3]					N	+	
As[3]		C			N	+	
As[3]		DNA	N	+	Dg	L	
As[3]		DNA			N	+	Dg	L
As[3]; As[5]		C			N	+	O	
As[3]		Di	M		N	+	L	
As[3]		C			N	+	N	

Table 3-7. Genotoxicity of Inorganic Arsenic *In Vitro*

					Rs				
As^{3}		DNA			–		–		
As^{3}; As^{5}						+			
As^{3}; As^{5}						+			
As^{3}; As^{5}						+			
As^{3}						+			
As^{3}						+			
As^{3}						+			
As^{3}						+			
As^{3}						+			
As^{3}						+			
As^{3}						+			
As^{3}						+			
As^{5}						–			
As^{3}						+			

Table 3-7. Genotoxicity of Inorganic Arsenic *In Vitro*

Species	Endpoint			Results		
				With activation	Without activation	
As^{3+}	[illegible]	[illegible]		Negative	+	[illegible]
As^{3+}	[illegible]	[illegible]		Negative	+	Reduced [illegible]
As^{3+}; As^{5+}	[illegible]		PARP activity	Negative	+	[illegible]
As^{3+}	[illegible]		DNA repair	+	+	Cell [illegible]
As^{3+}	[illegible]		DNA strand	Negative	-	[illegible]
As^{3+}	[illegible]		DNA repair	Negative	+	[illegible]
As^{3+}	[illegible]		Cell [illegible]	Negative	+	Marked [illegible]
As^{3+}	[illegible]		[illegible] DNA [illegible]	Negative	+	[illegible]
As^{3+}	Methylation	Enzyme		Negative	[illegible]	Other [illegible]
As^{3+}	Methylation		Clastogenicity	Negative	+	Marked [illegible]
As^{3+}; As^{5+}	[illegible]	[illegible]				
As^{3+}	Methylation		Mitotic activity	Negative	+	Other [illegible]
As^{3+}; As^{5+}	Methylation	Clastogenicity		Negative	+	Marked [illegible]
As^{3+}	Methylation	Clastogenicity		Negative	+	Slight [illegible]
As^{3+}	Metabolic [illegible]		[illegible]	Negative	+	Less [illegible]
As^{3+}	Methylation [illegible]		Mitotic [illegible]	Negative	+	Liver [illegible]
As^{3+}	Chromosome [illegible]	[illegible]	Negative	–	Liver [illegible]	
As^{3+}	Chromosome [illegible]	[illegible]	Negative	–	Reduced [illegible]	
As^{3+}	Chromosome [illegible]	DNA [illegible] DNA-		Negative	+	[illegible]
As^{3+}	Chromosome [illegible]	DNA [illegible]		Negative	+	Liver [illegible]
As^{3+}	Chromosome [illegible]	[illegible]		Negative	+	[illegible]

Table 3-7. Genotoxicity of Inorganic Arsenic *In Vitro*

| | | |

Table 3-7. Genotoxicity of Inorganic Arsenic *In Vitro*

Species	Endpoint					Results			
						With Activation		Without Activation	
As^{3}	Chromosome Aberrations					Negative	+		
As^{3}	Chromosome Aberrations	Cytotoxicity		Negative	–				
As^{3}	Sister Chromatid Exchange		Negative	–					
As^{3}	Sister Chromatid Exchange	Clastogenicity				Negative	+		
As^{3}	Sister Chromatid Exchange	Clastogenicity				Negative	+		
As^{3}	Sister Chromatid Exchange (SCE)					Negative	–		
As^{3}	Sister Chromatid Exchange (SCE)					Negative	–		
As^{3}	Sister Chromatid Exchange	Mutagenicity				Negative	+		
As^{3}	Sister Chromatid Exchange	Mutagenicity				Negative	+		
As^{3}	Sister Chromatid Exchange	Mutagenicity				Negative	+		
As^{5}	Mutation				DNA damage	Negative	–	Positive	
As^{5}	Unscheduled DNA Synthesis	Clastogenicity				Negative	+	Negative	
As^{5}	Unscheduled DNA Synthesis	Clastogenicity				Negative	–	Negative	
As^{5}	Unscheduled DNA Synthesis	Clastogenicity				Negative	+	Positive	
As^{5}	Unscheduled DNA Synthesis	Cytotoxicity				Negative	–	Positive	
As^{5}	Unscheduled DNA Synthesis	Cytotoxicity				Negative	+	Positive	
As^{5}	Mutation	Cytotoxicity		Negative	–	Positive			
As^{5}	Mutation	Cytotoxicity		Negative	–	Positive			

Table 3-7. Genotoxicity of Inorganic Arsenic *In Vitro*

						Rsa			
As[5]	Chsa	Cln			Ndel	+			
As[5]	Sy		Ndel	–	Le				
As[5]	Sy	Cln			Ndel	+	Ly		
As[5]	Sy	Cln			Ndel	+	Le		
As[5]	Sy	Sid			Ndel	+	Le		
As[5]	Sy	Mga			Ndel	+	Le		
As[5]	Sy	Mga			Ndel	+	DiPad		

DNA

exposed to 22, but not 2.2 or 0.20, mg As/m^3 as arsenic trioxide on days 9–12 of gestation (Nagymajtenyi et al. 1985).

Investigations of genotoxic effects of ingested arsenic have yielded mixed results. A study of p53 mutations in arsenic-related skin cancers from patients in Taiwan exposed to arsenic from drinking water found a high rate of p53 mutations and different types of p53 mutations compared with those seen in UV-induced skin cancers (Hsu et al. 1999); similar results have been found in mice (Salim et al. 2003). In humans exposed to Fowler's solution (potassium arsenite, usually taken at a dose of about 0.3 mg As/kg/day [Holland 1904]), increased sister chromatid exchanges, but no increase in chromosomal aberrations, was reported in one study (Burgdorf et al. 1977), while just the converse (increased aberrations but no increase in sister chromatid exchange) was reported in another (Nordenson et al. 1979). Moore et al. (1997a) reported an exposure-dependent increase in the occurrence of micronucleated cells in a Chilean male population chronically exposed to high and low arsenic levels in their drinking water (average concentrations, 600 and 15 µg As/L, respectively), and noted that chromosome breakage was the major cause of micronucleus (MN) formation. Vig et al. (1984) found no significant differences in the frequency of chromosomal aberrations or sister chromatid exchanges between two populations in Nevada with differing levels of arsenic in their drinking water (mean concentrations of 5 and 109 µg/L). In animal studies, an increased incidence of chromosomal abnormalities was detected in rats given oral doses of sodium arsenate (4 mg As/kg/day) for 2–3 weeks (Datta et al. 1986), but no consistent increase in chromosomal aberrations was detected in bone marrow cells or spermatogonia from mice given sodium arsenite (about 50 mg As/kg/day) for up to 8 weeks (Poma et al. 1987). These studies suggest that ingested arsenic may cause chromosomal effects, but these data are too limited to draw a firm conclusion.

Organic Arsenicals. The genotoxicity of the organic arsenicals has not been as thoroughly studied, but several tests indicate that DMA and roxarsone may be able to cause chromosome aberrations, mutations, and deoxyribonucleic acid (DNA) strand breaks (see Table 3-8). An increased number of DNA strand breaks were detected in lung and other tissues of mice and rats given oral doses of ~1,500 mg/kg DMA (Okada and Yamanaka 1994; Yamanaka et al. 1989a); this effect appeared to be related to the formation of some active oxygen species. These breaks were largely repaired within 24 hours, so the relevance with respect to health risk is uncertain.

Table 3-8. Genotoxicity of Organic Arsenic

Chemical	Species	Test System	Endpoint	Activation	Result	Reference
Prokaryotic organisms:		*in vitro*				
Dimethylarsinic acid		*Escherichia coli*	Gene mutation	Not tested	+	Nesnow et al. 1983
Roxarsone		*Salmonella typhimurium*	Gene mutation	–	–	NTP 1991
Eukaryotic organisms: *in vitro*						
Arsenobetaine	Human		Cytogenetic analysis	Not tested	+	Ochi et al. 1986
Arsenocholine	Chicken		Transformation	Not tested	–	Egami et al. 1989
Dimethylarsinic acid		Human fibroblasts	Micronucleus formation	Not tested	–	Endo et al. 1989
Dimethylarsinic acid		Human lymphocytes	Sister chromatid exchange	Not tested	–	Ramel et al. 1984
Dimethylarsinic acid		Human lymphocytes	Unscheduled DNA synthesis	Not tested	+	Mahler et al. 1980
Dimethylarsinic acid		Human lymphocytes	Single-strand DNA breaks	Not tested	+	Nesnow et al. 1983
Dimethylarsinic acid		Human lymphocytes	DNA repair	+	+	Nesnow et al. 1983
Dimethylarsinic acid		Human lymphocytes	DNA repair	Not tested	+	Rimington et al. 1988
Dimethylarsinic acid		Human lymphocytes	DNA damage	Not tested	+	Tezuka et al. 1989
Dimethylarsinic acid		Human lymphocytes	DNA repair	Not tested	+	Nesnow et al. 1983
Dimethylarsinic acid		Human lymphocytes	DNA-protein cross-links	Not tested	+	Nesnow et al. 1983
Dimethylarsinic acid		Human lymphocytes	DNA repair	Not tested	+	Nesnow et al. 1983
Dimethylarsinic acid		Human lymphocytes	Cytogenetic analysis	Not tested	+	Ochi et al. 1986
Dimethylarsinic acid		Mouse lymphoma cells (L5178Y +/- TK)	Gene mutation	Not tested	+	Amacher and Turner 1985
Dimethylarsinic acid		Chinese hamster ovary cells	Micronucleus formation	Not tested	+	Endo et al. 1989
Dimethylarsinic acid		Chinese hamster lung cells	Cytogenetic analysis	Not tested	+	Ueda et al. 1987
Dimethylarsinic acid		Chinese hamster ovary cells	Cytogenetic analysis	Not tested	+	Nesnow et al. 1983

Table 3-8. Genotoxicity of Organic Arsenic

				Rsu			
Cltfon Sjse		(gnEdpn		LtV tlno	LtV tlno		Rfe
Dijpo id		Chdtg adpbtBY	Cbn lne	+	+		ldfa 2
Dijpo id		Chdtf Y le	Tjtd itde	Ndel	+	Egtda	9
Mjid tdtd		fle	Cbn lne	Ndel	+	OgQtda	0
Mjpo id		Chdtf Y le	Tjtd itde	Ndel	+	Egtda	9
Rne		*Drosophila melanogaster*	Sxkd ice	Ndel	–	NTP 9	
Rne	Rtjp	DNA ld	tde	Ndel	+	Stda	0
Rne	A3fo	BALB3T3e	Tfon pd gy	Ndel	–	Mtda	9
Rne	Mejn	(.)fs	Tigfda ida	Ndel	+	NTP 9	
Ejgn *in vivo*		)			+		
Dijpo id		Rtjp DNA ig	kirtg	Ndel	+	ld	Ofd
Dijpo id		Mdjp DNA tde	irtcs	Ndel	+	ld	fd
Dijpo id		Mdjp DNA ig	kirtg	Ndel	+	ld	fd
Dijpo id		Mdjp DNA ig	kirtg	Ndel	–	ld	fd
Dijpo id		Mdjp DNA ld	fon	Ndel	+	ld	fd
Dijpo id		Mdjn Ajgin	tde	Ndel	+	ldfe	fd

–tgd-ed DNA -jd

3.4 TOXICOKINETICS

There is an extensive database on the toxicokinetics of inorganic arsenic. Most studies have been performed in animals, but there are a number of studies in humans as well. These studies reveal the following main points:

- Both arsenate and arsenite are well absorbed by both the oral and inhalation routes. Absorption by the dermal route has not been well characterized, but is low compared to the other routes. Inorganic arsenic in soil is absorbed to a lesser extent than solutions of arsenic salts.

- The rate of absorption of arsenic in highly insoluble forms (e.g., arsenic sulfide, lead arsenate) is much lower than that of more soluble forms via both oral and inhalation routes.

- Once absorbed, arsenites are oxidized to arsenates and methylated. This process may then be repeated to result in dimethylated arsenic metabolites.

- Distribution of arsenic in the rat is quite different from other animal species, suggesting that the rat is probably not an appropriate toxicokinetic model for distribution, metabolism, or excretion of arsenic by humans.

- The As(+3) form undergoes enzymic methylation primarily in the liver to form MMA and DMA. The rate and relative proportion of methylation production varies among species. The rate of methylation may also vary considerably among tissues.

- Most arsenic is promptly excreted in the urine as a mixture of As(+3), As(+5), MMA, and DMA; DMA is usually the primary form in the urine. Smaller amounts are excreted in feces. Some arsenic may remain bound to tissues, depending inversely on the rate and extent of methylation.

Less information is available for the organic arsenicals. It appears that both MMA and DMA are well absorbed, but are rapidly excreted in the urine and feces. MMA may be methylated to DMA, but neither MMA nor DMA are demethylated to yield inorganic arsenic.

A review of the evidence that supports these conclusions is presented below.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Since arsenic exists in air as particulate matter, absorption across the lung involves two processes: deposition of the particles onto the lung surface, and absorption of arsenic from the deposited material. In lung cancer patients exposed to arsenic in cigarette smoke, deposition was estimated to be about 40% and absorption was 75–85% (Holland et al. 1959). Thus, overall absorption (expressed as a percentage of inhaled arsenic) was about 30–34%. In workers exposed to arsenic trioxide dusts in smelters, the amount of arsenic excreted in the urine (the main route of excretion; see Section 3.4.4) was about 40–60% of the estimated inhaled dose (Pinto et al. 1976; Vahter et al. 1986). Absorption of arsenic trioxide dusts and fumes (assessed by measurement of urinary metabolites) correlated with time weighted average arsenic air concentrations from personal breathing zone air samplers (Offergelt et al. 1992). Correlations were best immediately after a shift and just before the start of the next shift. Although the percent deposition was not measured in these cases, it seems likely that nearly all of the deposited arsenic was absorbed. This conclusion is supported by intratracheal instillation studies in rats and hamsters, where clearance of oxy compounds of arsenic (sodium arsenite, sodium arsenate, arsenic trioxide) from the lung was rapid and nearly complete (60–90% within 1 day) (Marafante and Vahter 1987; Rhoads and Sanders 1985). In contrast, arsenic sulfide and lead arsenate were cleared more slowly (Marafante and Vahter 1987), indicating that the rate of absorption may be lower if the inhaled arsenic is in a highly insoluble form. There are no data to suggest that absorption of inhaled arsenic in children differs from that in adults.

No studies were located regarding absorption of organic arsenicals in humans or animals after inhalation exposure. However, DMA instilled in the lungs of rats was absorbed very rapidly (half-time of 2.2 minutes) and nearly completely (at least 92%) (Stevens et al. 1977b). This indicates that organic arsenicals are likely to be well absorbed by the inhalation route.

3.4.1.2 Oral Exposure

Several studies in humans indicate that arsenates and arsenites are well absorbed across the gastrointestinal tract. The most direct evidence is from a study that evaluated the 6-day elimination of arsenic in healthy humans who were given water from a high-arsenic sampling site (arsenic species not specified) and that reported approximately 95% absorption (Zheng et al. 2002). A similar absorption efficiency can be estimated from measurements of fecal excretion in humans given oral doses of arsenite,

where <5% was recovered in the feces (Bettley and O'Shea 1975). This indicates absorption was at least 95%. These results are supported by studies in which urinary excretion in humans was found to account for 55–87% of daily oral intakes of arsenate or arsenite (Buchet et al. 1981b; Crecelius 1977; Kumana et al. 2002; Mappes 1977; Tam et al. 1979b). In contrast, ingestion of arsenic triselenide (As_2Se_3) did not lead to a measurable increase in urinary excretion (Mappes 1977), indicating that gastrointestinal absorption may be much lower if highly insoluble forms of arsenic are ingested. There are no data to suggest that absorption of arsenic from the gut in children differs from that in adults.

These observations in humans are supported by a number of studies in animals. Fecal excretion of arsenates and arsenites ranged from 2 to 10% in monkeys and mice, with 70% or more appearing in urine (Charbonneau et al. 1978a; Vahter 1981; Vahter and Norin 1980). Oral absorption of [^{73}As] labeled sodium arsenate in mice was unaffected by dose (0.0005–5 mg/kg) as reflected in percentage of dose excreted in feces over 48 hours (Hughes et al. 1994). Absorption ranged from 82 to 89% at all doses. Gonzalez et al. (1995) found that the percentage of arsenate that was absorbed in rats decreased as the dose increased from 6 to 480 µg, suggesting saturable, zero-order absorption of arsenate in this species. Hamsters appear to absorb somewhat less than humans, monkeys, and mice, since fecal excretion usually ranges from 10 to 40% (Marafante and Vahter 1987; Marafante et al. 1987a; Yamauchi and Yamamura 1985). Rabbits also appear to absorb less arsenate than humans, monkeys, or mice after oral exposure (Freeman et al. 1993). After a gavage dose of 1.95 mg/kg sodium arsenate, 45% of the arsenate was recovered in feces in males and 52% in females. As in humans, when highly insoluble arsenic compounds are administered (arsenic trisulfide, lead arsenate), gastrointestinal absorption is reduced 20–30% (Marafante and Vahter 1987).

Bioavailability of arsenic was measured in rabbits ingesting doses of smelting soils that contained arsenic primarily in the form of sulfides (Freeman et al. 1993). Bioavailability was assessed by comparing the amounts of arsenic that was excreted after ingestion of the soil to that excreted after an intravenous dose of sodium arsenate. The bioavailability of the arsenic in the ingested soil was 24±3.2% and that of sodium arsenate in the gavage dose was 50±5.7%. Approximately 80% of the arsenic from ingested soil was eliminated in the feces compared with 50% of the soluble oral dose and 10% of the injected dose. In another study, rabbits dosed with sodium arsenite (0.8 mg As/kg) had 5 times greater blood arsenic concentrations than rabbits dosed with arsenic-containing soil (2.8 mg As/kg), suggesting a lower bioavailability of the arsenic in soil (Davis et al. 1992).

Studies of the bioavailability of arsenic suggest that absorption of arsenic in ingested dust or soil is likely to be considerably less than absorption of arsenic from ingested salts (Davis et al. 1992, 1996; EPA 1997g; Freeman et al. 1993, 1995; Pascoe et al. 1994; Rodriguez et al. 1999). Oral absorption of arsenic in a group of three female Cynomolgus monkeys from a soluble salt, soil, and household dust was compared with absorption of an intravenous dose of sodium arsenate (Freeman et al. 1995). Mean absolute percentage bioavailability based on urine arsenic excretion was reported at 67.6±2.6% (gavage), 19.2±1.5% (oral dust), and 13.8±3.3% (oral soil). Mean absolute percentage bioavailability based on blood arsenic levels was reported at 91.3±12.4% (gavage), 9.8±4.3% (oral dust), and 10.9±5.2% (oral soil). The arsenic in the dust and soil was approximately 3.5–5-fold (based on levels in the urine) and 8–9-fold (based on levels in the blood) less bioavailable than arsenic in solution. A study in beagle dogs fed with soil containing As_2O_5 or treated with intravenous soluble arsenic found that compared to injection the bioavailability of arsenic from ingested soil was 8.3±2.0% (Groen et al. 1993). The bioavailability of arsenic in soil has been studied in juvenile swine that received daily oral doses of soil or sodium arsenate (in food or by gavage) for 15 days (EPA 1997g). The soils were obtained from various mining and smelting sites and contained, in addition to arsenic at concentrations of 100–300 µg/g, lead at concentrations of 3,000–14,000 µg/g. The arsenic doses ranged from 1 to 65.4 µg/kg/day. The fraction of the arsenic dose excreted in urine was measured on days 7 and 14 and the relative bioavailability of the soil-borne arsenic was estimated as the ratio of urinary excretion fractions, soil arsenic:sodium arsenate. The mean relative bioavailability of soil-borne arsenic ranged from 0 to 98% in soils from seven different sites (mean±SD, 45%±32). Estimates for relative bioavailability of arsenic in samples of smelter slag and mine tailings ranged from 7 to 51% (mean±SD, 35%±27). Rodriguez et al. (1999) used a similar approach to estimate the relative bioavailability of arsenic in mine and smelter wastes (soils and solid materials) in juvenile swine. Samples included iron slag deposits and calcine deposits and had arsenic concentrations that ranged from 330 to 17,500 µg/g. Relative bioavailability (waste:sodium arsenate) ranged from 3 to 43% for 13 samples (mean, 21%) and was higher in iron slag wastes (mean, 25%) than in calcine wastes (mean, 13%).

Bioavailability of arsenic from soil is reduced by low solubility and inaccessibility due to the presence of secondary reaction products or insoluble matrix components (Davis et al. 1992). This is supported by studies conducted with *in vitro* simulations of the gastric and/or intestinal fluids (Hamel et al. 1998; Rodriguez et al. 1999; Ruby et al. 1996, 1999; Williams et al. 1998). When soils containing arsenic are incubated in simulated gastrointestinal fluids, only a fraction of the arsenic becomes soluble. Estimates of the soluble, or bioaccessible, arsenic fraction have ranged from 3 to 50% for various soils and mining and

smelter waste materials (Rodriguez et al. 1999; Ruby et al. 1996); these estimates are similar to *in vivo* estimates of the relative bioavailability of arsenic in these same materials (Ruby et al. 1999).

Based on urinary excretion studies in volunteers, it appears that both MMA and DMA are well absorbed (at least 75–85%) across the gastrointestinal tract (Buchet et al. 1981a; Marafante et al. 1987b). This is supported by studies in animals, where at least 75% absorption has been observed for DMA (Marafante et al. 1987b; Stevens et al. 1977b; Yamauchi and Yamamura 1984) and MMA (Yamauchi et al. 1988).

3.4.1.3 Dermal Exposure

No quantitative studies were located on absorption of inorganic arsenicals in humans after dermal exposure. Percutaneous absorption of [^{73}As] as arsenic acid (H_3AsO_4) alone and mixed with soil has been measured in skin from cadavers (Wester et al. 1993). Labeled arsenic was applied to skin in diffusion cells and transit through the skin into receptor fluid measured. After 24 hours, 0.93% of the dose passed through the skin and 0.98% remained in the skin after washing. Absorption was lower with [^{73}As] mixed with soil: 0.43% passed through the skin over 24 hours and 0.33% remained in the skin after washing.

Dermal absorption of arsenic has been measured in Rhesus monkeys (Wester et al. 1993). After 24 hours, 6.4% of [^{73}As] as arsenic acid was absorbed systemically, as was 4.5% of [^{73}As] mixed with soil. Uptake of arsenic into blood or tissues was undetectable for up to 24 hours in rats whose tails were immersed in solutions of sodium arsenate for 1 hour. However, arsenic began to increase in blood, liver, and spleen over the next 5 days (Dutkiewicz 1977). The rate of uptake was estimated to be 1–33 μg/cm^2/hour. These findings suggest that dermal exposure leads initially to arsenic binding to skin, and that the bound arsenic may slowly be taken up into the blood, even after exposure ends.

No studies were located on absorption of organic arsenicals in humans or animals after dermal exposure.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located on the distribution of arsenic in humans or animals after inhalation exposure, but intratracheal administration of arsenic trioxide to rats resulted in distribution of arsenic to the liver, kidney, skeleton, gastrointestinal tract, and other tissues (Rhoads and Sanders 1985). This is consistent

with data from oral and parenteral studies (below), which indicate that absorbed arsenic is distributed throughout the body.

No studies were located regarding the distribution of organic arsenicals in humans or animals after inhalation exposure. However, DMA administered to rats by the intratracheal route was distributed throughout the body (Stevens et al. 1977b), suggesting that inhalation of organic arsenicals would also lead to widespread distribution.

3.4.2.2 Oral Exposure

Analysis of tissues taken at autopsy from people who were exposed to background levels of arsenic in food and water revealed that arsenic is present in all tissues of the body (Liebscher and Smith 1968). Most tissues had about the same concentration level (0.05–0.15 ppm), while levels in hair (0.65 ppm) and nails (0.36 ppm) were somewhat higher. This indicates that there is little tendency for arsenic to accumulate preferentially in any internal organs. However, exposure levels may not have been high enough to cause elevated levels in tissues. Arsenic exposure may have been low enough that the methylation process in the body resulted in limited accumulation in internal organs. Tissue analysis of organs taken from an individual following death from ingestion of 8 g of arsenic trioxide (about 3 g of arsenic) showed a much higher concentration of arsenic in liver (147 μg/g) than in kidney (27 μg/g) or muscle, heart, spleen, pancreas, lungs, or cerebellum (11–12 μg/g) (Benramdane et al. 1999). Small amounts were also found in other parts of the brain (8 μg/g), skin (3 μg/g), and hemolyzed blood (0.4 μg/g). Many studies have been performed where arsenic levels in hair and nails have been measured and correlations with exposure analyzed. Some of these studies are discussed in Section 3.8, Biomarkers of Exposure.

Inorganic arsenic passes easily through the placenta. High levels of arsenic were found in the liver, kidney, and brain during autopsy of an infant prematurely born to a young mother who had ingested inorganic arsenic at week 30 of gestation (Lugo et al. 1969). Arsenic was detected in human breast milk at concentrations of 0.00013–0.00082 ppm in a World Health Organization study (Somogyi and Beck 1993). Arsenic concentrations were 0.0001–0.0044 ppm in human milk sampled from 88 mothers on the Faroe Islands whose diets were predominantly seafood (Grandjean et al. 1995). Exposures to arsenic from the seafood diet in this population was most likely to organic "fish arsenic." In a population of Andean women exposed to high concentrations (about 200 ppb) of inorganic arsenic in drinking water, concentrations of arsenic in breast milk ranged from about 0.0008 to 0.008 ppm (Concha et al. 1998b).

Studies in mice and hamsters given oral doses of arsenate or arsenite have found elevated levels of arsenic in all tissues examined (Hughes et al. 2003; Vahter and Norin 1980; Yamauchi and Yamamura 1985), including the placenta and fetus of pregnant females (Hood et al. 1987, 1988). Inorganic arsenic crosses the placental barrier and selectively accumulates in the neuroepithelium of the developing animal embryo (Hanlon and Ferm 1977; Lindgren et al. 1984). In mice, radiolabel from orally administered 74-As was widely distributed to all tissues, with the highest levels in skin, kidney, and liver (Hughes et al. 2003). No obvious differences between As(+3) and As(+5) were found, although residual levels after 24 hours tended to be higher for As(+3) than As(+5) (Vahter and Norin 1980). In hamsters, increases in tissue levels were noted after oral treatment with As(+3) for most tissues (hair, kidney, liver, lung, skin, muscle), with the largest increases in liver and lung (Yamauchi and Yamamura 1985). Liver and kidney arsenic concentations increased with dose in dogs fed arsenite in the diet for 6 months (Neiger and Osweiler 1992).

No studies were located on the distribution of organic arsenicals in humans following oral exposure, but MMA and DMA formed *in vivo* by methylation of inorganic arsenic in hamsters appears to be distributed to all tissues (Takahashi et al. 1988; Yamauchi and Yamamura 1985). This is supported by studies in animals, in which MMA and DMA were found in all tissues after acute oral doses (Stevens et al. 1977b; Yamauchi and Yamamura 1984; Yamauchi et al. 1988).

3.4.2.3 Dermal Exposure

No studies were located regarding distribution of inorganic or organic arsenicals in humans or animals after dermal exposure.

3.4.2.4 Other Routes of Exposure

Studies in mice, rabbits, and monkeys injected intravenously with solutions of arsenite or arsenate confirm that arsenic is widely distributed throughout the body (Lindgren et al. 1982; Marafante and Vahter 1986; Vahter and Marafante 1983; Vahter et al. 1982). Shortly after exposure, the concentration of arsenic tends to be somewhat higher in liver, kidney, lung, and gastrointestinal epithelium (Hughes et al. 2000; Lindgren et al. 1982; Vahter and Marafante 1983; Vahter et al. 1982), but levels tend to

equilibrate over time. Arsenate shows a tendency to deposit in skeletal tissue that is not shared by arsenite (Lindgren et al. 1982, 1984), presumably because arsenate is an analog of phosphate.

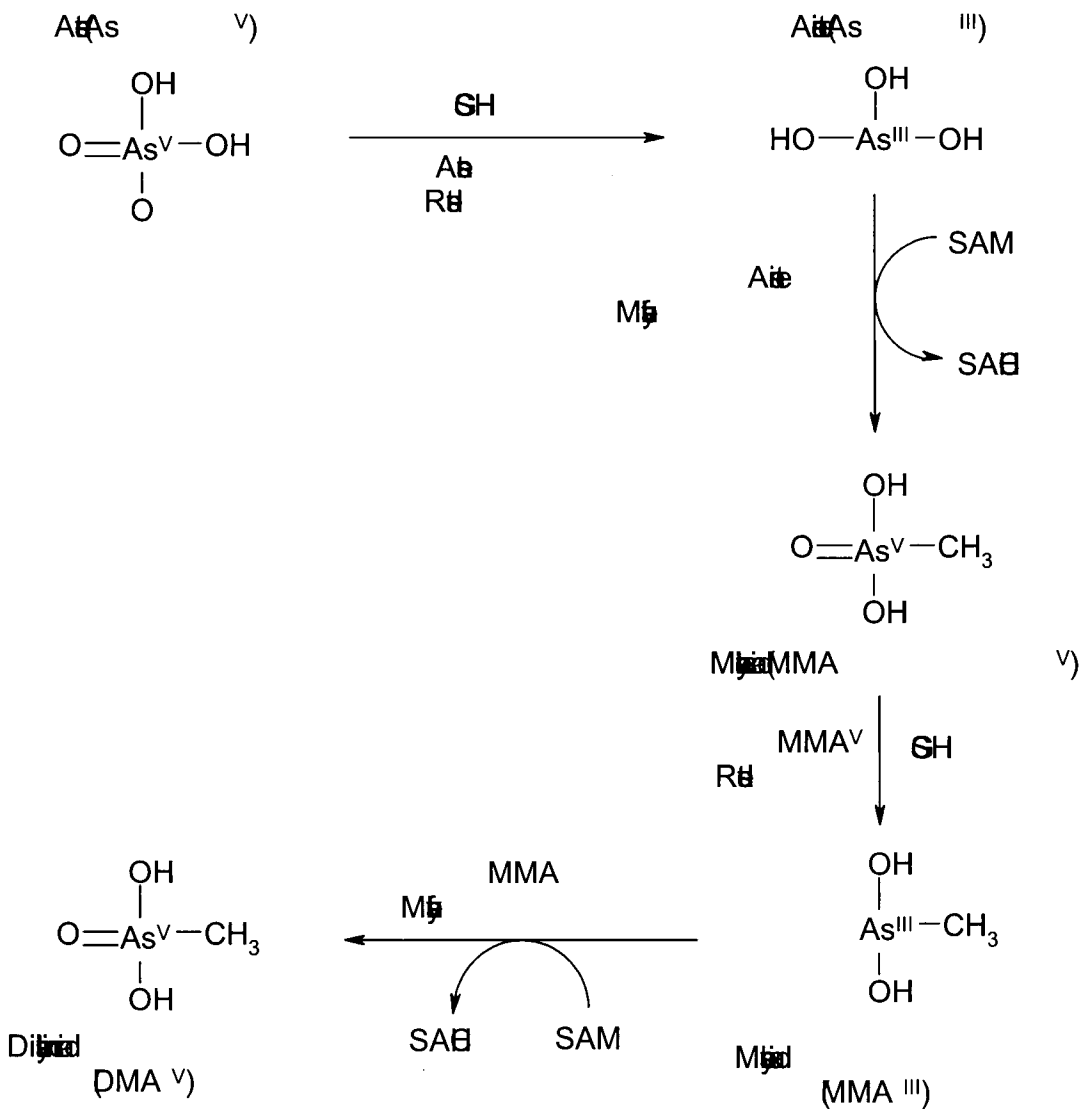
The distribution of arsenic in the rat is quite different from other animal species. Following intramuscular injection of carrier-free radio-arsenate in rats, most of the injected arsenic became bound to hemoglobin in red blood cells, and very little reached other tissues (Lanz et al. 1950). However, similar experiments in dogs, mice, guinea pigs, rabbits, and chicks found very little uptake of arsenic into the blood in these species (cats gave intermediate results).

3.4.3 Metabolism

The metabolism of inorganic arsenic has been extensively studied in humans and animals, and is diagrammed in Figure 3-5. Two basic processes are involved: (1) reduction/oxidation reactions that interconvert As(III) and As(V), and (2) methylation reactions, which convert arsenite to MMA and DMA. The resulting series of reactions results in the reduction of inorganic arsenate to arsenite (if necessary), methylation to MMA(V), reduction to MMA(III), and methylation to DMA(V). These processes appear to be similar whether exposure is by the inhalation, oral, or parenteral route. The human body has the ability to change inorganic arsenic to less toxic organic forms (i.e., by methylation) that are more readily excreted in urine. In addition, inorganic arsenic is also directly excreted in the urine. It is estimated that by means of these two processes, more than 75% of the absorbed arsenic dose is excreted in the urine (Marcus and Rispin 1988), although this may vary with the dose and exposure duration. This mechanism is thought to have an upper-dose limit which, when overwhelmed, results in a higher incidence of arsenic toxicity. This is supported by a case report of an individual who died 3 days after ingesting 8 g of arsenic trioxide (about 3 g of arsenic) (Benramdane et al. 1999). Only 20% of the total arsenic in all tissues analyzed was methylated (14% MMA, 6% DMA), while 78% remained as arsenite and 2% as arsenate.

The majority of the evidence characterizing the metabolic pathways of arsenic is derived from analysis of urinary excretion products. Exposure of humans to either arsenates or arsenites results in increased levels of inorganic As(+3), inorganic As(+5), MMA, and DMA in urine (Aposhian et al. 2000a, 2000b; Buchet et al. 1981a, 1981b; Concha et al. 1998a, 1998b; Crecelius 1977; Kurttio et al. 1998; Lovell and Farmer 1985; Smith et al. 1977; Tam et al. 1979b; Vahter 1986). Similar results are obtained from studies in mice (Vahter 1981; Vahter and Envall 1983), hamsters (Hirata et al. 1988; Marafante and Vahter 1987; Takahashi et al. 1988), and rabbits (Maiorino and Aposhian 1985; Marafante et al. 1985; Vahter and Marafante 1983). Until recently, little distinction was made between MMA(V) and MMA(III) in the

Figure 3-5. Inorganic Arsenic Biotransformation Pathway



urine in most studies, and the assumption was that the majority of MMA in the urine was MMA(V); however, a more recent evaluation has demonstrated that the methylated arsenic atom may be in either valance state (Aposhian et al. 2000a, 2000b).

The relative proportions of As(+3), As(+5), MMA, and DMA in urine can vary depending upon the chemical administered, time after exposure, route of exposure, dose level, and exposed species. In general, however, DMA is the principal metabolite following long-term exposure, with lower levels of inorganic arsenic [As(+3) and As(+5)] and MMA. In humans, the relative proportions are usually about 40–75% DMA, 20–25% inorganic arsenic, and 15–25% MMA (Buchet et al. 1981a; Hopenhayn et al. 2003b; Loffredo et al. 2003; Mandal et al. 2001; Smith et al. 1977; Tam et al. 1979b; Tokunaga et al. 2002; Vahter 1986). With relatively constant exposure levels, these metabolic proportions remain similar over time (Concha et al. 2002), and appear to be similar among family members (Chung et al. 2002). One study of groups of women and children in two villages in Argentina showed that children ingesting large amounts of arsenic in their drinking water (200 µg/L) excreted about 49% inorganic arsenic and 47% DMA (Concha et al. 1998b). This compared to 32% inorganic arsenic and 66% DMA for the women in the study. This may indicate that metabolism of arsenic in children is less efficient than in adults. The rabbit has a ratio of metabolites similar to human adults (Maiorino and Aposhian 1985), suggesting that this may be the best animal model for toxicokinetics in humans. In contrast, the guinea pig, marmoset, and tamarin monkey do not methylate inorganic arsenic (Healy et al. 1998; Vahter and Marafante 1985; Vahter et al. 1982; Zakharyan et al. 1996); thus, they may be poor models for humans.

Reduction of arsenate to arsenite can be mediated by glutathione (Menzel et al. 1994). Scott et al. (1993) showed that glutathione forms complexes with both arsenate and arsenite *in vitro*, and that glutathione is oxidized (and arsenate reduced) in the glutathione-arsenate reaction. Studies *in vitro* indicate that the substrate for methylation is As(+3), and that As(+5) is not methylated unless it is first reduced to As(+3) (Buchet and Lauwerys 1985, 1988; Lerman et al. 1983). The main site of methylation appears to be the liver, where the methylation process is mediated by enzymes that utilize S-adenosylmethionine as cosubstrate (Buchet and Lauwerys 1985, 1988). Under normal conditions, the availability of methyl donors (e.g., methionine, choline, cysteine) does not appear to be rate limiting in methylating capacity, either in humans (Buchet et al. 1982) or in animals (Buchet and Lauwerys 1987; Buchet et al. 1981a). However, severe dietary restriction of methyl donor intake can result in significant decreases in methylating capacity (Buchet and Lauwerys 1987; Vahter and Marafante 1987).

Arsenic methyltransferase and MMA methyltransferase activities have been purified to homogeneity from cytosol of rabbit liver (Zakharyan et al. 1995), Rhesus monkey liver (Zakharyan et al. 1996), and rat liver (Thomas et al. 2004). It appears that a single protein catalyzes both activities. This activity transfers a methyl group from S-adenosylmethionine to As(+3) yielding MMA, which is then further methylated to DMA. Reduced glutathione is probably a co-factor *in vivo*, but other thiols can substitute *in vitro* (L-cysteine, dithiothreitol). The substrate saturation concentration for rabbit arsenite methyltransferase is 50 μM, for MMA methyltransferase it is 1,000 μM. The purified activity is specific for arsenite and MMA; selenite, selenate, selenide, and catechols do not serve as substrates. Recently, Thomas et al. (2004) reported cloning the gene for an S- adenosylmethionine-dependent methyltransferase from rat liver cytosol that catalyzes the conversion of arsenic to methylated and dimethylated species. It bears a high similarity to translations of *cyt19* genes in both the mouse and the human.

Studies in mice indicate that exposure to arsenic does not induce arsenic methylation activity (Healy et al. 1998). Mice receiving up to 0.87 mg As/kg/day as sodium arsenate in drinking water for 91 days had the same arsenic methylating activity as unexposed controls. Specific activities were highest in testis (1.45 U/mg) followed by kidney (0.70 U/mg), liver (0.40 U/mg), and lung (0.20 U/mg). None were affected by arsenic exposure.

Since the methyl derivatives of arsenic generally appear to be less toxic than inorganic arsenic (see Section 3.2), and since methylation tends to result in lower tissue retention of inorganic arsenic (Marafante and Vahter 1984, 1986; Marafante et al. 1985; Vahter and Marafante 1987), the methylation process is usually viewed as a detoxification mechanism. However, several recent studies showing an elevated toxicity of MMA(III) relative even to As(III) in cultured human liver cells (Petrick et al. 2000, 2001) have called this assumption into question. Because methylation is an enzymic process, an important issue is the dose of arsenic that saturates the methylation capacity of an organism, resulting in a possible increased level of the more toxic As(III) in tissues, or whether or not such a dose exists. Limited data from studies in humans suggest that methylation may begin to become limiting at doses of about 0.2–1 mg/day (0.003–0.015 mg/kg/day) (Buchet et al. 1981b; Marcus and Rispin 1988). However, these observations are relatively uncertain since they are based on data from only a few subjects, and the pattern of urinary excretion products in humans who ingested high (near lethal) oral doses or were exposed to elevated levels in the workplace is not much different from that in the general population (Lovell and Farmer 1985; Vahter 1986). Furthermore, the nutrient intakes reported by Engel and Receveur (1993) were sufficient to accommodate the body stores of methyl groups needed for arsenic biomethylation. At the highest arsenic level reported in the endemic area, the biomethylation process required only a few

percent of the total daily methyl intake (Mushak and Crocetti 1995). Thus, the dose rate at which methylation capacity becomes saturated cannot be precisely defined with current data.

With the exception of arsenosugars, which may undergo extensive metabolism, organic arsenicals appear to undergo little metabolism. Humans who ingested a dose of MMA converted a small amount (about 13%) to DMA (Buchet et al. 1981a), and several studies in hamsters have noted the formation of low levels of the trimethyl derivative (trimethylarsine oxide, $(CH_3)_3AsO$) (Yamauchi and Yamamura 1984; Yamauchi et al. 1988). However, the methylarsenates are not demethylated to inorganic arsenic either in humans (Buchet et al. 1981a; Marafante et al. 1987b) or in animals (rats and hamsters) (Stevens et al. 1977b; Yamauchi and Yamamura 1984; Yoshida et al. 2001).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

As noted previously (see Section 3.4.1.1), urinary excretion of arsenic appears to account for 30–60% of the inhaled dose (Holland et al. 1959; Pinto et al. 1976; Vahter et al. 1986). Since the deposition fraction usually ranges from about 30 to 60% for most respirable particles (EPA 1989b), this suggests that nearly all arsenic that is deposited in the lung is excreted in the urine. The time course of excretion in humans exposed by inhalation has not been thoroughly investigated, but urinary arsenic levels in workers in a smelter rose within hours after they came to work on Monday and then fell over the weekend (Vahter et al. 1986). This implies that excretion is fairly rapid, and this is supported by intratracheal studies in rats (Rhoads and Sanders 1985) and hamsters (Marafante and Vahter 1987), where whole-body clearance of administered arsenate or arsenite occurred with a half-time of 1 day or less. However, small amounts of arsenic may remain bound in the lung, and only be cleared with a half-time of several months (Rhoads and Sanders 1985). The primary forms of arsenic found in the urine of inhalation-exposed humans are DMA and MMA, with inorganic arsenic comprising <25% of the total urinary arsenic (Apostoli et al. 1999).

No studies were located regarding the excretion of organic arsenicals by humans or animals after inhalation exposure. However, rats that were given a single intratracheal dose of DMA excreted about 60% in the urine and about 8% in the feces within 24 hours (Stevens et al. 1977b). This indicates that organic arsenicals are likely to be promptly excreted after inhalation exposure.

3.4.4.2 Oral Exposure

Direct measurements of arsenic excretion in humans who ingested known amounts of arsenite or arsenate indicate that very little is excreted in the feces (Bettley and O'Shea 1975), and that 45–85% is excreted in urine within 1–3 days (Apostoli et al. 1999; Buchet et al. 1981a; Crecelius 1977; Mappes 1977; Tam et al. 1979b). At low exposure levels, urinary arsenic levels generally increase linearly with increasing arsenic intake (Calderon et al. 1999). During lactation, a very small percent of ingested arsenic may also be excreted in the breast milk (Concha et al. 1998a). A similar pattern of urinary and fecal excretion is observed in hamsters (Marafante and Vahter 1987; Yamauchi and Yamamura 1985) and mice (Vahter and Norin 1980); this pattern is typically modeled as a biphasic process (e.g., Hughes et al. 2003). Generally, whole body clearance is fairly rapid, with half-times of 40–60 hours in humans (Buchet et al. 1981b; Mappes 1977). Clearance is even more rapid in mice and hamsters, with 90% removed in 2 days (Hughes et al. 2003; Marafante and Vahter 1987; Vahter 1981; Vahter and Norin 1980).

Studies in humans indicate that ingested MMA and DMA are excreted mainly in the urine (75–85%), and this occurs mostly within 1 day (Buchet et al. 1981a; Marafante et al. 1987b). This is supported by studies in rats and hamsters, although in animals excretion is more evenly distributed between urine and feces (Marafante et al. 1987b; Stevens et al. 1977b; Yamauchi and Yamamura 1984; Yamauchi et al. 1988).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion of inorganic arsenicals in humans or animals following dermal exposure. In rats, arsenic absorbed through the tail was excreted approximately equally in urine and feces, similar to the excretion pattern following oral exposure (Dutkiewicz 1977).

No studies were located regarding excretion of organic arsenicals in humans or animals following dermal exposure.

3.4.4.4 Other Routes of Exposure

Excretion of arsenate and arsenite following parenteral exposure of animals is similar to that seen following oral exposure. In rabbits and mice, urinary excretion within 8 hours usually accounts for about

50–80% of the dose (Maehashi and Murata 1986; Maiorino and Aposhian 1985; Vahter and Marafante 1983). Somewhat lower levels (30–40%) are excreted in the urine of marmoset monkeys (Vahter and Marafante 1985; Vahter et al. 1982), probably because of the absence of methylation in this species. Whole-body clearance studies in mice indicate that arsenate is over 65% removed within 24 hours, while arsenite is about 86% removed at 24 hours (Lindgren et al. 1982). A relatively small proportion of an injected dose of arsenic V (10% for rats, 4% for mice, and <2% for hamsters, guinea pigs, and rabbits) was found to be excreted into the bile within the first 2 hours post-injection (Csanaky and Gregus 2002). Following arsenic III injection, a much greater percentage (92% for guinea pigs and 75% for rats) of the arsenic was found in the bile in the first 2 hours after administration (Csanaky and Gregus 2002).

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

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

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

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

1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-6 shows a conceptualized representation of a PBPK model.

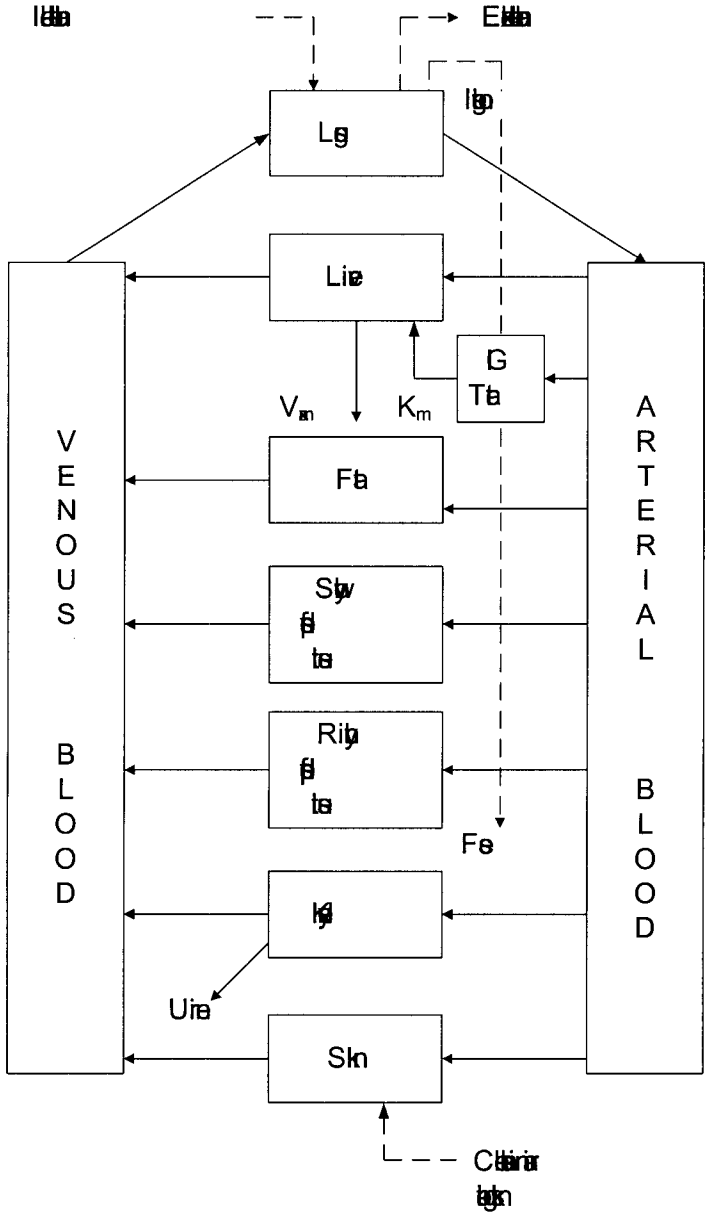
If PBPK models for arsenic exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

PBPK models for arsenic are discussed below.

3.4.5.1 Summary of PBPK Models

The Mann model (Gentry et al. 2004; Mann et al. 1996a, 1996b), Yu model (Yu 1998a, 1998b; Yu 1999a, 1999b), and Menzel model (Menzel et al. 1994) are the PBPK models for arsenic currently available. The Mann model simulates the absorption, distribution, metabolism, elimination, and excretion of As(+3), As(+5), MMA, and DMA after oral and inhalation exposure in mice, hamsters, rabbits, and humans. The Yu model simulates the absorption, distribution, metabolism, elimination, and excretion of As(+3), As(+5), MMA, and DMA after oral exposure to inorganic arsenic in mice, rats, or humans. The Menzel

Figure 3-6. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



model is a preliminary model that predicts internal organ burden of arsenic during specific oral exposures, simulating the metabolism, distribution to organs and binding to organs in mice, rats, and humans.

3.4.5.2 Arsenic PBPK Model Comparison

The Mann model is a well-derived model, consisting of multiple compartments and metabolic processes, and modeling four chemical forms of arsenic (two organic and two inorganic), which has been validated using experimental data. The Yu model has more compartments than the Mann model, also models metabolism and fate of four forms of arsenic, and has likewise been validated using experimental data. The Menzel model is still preliminary and has not been validated.

3.4.5.3 Discussion of Models

The Mann Model

Risk assessment. The Mann model was not used for risk assessment.

Description of the model. The Mann model was initially developed to simulate oral, intratracheal, and intravenous exposure to arsenic in rabbits and hamsters (Mann et al. 1996a). In a companion paper, the model was expanded to include inhalation exposure and extrapolated and applied to humans (Mann et al. 1996b). A subsequent paper further expanded the model to include mice (Gentry et al. 2004).

The model consists of six tissue compartments: blood, liver, kidneys, lungs, skin, and other tissues. The blood compartment is divided into plasma and red blood cell subcompartments, considered to be at equilibrium. Three routes of exposure are considered in the model. Oral exposure is considered to enter the liver from the gastrointestinal tract via first-order kinetics. Intratracheal exposure results in deposition into the pulmonary and tracheo-bronchial regions of the respiratory tract. Uptake into blood from the pulmonary region is considered to be via first order kinetics into plasma, uptake from the tracheo-bronchial region is by both transfer into plasma and transport into the gastrointestinal tract. Intravenous injection results in a single bolus dose into the plasma compartment.

Metabolism in the model consists of oxidation/reduction and two methylation reactions. The oxidation/reduction of inorganic arsenic was modeled as a first order process in the plasma, with

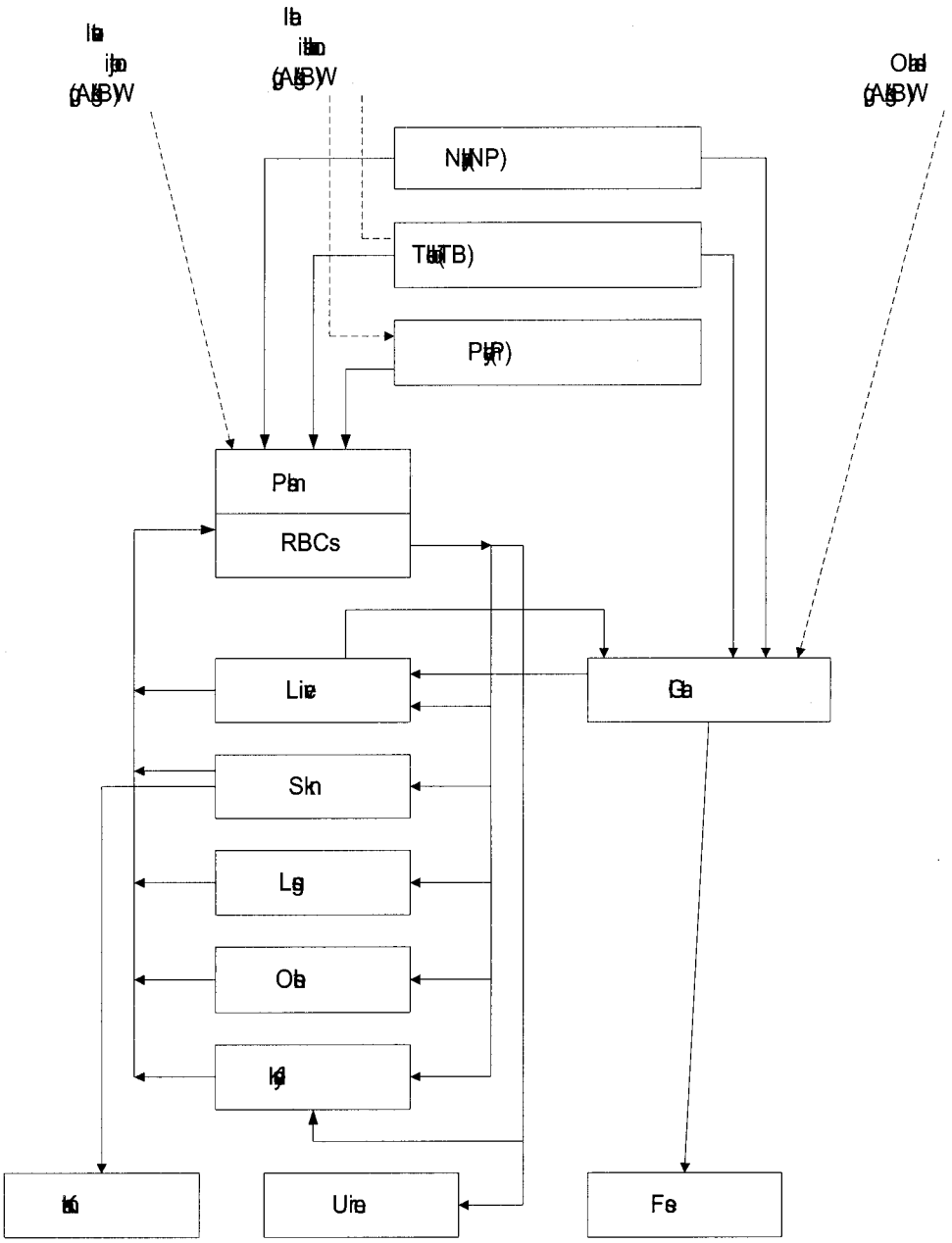
reduction also included in the kidneys. Methylation of As(+3) was modeled as a two-step process occurring in the liver according to Michaelis-Menton kinetics.

Most physiological parameters were derived by scaling to body weight (Lindstedt 1992). In cases where parameters were not available (absorption rates, tissue affinity, biotransformation), estimates were obtained by fitting. This was done by duplicating the initial conditions of published experiments in the model, varying the unknown parameters and comparing the results of the simulation to the reported results. Tissue affinity constants were estimated using reported arsenic levels in tissues at various times after exposure. Metabolic rate constants and absorption rate constants were estimated using data for excretion of arsenic metabolites in urine and feces. Figure 3-7 shows the animal model and Tables 3-9 through 3-12 provide the parameters used in the animal model. The human model is similar to the animal models with adjustments for body weight and absorption and metabolic rates. A naso-pharynx compartment is included in the human model, which was not present in the animal models. Penetration and deposition in the respiratory tract are based on the log-normal particle size distribution of the aerosol. Metabolic and absorption rate constants were fitted using experimental data on urinary excretion of arsenic following a single oral dose of As(+3) (Buchet et al. 1981a) or As(+5) (Tam et al. 1979b) in human volunteers. The lung absorption rate constant was obtained by fitting the total urinary excretion of arsenic as predicted with the model to experimental data obtained from occupational exposure to arsenic trioxide (Offergelt et al. 1992). Figure 3-8 shows the human model, and Tables 3-13 and 3-14 provide the data and constants used in the human model.

Validation of the model. The model was generally successful in describing the disposition of an intravenous dose of sodium arsenate in rabbits over a 24-hour period (Marafante et al. 1985). Discrepancies included a 6–7-fold overestimation of levels in skin at 24 hours and underestimation of As(+5) in plasma in the hour following injection. A statistical assessment of how well the model fit the empirical data was not presented. In hamsters, the model was also generally predictive of oral and intratracheal exposures (Marafante and Vahter 1987). Generally, predictions were better for the exposures to As(+5) than for those to As(+3).

The human model was validated using data from studies of repeated oral intake of sodium arsenite in human volunteers (Buchet et al. 1981b), occupational exposure to arsenic trioxide and elemental arsenic (Vahter et al. 1986), and community exposure to As(+5) via drinking water (Harrington et al. 1978; Valentine et al. 1979). Simulations were generally in good agreement with the experimental data.

Figure 3-7. Parameters Used in the Mann PBPK Model for Animals



Source: Mann et al. 1996b

Table 3-9. Parameters Used in the Mann PBPK Model for Animals

Parameter	Rat	Mouse
Blood flow (L/hr/kg$^{2/3}$)	2.3	1.7
Organ volumes (L/kg)		
Liver	0.12	0.08
Kidney	0.02	0.02
Lung	0.03	0.01
Skin	0.14	0.07
Organ flow (fraction of cardiac output)		
Other	0.18	0.12
Lung uptake (fraction of dose)		
Skin	0.05	0.06
Skin uptake	0.01	0.01
Blood partition coefficients		
Calculated	0.6	0.8
Liver (basic)	0.12	0.12
Liver (acidic)	0.09	0.09
Kidney	0.10	0.07
Lung	0.13	0.07
Skin	0.08	0.12
Other	0.12	0.12
Clearance (L/hr/kg$^{2/3}$)		
Urinary Clearance	0.10	0.16
Slowly reversible binding	0.16	0.16
Tissue binding (mg/L)	0.3	0.1

Source: Mann et al. 1996a

PBPK = physiologically based pharmacokinetic

Table 3-10. Tissue Affinity Constants (K_{ij}) Obtained for the Mann PBPK Model for Animals by Fitting for Rabbits and Hamsters

	K_{ij}			
Tie(*i*)	A¥	A(II)	MMA	DMA
Liv	1	2	0	1
Kid	0	2	0	5
Lg	1	1	1	2
Skn	1	6	6	1
Ob	0	0	1	1

SaMa

DMA = MMA = PBPK

Table 3-11. Metabolic Rate Constants for the Mann PBPK Model for Animals Obtained by Fitting for Rabbits and Hamsters

SeMa

PBPK

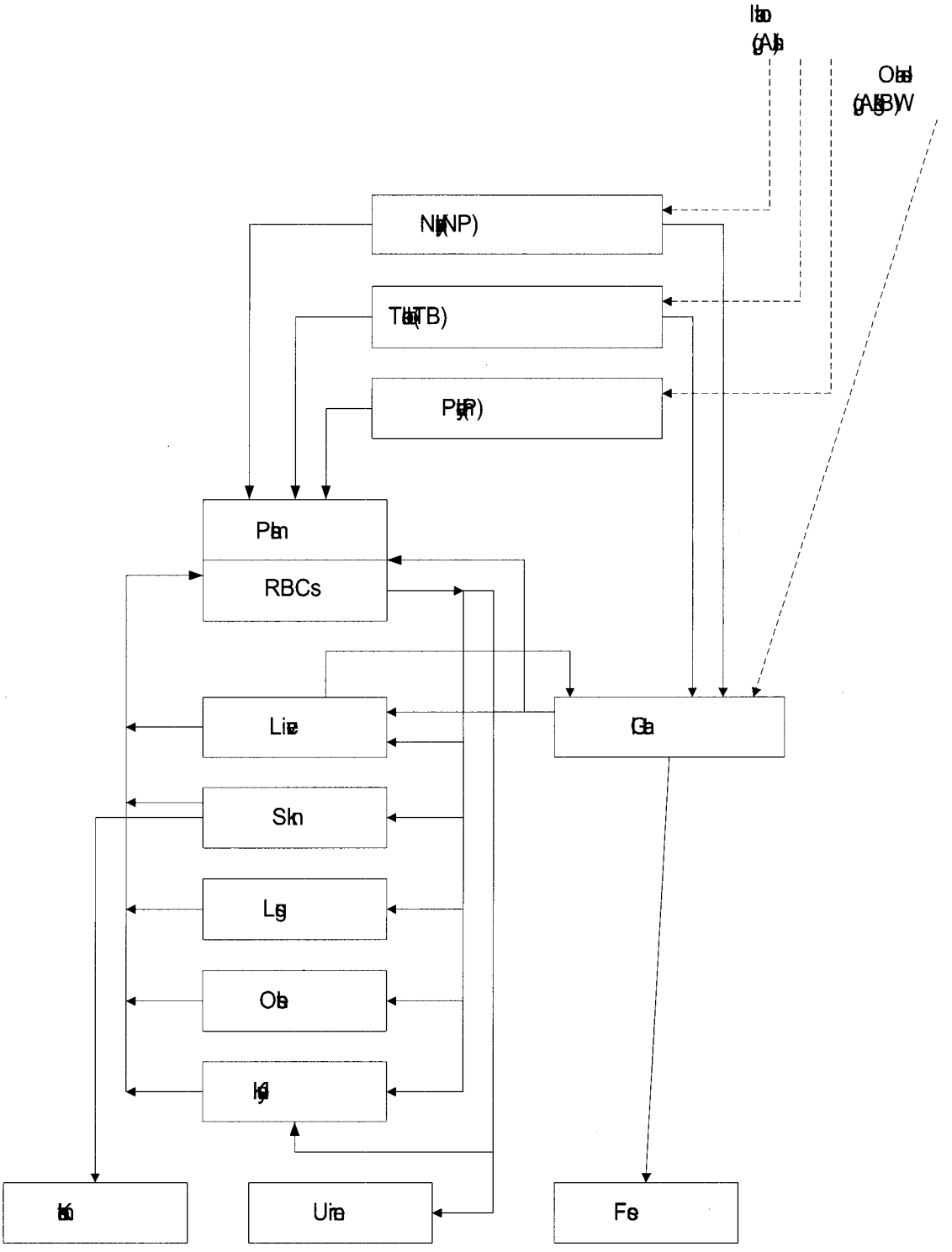
Table 3-12. Fitted Gastrointestinal Tract and Lung Absorption Half-time for the Hamster for the Mann PBPK Model

Aisqch	Lg		
A			
$Na_3(AsO_4)$	θ		2
$Pb_3(AsO_4)$	θ		θ
As_2O_5	2		—
A(III)			
$NaAsO_2$	θ		2
As_2S_3	θ		2
As_2O_3	2		—
DMA	θ		—

SeMa

DMA =PBPK

Figure 3-8. Parameters Used in the Mann PBPK Model for Humans



SeMaeB

Table 3-13. Physiological Data Used in the Mann PBPK Model for Humans

P	Og		Uits	
Bdn			bm	3
Og		Liv	g	6
		Kdy	g	8
		Lg	g	8
		Skn	g	3
		Obs	g	7
Ldn		Stn	bm	2
		Stn ibe	bm	9
Bdv		Cdp Lin		9
		Liv bc	Lin	0
		Liv bc	Lin	0
		Kdy	Lin	6
		Lg	Lin	0
		Skn	Lin	6
		Obs	Lin	0
Cin				
Mn			g	7
Fn			g	0
Cn				
Bn			bin	6
Stn			cm	8
Np			cm 2	7
Thn			cm 2	3
Py			cm 2	7
Thy			cm 2	6

Sa M

PBPK

Table 3-14. Tissue Affinity Constants (K_{ij}) Obtained by Fitting the Mann PBPK Animal Model for Use with Humans

	K_{ij}			
Tie()	A¥	A(I)	MMA	DMA
Li	1	2	0	1
K	0	2	0	5
Lg	1	1	1	2
Skn	1	6	6	1
Rd b b	2	5	2	2
Ob	0	0	1	1

Se M

DMA MMA PBPK

The predictions of tissue distribution, metabolism, and elimination of arsenic compounds from the mouse model were compared with experimental data, and showed generally good agreement. The model tended to overpredict the concentration of organic arsenicals in the lungs, and to a lesser extent in the kidneys and liver, while for inorganic arsenic, the model overpredicted the levels of arsenic (V) present in the urine of acutely-exposed mice.

Target tissues. Levels in skin were not well predicted by this model in animals. Results for the lung were not presented, except for the mouse model, which tended to overpredict lung levels. The human model was only used to predict urinary metabolites.

Species extrapolation. Species extrapolation was not attempted in this model. However, tissue affinities derived for the rabbit and hamster models were used in the human model.

Interroute extrapolation. Interroute extrapolation was not attempted in this model.

The Menzel Model

Risk assessment. The Menzel model was not used for risk assessment.

Description of the model. The Menzel model was developed to simulate oral exposure to arsenic from drinking water and food. Inhalation of arsenic in the particulate phase or as arsine gas is not considered. The chemical species in drinking water is assumed to be As(+5).

The model consists of two sets of compartments: those in which the pools of arsenic are not influenced by blood perfusion, and those in which blood perfusion does determine arsenic burden. The former set of compartments includes the gut, feces, hair, bladder, and urine. The latter set of compartments included lung, liver, fat, skin, kidney, and other tissues. Oral exposure is considered to enter the liver from the gastrointestinal tract.

The model followed that of Anderson and coworkers (Anderson et al. 1987; Ramsey and Anderson 1984). Data from mice were used to test predictions of absorption. Excretion is considered to be rapid and complete into the urine, with no reabsorption from the kidney. Fecal arsenic content accounts for unabsorbed arsenic excreted in the bile, and complex arsenic species from food. Metabolism includes

reduction by glutathione and methylation. Arsenic accumulation in the skin, hair and nails was included by assuming that arsenic binds irreversibly to protein sulfide groups in hair and nails.

Validation of the model. The model was preliminary and has not been validated.

Target tissues. Target tissues have not yet been modeled.

Species extrapolation. Species extrapolation was not attempted in this model.

Interroute extrapolation. Interroute extrapolation was not attempted in this model.

The Yu Model

Risk assessment. The Yu model was not used for risk assessment.

Description of the model. The Yu model was developed to simulate oral exposure to arsenic in mice and rats (Yu 1998a, 1998b), and was later adapted for oral exposures in humans (Yu 1999a, 1999b). Inhalation of arsenic in the particulate phase or as arsine gas is not considered. As(+3), As(+5), MMA, and DMA were all considered in the model, though the movements of MMA and DMA were not considered.

The model consists of eight tissue compartments: intestine, skin, muscle, fat, kidney, liver, lung, and vessel-rich group (VRG, e.g., brain); in the human model, the VRG and kidney compartments were combined. Only oral exposure was considered. Absorption is based on absorption to the stomach, which then passes the arsenic to the gastrointestinal tract. From the gastrointestinal tract, arsenic is either transferred to the blood or excreted in the feces.

The physiological parameters for the model were obtained from published values in the literature. Tissue/blood partition coefficients were based on the postmortem blood and tissue concentrations from a fatal human poisoning case study (Saady et al. 1989). Tissue volumes and blood flow rates were based on published values from a number of sources (EPA 1988e; Reitz et al. 1990). Absorption and excretion rate constants were based on experimental observations of blood concentrations and urinary and fecal excretion following oral administration of inorganic arsenic (Odanaka et al. 1980; Pomroy et al. 1980). Metabolic rate constants for the methylation and dimethylation of inorganic arsenic were also based on

experimental observations (Buchet et al. 1981a; Crecelius 1977). Figure 3-9 shows the model and Table 3-15 provides the parameters used for each species.

Validation of the model. The model was generally successful at predicting the urinary excretion 48 hours after administration of 5 mg/kg inorganic arsenic in both rats and mice. After 48 hours, the observed/predicted ratios associated with excreted doses ranged from 0.78 to 1.11 for the mouse and from 0.85 to 0.93 for the rat. However, the model overpredicted the amount of inorganic arsenic found in the feces of mice at 24 and 48 hours, and overpredicted the amount of DMA formed by exposed mice at 48 hours. In rats, the model overestimated the urinary and fecal excretion of inorganic arsenic at 24 hours postexposure, though at 48 hours, measured values all fell within the predicted ranges. The human model was also generally successful at predicting the urinary excretion of arsenic compounds following oral exposure, based on results of controlled human exposure studies (Buchet et al. 1981a; Vahter 1983). In general, however, the model underpredicts excretion at early time points and overpredicts at later time points, with 24 hours being the time at which its predictive capabilities agreed most strongly with available data.

The ability of the model to predict tissue burdens was not compared to actual data for any species.

Target tissues. Model predictions of tissue burdens were not compared to actual data. The model accurately predicted, with a few exceptions, the urinary and fecal excretion of inorganic arsenic and its metabolites in rats, mice, and humans.

Species extrapolation. Species extrapolation beyond rats and mice was not attempted using this model. The human model has not been compared to, or linked with, either of the rodent models.

Interroute extrapolation. Interroute extrapolation was not attempted using this model.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Arsenic absorption depends on its chemical form. In humans, As(+3), As(+5), MMA, and DMA are orally absorbed ≥75%. Arsenic is also easily absorbed via inhalation. Absorption appears to be by passive diffusion in humans and mice, although there is evidence (Gonzalez et al. 1995) for a saturable

Figure 3-9. Parameters Used in the Yu PBPK Model for Animals

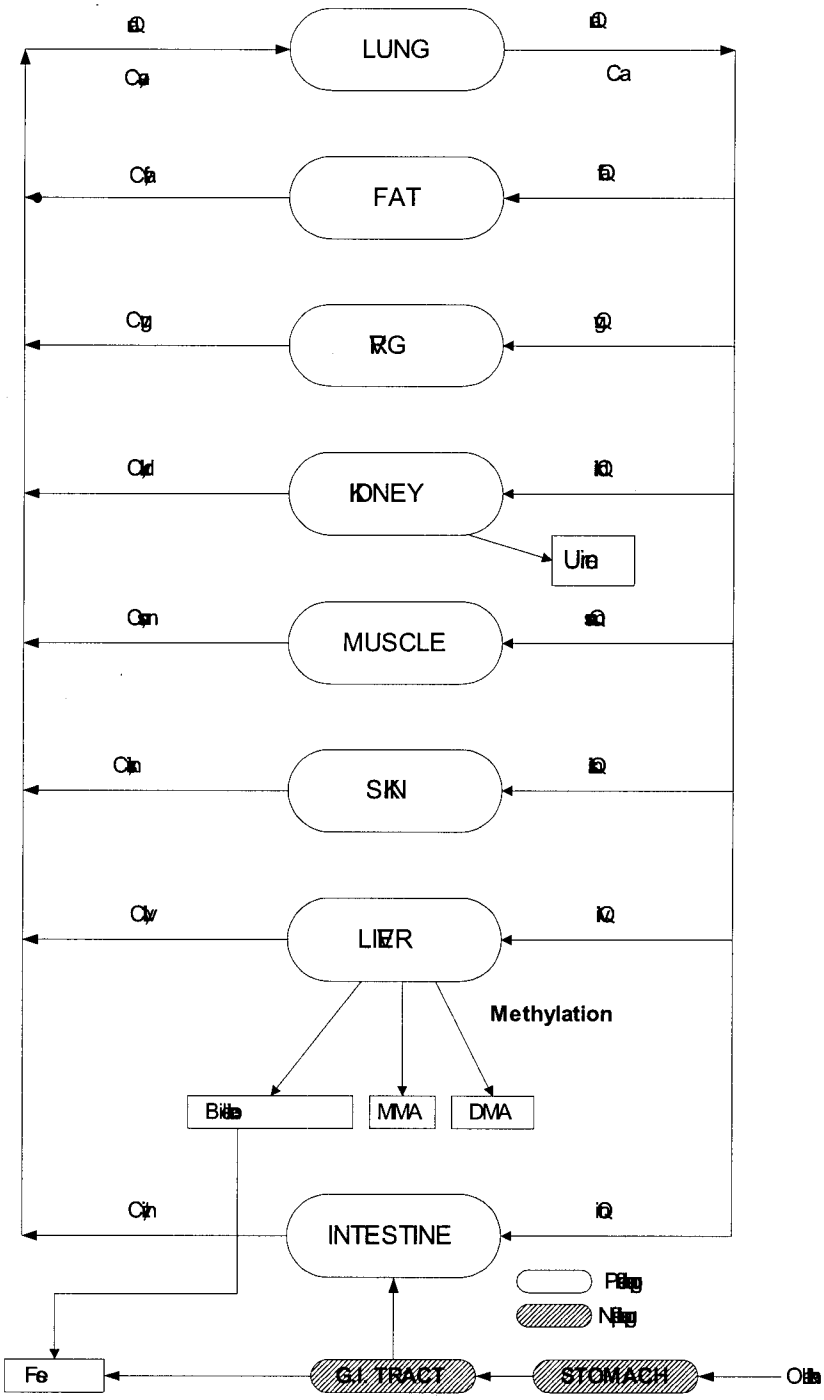


Table 3-15. Parameters Used in the Yu PBPK Model

	Mo	Ra		Hu	
Pa				As III As V MMA DMA)	
Ble	0	0	2		
Sk	0	0	2		
RG	0	0	Co		
Mu	0	0	2		
Fa	—	0	0		
Ki	0	3	1		
Liv	0	0	2		
Lg	0	0	1		
Bl (L)					
Ble	0	2	0		
Sk	0	0	0		
RG	3	0	NA		
Mu	3	2	2		
Fa	—	2	5		
Ki	2	2	2		
Liv	2	2	0		
Lg	NR	NR	2		
Tis (L)					
Ble	0	0	0		
Sk	3	5	0		
RG	0	0	NA		
Mu	9	2	0		
Fa	—	5	2		
Ki	0	6	2		
Liv	5	2	2		
Lg	2	0	0		
Mo					
(MMA) (µ/	0	0	2		
(DMA) (µ/	0	0	2		
K (MMA) (µ/	0	2		0	
K (DMA) (µ/	2	2		0	
Fi				As III As V MMA DMA)	
K_{SI} ($^{-1}$)	0	0		2	
K_{AI} ($^{-1}$)	5	0		2	
K_{e} ($^{-1}$)	0	0		0	
K_{ur} ($^{-1}$)	2	0		0	
K_{bi} ($^{-1}$)	0	0		0	

NA = NR =

carrier-mediated cellular transport process for arsenate in rats (for review, see Rosen, 2002). Dermal absorption appears to be much less than by the oral or inhalation routes. Bioavailability of arsenic from soil appears to be lower via the oral route than it is for sodium salts of arsenic. Arsenic in soil may form water insoluble compounds (e.g., sulfides), which are poorly absorbed.

Arsenic and its metabolites distribute to all organs in the body; preferential distribution has not been observed in human tissues at autopsy or in experiments with animal species other than rat (in which arsenic is concentrated in red blood cells). Since the liver is a major site for the methylation of inorganic arsenic, a "first-pass" effect is possible after gastrointestinal absorption; however, this has not been investigated in animal models.

Arsenic and its metabolites are largely excreted via the renal route. This excretion mechanism is not likely to be saturated within the dose range expected from human exposure. Excretion can also occur via feces after oral exposure; a minor excretion pathway is nails and hair. The methylation of inorganic arsenic is the major detoxification pathway. The proportion of metabolites recovered in urine [As(+3), As(+5), MMA, DMA] are roughly consistent in humans regardless of the exposure scenario. However, interindividual variation is great enough that it cannot be determined if capacity limitation may occur in some individuals.

The manifestation of arsenic toxicity depends on dose and duration of exposure. Single oral doses in the range of 2 mg As/kg and higher have caused death in humans. Doses as low as 0.05 mg As/kg/day over longer periods (weeks to months) have caused gastrointestinal, hematological, hepatic, dermal, and neurological effects. These effects appear to be a result of direct cytotoxicity. Long-term exposure (years) to drinking water at levels as low as 0.001 mg As/kg/day have been associated with skin diseases and skin, bladder, kidney, and liver cancer. Long-term inhalation exposure to arsenic has also been associated with lung cancer at air levels as low as 0.05–0.07 mg/m^3. It is not clear at this time why long-term toxicity is different between the oral and inhalation routes, given that arsenic is easily absorbed into the systemic circulation by both routes.

Studies in mice and rats have shown that arsenic compounds induce metallothionein, a metal-binding protein thought to detoxify cadmium and other heavy metals, *in vivo* (Albores et al. 1992; Hochadel and Waalkes 1997; Kreppel et al. 1993; Maitani et al. 1987a). The potency of arsenic compounds in inducing metallothionein parallels their toxicity (i.e., As(+3) > As(+5) > MMA > DMA). For cadmium, it is thought that metallothionein binds the metal, making it biologically inactive. For arsenic, however, only

a small percentage of the administered metal is actually bound to metallothionein (Albores et al. 1992; Kreppel et al. 1994; Maitani et al. 1987a). *In vitro* studies have shown that affinity of arsenic for metallothionein is much lower than that of cadmium or zinc (Waalkes et al. 1984). It has been proposed that metallothionein might protect against arsenic toxicity by acting as an antioxidant against oxidative injury produced by arsenic (NRC 1999).

3.5.2 Mechanisms of Toxicity

Effect of Metabolism on Toxicity. The effect of metabolism on toxicity appears to depend on dose. In relatively high oral exposures (≥0.05 mg/kg/day), it is likely that methylation capacity is not adequate to prevent cytotoxic levels of As(III) from reaching tissues. Saturation of methylating enzymes may in theory result in the buildup of MMA(III), which is also believed to be cytotoxic (Petrick et al. 2000). At lower long-term doses, which have been associated with cancer, the relationship between metabolism and toxicity is the object of debate. The demand of arsenic on cellular methylating capacity (particularly the co-factor S-adenosylmethionine) may also lower the efficiency of other cellular methyltransferases, although evidence for this is limited, and may vary with the form of arsenic (e.g. arsenite vs. arsenate). These effects on DNA methylating activity are discussed below.

Target Organ Toxicity. Relatively high-dose acute- and intermediate-duration toxicity appears to be the result of arsenic cytotoxicity. Reduced inorganic arsenic [As(+3)] may react with sulfhydryl groups in proteins and inactivate target enzymes. A particular target in the cell is the mitochondrion, which accumulates arsenic (Goyer 1991). Arsenic inhibits succinic dehydrogenase activity and can uncouple oxidative phosphorylation; the resulting fall in ATP levels affects virtually all cellular functions (Na+/K+ balance, protein synthesis, etc.).

Mechanistic studies of arsenic toxicity have suggested a role of the generation of reactive oxygen species in the toxicity of inorganic arsenic (Bernstam and Nriagu 2000; Kitchin and Ahmad 2003; Shi et al. 2004; Wu et al. 2001). Both *in vivo* and *in vitro* studies of arsenic-exposed humans and animals have indicated the possible involvement of increased lipid peroxidation (Mukherjee et al. 2004; Pi et al. 2002), superoxide production (Kessel et al. 2002; Lynn et al. 2000), hydroxyl radical formation (Nishikawa et al. 2002), blood nonprotein sulfhydrals (Pi et al. 2002), and/or oxidant-induced DNA damage (Matsui et al. 1999; Nesnow et al. 2002; Nishikawa et al. 2002). Reduction of cellular oxidant defense by treatment with glutathione depleting agents results in an increased sensitivity of cells to arsenic toxicity (Davison et

al. 2003). It is noteworthy that the same oxidative processes that are thought to lead to cellular damage may also result in genotoxicity and eventual carcinogenesis.

Carcinogenesis. The EPA and the International Agency for Research on Cancer (IARC) classify arsenic as a carcinogen for which there is sufficient epidemiological evidence to support a causal relationship between exposure to arsenic and skin cancer. Unlike the large majority of substances considered as human carcinogens based on epidemiological evidence, arsenic alone will not induce cancer in most rodent models, although it has been shown to be a complete transplacental carcinogen in mice (Waalkes et al. 2003a, 2004a, 2004b, 2004c). The genotoxicity database for arsenic indicates that it does not acutely induce point mutations, but delayed (~8 days) mutagenesis, oxidative DNA mutations, chromosomal aberrations, and sister chromatid exchanges have been reported (see Tables 3-13 and 3-14). Arsenic can also potentiate mutagenicity observed with other chemicals. This potentiation may be the result of direct interference by arsenic with DNA repair processes, perhaps by inhibiting DNA ligase (Li and Rossman 1989) or other DNA repair enzymes (Ahsan et al. 2003; Andrew et al. 2003a, 2003b; Danaee et al. 2004). Finally, arsenic can also induce DNA amplification (Lee et al. 1988).

It has been hypothesized that methylation changes in genes or their control regions can lead to altered gene expression, and potentially, carcinogenesis (Baylin et al. 1998; Chen et al. 2003b; Chung et al. 2002; Costa 1995). A study of exposed humans in Taiwan suggested that subjects with lower secondary methylation indices, as indicated by the ratio of DMA to MMA in the urine, have an increased risk of bladder cancer (Chen et al. 2003b), particularly in subjects with high exposure levels. Effects of arsenic on DNA methylation have been studied in two cell culture systems. In the first, arsenite exposure in the human lung adenocarcinoma cell line A549 resulted in hypermethylation of cytosine in the promoter region of the tumor suppressor gene p53 (Mass and Wang 1997). In the second, hypomethylation throughout the genome was found in a rat liver cell line (TRL 1215) that had been exposed to submicromolar sodium arsenite for 18 weeks; these cells exhibited aberrant gene expression and had undergone malignant transformation, as demonstrated by the induction of tumors when injected into Nude mice (Zhao et al. 1997).

Inorganic arsenic exposure has been shown to modify the expression of a variety of genes related to cell growth and defense (Liao et al. 2004a; Rea et al. 2003), including the tumor suppressor gene p53 (Hsu et al. 1999; Mass and Wang 1997; Salazar et al. 2004), as well as alter the binding of nuclear transcription factors (Kaltreider et al. 1999).

The tissue-specificity of arsenic carcinogenicity in humans is being studied in primary human epidermal keratinocytes (Germolec et al. 1997a). Low micromolar concentrations of sodium arsenite resulted in neoplasia accompanied by increased mRNA transcripts and secretion of growth factors including granulocyte macrophage-colony stimulating factor (GM-CSF), transforming growth factor alpha (TGF-α), and the cytokine tumor necrosis factor alpha (TNF-α). Arsenic in drinking water also increased the number of skin papillomas in transgenic mice in which dermal application of phorbol esters induces papillomas (genetically initiated mice), although it did not do so alone. These results support a hypothesis that chronic low-level exposure to arsenic stimulates keratinocyte secretion of growth factors, the resulting increased cellular division (and concomitant DNA replication) allows greater opportunities for genetic damage to occur.

Recent evidence has suggested that the carcinogenic effects of arsenic may result from a cocarcinogenic effect of arsenic, rather than direct carcinogenic action. Two studies (Burns et al. 2004; Rossman et al. 2001) have reported that while arsenic exposure (up to 10 mg/L in the drinking water) alone did not result in the formation of skin tumors in mice, co-exposure to arsenic and ultraviolet light had a greater than additive effect on skin tumor formation, with greater numbers and size of tumors compared to ultraviolet light alone. While the precise mechanisms of this effect has not been elucidated, Pi et al. (2005) have reported that long-term exposure of cells to low levels of inorganic arsenic confers resistance to apoptosis through a phosphorylated PKB-related mechanism. A resistance to apoptosis would allow for the expansion of otherwise-damaged cells, and could result in an enhanced carcinogenic effect. Several recent reviews (Rossman 2003; Rossman et al. 2004) have further discussed arsenic-related cocarcinogenesis.

3.5.3 Animal-to-Human Extrapolations

The usefulness of animal models for toxicity studies with arsenic is significantly limited by two major factors. First and most importantly, no animal model exists for the health effect of greatest concern for human exposure: carcinogenicity in skin and other organs after oral exposure. Second, the pattern of metabolism in humans (significant excretion of the methylated forms of arsenic) is unlike that of most other mammalian species (the mouse and rabbit may be exceptions). The ratios of inorganic to organic arsenic excreted also vary between species. The rat sequesters arsenic in its erythrocytes and is not a suitable model for human toxicity.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

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

There is little evidence to suggest that arsenic functions as an endocrine disruptor. An association has been demonstrated between exposure to arsenic in drinking water and increased incidence of diabetes mellitus (Rahman et al. 1998; Tsai et al. 1999; Tseng et al. 2000; Wang et al. 2003), although dose-response relationships are not available and the mechanism of action for this response has not been

characterized. No other relevant data were located in humans or animals. Data on general effects of arsenic compounds on the endocrine system are presented in Sections 3.2.1.2 and 3.2.2.2 above.

No in vitro studies were located regarding endocrine disruption of arsenic.

3.7 CHILDREN'S SUSCEPTIBILITY

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

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

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

sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

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

Arsenic has been recognized as a human toxicant for many centuries, and the symptoms of acute poisoning are well known. Children who are exposed to high levels of arsenic exhibit symptoms similar to those seen in adults, including respiratory, cardiovascular, dermal, and neurological effects, and vomiting if the arsenic is ingested (Borgono et al. 1980; Foy et al. 1992; Kersjes et al. 1987; Mazi et al. 2001; Rosenberg 1974; Zaldívar 1974; Zaldívar and Gullier 1977). Arterial thickening of the pancreas was observed in five children who died in Chile after chronic exposure to arsenic (Rosenberg 1974). Foy et al. (1992) described systemic effects of chronic arsenic exposure in children in a village near a tin and tungsten mining operation in Thailand. The arsenic concentration in water samples from 35 shallow wells averaged 0.82 mg As/L (range, 0.02–2.7 mg As/L). Piped water (available in some homes) had a concentration of 0.07 mg As/L. A survey of skin manifestations of arsenic poisonings was conducted in the autumn of 1987. The case reports of four children were presented. All of the children had hyperkeratosis and hyperpigmentation of the extremities, including tibia, palms, and soles. In addition, one child had developed weakness 3 years previously and had anorexia and a chronic cough for 1 year. She had been held back twice in school as a slow learner. On examination, she had a runny nose and weakness of her wrist joints. The liver was about 4 finger-breadths below the right costal margin with a sharp but tender edge. Blood arsenic levels ranged from 0.087 to 0.46 μg/mL and the arsenic level in hair ranged from 14.4 to 20 μg/g. The authors concluded that the finding of typical skin manifestations of chronic arsenic poisoning suggests that it may take a considerably shorter period of time to develop these

manifestations than previously thought. However, it is not known what effect co-exposure to tin and tungsten might have had on skin manifestations in these children.

Wasserman et al. (2004) conducted a cross-sectional evaluation of intellectual function in 201 children 10 years of age whose parents were part of a larger cohort in Bangladesh. Intellectual function was measured using tests drawn from the Wechsler Intelligence Scale for Children; results were assessed by summing related items into Verbal, Performance, and Full-Scale raw scores. The children were divided into four exposure groups, representing <5.5, 5.6–50, 50–176, or 177–790 μg As/L drinking water. After adjustment for confounding factors, a dose-related effect of arsenic exposure was seen on both Performance and Full-Scale scores; for both end points, exposure to 50 μg/L or greater resulted in statistically significant differences, relative to the lowest exposure group (<5.5 μg/L). In an evaluation of neurobehavioral effects in Taiwanese children exposed to low (0.0017–0.0018 mg As/kg/day) or high (0.0034–0.0042 mg As/kg/day) levels of inorganic arsenic in the drinking water, children in the low exposure group showed decreased performance in the switching attention task, while children in high exposure group showed decreased performance in both the switching attention task and in tests of pattern memory, relative to unexposed controls (Tsai et al. 2003). Similarly, Calderon et al. (2001, 2004) reported that elevated levels of urinary arsenic in Mexican children were correlated with poorer performance on tests evaluating long-term memory and linguistic abstraction. Thus, it appears that exposure of children to inorganic arsenic may result in detrimental effects on neurobehavioral parameters.

Wulff et al. (1996) conducted a retrospective study of a cohort of children born between 1961 and 1990 in the municipality of Skelleftea, Sweden, where a smelter released arsenic and other pollutants including lead, copper, cadmium, and sulfur dioxide. Childhood cancer incidences among children born in the vicinity of the smelter (i.e., within 20 km) and distant from the smelter (>20 km) were compared with expected incidences based on Swedish national statistics. There appeared to be an increased risk of childhood cancer (all types combined) among children born in the vicinity of the smelter (SIR=195, 95% CI=88–300, based on 13 cases observed and 6.7 expected), but the increase was not statistically significant, and in any event, the role of arsenic in any finding from this study is confounded by the presence of other metals. The number of cases (n=42) was very close to the expected number (n=41.8) among children born distant from the smelter. Similar results were reported in a study by Moore et al. (2002a), which did not find increased incidence ratios for all childhood cancers or for childhood leukemias in children from an area of Nevada with high arsenic exposures.

Inorganic arsenic has been characterized as a developmental toxicant. It is known to cross the placental barrier and selectively accumulate in the neuroepithelium of the developing animal embryo (Hanlon and Ferm 1977; Lindgren et al. 1984). Studies in animals have also revealed that various fetal malformations occur after embryonic exposure to arsenic *in vitro*; neural tube defects are the predominant and consistent malformation in these studies (Chaineau et al. 1990; Mirkes and Cornel 1992; Morrissey and Mottet 1983; Mottet and Ferm 1983; Tabacova et al. 1996; Willite and Ferm 1984; Wlodarczyk et al. 1996). *In vivo* studies have shown that high doses of ingested arsenic can produce developmental effects (fetal mortality, skeletal defects), but generally only at maternally toxic doses (Baxley et al. 1981; Holson et al. 1999, 2000; Hood and Harrison 1982; Hood et al. 1978; Nemec et al. 1998; Stump et al. 1999). A series of recent studies showed an increased incidence of tumors in the offspring of mice exposed to arsenic from gestational day 8 through day 18 (Waalkes et al. 2003a, 2004a, 2004b, 2004c) (see Section 3.2.2.6 for further details). In humans, acute prenatal exposure to high doses of inorganic arsenic can result in miscarriage and early neonatal death (Bollinger et al. 1992; Lugo et al. 1969). Although several studies have reported marginal associations between prolonged low-dose human arsenic exposure and adverse reproductive outcomes, including spontaneous abortion, stillbirth, developmental impairment, and congenital malformation (Ahmad et al. 2001; Aschengrau et al. 1989; Chakraborti et al. 2003c; Hopenhayn-Rich et al. 2000; Nordstrom et al. 1978a, 1979b; Yang et al. 2003; Zierler et al. 1988), none of these studies have provided convincing evidence for such effects or information concerning possible dose-response relationships.

There is no evidence for differences in absorption of arsenic in children and adults. Ingestion of arsenic in dirt may be an important route of exposure for young children. A study that used a synthetic gastric juice designed to mimic gastric conditions in a 2-year-old child found that absorption of arsenic from contaminated soil was likely to be up to 5 times lower than the total concentration of arsenic in the soil (Williams et al. 1998). As previously mentioned, arsenic crosses the placenta and preferentially accumulates in the embryonic neuroepithelium. In addition, arsenic is known to be present in breast milk at low concentrations. Arsenic concentrations were low in human milk sampled from 88 mothers in the Faroe Islands (0.0001–0.0044 ppm), where the diet is predominantly seafood (exposures were primarily to "fish arsenic" [Grandjean et al. 1995]), in a population of Andean women (0.0008–0.008 ppm) exposed to high concentrations of inorganic arsenic in drinking water (Concha et al. 1998b), and in a World Health Organization survey (0.00013–0.00082 ppm) (Somogyi and Beck 1993). There is no information in the literature describing storage of arsenic in maternal tissues. There is some evidence that metabolism of arsenic in children is less efficient than in adults. Children in two villages in Argentina ingesting large amounts of arsenic in their drinking water (200 µg/L) excreted about 49% inorganic arsenic and 47%

DMA, compared to 32% inorganic arsenic and 66% DMA for the women in the study (Concha et al. 1998b). No PBPK models specifically targeted at fetuses, infants, or children, or pregnant or lactating women were found in the literature. There are no biomarkers that have been specifically identified for children exposed to arsenic. In addition, no unique interactions of arsenic with other chemicals have been identified in children.

The mechanism of toxic action of arsenic in the mammalian cell may involve inhibition of proliferation of cells (Dong and Luo 1993; Jha et al. 1992; Petres et al. 1977). In addition, high-dose arsenic impairs assembly and disassembly of microtubules, thus interfering with mitotic spindle formation and embryonal cell division (Leonard and Lauwerys 1980; Li and Chou 1992; Mottet and Ferm 1983). Arsenic compounds also cause chromosomal aberrations (Jha et al. 1992; Leonard and Lauwerys 1980), which may disrupt cell cycling. The direct toxic effects of high levels of arsenic in the developing embryo result not from a difference in the mechanism of toxicity during development, but rather from the existence of a unique target tissue, the neuroepithelium. The process of neurulation involves cell shape changes, cytokinesis, and cell adhesion, which are dependent upon cytoskeletal elements that are functionally affected by arsenic (Dallaire and Beliveau 1992; Edelman 1992; Gunn et al. 1992; Li and Chou 1992; Moriss-Kay et al. 1994; Scheonwolf and Smith 1990; Taubeneck et al. 1994). However, since arsenic is known to affect vasculature, and since altered placental and/or embryonal vasculature has been suggested as a mechanism leading to neural tube defects, the embryo may be sensitive to this manifestation of arsenic toxicity.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, 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 arsenic 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 arsenic 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 Arsenic

Arsenic levels in blood, urine, hair, and nails have all been investigated and used as biological indicators of exposure to arsenic. Since arsenic is cleared from blood within a few hours (Tam et al. 1979b; Vahter 1983), measurements of blood arsenic reflect exposures only within the very recent past. Typical values in nonexposed individuals are less than 1 µg/L (Heydorn 1970; Hindmarsh and McCurdy 1986; Valentine et al. 1979). Consumption of medicines containing arsenic is associated with blood values of 100–250 µg/L, while blood levels in acutely toxic and fatal cases may be 1,000 µg/L or higher (Driesback 1980).

However, blood levels do not appear to be reliable indicators of chronic exposure to low levels of arsenic. For example, there was no correlation between the level of arsenic in blood of residents and the level of arsenic in drinking water in several U.S. communities where water levels ranged from about 6 to 125 µg/L (Valentine et al. 1979, 1981). Consequently, measurement of blood arsenic is not generally considered to be a reliable means of monitoring human populations for arsenic exposure.

As discussed in Section 3.4.4, most arsenic that is absorbed from the lungs or the gastrointestinal tract is excreted in the urine, mainly within 1–2 days. For this reason, measurement of urinary arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure, and this approach has proved useful in identifying above-average exposures in populations living near industrial point sources of arsenic (e.g., Milham and Strong 1974; Polissar et al. 1990). By the inhalation route, several researchers have found that there is a good quantitative correlation between the concentration of arsenic in workplace air (C_{air}, µg/m^3) and the concentration in the urine (C_{urine}, µg/L) of exposed workers. For example, Pinto et al. (1976) found a linear relationship for exposures ranging up to 150 µg/m^3, given by the following equation:

$$C_{air}=0.3\ C_{urine}$$

More recently, Enterline et al. (1987a) reinvestigated this relationship over a wider range of exposures (up to 3,500 µg/m^3), and found that the curve tended to be concave upward, as given by the following equation:

$$C_{air}=0.0064\ (C_{urine})^{1.94}$$

This indicates that at higher exposure levels, a higher fraction of the dose is excreted in urine, although the toxicokinetic basis for this is not certain. Numerous studies have used above-average urinary levels (i.e., higher than about 100 µg/L) as evidence of recent arsenic ingestion (e.g., Borgono et al. 1980; Fincher and Koerker 1987; Franzblau and Lilis 1989; Goldsmith and From 1986; Kyle and Pease 1965; Valentine et al. 1981), but a quantitative relation between ingested arsenic and urinary excretion levels has only recently been reported. Calderon et al. (1999) found a quantitative correlation between the log of the mean total urinary arsenic concentration/creatinine (TAs/c, µg/mg) of people living in areas with

arsenic-contaminated drinking water sources and the log of the inorganic arsenic concentration in the drinking water (InAs, µg/L). The equation for the regression line is:

$$TAs/c=10^{-2.57} \times (InAs)^{0.63}$$

where -2.57 and 0.63 are the intercept and slope, respectively, for the regression of the log10-transformed data. Mixed model regression analysis showed that the log of estimated arsenic intake from drinking water (µg/day) is also a good predictor of Tas/c excretion (Calderon et al. 1999).

There is some indication that speciation of urinary arsenic may indicate the extent of past cumulative exposure to arsenic. Hsueh et al. (1998a) reported higher levels of DMA and MMA in the urine of individuals with higher cumulative past exposure to inorganic arsenic. Speciated urinary arsenic is also a recommended biomarker for recent inorganic arsenic exposure. Walker and Griffin (1998) used the EPA Exposure Assessment Model and a number of site-specific data covering environmental and biological factors to predict total and speciated urinary arsenic concentrations for children living near high levels of arsenic-contaminated soil. There was reasonable agreement between the measured and predicted speciated urinary arsenic concentrations.

An important limitation to the use of total urinary arsenic as a biomarker of exposure is that arsenobetaine is excreted (unmetabolized) in urine after ingestion of certain seafoods (Brown et al. 1990; Kalman 1987; Tam et al. 1982). Since "fish arsenic" is essentially nontoxic, analytical methods based on total urinary arsenic content may overestimate exposures to arsenic species that are of health concern. As discussed in Section 7.1, there are adequate methods for distinguishing arsenobetaine from other forms of arsenic in urine (inorganic, MMA, DMA), although these are not convenient to use as a routine screening method.

Arsenic tends to accumulate in hair and nails, and measurement of arsenic levels in these tissues may be a useful indicator of past exposures. Normal levels in hair and nails are 1 ppm or less (Choucair and Ajax 1988; Franzblau and Lilis 1989). These values may increase from several-fold to over 100-fold following arsenic exposure (Agahian et al. 1990; Bencko et al. 1986; de Peyster and Silvers 1995; Karagas et al. 1996; Landau et al. 1977; Milham and Strong 1974; Southwick et al. 1981; Valentine et al. 1979; Yamauchi et al. 1989) and remain elevated for 6–12 months (Choucair and Ajax 1988). Minimum exposure levels that produce measurable increases in arsenic levels in hair and nails have not been precisely defined. For hair, ingestion of 50–120 ppb of arsenic in drinking water produced only a marginal effect, but a clear increase was noted at 393 ppb (Valentine et al. 1979). Inhalation exposure of

workers to about 0.6 μg/m^3 of arsenic in air significantly increased average levels in nails (Agahian et al. 1990), although there was wide variation between individuals.

Analysis of hair may yield misleading results due to the presence of arsenic adsorbed to the external surface, but this can be minimized by collecting samples from close to the scalp or from unexposed areas and by washing the hair before analysis (e.g., Paschal et al. 1989). Similarly, extensive washing of nails is required to remove exogenous contamination (Agahian et al. 1990). The relationship between consumption of food items and levels of arsenic in toenails has recently been evaluated by MacIntosh et al. (1997) using standard multivariate regression models. This approach does not appear to be highly reliable, but may be sufficient for exploring associations between diet and disease. Kurttio et al. (1998) used linear regression models to show that there is a good association between arsenic concentration in hair (mg/kg) and total arsenic concentration in urine (μg/L), arsenic concentration in drinking water (μg/L) or daily intake of arsenic (μg/day). A 10 μg/L increase in the drinking water concentration or a 10–20 μg/day increase in daily arsenic intake corresponded to a 0.1 mg/kg increase in the arsenic concentration in hair. It is also important to note that the measurement of arsenic in hair and fingernails is a process not readily accessible to many clinical offices.

3.8.2 Biomarkers Used to Characterize Effects Caused by Arsenic

As discussed in Section 3.2, the characteristic pattern of skin changes caused by arsenic (hyperkeratinization, hyperpigmentation) is probably the most sensitive and diagnostic clinical indicator of chronic exposure to arsenic. However, no means has been developed for detecting these effects except by routine dermatological examination.

Peripheral neuropathy is another characteristic effect of arsenic exposure, and several researchers have investigated decreased nerve conduction velocity or amplitude as a biomarker for peripheral neuropathy. While effects can usually be detected in individuals with clinical signs of neuropathy (e.g., Goebel et al. 1990; Jenkins 1966; Le Quesne and McLeod 1977; Morton and Caron 1989; Murphy et al. 1981), effects are only marginal (Hindmarsh et al. 1977; Landau et al. 1977; Valentine et al. 1981) or undetectable (Kreiss et al. 1983; Southwick et al. 1981) in exposed populations without obvious clinical signs of toxicity. This indicates that this approach is probably not sufficiently sensitive to detect neurological effects earlier than by standard neurological examination (Hindmarsh and McCurdy 1986). Also, decreases in nerve conduction velocity or amplitude are not specific for arsenic-induced neuropathy.

Arsenic is known to affect the activity of a number of enzymes, and some of these may have potential as biomarkers of effect. Most promising is the spectrum of effects caused by arsenic on the group of enzymes responsible for heme synthesis and degradation, including inhibition of coproporphyrinogen oxidase and heme synthetase (Woods and Fowler 1978; Woods and Southern 1989) and activation of heme oxygenase (Sardana et al. 1981). Menzel et al. (1998) has examined the *in vitro* induction of human lymphocyte heme oxygenase 1(HO1) as a biomarker of arsenite exposure. Arsenite did induce *de novo* synthesis of HO1 in human lymphoblastoid cells, but it has not been determined if the same response is induced *in vivo*. It has been shown in animals that these arsenic-induced enzymic changes result in increased urinary levels of uroporphyrin, coproporphyrin, and bilirubin (Albores et al. 1989; Woods and Fowler 1978), and it has been shown that these effects can be detected in the urine of arsenic-exposed humans (Garcia-Vargas and Hernandez-Zavala 1996). Therefore, altered urinary levels of these heme-related compounds could serve as a biomarker of effect. However, it is known that numerous other toxic metals also have similar effects on heme metabolism (Albores et al. 1989; Sardana et al. 1981; Woods and Southern 1989), so it is likely that these effects would not be specific for arsenic.

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

3.9 INTERACTIONS WITH OTHER CHEMICALS

A number of researchers have found that arsenic compounds tend to reduce the effects of selenium (Hill 1975; Howell and Hill 1978; Kraus and Ganther 1989; Levander 1977; Miyazaki et al. 2003; Moxon et al. 1945; Schrauzer 1987; Schrauzer et al. 1978). Likewise, selenium can decrease the effects of arsenic, including clastogenicity (Beckman and Nordenson 1986; Biswas et al. 1999; Sweins 1983), delayed mutagenesis (Rossman and Uddin 2005), cytotoxicity (Babich et al. 1989; Rossner et al. 1977; Styblo and Thomas 2001), and teratogenicity (Holmberg and Ferm 1969). The mechanism of this mutual inhibition of effects is not known, but may be related to the formation of a complex that is excreted more rapidly than either arsenic or selenium alone (Cikrt et al. 1988; Hill 1975; Levander 1977; Levander and Baumann 1966) or due to selenium-induced changes in arsenic methylation (Styblo and Thomas 2001; Walton et al. 2003). There is little direct evidence that variations in selenium exposure in humans lead to significant increases or decreases in arsenic toxicity, although copper smelter workers who developed lung cancer had lower tissue levels of selenium than workers who did not develop lung tumors (Gerhardsson et al. 1985, 1988). This suggests that selenium deficiency could significantly increase the

risk of lung cancer following inhalation exposure to arsenic, but it is difficult to distinguish cause from effect in such a study.

The interaction between cigarette smoking, inhalation of arsenic, and the risk of lung cancer has not been extensively investigated. Smoking appeared to increase lung cancer risk synergistically (multiplicatively) in one study of smelter workers (Pershagen et al. 1981), although the data are not adequate to exclude a simple additive interaction (Thomas and Whittemore 1988). Cigarette smoking has been shown to increase the occurrence of lung cancer in people with high levels of arsenic in the drinking water (Chiou et al. 1995; Tsuda et al. 1995a). Suggestive evidence of a positive interaction between arsenic and benzo(a)pyrene has also been noted for induction of lung adenocarcinomas in hamsters (Pershagen et al. 1984a).

Co-exposure to ethanol and arsenic may exacerbate the toxic effects of arsenic. Simultaneous exposure of rats to ethanol (10% in drinking water) and arsenic (dose not stated) for 6 weeks produced a significant increase in the concentration of arsenic in the kidney, a nonsignificant increase of arsenic in the liver and a significant increase in the concentration of glutathione in the liver, compared to rats treated with either ethanol or arsenic alone (Flora et al. 1997a, 1997b). Histological damage to the liver, but not the kidneys, was increased in rats treated with both ethanol and arsenic compared to those receiving only arsenic.

Studies of rats exposed to arsenic, lead, and cadmium, alone or in combination, have revealed mainly additive or subadditive effects on body weight, hematological parameters, and enzymes of heme synthesis (Mahaffey and Fowler 1977; Mahaffey et al. 1981). Similarly, studies of the tissue levels of arsenic in rats fed arsenic with or without lead or cadmium revealed only limited evidence of any toxicokinetic interactions (Mahaffey et al. 1981). Pretreatment of rats with a nontoxic dose of cadmium had no effect on the lethality of a high dose of arsenic and did not reduce arsenic-induced hepatotoxicity (Hochadel and Waalkes 1997). These data do not suggest that arsenic toxicity is likely to be significantly influenced by concomitant exposure to these metals. However, supplementation with zinc or chromium may be useful in reducing chronic arsenism. Arsenic has been shown to cause an increase in total plasma cholesterol; co-administration of chromium(III) counteracts this effect (Aguilar et al. 1997). Pretreatment of mice with zinc, at least 24 hours before injection with arsenic-73, reduced arsenic retention compared to controls that did not receive the zinc pretreatment or received it only a short time before the administration of arsenic (Kreppel et al. 1994). Zinc is an inducer of metallothionein, but this induction does not appear to be the mechanism that reduces arsenic toxicity because other inducers of

metallothionein did not reduce arsenic toxicity and arsenic elimination was increased by the zinc pretreatment.

Since methylation of arsenic is a detoxification mechanism, it is possible that chemicals that interfere with the methylation process could increase toxicity. This is supported by studies in animals in which reagents that inhibit methylation enzymes (e.g., periodate-oxidized adenosine) caused an increase in tissue levels of inorganic arsenic (Marafante and Vahter 1986; Marafante et al. 1985). Similarly, cellular glutathione levels appear to play a role in the methylation process, and treatment with reagents (e.g., phorone) that decrease glutathione levels increases arsenic toxicity (Buchet and Lauwerys 1987). Inadequate dietary intake of methionine, choline, or protein may also exacerbate arsenic toxicity. Rabbits pretreated with diets low in choline, methionine, or protein showed a significant increase in tissue retention of arsenic and a significant decrease in the excretion of dimethylarsinic acid (Vahter and Marafante 1987). The increased retention of arsenic in rabbits fed these deficient diets is likely to be due to a reduction in arsenic methylation. Thus, the toxic effects of chronic arsenic ingestion may be increased in populations that are also subject to malnutrition.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

No studies were located that identified an unusual susceptibility of any human subpopulation to arsenic. Several recent studies have evaluated possible sex-related differences in arsenic toxicity and carcinogenesis (Aposhian et al. 2000a, 2000b; Calderon et al. 1999; Loffredo et al. 2003; Mandal et al. 2001; Watanabe et al. 2001), but have not consistently identified differences. However, since the degree of arsenic toxicity may be influenced by the rate and extent of its methylation in the liver (see Section 3.4.3), it seems likely that some members of the population might be especially susceptible because of lower than normal methylating capacity. A study of exposed humans in Taiwan suggested that subjects with lower secondary methylation indices have an increased risk of bladder cancer (Chen et al. 2003a), particularly in subjects with high exposure levels. Reduced hepatic methylation could result from

dietary deficiency of methyl donors such as choline or methionine (Buchet and Lauwerys 1987; Vahter and Marafante 1987), although this is unlikely to be a concern for most people in the United States. While there is some evidence that methylation capacity does vary among individuals (e.g., Buchet et al. 1981a; Foà et al. 1984; Tam et al. 1979b), the basis of this variation and its impact on human susceptibility have not been established. One report did describe severe arsenic toxicity, including neuropathy, that developed only in a 5,10-methylenetetrahydrofolate-reductase (MTHFR) deficient member of a family that had been exposed to arsenic (Brouwer et al. 1992). The authors suggest that the MTHFR deficiency in this girl might explain the fact that of all the family members exposed to arsenic, only she developed severe clinical signs of arsenic poisoning. Liver disease does not appear to decrease methylation capacity in humans, at least at low levels of arsenic exposure (Buchet et al. 1982; Geubel et al. 1988).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

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

Tintinalli JE, Ruiz E, Krone RL, eds. 1996. Emergency medicine. A comprehensive study. American College of Emergency Physicians. 4th ed. New York, NY: The McGraw-Hill Companies, Inc.

Goldfrank RL, Flomenbaum NE, Lewin NA, et al., eds. 1998. Goldfrank's toxicologic emergencies. 6th ed. Stamford, CT: Appleton and Lange.

Ellenhorn MJ. 1997. Ellenhorn's medical toxicology. Diagnosis and treatment of human poisoning. Baltimore, MD: Williams & Wilkins.

3.11.1 Reducing Peak Absorption Following Exposure

No data were located regarding the reduction of absorption after inhalation exposure to arsenic.

There are a number of methods for reducing absorption of arsenic following oral exposure. In cases of acute high-dose exposure, the removal of arsenic from the gastrointestinal tract may be facilitated by

gastric lavage, stomach intubation, induced emesis, or use of cathartics (saline, sorbitol) within a few hours after ingestion (Agency for Toxic Substances and Disease Registry 1990a; Aposhian and Aposhian 1989; Campbell and Alvarez 1989; Driesback 1980; Ellenhorn and Barceloux 1988; EPA 1989e; Haddad and Winchester 1990; Kamijo et al. 1998; Stutz and Janusz 1988). However, the efficacy of several of these methods has been questioned by some authors, and in some cases, the treatments may be contraindicated. For example, vomiting and diarrhea often occur soon after ingesting arsenic, and therefore, use of an emetic or cathartic may not be necessary. Also, emesis should not be induced in obtunded, comatose, or convulsing patients (Campbell and Alvarez 1989; Ellenhorn and Barceloux 1988; EPA 1989e), and saline cathartics should be used with caution in patients with impaired renal function (Campbell and Alvarez 1989). A recent article by Vantroyen et al. (2004) described a case of a massive arsenic trioxide overdose that was successfully treated by continuous gastric irrigation with sodium bicarbonate, forced diuresis, and administration of BAL and DMSA. Treatments of this sort are unlikely to be required following low-level exposures.

Another possible approach for reducing absorption following oral exposure is to administer substances that bind the arsenic in the gastrointestinal tract. For example, activated charcoal is sometimes used for this purpose (Campbell and Alvarez 1989; EPA 1989e; Stutz and Janusz 1988), although the effectiveness of this treatment is not well established. Because pentavalent arsenic is a phosphate analogue, administration of phosphate-binding substance such as aluminum hydroxide might possibly be useful, but this has not been investigated. Sulfhydryl compounds might be given to bind trivalent arsenic, but it seems unlikely that these would be effective under the acid conditions in the stomach, and it is not clear that such complexes would have reduced gastrointestinal absorption.

Following dermal or ocular exposure to arsenic, several measures can be taken to minimize absorption. All contaminated clothing should be removed, and contacted skin should be immediately washed with soap and water. Eyes that have come in contact with arsenic should be flushed with copious amounts of clean water (EPA 1989e; Stutz and Janusz 1988).

3.11.2 Reducing Body Burden

Acute arsenic intoxication may require treatment with chelating agents such as dimercaprol (BAL) and D-penicillamine. Although body burden is not necessarily reduced, these chelators bind free arsenic and serve to reduce the body's pool of biologically active arsenic. Chelation therapy is most effective when instituted within a few hours after exposure, and efficacy decreases as time after exposure increases

(Agency for Toxic Substances and Disease Registry 1990a; Kajimo et al. 1998; McFall et al. 1998; Peterson and Rumack 1977).

In general, chelating agents should be used with caution, since they may have serious side effects such as pain, fever, hypotension, and nephrotoxicity (Ellenhorn and Barceloux 1988). Some water-soluble and less toxic analogues of BAL such as dimercaptosuccinic acid (DMSA), dimercaptopropyl phthalamadic acid (DMPA), and dimercaptopropane sulfonic acid (DMPS) are currently under investigation and may prove to be promising treatments for arsenic poisoning (Agency for Toxic Substances and Disease Registry 1990a; Aposhian and Aposhian 1989; Aposhian et al. 1997; Guha Mazumder 1996; Kreppel et al. 1995). However, a randomized placebo trial of 2,3-dimercaptosuccinic acid as a therapy for chronic arsenosis due to drinking contaminated water found no significant difference between patients treated with 2,3-dimercaptosuccinic acid and those treated with a placebo (Guha Mazumder et al. 1998a). N-acetylcysteine has been used in animals to chelate arsenic (Haddad and Winchester 1990), and a human case study reported N-acetylcysteine to be successful in treating a case of arsenic poisoning that was not responding well to BAL treatment (Martin et al. 1990). A recent article by Vantroyen et al. (2004) described a case of a massive arsenic trioxide overdose that was successfully treated by continuous gastric irrigation with sodium bicarbonate, forced diuresis, and administration of BAL and DMSA.

As discussed in Section 3.4.3, once arsenic has been absorbed into the blood stream, it undergoes methylation to yield MMA and DMA. These forms of arsenic are less toxic than inorganic arsenic and are cleared from the body by excretion in the urine. Therefore, if it were possible to enhance arsenic methylation, both body burden and toxicity of arsenic might be reduced. However, experimental evidence in animals and humans suggests that arsenic methylation is not enhanced to any significant degree by supplementation with methylation cofactors (Buchet and Lauwerys 1987; Buchet et al. 1982), presumably because it is enzyme level and not cofactor availability that is rate limiting in arsenic methylation.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

It is generally thought that trivalent arsenic exerts its toxic effects mainly by complexing with sulfhydryl groups in key enzymes within the body, thereby inhibiting critical functions such as gluconeogenesis and DNA repair (Aposhian and Aposhian 1989; Li and Rossman 1989). Therefore, administration of sulfhydryl-containing compounds soon after exposure could provide alternative target molecules for arsenic, and prevent inhibition of enzyme functions. In fact, many of the chelating agents discussed

above (BAL, DMSA, DMPA, DMPS, N-acetylcysteine) contain sulfhydryl groups, and this may account for their efficacy.

The mechanism by which pentavalent arsenic acts is less certain. Since pentavalent arsenic is reduced in the body to the trivalent state, pentavalent arsenic may act in a similar manner as described above for trivalent arsenic. If this is the case, efforts to inhibit the reduction of pentavalent arsenic would decrease its toxicity. However, no methods are currently recognized for blocking this reduction. Pentavalent arsenic may also exert effects by acting as a phosphate analogue. As a phosphate analogue, pentavalent arsenic could potentially affect a number of biological processes, including ATP production, bone formation, and DNA synthesis. However, any effort to interfere in normal phosphate metabolism could produce serious side effects, and no method is known for selectively interfering with arsenate metabolism.

3.12 ADEQUACY OF THE DATABASE

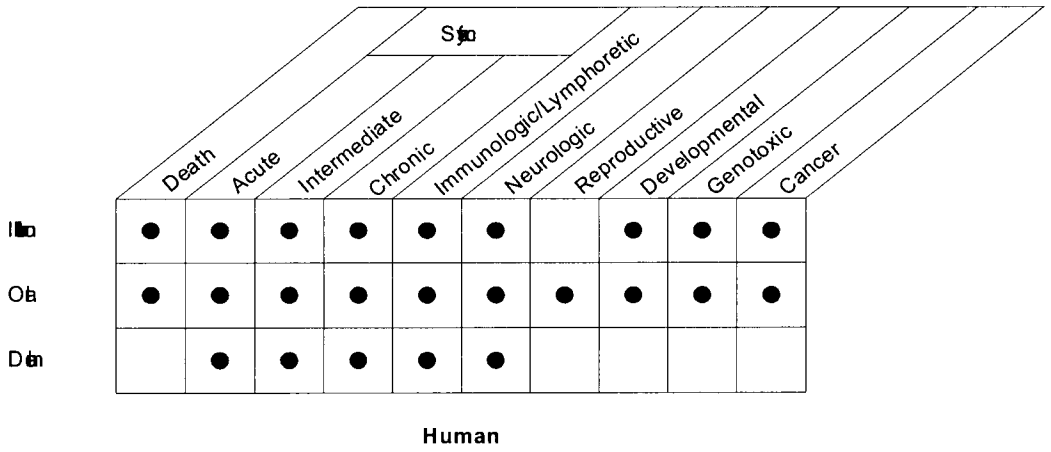
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of arsenic is available. Where adequate information is not available, 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 arsenic.

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

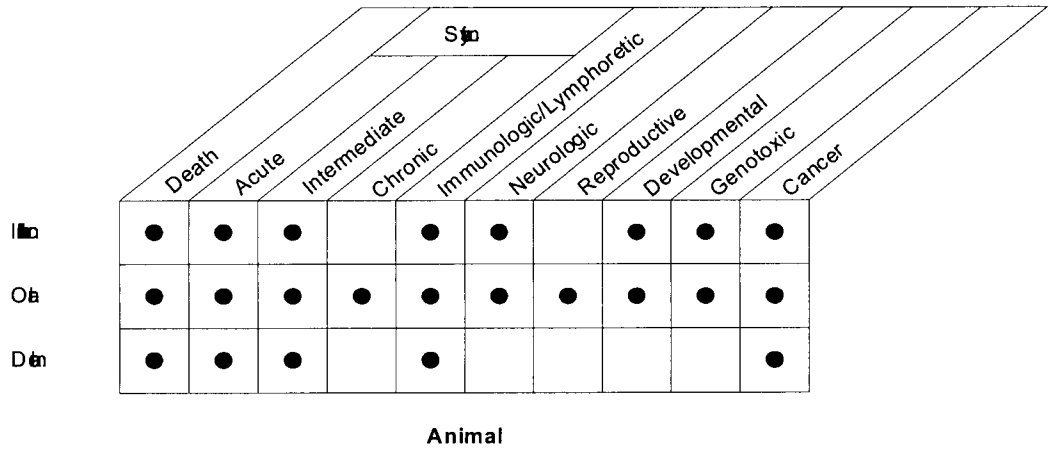
3.12.1 Existing Information on Health Effects of Arsenic

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to inorganic and organic arsenic are summarized in Figures 3-10 and 3-11, respectively. The purpose of these figures is to illustrate the existing information concerning the health effects of arsenic. Each dot in the figure indicates that one or more studies provide information associated with that particular effect.

Figure 3-10. Existing Information on Health Effects of Inorganic Arsenic



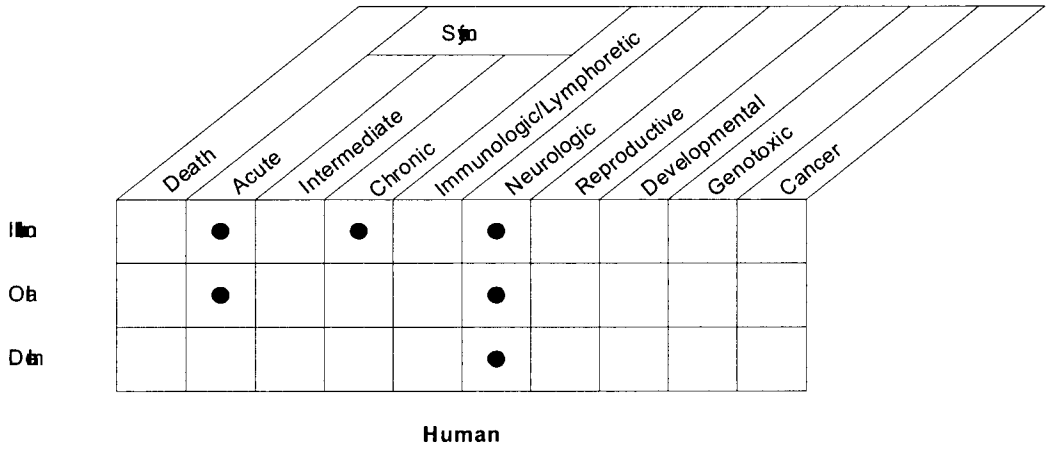
Human



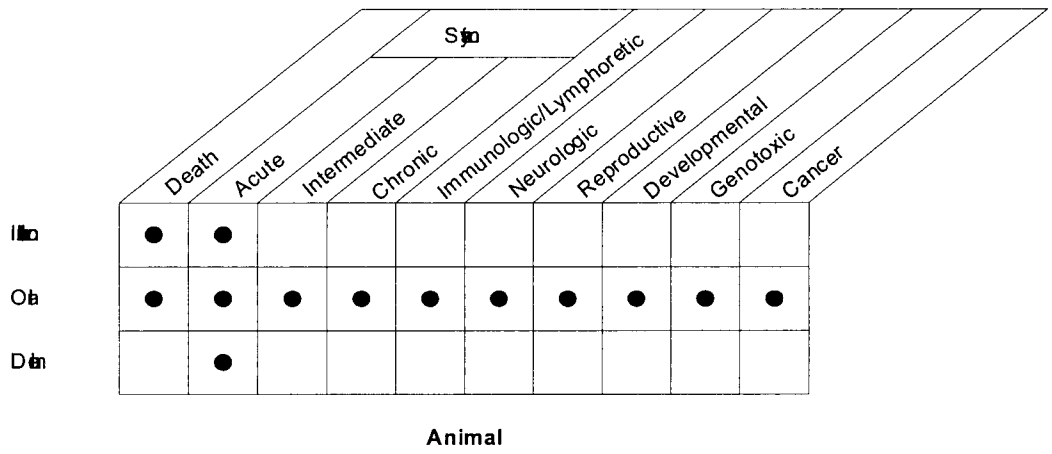
Animal

● Existing Studies

Figure 3-11. Existing Information on Health Effects of Organic Arsenic



Human



Animal

● Existing Studies

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.

As shown in Figure 3-10, there is a substantial database on the toxicity of inorganic arsenicals, both in humans and in animals. The oral route has been most thoroughly investigated, and reports are available on most end points of concern following acute, intermediate, and chronic exposure. The inhalation route has also been studied extensively, mainly in humans, with special emphasis on lung cancer. A number of noncancer end points have also been studied following inhalation exposure, but information on these effects is less extensive. Limited information on the effects of dermal exposure is also available in both humans and animals, focusing mainly on direct irritancy and dermal sensitization reactions. The absence of studies on other effects of inorganic arsenic following dermal exposure is probably not a critical data need, since dermal uptake of inorganic arsenic appears to be sufficiently limited that other routes of exposure (oral or inhalation) would almost always be expected to be of greater concern.

As shown in Figure 3-11, very little information is available on the effects of organic arsenic compounds in humans, although there are a number of studies in animals. These studies mainly involve the oral route, since all of these compounds are nonvolatile solids, although a few acute inhalation studies have been performed. Limited information is available on acute dermal lethality and dermal irritancy of some organic arsenicals, but data are lacking on other effects of organic arsenicals following dermal exposure. As discussed previously, in evaluating the adequacy of the database on arsenic, it is important to keep in mind that most studies in animals indicate that they are quantitatively less sensitive to arsenic than humans. For this reason, data from animal studies should be used to draw inferences about effects in humans only with caution.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. There is only limited information on the effects of acute inhalation exposure to arsenic in humans, but the chief symptoms appear to be irritation of the respiratory and gastrointestinal tracts (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Dunlap 1921; Ide and Bullough 1988; Morton and Caron 1989; Pinto and McGill 1953). Quantitative data are lacking, but

effects generally appear to be mild even at high-exposure levels. On this basis, it seems that risks of acute effects are probably low for inhalation exposures in the environment or near waste sites. Research to obtain a quantitative acute inhalation NOAEL value that could be used to derive an acute inhalation MRL would, therefore, be useful but not critical. There are numerous case studies in humans on the acute oral toxicity of arsenic, and the main end points (gastrointestinal irritation, pancytopenia, hepatic injury, neuropathy) are well characterized (Armstrong et al. 1984; Fincher and Koerker 1987). A provisional acute oral MRL of 0.005 mg As/kg/day was derived for inorganic arsenic based on a LOAEL for gastrointestinal symptoms and facial edema reported by Mizuta et al. (1956). Additional studies to define an acute oral NOAEL would be useful to reduce uncertainty in the MRL derivation. Acute dermal exposure is unlikely to cause serious systemic injury, but it can lead to contact dermatitis and skin sensitization (Holmqvist 1951; Pinto and McGill 1953). However, available data do not permit a quantitative estimate of the concentration of arsenic on the skin or in air, dust, soil, or water that causes these effects. Further research would be valuable to obtain a quantitative NOAEL for direct dermal effects, since humans may have dermal contact with contaminated soil or water near hazardous waste sites.

No information was located on the acute toxicity of organic arsenicals in humans. Acute lethality and systemic toxicity data exist for several compounds by both oral and inhalation exposure of animals, and these data suggest that the organic derivatives of arsenic may cause effects similar to the inorganic forms, but only at higher doses (Kaise et al. 1989; NTP 1989b; Rogers et al. 1981; Stevens et al. 1979). Even though these compounds appear to be less toxic than inorganic arsenic, additional studies (especially in humans) would be valuable, since acute oral, inhalation, or dermal exposures may occur during manufacture or use of agricultural organic arsenicals, or at waste sites where organic arsenicals have been deposited. Derivation would be useful, but not critical, since those coming into contact with organic arsenic compounds might be regulated under OSHA and/or wear protective clothing as recommended by manufacturers.

Intermediate-Duration Exposure. Intermediate-duration inhalation exposure of humans to arsenic appears to result in respiratory tract irritation (occasionally including perforation of the nasal septum) and mild gastrointestinal tract irritation (Ide and Bullough 1988). Quantitative data are too limited (only one study, of one individual) to derive an intermediate-duration inhalation MRL. Further studies to define the NOAEL for intermediate-duration inhalation exposure of humans would be valuable, since humans could be exposed to arsenic-containing airborne dusts near smelters, chemical plants, or waste sites. Effects of intermediate-duration oral exposure are similar to those of acute oral exposure, but may also include

development of vascular injury and a characteristic group of skin changes (Franzblau and Lilis 1989; Holland 1904; Wagner et al. 1979). Most studies indicate that these effects occur at doses of about 0.05 mg As/kg/day or higher, but the data do not provide a firm basis for identifying the intermediate-duration NOAEL. For this reason, no intermediate-duration oral MRL has been derived. Further studies to establish the NOAEL would be valuable, since humans could have intermediate-duration oral exposures to arsenic through ingestion of contaminated soil or water near smelters, chemical factories, or waste sites. Since dermal effects appear to be restricted to acute irritancy, intermediate-duration dermal studies are probably not essential.

No information was located on the intermediate-duration toxicity of organic arsenicals in humans. The intermediate-duration oral toxicities of roxarsone, MMA, and DMA have been investigated in animals (Edmonds and Baker 1986; Jaghabir et al. 1989; Kerr et al. 1963; NTP 1989b; Prukop and Savage 1986; Siewicki 1981), but data are lacking for any compound by the inhalation route. Further studies on the intermediate-duration oral, inhalation, and dermal toxicity of these compounds would be valuable, especially in humans, since people may be exposed to organic arsenicals during their manufacture or use, or from materials deposited in waste sites.

Chronic-Duration Exposure and Cancer. The target tissues of chronic-duration exposure of humans to inorganic arsenic are the same as for intermediate-duration exposure for both the oral and inhalation routes. Effects of dermal exposure appear to be restricted to direct irritation of exposed surfaces. Therefore, chronic-duration studies are probably not essential for the dermal route. Quantitative data from one study identify an inhalation exposure level of about 0.1 mg As/m^3 as the LOAEL for skin changes (Perry et al. 1948), but because there are no additional supporting studies and a NOAEL is not clearly established, a chronic-duration inhalation MRL has not been derived. Additional studies in humans to define the chronic inhalation NOAEL for dermal or other effects would be valuable, since humans may be chronically exposed to arsenic dusts in air near smelters, chemical factories, or waste sites. Chronic oral exposure data from studies in humans indicate that the LOAEL for skin lesions and other effects is probably about 0.01–0.02 mg As/kg/day (10–20 µg As/kg/day), and that the NOAEL is probably between 0.0004 and 0.0009 mg As/kg/day (0.4–0.9 µg As/kg/day) (Cebrián et al. 1983; Hindmarsh et al. 1977; Southwick et al. 1981; Tseng 1977; Tseng et al. 1968). The NOAEL of 0.0008 mg As/kg/day from the study by Tseng et al. (1968) is appropriate for derivation of a chronic-duration oral MRL, but an uncertainty factor of 3 was required to account for the fact that the population that constituted the no-effect group were relatively young (possibly decreasing the ability to detect dermal

or other effects). For this reason, further epidemiological studies to provide additional support for the threshold dose for arsenic in humans would be valuable.

There are numerous studies in humans that support the carcinogenic effects of inorganic arsenic from inhalation exposure (Enterline et al. 1987a, 1987b, 1995; Järup and Pershagen 1991; Järup et al. 1989; Lee-Feldstein 1986; Welch et al. 1982) and oral exposure (Chen et al. 1986, 1988b, 1992; Chiou et al. 1995; Ferreccio et al. 1996; Hsueh et al. 1995; Lander et al. 1975; Liu and Chen 1996; Lüchtrath 1983; Smith et al. 1992; Tseng 1977; Tseng et al. 1968; Yu et al. 1992; Zaldívar 1974; Zaldívar et al. 1981). Quantitative slope factors have been derived for both routes. There is a noticeable absence, however, of 2-year animal carcinogenicity studies for either the inhalation or oral route of exposure (Chan and Huff 1997). In light of the ongoing controversy over the reasons for the absence of a carcinogenic effect in animals, it seems prudent to firmly establish a negative effect in a 2-year study. The carcinogenic effects of chronic dermal exposure to inorganic arsenicals have not been studied, but dermal exposure is a relatively minor route of exposure, and these studies would not be a top priority.

The mechanism of arsenic carcinogenicity is not known, although the current view is that it functions mainly as a promoter or cocarcinogen. Further studies on the mechanism of arsenic toxicity would be particularly valuable to improve our ability to evaluate human cancer risks from inhalation or oral exposures that might occur near waste sites. Also, mechanistic studies could help in the evaluation of cancer risks from organic derivatives (see below).

There is very little information on the chronic toxicity of organic arsenicals. One study of workers exposed to arsanilic acid did not identify any adverse effects, but no systematic, clinical, or toxicological examinations of exposed people were performed (Watrous and McCaughey 1945). A chronic-duration study in rats and mice given roxarsone in the diet did not reveal any obvious clinical effects (Prier et al. 1963). These data suggest that the organic arsenicals have low chronic toxicity, but further studies (especially of humans exposed during manufacture or use of organic arsenicals) would be valuable in deriving estimates of safe exposure limits.

No information was located on carcinogenic effects of organic arsenicals in humans. The carcinogenic potential of roxarsone has been investigated in rats and mice (NTP 1989b); this study detected only equivocal evidence of carcinogenicity in male rats, with no evidence of carcinogenicity in female rats or in male or female mice. However, the cancer potential for other organic arsenic compounds has not been studied in chronic bioassays. Since MMA and DMA are formed from inorganic arsenic *in vivo* by

methylation in the liver, chronic studies of the carcinogenic potential of these compounds would be valuable. Studies of humans exposed in the workplace would probably be preferable to studies in animals, since animals appear to be less susceptible to the carcinogenic effects of arsenic than humans. Studies on cancer risk following chronic dermal exposure to organic arsenicals are probably not essential.

Genotoxicity. There are several studies that suggest that inorganic arsenic may cause genotoxicity (mainly chromosomal effects) in exposed humans (Burgdorf et al. 1977; Nordenson et al. 1978), and this is supported by numerous studies in animals (Datta et al. 1986; DeKnudt et al. 1986; Nagymajtenyi et al. 1985) and cultured cells (Beckman and Nordenson 1986; Casto et al. 1979; DiPaulo and Casto 1979; Lee et al. 1985; Nakamuro and Sayato 1981; Nishioka 1975; Oberly et al. 1982; Okui and Fujiwara 1986; Sweins 1983; Ulitzer and Barak 1988; Zanzoni and Jung 1980). The mechanism of genotoxicity is not known, but may be due to the ability of arsenite to inhibit DNA repair enzymes (Li and Rossman 1989) or to alter apoptosis (Pi et al. 2005) or the ability of arsenate to act as a phosphate analog. Further studies to improve our understanding of the mechanism of genotoxicity would be valuable, since this could aid in the understanding of arsenic-induced cancer risk.

Reproductive Toxicity. No information was located regarding the effect of inorganic arsenic on gametogenesis or reproductive organ pathology in humans, and few reproduction studies were located in animals. Available animal studies did not find evidence for reproductive effects following inhalation or oral exposure (Holson et al. 1999, 2000), except for a trend toward decreased pups per litter in mice in a 3-generation study (Schroeder and Mitchner 1971) that is consistent with embryolethality observed in developmental studies of inorganic arsenic. Studies on spermatogenesis and reproductive success in arsenic-exposed workers would be valuable in evaluating whether there are significant reproductive risks of arsenic in humans, and this could be further strengthened by studies including histopathological examination of reproductive tissues (which was not done in the existing studies) in animals.

No information was located on reproductive effects of organic arsenicals in humans, but one study in animals indicated that oral exposure of male mice to MMA could result in a marked decrease in litter production in untreated females (Prukop and Savage 1986). This suggests that spermatogenesis or mating behavior may have been adversely affected, and further studies would be valuable to investigate the mechanism of this effect and whether other organic arsenicals produce similar effects.

Developmental Toxicity. There are several epidemiological studies that suggest that inhalation (Nordstrom et al. 1978a, 1978b, 1979a, 1979b) or oral (Aschengrau et al. 1989; Zierler et al. 1988)

exposure to inorganic arsenic might increase the risk of low birth weight, congenital defects, or abortion in exposed women. These studies do not establish that arsenic was responsible, since all involved exposures to other chemicals or risk factors, but do suggest that additional studies on developmental parameters in humans exposed to arsenic would be valuable in determining whether this is an effect of concern. Studies in animals support the view that oral, inhalation, and parenteral exposure to inorganic arsenic can all increase the incidence of fetotoxicity and teratogenicity, although this appears to occur only at doses that are toxic or even lethal to the dams (Baxley et al. 1981; Beaudoin 1974; Carpenter 1987; Ferm and Carpenter 1968; Ferm et al. 1971; Hanlon and Ferm 1986c; Holson et al. 1999, 2000; Hood and Bishop 1972; Hood and Harrison 1982; Hood et al. 1978; Mason et al. 1989; Nagymajtenyi et al. 1985; Nemec et al. 1998; Stump et al. 1999; Willhite 1981). Thus, additional studies in animals may be useful in defining the mechanisms of these developmental effects and in identifying the time of maximum susceptibility of the fetus, but such studies probably will not help identify a safe exposure level for humans.

No information was located regarding developmental effects in humans after oral or inhalation exposure to organic arsenicals. One oral study and two intraperitoneal ingestion studies in animals indicate that MMA and DMA can produce developmental effects, but only at levels that cause maternal toxicity (Hood et al. 1982; Rogers et al. 1981; Willhite 1981). However, in view of the apparent differences in susceptibility between animals and humans, it would be valuable to investigate whether there are any measurable effects on development in humans exposed to organic arsenicals in the workplace or the environment.

Immunotoxicity. No studies were located on immunotoxic effects in humans after oral exposure to inorganic arsenic. One inhalation study in humans (Bencko et al. 1988), one oral study in animals (Kerkvliet et al. 1980), and one intratracheal instillation study in animals (Sikorski et al. 1989) suggest that arsenic causes little or no functional impairment of the immune system, but one inhalation study in animals found decreased pulmonary bactericidal activity and increased susceptibility to streptococcal infection in exposed mice (Aranyi et al. 1985). Additional studies (both in humans and animals) would be valuable to investigate this end point further. Dermal exposure of humans to high levels of arsenic dusts may cause dermal sensitization (Holmqvist 1951), but the dose and time dependence of this phenomenon are not known. Studies to determine whether dermal sensitization occurs in people with low level dermal exposures to arsenic in dust or soil, such as might occur for residents near an arsenic-containing waste site, would be valuable in assessing the significance of this effect to nonoccupationally exposed populations.

No information was located on the immunotoxicity of organic arsenicals in humans or animals. Since there are suggestions that inorganic arsenic may cause some changes in the immune system, studies on possible immune effects of the common organic arsenicals might be helpful.

Neurotoxicity. There is convincing evidence from studies in humans that inorganic arsenic can cause serious neurological effects, both after inhalation (Beckett et al. 1986; Danan et al. 1984; Morton and Caron 1989) and oral exposure (Armstrong et al. 1984; Feldman et al. 1979; Fincher and Koerker 1987; Huang et al. 1985; Landau et al. 1977; Mizuta et al. 1956; Silver and Wainman 1952). This is based mainly on clinical observations and neurological examinations of exposed persons and is confirmed by histological examination of nerve biopsy specimens. Available studies provide a reasonable estimate of LOAEL and NOAEL values by the oral route, but similar data are lacking for the inhalation route. Further studies designed to identify the threshold for neurological effects in humans exposed by the inhalation route would be valuable, since humans may be exposed to arsenic dusts in air from smelters, chemical factories, or waste sites. Animals appear to be much less susceptible than humans to the neurological effects of inorganic arsenic, so studies in animals would probably not help in estimation of a safe exposure limit.

No information was located on neurological effects of organic arsenicals in humans, but clear clinical and histological signs of neurotoxicity have been noted in pigs given repeated oral doses of roxarsone (Edmonds and Baker 1986; Kennedy et al. 1986; Rice et al. 1985). These findings suggest that more extensive investigations of the neurotoxic potential of roxarsone and other organic arsenicals would be valuable to determine the potential human health risk from these compounds, since humans could be exposed during the manufacture or use of these compounds, or near waste sites where they have been deposited.

Epidemiological and Human Dosimetry Studies. Numerous epidemiologic studies of humans exposed to inorganic arsenic by the oral and inhalation routes constitute the database on arsenic-related cancer and noncancer human health effects. As with virtually all epidemiologic investigations, these studies are limited by possible confounding from factors such as smoking, exposure to other chemicals, and differences in population characteristics (e.g., nutritional state, metabolism, and toxicokinetics) that inhibit extrapolation of study results to a wider population. Moreover, many of these studies lack good dose estimates for study participants. Some studies lack quantitative data altogether. For this reason, improved data on confounding factors and improved methods of human dosimetry would be valuable in

any further human epidemiologic studies of arsenic, either in the workplace or in the general environment. Recent work has broadened the qualitative dose-response information beyond the highly exposed Taiwanese population, but additional studies of persons with lower exposure levels would be especially valuable for risk assessments for the U.S. population. From a public health standpoint, well designed studies of common noncancer health outcomes (e.g., cardiovascular disease and diabetes) could be more important than additional studies of cancer. Availability of methods for biomonitoring of exposure are discussed below.

Biomarkers of Exposure and Effect.

Exposure. There are sensitive and specific methods for measuring arsenic in blood, urine, hair, nails, and other tissues, and this is the approach normally employed for measuring arsenic exposure in humans. Usually total arsenic is measured, but methods are available for measuring inorganic arsenic and each of the organic derivatives separately. Urinary levels are generally considered to be the most reliable indication of recent exposures (Enterline et al. 1987a; Milham and Strong 1974; Pinto et al. 1976; Polissar et al. 1990), but if a high urinary level is present, care must be taken to account for the presence of nontoxic forms of arsenic from the diet. Blood levels are sometimes used to evaluate the status of acutely poisoned individuals (Driesback 1980; Heydorn 1970; Hindmarsh and McCurdy 1986; Valentine et al. 1979, 1981), but this approach is not generally useful for biomonitoring of long-term exposure to low levels. Hair and nails provide a valuable indication of exposures that occurred 1–10 months earlier (Agahian et al. 1990; Bencko et al. 1986; Choucair and Ajax 1988; Landau et al. 1977; Milham and Strong 1974; Southwick et al. 1981; Valentine et al. 1979; Yamauchi et al. 1989), although care must be taken to exclude external contamination of these samples. Cumulative urinary arsenic levels may be used to derive a quantitative estimate of exposure (Enterline et al. 1987a; Pinto et al. 1976), but data on the quantitative relation between exposure and arsenic levels in nails and hair were not located. Efforts to establish an algorithm for estimating past exposure levels from hair or nail levels would be valuable in quantifying average long-term exposure levels in people where repeated urinary monitoring is not feasible.

Effect. The effects of arsenic are mainly nonspecific, but the combined presence of several of the most characteristic clinical signs (e.g., nausea, diarrhea, peripheral neuropathy, anemia, vascular lesions, hyperkeratinization, hyperpigmentation) is usually adequate to suggest arsenic intoxication. Although there are standard clinical methods for detecting and evaluating each of these effects, there are no recognized methods for identifying early (preclinical) effects in exposed persons. Neurophysiological

measurements of nerve conduction velocity or amplitude have been investigated (Goebel et al. 1990; Jenkins 1966; Le Quesne and McLeod 1977; Morton and Caron 1989; Murphy et al. 1981), but at present, this approach does not seem to offer much advantage over a standard neurological examination. Changes in urinary excretion levels of several heme-related metabolites appear to be a good indication of preclinical effects of arsenic toxicity in animals (Albores et al. 1989; Sardana et al. 1981; Woods and Fowler 1978; Woods and Southern 1989), but this has not been established in humans and is not specific for arsenic-induced effects. Further efforts to develop these approaches and to identify other more specific biochemical or physiological indicators of arsenic-induced effects would be very valuable in monitoring the health of persons exposed to low levels of arsenic in the environment or near waste sites.

Absorption, Distribution, Metabolism, and Excretion. Available data from toxicokinetic studies in humans reveal that arsenates and arsenites are well absorbed following both oral and inhalation exposure. Data on distribution are limited, but it appears that arsenic is transported to nearly all tissues. Metabolism involves mainly reduction-oxidation reactions that interconvert As(+5) and As(+3) and methylation of As(+3) to yield MMA and DMA. Most arsenic is rapidly excreted in the urine as a mixture of inorganic arsenics, MMA, and DMA, although some may remain bound in tissues (especially skin, hair, and fingernails). These findings are strongly supported by numerous studies in animals. Because methylation represents a detoxification pathway, an area of special interest is the capacity of the human body to methylate inorganic arsenic. Limited data suggest that the methylation system might begin to become saturated at intakes of about 0.2–1 mg As/day (Buchet et al. 1981b; Marcus and Rispin 1988), but this is uncertain. Further studies to define the rate and saturation kinetics of whole-body methylation in humans would be especially helpful in evaluating human health risk from the low levels of arsenic intake that are usually encountered in the environment. Along the same line, further studies to determine the nature and magnitude of individual variations in methylation capacity and how this depends on diet, age, and other factors would be very useful in understanding and predicting which members of a population are likely to be most susceptible.

The toxicokinetics of dermal exposure have not been studied. It is usually considered that dermal uptake of arsenates and arsenites is sufficiently slow that this route is unlikely to be of health concern (except that due to direct irritation), but studies to test the validity of this assumption would be valuable. Also, dermal uptake of organic arsenicals could be of concern, and quantitative data on the rate and extent of this would be helpful in evaluating risks from application of arsenical pesticides or exposures to organic arsenicals in waste sites.

Comparative Toxicokinetics. Available toxicity data indicate that arsenic causes many of the same effects in animals that are observed in humans, but that animals are significantly less sensitive. The basis for this difference in susceptibility is not certain but is probably mainly a result of differences in absorption, distribution, metabolism, or excretion. For example, rats strongly retain arsenic in red blood cells (Lanz et al. 1950), while humans (and most other species) do not. Similarly, marmoset monkeys do not methylate inorganic arsenic (Vahter and Marafante 1985; Vahter et al. 1982), while humans and other animal species do. Because of these clear differences in toxicity and toxicokinetics between species, further comparative toxicokinetic studies that focus on the mechanistic basis for these differences would be very valuable. At a minimum, this would help clarify which laboratory species are the most useful models for humans and could ultimately lead to development of a PBPK model that would permit reliable extrapolation of observations across species.

Methods for Reducing Toxic Effects. There are a number of general methods for reducing the absorption of arsenic in the gastrointestinal tract and skin, but there are currently no methods for reducing the absorption of arsenic from the lungs. The removal of arsenic from the gastrointestinal tract is usually facilitated by the use of emetics, cathartics, lavages, or activated charcoal (Agency for Toxic Substances and Disease Registry 1990a; Aposhian and Aposhian 1989; Campbell and Alvarez 1989; Driesback 1980; Ellenhorn and Barceloux 1988; EPA 1989e; Haddad and Winchester 1990; Mitra et al. 2004; Stutz and Janusz 1988). Studies that investigate the effects of phosphate-binding chemicals (aluminum hydroxide) and nonabsorbable sulfhydryl compounds on the absorption of pentavalent and trivalent arsenic, respectively, may be useful in developing treatments that are more specific to arsenic intoxication. Once arsenic is in the body, treatment usually involves the use of one or more chelators, such as BAL or penicillamine. However, these agents often exhibit adverse side effects (Agency for Toxic Substances Disease Registry 1990a; Ellenhorn and Barceloux 1988), and are generally only applied following high-dose acute exposure. Further studies investigating the efficacy of less toxic arsenic chelators, such as DMSA, DMPA, DMPS, and N-acetyl cysteine, may lead to the development of safer treatment methods. Studies on the efficacy of chelators and agents to enhance methylation and elimination in treatment of chronic arsenic exposure would also be helpful, as available treatment methods for chronic arsenic exposure are limited. Trivalent arsenic is generally believed to exert toxic effects by binding to the vicinal sulfhydryl group of key enzymes, thereby interfering with a number of biological processes, such as gluconeogenesis and DNA repair (Li and Rossman 1989; Szinicz and Forth 1988). Since pentavalent arsenic may need to be reduced in the body to the trivalent state before it can exert toxic effects, studies that investigate methods for blocking this conversion may lead to a method for interfering with the mechanism of action for pentavalent arsenic. A recent study has shown that insufficient intake of

calcium, animal protein, folate, and fiber may enhance the toxic effects of inorganic arsenic (Mitra et al. 2004), but it is not known if dietary supplementation will prove effective in patients who already show arsenic-induced symptoms.

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

A majority of the data on the effects of exposure of humans to arsenic has focused on adults. Although a few studies of acute poisoning and chronic exposure specifically describe children (Borgono et al. 1980; Concha et al. 1998a, 1998b, 1999; Foy et al. 1992; Kersjes et al. 1987; Rosenberg 1974; Zaldívar 1974; Zaldívar and Guillier 1977), in general, data are lacking. Specifically, although there is a substantial database on the effect of arsenic on animal development, there are few data describing developmental effects in humans. Additional research in this area, using populations in areas of endemic arsenic exposure, would be useful.

Although there is no reason to suspect that the pharmacokinetics of arsenic differs in children and adults, there are few data available on this topic. Research on absorption, distribution, metabolism, and excretion in children would aid in determining if children are at an increased risk, especially in areas where chronic exposure to an environmental source occurs. With regard to exposure during development, additional research on maternal kinetics, and transfer via breast milk would be useful in obtaining a more complete picture of prenatal and neonatal development, especially with regard to neural development and the possible development of childhood cancer.

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

3.12.3 Ongoing Studies

A number of researchers are continuing to investigate the toxicity and toxicokinetics of arsenic. Table 3-16 summarizes studies being sponsored by agencies of the U.S. federal government. Additional research is being sponsored by industry groups and other agencies, and research is also ongoing in a number of foreign countries.

Table 3-16. Ongoing Studies on Health Effects of Arsenic, Federally Funded

Investigator	Affiliation	Title		Sponsor
Ayala-Fierro, F.	University of Arizona	Toxicity of Arsenic	Determination of *in vitro* and *in vivo*	NIEHS
Boyd, W.	Southern Cross University	Arsenic Toxicity	Biochemical and cellular	National Health and Medical Research Council, Australia
Burns, F.	Columbia University	Effects of Arsenic	Chromosomal	NIEHS
Burns, F.	Columbia University	Effects of Arsenic	Mechanisms of chromosomal	NIEHS
Byrd, D.	University of California	Arsenic	Neurotoxicity	NIEHS
Del Razo, L.	Mexican Institute	Arsenic	Urinary	National Institute of Public Health, Mexico
Del Razo, L.	University of Arizona	Arsenic	Cellular	NIEHS
Del Razo, L.	University of California

Table 3-16. Ongoing Studies on Health Effects of Arsenic, Federally Funded

Table 3-16. Ongoing Studies on Health Effects of Arsenic, Federally Funded

Ite	Affiio	Tie		Spo
Sip,AeH	Uie	ijfCiea BjeCiea	A pei ieiyiegfo ied ieed igmeb igfeiiig ev	EPA
Sie,eR	DeCe	ieNepea	Aši)eAP 1ey iejjo	NIEEI
SqeEieT	NeeUiey	MieCpe NeNeeY	Aiee ieeeie	EPA
SpMiea	UiejfNb	Cea CeHNbCea	Aieee eee ea	EPA
Tpn SeR		Meee

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Arsenic appears in Group 15 (V) of the periodic table, below nitrogen and phosphorus. In compounds, arsenic typically exists in one of three oxidation states, -3, +3, and +5 (Carapella 1992). Arsenic compounds can be categorized as inorganic, compounds without an arsenic-carbon bond, and organic, compounds with an arsenic-carbon bond. Information regarding the chemical identity of arsenic and some common inorganic and organic arsenic compounds are located in Tables 4-1 and 4-2, respectively.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of arsenic and some common inorganic and organic arsenic compounds is located in Tables 4-3 and 4-4, respectively.

Arsenic is classified chemically as a metalloid, having both properties of a metal and a nonmetal; however, it is frequently referred to as a metal. Elemental arsenic or metallic arsenic (As(0)) normally occurs as the α-crystalline metallic form, which is a steel gray and brittle solid. The β-form is a dark gray amorphous solid. Other allotropic forms of arsenic may also exist (Carapella 1992).

Table 4-1. Chemical Identity of Arsenic and Selected Inorganic Arsenic Compounds[a]

Chac Aisc		Aisiad Aiapl Aiaiss		
Syn	Aiaphl iegic laic	Oac id	Aiiid Aiaiad gliic ipl	Aiiid(III)ia iaiad iaiac
Rigil in	Ndl	Fi-H Di Di Lig Cla	Ndl	laAisc AiaAin
Chin As		H_3AsO_4	As_2O_5	As_2O_3
Chia	As	HO—As(=O)-OH (OH)	$[As^{5}]_2[O^{2}]_5$	$[As^{3}]_2[O^{2}]_3$
Ilain				
CAS ig				
NIOSHRTECS [b]	C	C C	C	
EPA la D		D P D P	D P	
OMTADS	Ndl	Ndl Ndl		Ndl
DOTJNNAIMO ip	UNMO 6	UN5 [UN5 MO Tl	UNMO 6	UNMO 6
EDB				
EINECS				
NCI	Ndl	Ndl Ndl		Ndl

Table 4-1. Chemical Identity of Arsenic and Selected Inorganic Arsenic Compounds[a]

Chemical name	Chemical formula		Synonyms	Trade name	Structural formula
Synonym	Chemical formula	Molecular weight			
Registered trademark	Pesticide code number				
Calcium arsenate	$Ca_3(AsO_4)_2$	398.08		Sodium arsenate	Na_2HAsO_4	185.92	$NaAsO_2$	129.91	
Identification numbers					
CAS registry					
NIOSH/RTECS[b]					
EPA hazardous waste					
OHM/TADS					
DOT/UN/NA/IMO shipping					
HSDB					
EINECS					
NCI					

[a]All information in this table was obtained from HSDB unless otherwise noted.
[b]RTECS data.

CAS = Chemical Abstracts Service; DOT/UN/NA/IMO = Department of Transport/United Nations/North America/International Maritime Organization; EINECS = European Inventory of Existing Commercial Chemical Substances; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH/RTECS = National Institute for Occupational Safety and Health/Registry of Toxic Effects of Chemical Substances; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System

Table 4-2. Chemical Identity of Selected Organic Arsenic Compounds[a]

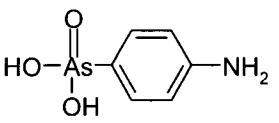
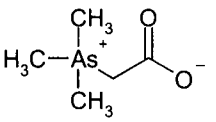
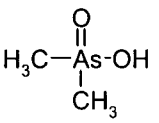
Cmc	Aidcid	Ae	Dijnid		
Sjn	Aijc (Ai			Fiimn jn tjd ida	Cjid jda idDMA;DMAA
RjdNdl				Ndl	(A,Pj6 REC6
Cdn C		$_6H_8AsNO_3$		$C_5H_1AsO_2$	$C_2H_7AsO_2$
Cda					
Idfn					
CAS jy		6		6	6
NIOSHRTECS [b]		CF6	C6	C6	
EPA dv D0				Ndl	UD0
OMTADS		Ndl		Ndl	Ndl
DOTJNNAMO		Ndl		Ndl	UNMO6
EDB		2	No	l	6
EINECS		l	No	l	0
NCI		Ndl		Ndl	Ndl

Table 4-2. Chemical Identity of Selected Organic Arsenic Compounds[a]

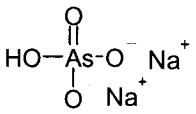
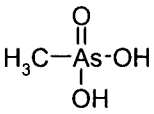
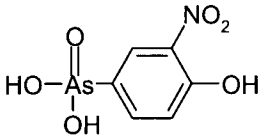
Characteristic	Dimethylarsinic acid	Methylarsonic acid	Roxarsone
Synonym	DSMA; cacodylic acid	Arsenic, methyl-	Roxarsone
Registered trade name	Ansar 170; Ansar 529; DSMA Liquid; Dimethyl; Ercoblue; Ercochem 101; Ercodry; Methar 30; Phytar 138; DSMA Liquid; Dimethyl-Tech; Arsinic acid, dimethyl-, sodium salt; DSMA Liquid; Dimethyl-Tech; Ercoblue; Ercodry; Sodium cacodylate	None	None
Chemical formula	$C_2H_6AsNaO_2$	$CH_5AsO_3Na_2$	CH_5AsO_3	$C_6H_6AsNO_6$
Chemical structure			
Identification numbers				
CAS registry	75-60-5	124-65-2	144-21-8	121-19-7
NIOSH RTECS[b]	PAA750000	PAA700000	CE5600000	
EPA hazardous waste	D004	D004	D004	
OHM/TADS	None	None	None	None
DOT/UN/NA/IMO shipping	None	None	None	None
HSDB	7	6	8	
EINECS	200-540-9	204-718-1	205-687-8	
NCI	None	None	C61	

Table 4-2. Chemical Identity of Selected Organic Arsenic Compounds[a]

Characteristic	Synonyms	Structure	Synonyms	Structure
Systematic name	Arsanilic acid		Sodium cacodylate	
	4-aminobenzenearsonic acid		sodium dimethylarsinate	
	p-aminophenylarsonic acid		sodium salt	
	p-arsanilic acid			
Registered trade name	None		Ansar 8100	Ansar 8200
			Encycle; Phytar 560	Target MSMA; Phytar 53;
			Reactect 6	Daconate 6
				Bueno MSMA Magnum 6
				Drexel Razor Razor Pro
				Ansar Silver 6
Chemical formula	$C_6H_7AsNO_3Na$		$C_2H_6AsO_2Na$	CH_4AsO_3Na
Chemical structure				
Identification numbers				
CAS registry				
NIOSH RTECS[b]	CF		C	PA
EPA hazardous waste	D	D	D	
OHM/TADS	None	None		None
DOT/UN/NA/IMO shipping	UN	UN	No	
HSDB				
EINECS				
NCI	C	No		C

[a]All information in this table from HSDB unless otherwise noted.
[b]RTECS unless otherwise noted.

CAS = Chemical Abstracts Service; DOT/UN/NA/IMO = Department of Transport/United Nations/North America/International Maritime Organization; EINECS = European Inventory of Existing Commercial Chemical Substances; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-3. Physical and Chemical Properties of Arsenic and Selected Inorganic Arsenic Compounds[a]

Pp	Aic	Aiid	Aic ld	Aiid
Mg				
Cb	Sig			
Pp	St	St	St	St
Mgin	°C	5 °C	D °C	°C °C
Bigin	°C	LH	°C	°C
Dy				
Od	Os	No	No	Os
Od				
	Nd	Nd	Nd	Nd
Air	Nd	Nd	Nd	Nd
Sy				
		°C	°C	°C
Og Nd		St	St Pi	
Oh	Nd	Nd	St St	
Pi				
Lg	Nd	Nd	Nd	Nd
Lg	Nd	Nd	Nd	Nd
	No		Nd	Nd
		Nd	Nd	°C
Ai	Nd	Nd	Nd	Nt
Fi	Nd	Nd	Nd	Nd
Fi	Nd	Nd	Nd	Nd
Cl Nd		Nd	Nd	Nd
El Nd		Nd	Nd	Nd

Table 4-3. Physical and Chemical Properties of Arsenic and Selected Inorganic Arsenic Compounds[a]

Pp	Cn			Dn	Sn	
M	2	6	8	2		
Cb	Cb	Db	g	Cb	d	
P	St	St	St[d]	St		
M	D	2 °C	3 °C[d]	N		
B	N	N	N	N		
D	2	3	3 2 °C	d	3	
Od	Ob		d	Ob	d	N
Od						
W	N	N	N	N		
Air	N	N	N	N		
St						
W	C	°C	St		F	
Og				Sl	Sl	
Ob	St	St		Sl	N	
P						
LgK w	N	N	N	N		
LgK o	N	N	N	N		
K a	N	N				
	°C	N	N	N		
At	N	N	N	N		
F	N	N	N	N		
F	N	N	N	N		
C	N	N	N	N		
E	N	N	N	N		

[a] Al
[b]
[c] NRC 9
[d]

Table 4-4. Physical and Chemical Properties of Selected Organic Arsenic Compounds[a]

Property	Arsenic acid	Arsenous acid	Dimethylarsinic acid
Molecular weight		[b]	
Color			
Physical state		[b]	
Melting point	°C	°C [b]	°C
Boiling point			°C
Density			
Odor			
Odor threshold			
Water			
Air			
Solubility			
Water			°C
Organic solvents			
Acidity			
Partition coefficients			
Log K_{ow}			
Log K_{oc}			
pK_a		[c]	
Bioconcentration factor			
Soil organic carbon partition coefficient			
Atmospheric photodegradation			
Flammability			
Explosivity			
Conversion factor			
Explosive limits			

Table 4-4. Physical and Chemical Properties of Selected Organic Arsenic Compounds[a]

Table 4-4. Physical and Chemical Properties of Selected Organic Arsenic Compounds[a]

Pp	Diin	Sin	Sin
M			
Cb		C	
P	St	St	St
M	°C	°C	°C
B	Nd	Nd	Nd
D	[3]	°C	Nd
Od	No	Ob	Ob
Od			
	Nd	Nd	Nd
Air	Nd	Nd	Nd
St			
	°C	°C	°C
Og	St	Nd	Is
Aid	Nd	Nd	Nd
P			
LgK		No	
LgK	Nd	Nd	Nd
K	K		K
	[7]	Nd	[8]
	Nd	Nd	Nd
At	Nd	Nd	Nd
F	Nd	Nd	Nd
F	No		
C	Nd	Nd	Nd
E	Nd	Nd	Nd

[a]Al
[b]C
[c]T

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

5.1 PRODUCTION

Arsenic is widely distributed in the Earth's crust, which contains about 3.4 ppm arsenic (Wedepohl 1991). It is mostly found in natural minerals, such as realgar (As_4S_4), orpiment (As_2S_3), and arsenolite (As_2O_3), and only found in its elemental form to a small extent. There are over 150 arsenic-bearing minerals (Budavari et al. 2001; Carapella 1992).

Arsenic is presently obtained as a byproduct of the smelting of copper, lead, cobalt, and gold ores. Arsenic trioxide is volatilized during smelting and accumulates in the flue dust, which may contain up to 30% arsenic trioxide. The crude flue dust is further refined by mixing with small amounts of galena or pyrite to prevent the formation of arsensites and roasting to yield arsenic trioxide of 90–95% purity. By successive sublimations, a purity of 99% can be obtained. Arsenic metal can be prepared by the reduction of arsenic oxide with charcoal. Demand for metallic arsenic is limited and thus, about 95% of arsenic is marketed and consumed in combined form, principally as arsenic trioxide, which is subsequently converted to arsenic acid (Brooks 2003; Carapella 1992; Hanusch et al. 1985).

Since 1985, when the ASARCO smelter in Tacoma, Washington ceased operation, there has been no domestic production of arsenic and consequently, the United States remains entirely dependent on imports (Brooks 2003; U.S. Bureau of Mines 1988, 1990). Prior to its cessation, U.S. production of arsenic trioxide had been 7,300 metric tons in 1983, 6,800 metric tons in 1984, and 2,200 metric tons in 1985 (U.S. Bureau of Mines 1988). In 2003, arsenic trioxide was obtained from the treatment of nonferrous ores or concentrates in 14 countries. In 2003, the world's largest producer of arsenic trioxide was China, followed by Chile and Peru. China is the world leader in the production of commercial-grade arsenic metal. The United States, with an apparent demand of 21,600 metric tons in 2003, is the world's leading consumer of arsenic (Brooks 2003).

Tables 5-1 and 5-2 list facilities in each state that manufacture or process arsenic and arsenic compounds, respectively, as well as the intended use and the range of maximum amounts of arsenic or arsenic compounds that are stored on site. In 2002, there were 61 and 501 reporting facilities that produced, processed, or used arsenic and arsenic compounds, respectively, in the United States. The data listed in Tables 5-1 and 5-2 are derived from the Toxics Release Inventory (TRI02 2005). Only certain types of

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

State[a]	Number of facilities	Minimum reported amount released (pounds)[b]	Maximum reported amount released (pounds)[b]	Activities[c]
AK	1	0	9,[illegible]	
AL	8	0	9,[illegible]	
AR	4	0	9,[illegible]	
AZ	8	0	9,[illegible]	
CA	0	0	9,[illegible]	
CO	8	0	9,[illegible]	
FL	9	0	9,[illegible]	
GA	3	0	9,[illegible]	
HI	1	0	9,[illegible]	
IA	3	0	9,[illegible]	
ID	7	0	9,[illegible]	
IL	5	0	9,[illegible]	
IN	7	0	9,[illegible]	
KY	9	0	9,[illegible]	
LA	8	0	9,[illegible]	
MA	5	0	9,[illegible]	
MD	9	0	9,[illegible]	
MI	0	0	9,[illegible]	
MN	5	0	9,[illegible]	
MO	5	0	9,[illegible]	
MS	9	0	9,[illegible]	
NC	8	0	9,[illegible]	
ND	2	0	9,[illegible]	
NE	1	0	9,[illegible]	
NJ	9	0	9,[illegible]	
NM	2	0	9,[illegible]	
NV	5	0	9,[illegible]	
NY	3	0	9,[illegible]	
OH	4	0	9,[illegible]	
OK	9	0	9,[illegible]	
OR	5	0	9,[illegible]	
PA	2	0	9,[illegible]	
PR	3	0	9,[illegible]	
SC	8	0	9,[illegible]	
SD	1	0	9,[illegible]	
TN	8	0	9,[illegible]	
TX	2	0	9,[illegible]	
UT	8	0	9,[illegible]	

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

Sta[a]	Nu of Fac	Min Qua (lb/yr)	[b]	Max Qua (lb/yr)	[b]	Activities[c]
W	3	0		9	58	
W	8	0		9		
W	8	0		9		
W	1	0		9		

Se TRI2(Dat

[a] Pa
[b] Ac
[c] Ac

1 Pa
2 Ip
3 O
4 S
5 B

6 Ip
7 Re
8 Fa
9 At
0 R

1 Cl
2 M
3 Ad
4 Pe

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

State[a]	Number of facilities	Minimum amount handled (pounds)	[b]	Maximum amount handled (pounds)	[b]	Activities	[c]
AK	6	0		9		1,5,7,8,11	
AL	5		0	9		1,2,4,5,6,7,8,9,12	
AR	2	0		9		1,2,3,8,9,11	
AZ	2		0	9		1,2,4,5,6,7,8,9,10,11	
CA	8		0	9		1,2,4,5,6,7,8,9,11	
CO	8	0		9		1,3,4,5,6,7,12	
DE	1	0		9		1,5,9	
FL	2		0	9		1,3,4,5,7,8,11	
GA	5		0	9		1,2,4,5,6,7,8,11	
HI	6	0		9		1,5,7,8	
IA	2		0	9		1,3,4,5,6,7,8,9,12	
ID	6	0		9		1,3,5,6,7,8,12	
IL	8		0	9		1,2,4,5,6,7,8,10,11	
IN	3	0		9		1,2,4,5,6,7,8,11	
KS	2		0	9		1,3,4,5,6,7,11	
KY	2		0	9		1,2,4,5,6,7,8,10,11	
LA	0		0	9		1,2,4,5,6,7,8,12	
MA	8	0		9		1,4,5,7,8	
MD	3		0	9		1,4,5,7,8,12	
ME	1	0		9		1,5,7	
MI	2		0	9		1,2,4,5,6,7,8,9,11	
MN	1	0		9		1,3,5,6,7,8,12	
MO	2		0	9		1,2,4,5,6,7,8,11	
MS	2	0		9		1,2,4,5,6,7,8,12	
MT	8	0		0	1,2,3,5,6,7,11		
NC	5		0	9		1,2,4,5,6,7,8,10,11	
ND	0	0		9		1,5,6,7,11	
NE	5	0		9		1,3,4,5,6,7,12	
NH	2	0		9		1,5,7,8	
NJ	3		0	9		1,2,4,5,6,7,8,12	
NM	1	0		9		1,5,7,8	
NV	2	0		0	1,2,3,5,6,7,11		
NY	2		0	9		1,2,4,5,6,7,8,12	
OH	5		0	9		1,2,4,5,6,7,8,9,11	
OK	3		0	9		1,2,3,5,6,11	
OR	1		0	9		1,3,7,12	
PA	5		0	9		1,2,4,5,6,7,8,9,11	
PR	7	0		9		1,2,5,11	

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

Sta	a Nb Fa	Mi Qa b	Ma Qa b	Ac c
RI	7	0	9	7,8
SC	0	0	9	1,2,3,4,5,6,7,8,9,10,12
SD	5	0	9	1,5,6,8,12
TN	8	0	9	1,2,3,4,5,6,7,8,9,10,12
TX	28	0	9	1,2,3,4,5,6,7,8,9,10,12
UT	2	0	9	1,3,4,5,6,7,8,10,12
VA	23	0	9	1,2,3,4,5,6,7,8,9,10,12
WA	4	0	9	1,2,3,5,6,7,8,9,10,12
WI	3	0	9	1,2,3,4,5,6,7,9,11
WV	2	0	9	1,3,4,5,6,7,8,10,12
WY	9	0	9	1,3,4,5,6,7,8,10,12

Se TRI 2 Da a

[a] Pa fa
[b] An a a a
[c] Ac

1 Pa
2 Im
3 On
4 SD
5 Bu
6 Im
7 Re
8 Fa Co
9 Ac Co
10 Re
1 Ch Pa Ag
2 Ma Ag
3 Ad De Us
4 Pa

facilities were required to report. Therefore, this is not an exhaustive list. Current U.S. manufacturers of selected arsenic compounds are given in Table 5-3.

5.2 IMPORT/EXPORT

Since U.S. production ceased in 1985, all arsenic consumed in the United States is imported. Imports of arsenic have increased substantially since the mid-1980s, reaching 21,600 metric tons in 2003, of which 27,300 metric tons were as arsenic trioxide and 990 metric tons as the metal. China is the major import source for metallic arsenic from 2000 to 2003, supplying 78%, followed by Japan (16%) and Hong Kong (3%). China is also the major import source in 2000–2003 for arsenic trioxide, supplying 62%, followed by Chile (15%), Morocco (15%), and Mexico (4%) (Brooks 2003, 2005).

U.S. exports of metallic arsenic were 173 metric tons in 2003 and are estimated to be 200 metric tons in 2004 (Brooks 2005). In 2003, U.S. imports for consumption of arsenic and arsenic trioxide were approximately $9.9x10^5$ and $2.7x10^6$ kilograms, respectively (ITA 2005a, 2005b).

5.3 USE

In 2003, the United States was the world's largest consumer of arsenic, with an apparent demand of 21,600 metric tons. Production of wood preservatives, primarily CCA, CrO_3•CuO•As_2O_5, accounted for more than 90% of domestic consumption of arsenic trioxide. The remainder was used for the production of agricultural chemicals, including fertilizers, herbicides, and insecticides. The major U.S. producers of arsenical wood preservatives include Arch Wood Protection Inc., Georgia; Chemical Specialties Inc., North Carolina; and Osmose Wood Preserving Inc., New York (Brooks 2003). CCA is the most widely used wood preservative in the world. Wood treated with CCA is referred to as 'pressure treated' wood (American Wood Preservers Association 2000; Page and Loar 1993). In 1997, approximately 727.8 million cubic feet (20.6 million cubic meters) of wood products were pressure treated in the United States. CCA is a water-based product that protects several commercially available species of western lumber from decay and insect attack. It is widely used in treating utility poles, building lumber, and wood foundations. CCA comes in three types, A, B, and C, which contain different proportions of chromium, copper, and arsenic oxides. Type C, the most popular type, contains CrO_3, CuO, and As_2O_5 in the proportions 47.5, 18.5, and 34.0%, respectively. The retention levels are 0.25 pounds per cubic feet (pcf) for above ground use such as fencing and decking, 0.40 pcf for lumber used in ground contact such as

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

Cpn	Lto
Aid	
Ad Pd	Cp
Od Pd	Mig Te
Aid	
Fg Ld	Cp Nb Cl
Dd (DSMA)	
W Cp Cp	Sp Nd
Dd Cd Cpn	Tp Mi
Md (MSMA)	
Dd Cd Cpn	Tp Mi
Ag Cd Cp	Fg Nd

[a]D f R t (SRI) t SRI t

fence posts and deck posts, and 0.60 pcf for all weather wood foundations (Chicago Flameproof 2000; Permapost 2000). Piling used for fresh and saltwater contact should contain 0.80 and 2.5 pcf of CCA, respectively.

In 2003, U.S. manufacturers of arsenical wood preservative began a voluntary transition from CCA to other wood preservatives in wood products for certain residential uses, such as play structures, picnic tables, decks, fencing, and boardwalks. This phase out was completed on December 31, 2003; wood treated prior to this date could still be used and structures made with CCA-treated wood would not be affected. CCA-treated wood products continue to be used in industrial applications (Brooks 2003, 2005).

Metallic arsenic is used as an alloying element in ammunition and solders, as an anti-friction additive to metals used for bearings, and to strengthen lead-acid storage battery grids. In the past, the predominant use of arsenic was in agriculture. Organic arsenicals, namely dimethylarsinic acid (cacodylic acid), disodium methanearsonate (DSMA), sodium methanearsonate (MSMA), and arsenic acid, are still used as herbicides (Meister 1999). Cacodylic acid is also used as a silvicide (kills/controls trees and brush) and cotton defoliant. Pesticide use data from 1992 indicates that 6.0, 1.3, and 0.14 million pounds of MSMA, DSMA, and cacodylic acid, respectively, were applied to U.S. crops; the respective areas treated were 3.7, 0.76, and 0.17 million acres (Gianessi and Anderson 1995d). About 99.5% of these chemicals were applied to cotton. The remainder was applied to citrus and sod. Other organic arsenicals used in agriculture include arsanilic acid, sodium arsanilate, and 3-nitro-4-hydroxyphenylarsonic acid (roxarsone), which are antimicrobials used in animal and poultry feeds (Beerman 1994). While the U.S. Food and Drug Administration (FDA) has authorized the used of these compounds as medicinal feed additives, only one of the arsenical compounds may be used at a time as the sole source of organic arsenic in the feed (EPA 1998k). In 1999–2000, about 70% of the broiler industry added roxarsone to broiler poultry feed; concentrations of roxarsone in feed range from 22.7 to 45.4 g/ton (Garbarino et al. 2003).

From the mid-nineteenth century to the introduction of organic pesticides in the 1940s, inorganic arsenic compounds were the dominant pesticides available to farmers and fruit growers. Calcium arsenate was formerly used to control the boll weevil and cotton worm and was used as an herbicide. Lead arsenate was used on apple and other fruit orchards as well as on potato fields. Sodium arsenite was used to control weeds on railroad right-of-ways, potato fields, and in industrial areas, as well as in baits and to debark trees. Sodium arsenate had some application in ant traps. The use of inorganic arsenic compounds in agriculture has virtually disappeared beginning around the 1960s (Azcue and Nriagu 1994; Meister 1987; Merwin et al. 1994; Sanok et al. 1995). Food uses were voluntarily cancelled in 1993 as

was the use of arsenic acid as a defoliant on cotton plants; inorganic arsenic's remaining allowable uses are in ant baits and wood preservatives (EPA 1999a, 1999h). In 1987, EPA issued a preliminary decision to cancel the registration of most inorganic arsenicals used as nonwood pesticides (Loebenstein 1994) (see Chapter 8). According to the California Department of Pesticide Regulation, arsenic acid, arsenic pentoxide, and arsenic trioxide are registered currently as pesticides in the United States; there are no active registrants listed for calcium arsenate, lead arsenate, disodium arsenate, or sodium arsenite (DPR 2005).

High-purity arsenic (99.9999%) is used by the electronics industry for gallium-arsenide semiconductors for telecommunications, solar cells, and space research (Brooks 2005). Arsenic trioxide and arsenic acid were used as a decolorizer and fining agent in the production of bottle glass and other glassware (Carapella 1992).

Arsenic compounds have a long history of use in medicine. Inorganic arsenic was used as a therapeutic agent through the mid-twentieth century, primarily for the treatment of leukemia, psoriasis, and chronic bronchial asthma; organic arsenic antibiotics were extensively used in the treatment of spirochetal and protozoal disease (NRC 1999). The availability of inorganic arsenicals in Western medicines ended in the 1970s, although they may still be encountered in non-Western traditional medicines. By the 1980s, the only remaining medicinal organic arsenical was melarsoprol for treatment of the meningoencephalitic stage of African trypanosomiasis. Recently, there has been renewed interest in arsenic as a therapeutic agent, namely the use of arsenic trioxide in the treatment of acute promyelocytic leukemia (APL) (Gallagher 1998; Kroemer and de Thé 1999; Miller 1998; Wang 2001).

5.4 DISPOSAL

Wastes containing arsenic are considered hazardous wastes, and as such, their treatment, storage, and disposal are regulated by law (see Chapter 8). The main route of disposal of solid wastes containing arsenic is landfilling. EPA has promulgated rules and treatment standards for landfilling liquid arsenical wastes (EPA 1990e). Other disposal alternatives for arsenic-containing wastes include incineration and recycling. There is, however, essentially no recycling of arsenic from its principal uses in wood preservatives or agricultural chemicals (IRPTC 1990; U.S. Bureau of Mines 1990). Arsenic is not recovered from consumer end product scrap, such as treated wood. This scrap will most likely be disposed of in municipal landfills or municipal waste incinerators. No arsenic is recovered domestically from nonferrous smelting; however, process water and contaminated runoff from wood treatment plants

are reused and gallium arsenide scrap from semiconductor devices are processed for metal recovery (Brooks 2005).

CCA-treated wood is classified as non-hazardous waste under the Federal Resource Conservation and Recovery Act (RCRA). CCA-treated wood is disposed of with regular municipal trash (i.e., municipal solid waste, not yard waste). It should not be burned in open fires, stoves, residential boilers, or fire places and should not be composted or used as mulch. Treated wood from commercial or industrial applications may only be burned in commercial or industrial incinerators in accordance with state and federal regulations (EPA 2005a; Hickson 2000).

Arsenic 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 1995c). Disposal of wastes containing arsenic is controlled by a number of federal regulations (see Chapter 8).

6. POTENTIAL FOR HUMAN EXPOSURE

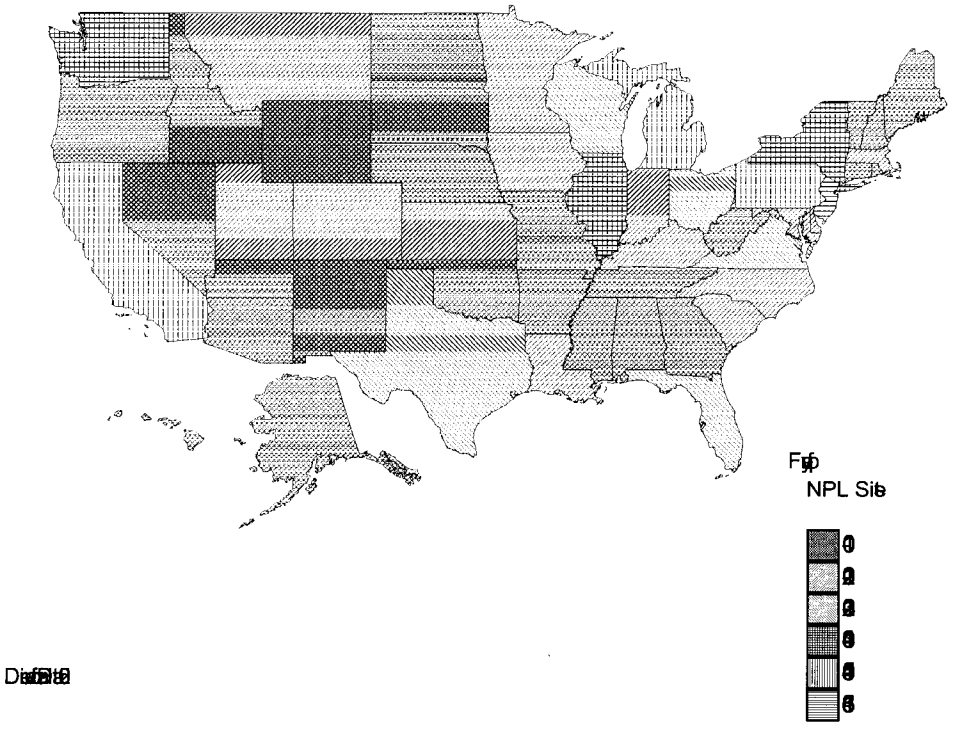
6.1 OVERVIEW

Arsenic has been identified in at least 784 of the 1,662 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2005). However, the number of sites evaluated for arsenic is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 778 are located within the United States, and 11, 3, and 2 are located in the Commonwealth of Puerto Rico, the Virgin Islands, and Guam (not shown).

Arsenic is widely distributed in the Earth's crust, which contains about 3.4 ppm arsenic (Wedepohl 1991). It is mostly found in nature in minerals, such as realgar (As_4S_4), orpiment (As_2S_3), and arsenolite (As_2O_3), and only found in its elemental form to a small extent. There are over 150 arsenic-bearing minerals (Budavari et al. 2001; Carapella 1992). While arsenic is released to the environment from natural sources such as wind-blown dirt and volcanoes, releases from anthropogenic sources far exceed those from natural sources. Anthropogenic sources of arsenic include nonferrous metal mining and smelting, pesticide application, coal combustion, wood combustion, and waste incineration. Most anthropogenic releases of arsenic are to land or soil, primarily in the form of pesticides or solid wastes. However, substantial amounts are also released to air and water.

Arsenic found in soil either naturally occurring or from anthropogenic releases forms insoluble complexes with iron, aluminum, and magnesium oxides found in soil surfaces, and in this form, arsenic is relatively immobile. However, under reducing conditions, arsenic can be released from the solid phase, resulting in soluble mobile forms of arsenic, which may potentially leach into groundwater or result in runoff of arsenic into surface waters. Soil microorganisms may convert inorganic arsenic to organic forms and may reduce small amounts to arsine that would volatilize into the atmosphere. In aquatic systems, inorganic arsenic occurs primarily in two oxidation states, As(V) and As(III). Both forms generally co-exist, although As(V) predominates under oxidizing conditions and As(III) predominates under reducing conditions. Water samples from a number of lakes and estuaries, mostly in California, show measurable concentrations of methylated species of arsenic (equivalent to 1–59% of total arsenic) (Anderson and Bruland 1991). The appearance of methylated species in bodies of water is a complex process that is not completely understood, but appears to be seasonal in pattern and correlated with ambient water temperature and the presences of algal blooms. Arsenic may undergo a variety of reactions in the

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



environment, including oxidation-reduction reactions, ligand exchange, precipitation, and biotransformation (EPA 1979, 1984a; Pongratz 1998; Welch et al. 1988). These reactions are influenced by Eh (the oxidation-reduction potential), pH, metal sulfide and sulfide ion concentrations, iron concentration, temperature, salinity, and distribution and composition of the biota (EPA 1979; Wakao et al. 1988). Much of the arsenic will adsorb to particulate matter and sediment. Arsenic released to air exists mainly in the form of particulate matter. Arsenic released from combustion processes will generally occur as highly soluble oxides. These particles are dispersed by the wind and returned to the earth in wet or dry deposition. Arsines that are released to the atmosphere as a result of microbial action are oxidized to nonvolatile species that settle back to the ground.

Because arsenic is a natural component of the Earth's crust, low levels of the element are found in all environmental media. Atmospheric levels of arsenic in remote locations (away from human releases) range from 1 to 3 ng/m^3, while concentrations in urban areas may range from 20 to 100 ng/m^3. Concentrations in water are usually <10 µg/L, although higher levels may occur near natural mineral deposits or anthropogenic sources. Natural levels of arsenic in soil usually range from 1 to 40 mg/kg, with a mean of 5 mg/kg, although much higher levels may occur in mining areas, at waste sites, near high geological deposits of arsenic-rich minerals, or from pesticide application. Arsenic is also found in many foods, at concentrations that usually range from 20 to 140 µg/kg. Arsenic concentrations may be substantially higher in certain seafoods, although much of it is in the form of arsenobetaine, a relatively nontoxic organic arsenic compound.. Drinking water generally contains an average of 2 µg/L of arsenic, although 12% of water supplies from surface water sources in the North Central region of the country and 12% of supplies from groundwater sources in the Western region have levels exceeding 20 µg/L. In January 2001, EPA adopted a new standard that arsenic levels in drinking water were not to exceed 10 µg/L, replacing the previous standard of 50 µg/L. The rule became effective February 22, 2002 and municipalities must comply with the new standard by January 23, 2005 (EPA 2001a).

For most people, diet is the largest source of exposure to arsenic, with average intakes of about 40 µg/day of total arsenic (i.e., arsenic in all of its forms). The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. However, most of the arsenic in seafood, particularly in fish and some shellfish, is found as the nontoxic organic form, arsenobetaine. Inorganic arsenic in seafood sampled in a market basket survey of inorganic arsenic in food ranged from <0.001 to 0.002 µg/g. U.S. dietary intake of inorganic arsenic has been estimated to range from 1 to 20 µg/day, with grains and produce expected to be significant contributors to dietary inorganic arsenic intake (Schoof et al. 1999a, 1999b). Intake of arsenic from air, soil, and water are usually much smaller than from food,

but exposure from these media may become significant in areas with naturally high levels of arsenic or with arsenic contamination. People who produce or use arsenic compounds in occupations such as nonferrous metal smelting, pesticide manufacturing or application, wood preservation, semiconductor manufacturing, or glass production may be exposed to substantially higher levels of arsenic, mainly from dusts or aerosols in air. Exposure at waste sites may occur by a variety of pathways, including inhalation of dusts in air, ingestion of contaminated soil or water, or through the food chain. The magnitude of the exposures may be substantial, but this can only be evaluated on a site-by-site basis.

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 2005k). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005k).

Arsenic has been identified in a variety of environmental media (air, surface water, leachate, groundwater, soil, and sediment) at 784 of the 1,662 current or former NPL hazardous waste sites (HazDat 2005). However, the number of sites evaluated for arsenic is not known. The frequency of these sites within the United States can be seen in Figure 6-1.

6.2.1 Air

Estimated releases of 2,574 pounds (~1.2 metric tons) of arsenic to the atmosphere from 61 domestic manufacturing and processing facilities in 2002, accounted for about 0.14% of the estimated total

environmental releases from facilities required to report to the TRI (TRI02 2005). Estimated releases of 178,541 pounds (~81 metric tons) of arsenic compounds to the atmosphere from 501 domestic manufacturing and processing facilities in 2002, accounted for about 0.04% of the estimated total environmental releases from facilities required to report to the TRI (TRI02 2005). These releases for arsenic and arsenic compounds are summarized in Tables 6-1 and 6-2, respectively.

Arsenic naturally occurs in soil and will be present in the atmosphere as airborne dust. It is also emitted from volcanoes and in areas of dormant volcanism (e.g., fumaroles). Gaseous alkyl arsenic compounds may be released from soil that has been treated with inorganic arsenic compounds as a result of biogenic processes (Schroeder et al. 1987; Tamaki and Frankenberger 1992). Arsenic naturally occurs in sea water and vegetation and is released into the atmosphere in sea salt spray and forest fires. Anthropogenic sources of arsenic include nonferrous metal smelting, coal, oil and wood combustion, and municipal waste incineration. Arsenic naturally occurs in coal and oil and therefore, coal- and oil-fired power plants release arsenic to the atmosphere in their emissions (Pacyna 1987). Arsenic's use in agriculture and industrial processes also contributes to its emissions. One important source of arsenic emissions is cotton ginning in which the cotton seeds are removed from the raw cotton.

EPA conducted a modeling study with the Assessment System for Population Exposure Nationwide (ASPEN) in which estimates of emissions of hazardous air pollutants were used to estimate air quality (Rosenbaum et al. 1999). Using 1990 data, the total emissions of arsenic in the conterminous 48 states, excluding road dust or windblown dust from construction or agricultural tilling was estimated to be 3.0 tons/day with 90% of emissions coming from point sources and 5% each from area and mobile sources. Nriagu and Pacyna (1988) and Pacyna et al. (1995) estimated worldwide emissions of arsenic to the atmosphere for 1983. Estimates of yearly emissions from anthropogenic sources ranged from 12,000 to 25,600 metric tons with a median value of 18,800 metric tons. Natural sources contributed 1,100–23,500 metric tons annually. Chilvers and Peterson (1987) estimated global natural and anthropogenic arsenic emissions to the atmosphere as 73,500 and 28,100 metric tons per year, respectively. Copper smelting and coal combustion accounted for 65% of anthropogenic emissions. A U.S. Bureau of Mines study on the flow of mineral commodities estimated that global emissions of arsenic from metal smelting, coal burning, and other industrial uses ranged from 24,000 to 124,000 metric tons per year compared to natural releases, mostly from volcanoes, ranging from 2,800 to 8,000 metric tons per year (Loebenstein 1994). U.S. emissions of arsenic to the atmosphere were estimated as 3,300 metric tons per year between 1979 and 1986 (Pacyna et al. 1995). There is evidence that anthropogenic emissions, at least from smelters, are lower than they had been in the early 1980s. Skeaff

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Arsenic[a]

| State[c] | RFs[d] | Releases to the environment[b] | | |

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Arsenic[a]

			R[illegible]								b					
											T[illegible]					
St[illegible]	c	RF[d]	Air[e]		W[illegible]	f	Ul[g]		Ld[illegible]	h	Ob[illegible]	i	Oi[illegible]	j	Of[illegible]	k	On[illegible]
W		1	0	3		0		2	0	2		0		2			
Tl[illegible]	6	2	0		5	2	0	5		2							

Se TRI[illegible]

[a] Th TRI [illegible] Th is co
[illegible] D [illegible]
[b] D in TRI [illegible]
[c] P [illegible]
[d] N [illegible]
[e] Th [illegible]
[f] St [illegible]
[illegible]
[g] Cl [illegible]
[h] Re Cl Re At (RCRA) [illegible] C [illegible]
[i] St [illegible]
[illegible]
[j] Th [illegible]
[k] Th [illegible] POTW

RF = [illegible] Ul = [illegible]

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

| | | |

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

Sta[c]	RF[d]	Air[e]	W[f]	Ul[g]	Lad[h]	Ob[i]	Oite[j]	Ote[k]	Ote
RI	1	0	8	0	0	0		8	0
SC	9	3	0	0	3	0	2	0	3
SD	2	1	2	0	0	0	5	0	5
TN	7	8	0	0	5	2	0	0	2
TX	2	0	6	0	0	3	0	3	5
UT	7	3	0	0	0	3	3	2	0
X	9	3	0	0	3	0	3	3	5
W	6	7	2	0	0	0	0	6	0
W	5	0	5	0	0	0	2	3	3
W	0	7	6	0	2	5	5	6	6
W	2	0	0	0	0	0	0	0	0
Ta									

Se TRI Da

[a] Ta TRI Th is
Da TRI
[c] Pa
[d] Ne
[e] Ta
[f] Sa
da
[g] Ca
[h] Re Ac (RCRA) Ta
[i] Sa
[j] Ta
[k] Ta PO W

RF = Ul =

and Dubreuil (1997) calculated 1993 arsenic emission factors for Canadian smelters and found them to be 14, 7, and 26% for lead, copper-nickel, and zinc smelters, respectively. Significant amounts of arsenic are released in stack gases from roasting gold ores (Environment Canada 1993). It is likely that air releases of arsenic decreased during the 1980s due to regulations on industrial emissions (EPA 1986f), improved control technology for coal-burning facilities, and decreased use of arsenical pesticides. The National Air Toxics Assessment reported that total anthropogenic emissions for arsenic compounds in the United States in 1996 were 355 tons/year (EPA 2005b).

Pirrone and Keeler (1996) compared trends of trace element emissions from major anthropogenic sources in the Great Lakes region with ambient concentrations observed in urban areas of the region. They found that arsenic emissions increased about 2.8% per year from 1982 to 1988 and then decreased steadily by about 1.4% per year to 1993. Coal combustion in electric utilities and in residential, commercial, and industrial facilities was an important source of arsenic in the region, accounting for about 69% of the total emissions. Iron-steel manufacturing accounted for about 13% of the region wide arsenic emissions and nonferrous metals production for 17%.

Arsenic in the particulate phase is the predominant (89–98.6%) form of arsenic in the troposphere (Matschullat 2000). Inorganic species, most commonly trivalent arsenic, is the dominant form of arsenic in the air over emission areas; methylated forms of arsenic are probably of minor significance. Arsenic-containing air samples of smelter or coal-fired power plant origin consist largely of trivalent arsenic in both vapor and particulate form (Pacyna 1987). Oxides are the primary species evolved from fossil fuel and industrial processes. Additionally, arsenic trisulfide has also been reported from coal combustion, organic arsines from oil combustion, and arsenic trichloride from refuse incineration.

Arsenic has been identified in 35 air samples collected from 1,662 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2005).

6.2.2 Water

Estimated releases of 978 pounds (~0.4 metric tons) of arsenic to surface water from 61 domestic manufacturing and processing facilities in 2002, accounted for about 0.05% of the estimated total environmental releases from facilities required to report to the TRI (TRI02 2005). Estimated releases of 103,575 pounds (~47 metric tons) of arsenic compounds to surface water from 501 domestic manufacturing and processing facilities in 2002, accounted for about 0.03% of the estimated total

environmental releases from facilities required to report to the TRI (TRI02 2005). These releases for arsenic and arsenic compounds are summarized in Tables 6-1 and 6-2, respectively.

Arsenic may be released to water from the natural weathering of soil and rocks, and in areas of vulcanism. Arsenic may also leach from soil and minerals into groundwater. Anthropogenic sources of arsenic releases to water include mining, nonferrous metals, especially copper, smelting, waste water, dumping of sewage sludge, coal burning power plants, manufacturing processes, urban runoff, and atmospheric deposition (Nriagu and Pacyna 1988; Pacyna et al. 1995). A contributory part of mining and coal burning power plants is leaching from abandoned mine tailing and fly ash waste piles. Significant amounts of arsenic are released in liquid effluents from gold-milling operations using cyanide (Environment Canada 1993). Nriagu and Pacyna (1988) and Pacyna et al. (1995) estimated global anthropogenic inputs of arsenic into rivers, lakes, and oceans for 1983; annual estimated inputs ranged from 11,600 to 70,300 metric tons with a median value of 41,800 metric tons.

Leaching of arsenic from soil, landfills, or slag deposits is a source of arsenic in groundwater (Francis and White 1987; Wadge and Hutton 1987). The arsenic in soil may be naturally-occurring or a result of the application of arsenic-containing pesticides or sludge. Wood treated with CCA is used widely in piers, piling and bulkheads and arsenic readily leaches from the treated wood (Sanders et al. 1994). Arsenic has been identified in 574 groundwater and 275 surface water samples collected from 1,662 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2005).

Arsenic was detected in 58% of samples of urban storm water runoff from 8 of 15 cities surveyed in the National Urban Runoff Program at concentrations ranging from 1 to 50.5 µg/L (Cole et al. 1984).

6.2.3 Soil

Estimated releases of 1.8 million pounds (~820 metric tons) of arsenic to soils from 61 domestic manufacturing and processing facilities in 2002, accounted for about 99% of the estimated total environmental releases from facilities required to report to the TRI (TRI02 2005). An additional 19,466 pounds (~8.8 metric tons), constituting about 1% of the total environmental emissions, were released via underground injection (TRI02 2005). Estimated releases of 397 million pounds (~180,000 metric tons) of arsenic compounds to soils from 501 domestic manufacturing and processing facilities in 2002, accounted for about 99% of the estimated total environmental releases from facilities required to report to the TRI (TRI02 2005). An additional 1.1 million pounds (~494 metric tons),

constituting about 0.3% of the total environmental emissions, were released via underground injection (TRI02 2005). These releases for arsenic and arsenic compounds are summarized in Tables 6-1 and 6-2, respectively.

The soil receives arsenic from a variety of anthropogenic sources, including ash residue from power plants, smelting operations, mining wastes, and municipal, commercial, and industrial waste. Ash from power plants is often incorporated into cement and other materials that are used for roads and construction. Arsenic may be released from such material into soil. Nriagu and Pacyna (1988) and Pacyna et al. (1995) estimated global anthropogenic inputs of arsenic into soil for 1983. Excluding mine tailings and smelter slag, annual estimated inputs ranged from 52,000 to 112,000 metric tons with a median value of 82,000 metric tons. Mine tailings and smelter slag were estimated to add an additional 7,200–11,000 and 4,500–9,000 metric tons, respectively. Old abandoned mine tailings undoubtedly contribute still more. Wood treated with CCA used in foundations or posts could potentially release arsenic into the surrounding soil. CCA preservatives have been shown to leach to varying degrees from wood, as well as through soils in both field and laboratory studies (Chirenje et al. 2003a; Hingston et al. 2001; Rahman et al. 2004; Stilwell and Graetz 2001). Arsenic may also be released on land through the application of pesticides and fertilizer. Senesi et al. (1999) reported the range of arsenic in 32 fertilizers as 2.2–322 ng/g. Roxarsone (3-nitro-4-hydroxyphenylarsonic acid), which was used to treat poultry feed in approximately 70% of the broiler poultry operations in 1999–2000, is excreted unchanged in the manure. Poultry litter (manure and bedding) is routinely used as fertilizer to cropland and pasture. In 2000, assuming 70% of the 8.3 billion broiler poultry produced in the United States were fed roxarsone-treated feed, the resulting manure would contain approximately $2.5x10^5$ kg of arsenic (Garbarino et al. 2003). Land application of sewage sludge is another source of arsenic in soil. Arsenic was detected in sewage sludge samples from 23 cities at concentrations of 0.3–53 µg/g (Mumma et al. 1984).

Arsenic has been identified in 515 soil and 347 sediment samples collected from 1,662 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2005).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Arsenic in soil may be transported by wind or in runoff or may leach into the subsurface soil. However, because many arsenic compounds tend to partition to soil or sediment under oxidizing conditions,

leaching usually does not transport arsenic to any great depth (EPA 1982c; Moore et al. 1988; Pantsar-Kallio and Manninen 1997; Welch et al. 1988). Arsenic is largely immobile in agricultural soils; therefore, it tends to concentrate and remain in upper soil layers indefinitely. Downward migration has been shown to be greater in a sandy soil than in a clay loam (Sanok et al. 1995). Arsenic from lead arsenate that was used for pest control did not migrate downward below 20 cm in one fruit orchard; in another orchard, 15 years after sludge amendments and deep plowing, essentially all arsenic residues remained in the upper 40 cm of soil (Merwin et al. 1994). Leaching of arsenic in polluted wetland soil was low; leaching was correlated with the amount of dissolved organic matter in the soil (Kalbitz and Wennrich 1998). The effect of soil characteristics, namely pH, organic matter content, clay content, iron oxide content, aluminum oxide content, and cation exchange capacity (CEC), on the adsorption of various metals to 20 Dutch surface soils was assessed by regression analysis (Janssen et al. 1997). The most influential parameter affecting arsenic adsorption was the iron content of the soil.

Arsenic that is adsorbed to iron and manganese oxides may be released under reducing conditions, which may occur in sediment or flooding conditions (LaForce et al. 1998; McGeehan 1996; Mok and Wai 1994). In addition to reductive dissolution, when nutrient levels are adequate, microbial action can also result in dissolution. Interestingly, drying of the previously flooded soil increases arsenic adsorption, possibly due to alterations in iron mineralogy (McGeehan et al. 1998).

Darland and Inskeep (1997) conducted a study to determine the effects of pH and phosphate competition on the transport of arsenate ($H_xAsO_4^{x-3}$) through saturated columns filled with a sand containing free iron oxides. At pH 4.5 and 6.5, arsenate transport was strongly retarded, while at pH 8.5, it was rapid. The enhanced transport of arsenate at pH 8 is consistent with the pH dependence of surface complexation reactions describing arsenate sorption by metal oxide minerals that can be categorized as a ligand exchange mechanism. Phosphate was shown to compete effectively with arsenate for adsorption sites on the sand, but the competition was not sufficient to desorb all of the arsenate in batch column experiments, even when the applied phosphate exceeded the column adsorption capacity by a factor of two. The researchers concluded that arsenate desorption kinetics may play an important role in the transport of arsenate through porous media. In a study looking at the effect of competing anions on the adsorption of arsenite and arsenate on ferrihydrite, the effect of phosphate on arsenate adsorption was greater at higher pH than at low pH and the opposite trend was observed for arsenite. While sulfate did not change the affinity of arsenate for ferrihydrite, sulfate reduced the adsorption of arsenite at pHs below 7.0 (Jain and Loeppert 2000).

Smith et al. (1999) investigated the sorption properties of both As(V) and As(III) in 10 Australian soils of widely different chemistry and mineralogy at commonly found arsenic levels. Adsorption of both arsenate and arsenite was rapid (1 hour). The amount of As(V) sorbed varied widely (1.7–62.0 L/kg); soils with lower amounts of oxidic material adsorbed much less arsenic than those with higher amounts of these minerals. Arsenate sorption was highly correlated with the iron oxide content of the soil and this factor probably accounts for much of the variation in soil adsorptivity. Considerable leaching of arsenic occurred at a site where cattle were treated with a dip containing arsenic (cattle dip site) that contained similar soil. Arsenite adsorption, which was investigated in four of the Australian soils, was sorbed to a lesser extent than was arsenate. This was attributed to soil minerology and the species of As(V) and As(III) present in solution; at pH 5–7, the dominant As(V) species are $H_2AsO_4^-$ and $HAsO_4^{2-}$ and neutral H_3AsO_3 is the dominant As(III) species. For soils containing low amounts of oxidic minerals, pH had little effect on As(V) sorption, while for oxidic soils, a decrease in sorption was evident as the pH increased. In contrast, As(III) sorption increased with increasing pH. Jain et al. (1999) reported similar results where arsinite (As(III) and arsenate (As(V)) were both found to bind strongly to iron oxides; however, the adsorption of arsenate decreases with increasing pH, while the adsorption of arsenite increases with increasing pH (Jain et al. 1999). As(III), which exists in a neutral form as arsenous acid, H_3AsO_3, (pK_a=9.23, 12.13, 13.4), is less strongly adsorbed on mineral surfaces than the oxyanions of arsenic acid, H_3AsO_4, (pK_a=2.22, 6.98, 11.53) (NRC 1999). Based on its pK_a values, arsenic acid would exist as a mixture of arsenate anions, $H_2AsO_4^-$ and $HAsO_4^{2-}$, under most environmental conditions (pH 5–9).

The practice of liming to remediate contaminated soils and mine tailings has the potential to mobilize arsenic. Experiments performed by Jones et al. (1997) indicate that the increased mobility appears to be consistent with the pH dependence of sorption reactions of arsenic on iron oxide minerals rather than dissolution-precipitation reactions involving arsenic. They recommend that remediation of acidic mine tailings or other arsenic-contaminated soils be carefully evaluated with respect to potential arsenic mobilization, especially at contaminated sites hydraulically connected to surface or groundwaters.

Transport and partitioning of arsenic in water depends upon the chemical form (oxidation state and counter ion) of the arsenic and on interactions with other materials present. Soluble forms move with the water, and may be carried long distances through rivers (EPA 1979). However, arsenic may be adsorbed from water onto sediments or soils, especially clays, iron oxides, aluminum hydroxides, manganese compounds, and organic material (EPA 1979, 1982c; Welch et al. 1988). Under oxidizing and mildly reducing conditions, groundwater arsenic concentrations are usually controlled by adsorption rather than

by mineral precipitation. The extent of arsenic adsorption under equilibrium conditions is characterized by the distribution coefficient, K_d, which measures the equilibrium partitioning ratio of adsorbed to dissolved contaminant. The value of K_d depends strongly upon the pH of the water, the arsenic oxidation state, and the temperature. In acidic and neutral waters, As(V) is extensively adsorbed, while As(III) is relatively weakly adsorbed. Trivalent inorganic arsenic exists predominantly as arsenous acid (H_3AsO_3) at environmental pH and is not strongly adsorbed to suspended solids and sediments in the water column. Pentavalent inorganic arsenic exists predominantly as $H_2AsO_4^-$ and $HAsO_4^{2-}$ in most environmental waters, which has considerably greater adsorption characteristics than arsenous acid. While in acidic and neutral waters, As(V) is more strongly adsorbed relatively to As(III), in high-pH waters (pH >9) aquifer K_d values are considerably lower for both oxidation states (Mariner et al. 1996). Sediment-bound arsenic may be released back into the water by chemical or biological interconversions of arsenic species (see Section 6.3.2).

Arsenic enters rivers from where mining operations occurred and are transported downstream, moving from water and sediment into biofilm (attached algae, bacterial, and associated fine detrital material), and then into invertebrates and fish. The source of arsenic in the water column may be resuspended sediment. While arsenic bioaccumulates in animals, it does not appear to biomagnify between tropic levels (Eisler 1994; Farag et al. 1998).

Most anthropogenic arsenic emitted to the atmosphere arises from high temperature processes (e.g., coal and oil combustion, smelting operations, and refuse incineration) and occurs as fine particles with a mass median diameter of about 1 μm (Coles et al. 1979; Pacyna 1987). These particles are transported by wind and air currents until they are returned to earth by wet or dry deposition. Their residence time in the atmosphere is about 7–9 days, in which time the particles may be transported thousands of kilometers (EPA 1982b; Pacyna 1987). Long-range transport was evident in analyzing deposition of arsenic in countries like Norway; there was no indication that the marine environment contributed significantly to the deposition (Steinnes et al. 1992). Atmospheric fallout can be a significant source of arsenic in coastal and inland waters near industrial areas. Scudlark et al. (1994) determined the average wet depositional flux of arsenic as 49 μg As/m^2/year for 2 sites in Chesapeake Bay, Maryland from June 1990 to July 1991. They found a high degree of spatial and temporal variability. The elemental fluxes derived predominantly from anthropogenic sources. Golomb et al. (1997) report average total (wet + dry) deposition rates to Massachusetts Bay of 132 μg/m^2/year, of which 21 μg/m^2/year was wet deposition during the period September 15, 1992 to September 16, 1993. Hoff et al. (1996) estimated the following arsenic loadings into the Great Lakes for 1994 (lake, wet deposition, dry deposition): Superior,

11,000 kg/year, 3,600 kg/year; Michigan, 5,000 kg/year, 1,800 kg/year; Erie, 5,500 kg/year, 1,800 kg/year; and Ontario, 3,000 kg/year, 580 kg/year. The measured dry deposition fluxes of arsenic at four sampling sites around Lake Michigan ranged approximately from 0.01 to 1.5 μg As/m^2/day; estimated inputs of arsenic into Lake Michigan were reported to be $1.4x10^3$ kg/year (Shahin et al 2000).

Terrestrial plants may accumulate arsenic by root uptake from the soil or by absorption of airborne arsenic deposited on the leaves, and certain species may accumulate substantial levels (EPA 1982b). Yet, even when grown on highly polluted soil or soil naturally high in arsenic, the arsenic level taken up by the plants is comparatively low (Gebel et al. 1998b; Pitten et al. 1999). Kale, lettuce, carrots, and potatoes were grown in experimental plots surrounding a wood preservation factory where waste wood was incinerated to investigate the amount and pathways for arsenic uptake by plants (Larsen et al. 1992). On incineration, the arsenate in the wood preservative was partially converted to arsenite; the arsenic emitted from the stack was primarily particle bound. Elevated levels of inorganic arsenic were found in the test plants and in the soil around the factory. Statistical analyses revealed that the dominating pathway for transport of arsenic from the factory to the leafy vegetables (kale) was by direct atmospheric deposition, while arsenic in the root crops (potatoes and carrots) was a result of both soil uptake and atmospheric deposition. Arsenic accumulation by plants is affected by arsenic speciation. Uptake of four arsenic species (arsenite, arsenate, methylarsonic acid, and dimethylarsinic acid) by turnips grown under soilless culture conditions showed that while uptake increased with increasing arsenic concentration in the nutrient, the organic arsenicals showed higher upward translocation than the inorganic arsenical (Carbonell-Battachina et al. 1999). The total amount of arsenic taken up by the turnip plants followed the trend methylarsenate (MMA)<dimethylarsinic acid (DMA)<arsenite<arsenate. In a similar experiment, conducted with tomato plants, the total amount of arsenic taken up by the tomato plants followed the trend DMA<MMA<arsenate≈arsenite, with arsenic concentrations in the plants increasing with increasing arsenic concentration in the nutrient solution. Arsenic was mainly accumulated in the root system (85%) with smaller amounts translocating to the fruit (1%). However, plants treated with MMA and DMA had higher arsenic concentrations in the shoots and fruit than those treated with arsenite or arsenate (Burlo et al. 1999). Terrestrial plants growing on land bordering arsenic-contaminated waters show relatively little arsenic content, even though the sediments have arsenic concentrations as high as 200 μg/g (Tamaki and Frankenberger 1992). Arsenic concentrations in vegetables grown in uncontaminated soils and contaminated soils containing arsenic, as well as other metals and organic contaminants, were generally <12 μg/kg wet weight. A maximum concentration of 18 μg/kg wet weight was found in unpeeled carrots grown in highly contaminated soil, which contained a mean arsenic concentration of 27 mg/kg dry weight (Samsøe-Petersen et al. 2002).

In a study by Rahman et al. (2004), CCA-treated lumber was used to construct raised garden beds to determine how far the components of CCA migrated in the soil and the uptake of these components by crops grown in the soil. CCA can be transferred to skin and subsequently ingested if children touch wood treated with CCA (Hemond and Solo-Gabriele 2004). Arsenic was found to diffuse laterally into the soil from the CCA-treated wood, with the highest concentrations found at 0–2 cm from the treated wood and a steady decline in concentration with increased distance. The highest average arsenic concentrations found in soil closest (0–2 cm) to the CCA-treated wood were 56 and 46 μg/g in loamy sand and sandy loam soils, respectively. At a distance of 30–35 cm from the CCA-treated wood, arsenic concentrations were approximately 7 μg/g in both soils. All samples were of the top 0–15 cm of soil. Crops grown in both soil types within 0–2 cm of the CCA-treated wood contained higher concentrations of arsenic, 0.186 and 10.894 μg/g for carrots without peal and bean leaves and stems, respectively, than those grown at 1.5 m from the CCA-treated wood, 0.006 and 0.682 μg/g for bean pods and bean leaves and stems, respectively. However, based on FDA guidelines on tolerance limits, these crops would be considered approved for human consumption. Studies by Chirenje et al. (2003a) also showed that elevated arsenic concentrations were found in surface (0–5 cm) soils immediately surrounding, within the first 0.3 m, of utility poles, fences, and decks made with CCA-treated wood. Factors such as the preservative formula, fixation temperature, post treatment handling, and timber dimensions of CCA-treated wood, as well as the pH, salinity, and temperature of the leaching media can affect the leach rates from CCA-treated wood (Hingston et al. 2001). In a study by Lebow et al. (2003), the use of a water repellent finish on CCA-treated wood significantly reduces the amount of arsenic, as well as copper and chromium, in the run-off water. It was also observed the exposure to UV radiation caused a significant increase in leaching from both finished and unfinished samples of CCA-treated wood.

Bioconcentration of arsenic occurs in aquatic organisms, primarily in algae and lower invertebrates. Both bottom-feeding and predatory fish can accumulate contaminants found in water. Bottom-feeders are readily exposed to the greater quantities of metals that accumulate in sediments. Predators may bioaccumulate metals from the surrounding water or from feeding on other fish, including bottom-feeders, which can result in the biomagnification of the metals in their tissues. An extensive study of the factors affecting bioaccumulation of arsenic in two streams in western Maryland in 1997–1998 found no evidence of biomagnification since arsenic concentrations in organisms tend to decrease with increasing tropic level (Mason et al. 2000). Arsenic is mainly accumulated in the exoskeleton of invertebrates and in the livers of fish. No difference were found in the arsenic levels in different species of fish, which included herbivorous, insectivorous, and carnivorous species. The major bioaccumulation transfer is

between water and algae, at the base of the food chain and this has a strong impact on the concentration in fish. National Contaminant Biomonitoring data produced by the Fish and Wildlife Service were used to test whether differences exist between bottom-feeders and predators in tissue levels of metals and other contaminants. No differences were found for arsenic (Kidwell et al. 1995). Bioconcentration factors (BCFs) measured in freshwater invertebrates and fish for several arsenic compounds ranged from 0 to 17, but a BCF of 350 was observed in marine oysters (EPA 1980a). The BCFs of bryophytes, invertebrates, and fish (livers) in Swedish lakes and brooks impacted by smelter emissions were 8,700, 1,900–2,200, and 200–800, respectively (Lither et al. 1995). In a study conducted at the Times Beach Confined Disposal Facility in Buffalo, New York, arsenic concentrations in tissue from zebra mussels exposed for 34 days were significantly higher than water column concentrations (Roper et al. 1996). Barnacles growing on CCA-treated wood docks accumulated arsenic (Weis et al. 1993). The highest concentrations of arsenic was found on the most recently treated wood. Biomagnification in aquatic food chains does not appear to be significant (EPA 1979, 1982b, 1983e; Mason et al. 2000), although some fish and invertebrates contain high levels of arsenic compounds.

6.3.2 Transformation and Degradation

6.3.2.1 Air

Arsenic is released into the atmosphere primarily as arsenic trioxide or, less frequently, in one of several volatile organic compounds, mainly arsines (EPA 1982b). Trivalent arsenic and methyl arsines in the atmosphere undergo oxidation to the pentavalent state (EPA 1984a), and arsenic in the atmosphere is usually a mixture of the trivalent and pentavalent forms (EPA 1984a; Scudlark and Church 1988). Photolysis is not considered an important fate process for arsenic compounds (EPA 1979).

6.3.2.2 Water

Arsenic in water can undergo a complex series of transformations, including oxidation-reduction reactions, ligand exchange, precipitation, and biotransformation (EPA 1979, 1984a; Sanders et al. 1994; Welch et al. 1988). Rate constants for these various reactions are not readily available, but the factors most strongly influencing fate processes in water include Eh, pH, metal sulfide and sulfide ion concentrations, iron concentrations, temperature, salinity, distribution and composition of the biota, season, and the nature and concentration of natural organic matter (EPA 1979; Farago 1997; Redman et

al. 2002; Wakao et al. 1988). No formation of arsine gas from marine environments has been reported (Tamaki and Frankenberger 1992).

Inorganic species of arsenic are predominant in the aquatic environment. In the pH range of natural waters, the predominant aqueous inorganic As(V) species are the arsenate ions, $H_2AsO_4^-$ and $HAsO_4^{2-}$; the predominant inorganic As(III) species is H_3AsO_3 (Aurillo et al. 1994; EPA 1982c). As(V) generally dominates in oxidizing environments such as surface water and As(III) dominates under reducing conditions such as may occur in groundwater containing high levels of arsenic. However, the reduction of arsenate to arsenite is slow, so arsenate can be found in reducing environments. Conversely, the oxidation of arsenite in oxidizing environments is moderately slow (half-life, 0.4–7 days in coastal systems) and therefore, arsenite can be found in oxidizing environments (Mariner et al. 1996; Sanders et al. 1994). The main organic species in freshwater are MMA and DMA; however, these species are usually present at lower concentrations than inorganic arsenic species (Eisler 1994). (The toxicities of MMA and DMA are discussed in Chapter 3.) Aquatic microorganisms may reduce the arsenate to arsenite and the methylated arsenicals MMA and DMA (Aurillo et al. 1994; Benson 1989; Braman and Foreback 1973; Edmonds and Francesconi 1987; Gao and Burau 1997; Sanders et al. 1994). Methylated species are also produced by the biogenic reduction of more complex organoarsenic compounds like arsenocholine or arsenobetaine. Water samples from a number of lakes and estuaries, mostly in California, show measurable concentrations of methylated arsenic (equivalent to 1–59% of total arsenic) (Anderson and Bruland 1991). Within the oxic photic zone, arsenate and DMA were the dominant species. A seasonal study of one lake demonstrated that DMA was the dominant form of arsenic in surface waters during late summer and fall. Methylated species declined and arsenate species increased when the lake turned over in late fall. Mono Lake, a highly alkaline body of water, and four rivers did not have measurable concentrations of methylated arsenic. It was hypothesized that the reason why methylated forms were not detected in Mono Lake was that the extremely high inorganic arsenic concentrations in the lake, 230 μM (17 mg/L), could overwhelm the analysis of small amounts of organic forms. Other possibilities are that the high alkalinity or very high phosphate levels in the water, 260 μM (25 mg/L), are not conducive to biogenic methylation. At typical freshwater concentrations, the barium ion, in forming barium arsenate, is the most likely metal capable of holding total dissolved metals to low concentrations (EPA 1979). Other metals considered were calcium, iron, and chromium. Both reduction and methylation of As(V) may lead to increased mobilization of arsenic, since As(III), dimethylarsinates, and monomethylarsonates are much less particle-reactive than As(V) (Aurillo et al. 1994). In the estuarial Patuxet River, Maryland, arsenate concentrations peaked during the summer, at 1.0 μg/L in 1988–1989 (Sanders et al. 1994). In contrast, winter to spring levels were around 0.1 μg/L. Arsenite

concentrations were irregularly present at low levels during the year. Peaks of DMA occurred at various times, particularly in the winter and late spring and appeared to be linked with algal blooms. The DMA peak declined over several months that was followed by a rise in MMA. The MMA was thought to be occurring as a degradation product of DMA. A similar seasonal pattern of arsenic speciation was observed in Chesapeake Bay. Arsenite methylation took place during the warmer months leading to changes down the main stem of the bay; arsensite production dominated the upper reaches of the bay and methylated species dominated the more saline lower reaches. In coastal waters, reduced and methylated species are present in lower concentrations, around 10–20% of total arsenic (Sanders et al. 1994). In groundwater, arsenic generally exists as the oxyanion of arsenate ($H_xAsO_4^{3-x}$) or arsenite ($H_xAsO_3^{3-x}$), or both; however, the distribution between arsenite and arsenate is not always predictable based on oxidation-reduction potential (Robertson 1989; Welch et al. 1988).

6.3.2.3 Sediment and Soil

The arsenic cycle in soils is complex, with many biotic and abiotic processes controlling its overall fate and environmental impact. Arsenic in soil exists in various oxidation states and chemical species, depending upon soil pH and oxidation-reduction potential. Arsenate [(As(V)] and arsenite [As(III)] exist as oxyanions in oxidized systems, while metallic arsenic [As(0)], arsine [As(-III)], and methylated forms of arsenic are thermodynamically stable in reduced systems, such as swamp and bogs. The arsenate and arsenite oxyanions have various degrees of protonation depending upon pH (EPA 1982b; McGeehan 1996). Under most environmental conditions, inorganic As(V) will exist as a mixture of arsenate anions, $H_2AsO_4^-$ and $HAsO_4^{2-}$, and inorganic As(III) will exist as H_3AsO_3. As(V) predominates in aerobic soils, and As(III) predominates in slightly reduced soils (e.g., temporarily flooded) (EPA 1982b). Transformations between the various oxidation states and species of arsenic occur as a result of biotic or abiotic processes (Bhumbla and Keefer 1994). Arsenicals applied to soils may be methylated by microorganisms to arsines, which are lost through volatilization, and organic forms may be mineralized to inorganic forms (Gao and Burau 1997). Microorganisms found in natural marine sediments and sediments contaminated with mine-tailings have also been shown to be capable of methylating arsenic under aerobic and anaerobic conditions. Cumulative arsine evolution from arsenical-amended soil followed the order: DMA>MMA>As(III)=As(V) (Reimer 1989). Arsenites are of greater environmental concern than arsenates because of their greater toxicity and higher mobility in soil (McGeehan 1996). Sulfidic mining wastes may contain arsenopyrite that oxidizes to forms arsinic acid, a highly mobile form of arsenic under acid conditions. Organoarsenical pesticides (e.g., MMA, DMA) applied to soil are metabolized by soil bacteria to alkylarsines, arsenate, and MMA. They may also be mineralized to

inorganic arsenic (Gao and Burau 1997; Hood 1985). The half-life of DMA in soil is about 20 days (Hood 1985). Degradation of ^{14}C-labelled monosodium methanearsonate (MSMA) was found to range from 1.7 to 10% in Sharkey clay soil and Dundee silty clay loam soil after 60 days, respectively. Sterilized soils were found to produce essentially no $^{14}CO_2$, indicating that soil bacteria contributed to the decomposition of MSMA (Von Endt et al. 1968). The degradation of MSMA in various soils was found to be dependent upon soil type, water content, and temperature. MSMA dissipated faster in finer textured soils with continuous flooding and under controlled laboratory conditions (<180 days) than under field conditions (approximately 350 days) (Akkari et al. 1986). Roxarsone (3-nitro-4-hydroxyphenylarsonic acid) used in poultry feed is found excreted unchanged in poultry litter (bedding and manure). Roxarsone found in poultry litter, which is used to amend agricultural soil, was found to degrade to arsenate in approximately 3-4 weeks upon composting (Garbarino et al. 2003). In addition, the arsenic in poultry litter was found to be easily mobilized by water; however, its leach rate from amended soils was slow enough that it accumulated in soils (Rutherford et al. 2003).

A sequential fractionation scheme was used to assess the chemical nature, and thus the potential bioavailability, of arsenic at cattle dip sites in Australia where sodium arsenite was used extensively in cattle dips from the turn of the century until the early 1950s (McLaren et al. 1998). Most sites contained substantial amounts, 13% on the average, of arsenic in the two most labile fractions indicating a high potential for bioaccessibility and leaching. The bulk of the arsenic appeared to be associated with amorphous iron and aluminum minerals in soil. Similarly, arsenic in soil and mine waste in the Tamar Valley in England was found to be concentrated in a fraction associated with iron and organic-iron (Kavanagh et al. 1997). Laboratory studies were performed to assess the phase partitioning of trace metals to sediment from the Coeur d'Alene River, a mining area of Idaho, and the release of metals under simulated minor and major flooding events (LaForce et al. 1998). Arsenic was primarily associated with the iron and manganese oxides as seen by its large release when these oxides were reduced. Arsenic levels were comparatively low in the organic fraction and remaining residual fraction and negligible in the extractible fractions.

6.3.2.4 Other Media

Carbonell-Barrachina et al. (2000) found the speciation and solubility of arsenic in sewage sludge suspensions to be affected by pH and Eh. Under oxidizing conditions, the solubility of arsenic was low, with a major portion of the soluble arsenic present as organic arsenic compounds, mainly dimethylarsinic acid. Under moderately reducing conditions (0–100 mV), the major inorganic species in solution was

arsinite, and the solubility of arsenic was increased due to dissolution of iron oxyhydroxides. Under strongly reducing conditions (-250 mV), arsenic solubility was decreased by the formation of insoluble sulfides. The pH of the solution was also found to influence the speciation and solubility of arsenic. At neutral pH, the solubility of arsenic was at its maximum, and decreased under acidic or alkaline conditions. Inorganic arsenic species were the dominant species at pH 5.0; at pH 6.5, the major soluble forms were organic arsenic species. The biomethylation of arsenic was limited at acidic pH, and was at its maximum at near neutral pH (Carbonell-Barrachina et al. 2000).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to arsenic depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of arsenic 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 arsenic 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 arsenic in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Arsenic in ambient air is usually a mixture of particulate arsenite and arsenate; organic species are of negligible importance except in areas of substantial methylated arsenic pesticide application or biotic activity (EPA 1984a). Mean levels in ambient air in the United States have been reported to range from <1 to 3 ng/m^3 in remote areas and from 20 to 30 ng/m^3 in urban areas (Davidson et al. 1985; EPA 1982c; IARC 1980; NAS 1977a). EPA conducted a modeling study with the Assessment System for Population Exposure Nationwide (ASPEN) in which estimates of emissions of hazardous air pollutants were used to estimate ambient concentrations (Rosenbaum et al. 1999). Using 1990 data to estimate total emissions of arsenic in the conterminous 48 states, excluding road dust or windblown dust from construction or agricultural tilling, the 25th percentile, median, and 75th percentile arsenic concentration were estimated to be 9, 20, and 30 ng/m^3, respectively. Maps illustrating the amount of toxic air pollutant emissions, including arsenic compounds, by county in 1996 for the 48 coterminous states of the United States as well as Puerto Rico and the Virgin Islands are available on the internet at http://www.epa.gov/ttn/atw/-nata/mapemis.html, as of March 2005. Schroeder et al. (1987) listed ranges of arsenic concentrations in

air of 0.007–1.9, 1.0–28, and 2–2,320 ng/m^3 in remote, rural, and urban areas, respectively. The average annual arsenic concentration in air at Nahant, Massachusetts, just north of Boston, between September 1992 and September 1993, was 1.2 ng/m^3; 75% of the arsenic was associated with fine (<2.5 μm) particles. The long-term means of the ambient concentrations of arsenic measured in urban areas of the Great Lakes region from 1982 to 1993 ranged from 4.2 to 9.6 ng/m^3 (Pirrone and Keeler 1996). Large cities generally have higher arsenic air concentrations than smaller ones due to emissions from coal-fired power plants (IARC 1980), but maximum 24-hour concentrations generally are <100 ng/m^3 (EPA 1984a). In the spring of 1990, aerosols and cloud water that were sampled by aircraft at an altitude of 1.2–3 km above the Midwestern United States had a mean mixed layer arsenic concentration of 1.6±0.9 ng/m^3 (Burkhard et al. 1994a). The mean arsenic concentration at a site 400 km to the northwest, directly downwind on most days, was 1.0±0.5 ng/m^3.

Arsenic was monitored at an application site in the San Joaquin Valley, California and at four sites in nearby communities in 1987 where sodium arsenite was used as a fungicide on tokay grapes (Baker et al. 1996). The maximum arsenic concentration measured 15–20 meters from the edge of the field was 260 ng/m^3. The maximum arsenic concentration at four community sites in the area was 76 ng/m^3. The concentration at an urban background site was 3 ng/m^3 (Baker et al. 1996). Sodium arsenite is no longer registered in California (Baker et al. 1996). The highest arsenic levels detected in the atmosphere were near nonferrous metal smelters, with reported concentrations up to 2,500 ng/m^3 (IARC 1980; NAS 1977a; Schroeder et al. 1987).

Arsenic air concentrations measured in several indoor public places (e.g., cafeteria, coffee house, music club, Amtrak train, and several restaurants) with environmental tobacco smoke (ETS) ranged from <0.1 to 1 ng/m^3, with a mean of 0.4±0.3 ng/m^3. Sites that were ETS-free (university office and library) had arsenic concentrations <0.13 ng/m^3 (Landsberger and Wu 1995). The Toxic Exposure Assessment at Columbia/Harvard (TEACH) study measured levels of various toxics in New York City air in 1999. Exposures were assessed in a group of 46 high school students in West Central Harlem. Mean arsenic concentrations in summer home outdoor, home indoor, and personal air of the participants were 0.37, 0.40, and 0.45 ng/m^3, respectively (Kinney et al. 2002). Arsenic concentrations in indoor and outdoor air collected as part of the National Human Exposure Assessment Survey (NHAXES) in Arizona ranged from 3.4 to 22.3 and from 3.5 to 25.7 ng/m^3, respectively, with 71 and 68% below the detection limit (1.8–14.3 ng/m^3) (O'Rourke et al. 1999).

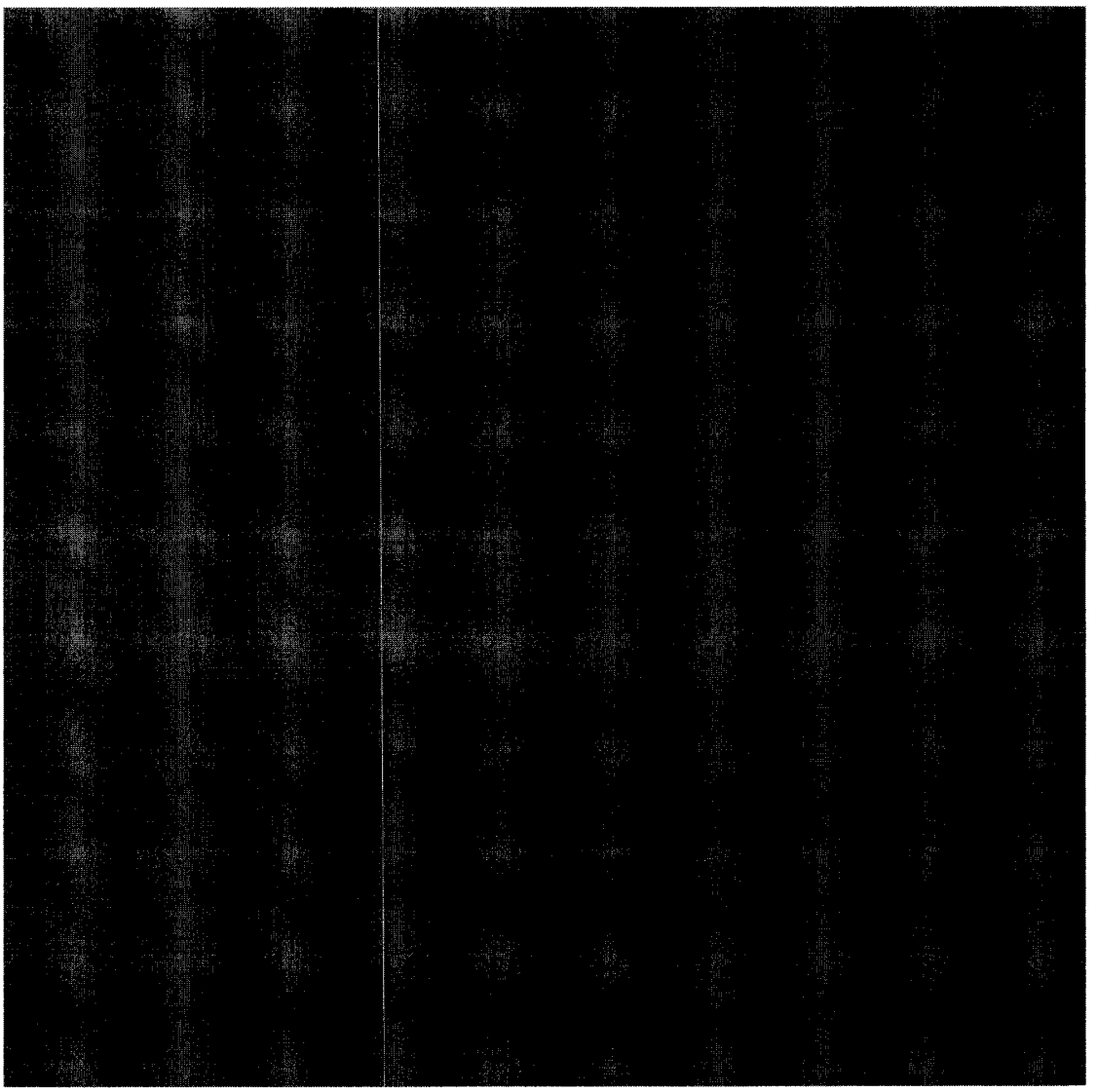
6.4.2 Water

Arsenic is widely distributed in surface water, groundwater, and finished drinking water in the United States. Surveys of arsenic concentrations in rivers and lakes indicate that most values are below 10 µg/L, although individual samples may range up to 1,000 µg/L (NAS 1977b; Page 1981; Smith et al. 1987; Welch et al. 1988). A survey of 293 stations in two nationwide sampling networks on major U.S. rivers found median arsenic levels to be 1 µg/L; the 75th percentile level was 3 µg/L (Smith et al. 1987). Arsenic was detected in 1,298 of 3,452 surface water samples recorded in the STORET database for 2004 at concentrations ranging from 0.138 to 1,700 µg/L in samples where arsenic was detected (EPA 2005c). Two streams in western Maryland that were the focus of a major bioaccumulation study in 1997–1998 had arsenic concentrations of 0.370±0.200 and 0.670±0.460 µg/L (Mason et al. 2000). Surface water will be impacted by runoff from polluted sites. In Whitewood Creek, South Dakota, where as much as 100 million tons of mining and milling waste derived from gold mining activities were discharged between 1876 and 1977, mean sediment arsenic levels were 1,920 µg/g; dissolved-phase and particulate phase arsenic levels in the creek water ranged from 20 to 80 and from 20 to 8,000 µg/L, respectively (Goddard 1987). River water sampled next to mine dumps during the rainy season in Zimbabwe had an arsenic concentration of 25 µg/L (Jonnalagadda and Nenzou 1996). An average arsenic concentration of 5.12 µg/L was reported in water from Moon Lake, a Mississippi River alluvial floodplain in northwest Mississippi. Intensive cultivation has occurred in this area, including cotton, soybeans, and rice (Cooper and Gillespie 2001). Hard-rock mining activities occurred in the southern part of Colorado and New Mexico north of Taos since the latter part of the 19th century until recently, which have impacted the Rio Grande and its tributaries. A mean arsenic concentration of approximately 0.8 µg/L was reported for the main stem of the Rio Grande sampled in June and September 1994. Arsenic concentrations in the Alamosa River, Colorado were 0.11 and 0.14 µg/L in June and September 1994, respectively, and 1.4 µg/L in Big Arsenic Spring, New Mexico in September 1994 (Taylor et al. 2001). Arsenic concentrations in water from watersheds in Black Hills, South Dakota, an area impacted by gold mining activities ranged from 2.5 to 55 µg/L and from 1.7 to 51 µg/L in unfiltered and filtered samples, respectively; concentrations from reference areas ranged from 1.1 to 3.4 µg/L and from 0.9 to1.9 µg/L in unfiltered and filtered samples, respectively (May et al. 2001). Arsenic concentrations ranged from 0.29 to 34.0 µg/L in water samples from Wakulla River and St. Joseph Bay North, along the Florida Panhandle; arsenic contamination in this area is likely to result from non-point source pollution (Philp et al. 2003).

Recent data on total arsenic in surface water from a number of seas and oceans show levels of <1 µg/L, except in the Antarctic Ocean and Southwest Pacific Oceans where the levels are 1.1 and 1.2 µg/L, respectively. Levels in coastal waters and estuaries are generally somewhat higher, in the range of 1–3 µg/L. However, estuarine water in Salinas, California had arsenic levels of 7.42 µg/L (Francesconi et al. 1994). The dissolved arsenic concentration in water at 40 sites in the Indian River Lagoon System in Florida ranged from 0.35 to 1.6 µg/L with a mean of 0.89±0.34 µg/L (Trocine and Trefry 1996). Thermal waters generally have arsenic levels of 20–3,800 µg/L, although levels as high as 276,000 µg/L have been recorded (Eisler 1994).

Arsenic levels in groundwater average about 1–2 µg/L, except in some western states with volcanic rock and sulfidic mineral deposits high in arsenic, where arsenic levels up to 3,400 µg/L have been observed (IARC 1980; Page 1981; Robertson 1989; Welch et al. 1988). In western mining areas, groundwater arsenic concentrations up to 48,000 µg/L have been reported (Welch et al. 1988). Arsenic concentrations in groundwater samples collected form 73 wells in 10 counties in southeast Michigan in 1997 ranged from 0.5 to 278 µg/L, with an average of 29 µg/L. Most (53–98%) of the arsenic was detected as arsenite (Kim et al. 2002). The U.S. Geological Survey mapped concentrations of arsenic in approximately 30,000 groundwater samples collected between 1973 and 1997; the counties in which at least 25% of wells exceed various levels are shown in Figure 6-2 (USGS 2005a). Most arsenic in natural waters is a mixture of arsenate and arsenite, with arsenate usually predominating (Braman and Foreback 1973; EPA 1982c, 1984a). Methylated forms have also been detected in both surface water and groundwater, at levels ranging from 0.01 to 7.4 µg/L (Braman and Foreback 1973; Hood 1985), with most values below 0.3 µg/L (Hood 1985). In a survey of shallow groundwater quality in the alluvial aquifer beneath a major urban center, Denver, Colorado, arsenic levels in the 30 randomly-chosen wells sampled had median levels of <1 µg/L; the maximum level was 33 µg/L (Bruce and McMahon 1996). Arsenic levels in groundwater sometimes exceeded the EPA maximum contaminant level (MCL), which was 50 µg/L at the time, in the Willamette Valley, Oregon and a nine-county region of southeastern Michigan (USGS 1999b, 1999c). In January 2001, the EPA lowered the MCL for arsenic from 50 to 10 µg/L (EPA 2001a). Areas of the world such as Bangladesh and West Bengal, India have shallow aquifers composed of arsenic-containing sediment. Arsenic is released into groundwater when the oxygen levels in the aquifer become low and iron and manganese oxyhydroxides that bind arsenic dissolve and release it into the surrounding water that the population relies on for drinking. In four villages that were targeted for a recent study, arsenic concentrations in drinking water ranged from 10 to 2,040 µg/L (Tondel et al. 1999).

Figure 6-2. Counties in Which at Least 25% of Wells Exceed Different Arsenic Levels



Arsenic has also been detected in rainwater at average concentrations of 0.2–0.5 µg/L (Welch et al. 1988). This range is consistent with that found in a 1997–1998 study in western Maryland, which was the focus of a major bioaccumulation study (Mason et al. 2000). Arsenic levels in wet deposition in the watershed as well as throughfall into the two streams were 0.345±0.392, 0.400±0.400, and 0.330±0.250 µg/L, respectively. Median arsenic concentrations in 30-day rainwater composite samples collected May-September 1994 from eight arctic catchments in northern Europe at varying distances and wind directions from the emissions of a Russian nickel ore mining, roasting, and smelting industry on the Kola Peninsula ranged from 0.07 to 12.3 µg/L (Reimann et al. 1997). Rain and snow samples were collected during the fall of 1996 and winter of 1997 at eight locations in a semi-circular pattern radiating out (2–15 km) in the direction of the prevailing wind from the Claremont incinerator located in New Hampshire. This incinerator processes 200 tons of solid waste per day. Arsenic concentrations in rainwater and snow ranged from 0.020 to 0.079 µg/L and from 0.80 to 1.28 µg/L, respectively (Feng et al. 2000).

Drinking water is one of the most important sources of arsenic exposure. Surveys of drinking water in the United States have found that more than 99% of public water supplies have arsenic concentrations below the EPA MCL, which was 50 µg/L at the time (EPA 1984a). In an EPA study of tap water from 3,834 U.S. residences, the average value was 2.4 µg/L (EPA 1982c). In January 2001, EPA adopted a new standard that arsenic levels in drinking water were not to exceed 10 µg/L, replacing the previous standard of 50 µg/L. The rule became effective February 22, 2002 and municipalities must comply with the new standard by January 23, 2005 (EPA 2001a).

Before the MCL for arsenic in drinking water was lowered from 50 to 10 µg/L, studies were undertaken to ascertain how different standards would affect compliance. One such survey sponsored by the Water Industry Technical Action Fund was the National Arsenic Occurrence Survey (NAOS). NAOS was based on a representational survey of public water systems defined by source type, system size, and geographical location. Additionally, it included a natural occurrence factor, a stratifying variable that could qualitatively describe the likelihood of arsenic occurrence in the supply. To predict finished water arsenic concentrations, data on the water treatment options, efficiency, and frequency of use were factored in. The results of the NAOS are presented in Table 6-3. The NAOS results are in general agreement with two older and more limited national surveys, EPA's National Inorganics and Radionuclides Survey (NIRS) and the Metropolitan Water District of Southern California Survey (MWDSC). The percentages of water systems that would be out of compliance are estimated to be 1.7,

Table 6-3. Regional Occurrence of Arsenic in U.S. Water Sources and Finished Drinking Water[a]

Occurrence in U.S. surface water sources				
	6	6	0	0
	8	2	4	0
	9	7	0	0
	2	6	0	0
	3	5	3	0
	3	2	3	0
	2	6	0	0
Occurrence in U.S. groundwater sources				
	7	2	7	0
	8	4	1	4
	8	4	2	0
	0	0	5	5
	6	2	5	0
	0	0	0	0
	2	3	8	4
Occurrence in U.S. finished surface water supplies				
	8	2	0	0
	9	8	0	0
	0	0	0	0
	3	2	0	0
	7	9	7	0
	4	4	0	2
	2	6	0	0
Occurrence in U.S. finished groundwater supplies				
	9	2	0	0
	8	4	1	4
	0	4	2	0
	6	2	2	3
	6	2	2	0
	0	6	0	0
	0	0	2	2

[a]

3.6, 9.3, and 20.7% for arsenic MCLs of 20, 10, 5, and 2 µg/L, respectively. Arsenic concentrations were determined in drinking in EPA Region V (Indiana, Illinois, Michigan, Minnesota, Ohio, and Wisconsin) as part of the National Human Exposure Assessment Survey (NHAXES); mean arsenic concentration in flushed and standing tap water were both 1.1 µg/L (Thomas et al. 1999). A recent review by Frost et al. (2003) of existing data from the EPA Arsenic Occurrence and Exposure Database, as well as additional data from state health and environmental departments and water utilities found that 33 counties in 11 states had estimated mean drinking water arsenic concentrations of 10 µg/L or greater. Eleven counties had mean arsenic concentrations of ≥20 µg/L, and two counties had mean arsenic concentrations of ≥50 µg/L (Frost et al. 2003).

The north central region and the western region of the United States have the highest arsenic levels in surface water and groundwater sources, respectively. In a study of drinking water from New Hampshire, arsenic concentrations ranged from <0.01 to 180 µg/L in the 793 households tested. More than 10% of the private wells had arsenic concentrations >10 µg/L, and 2.5% had levels >50 µg/L (Karagas et al. 1998). Domestic wells contained significantly higher arsenic concentrations than municipal wells with median concentrations of 0.5 and 0.2 µg/L, respectively (Peters et al. 1999). The highest arsenic levels in New Hampshire are associated with bedrock wells in the south eastern and south central part of the state. In a recent study of arsenic in well water supplies in Saskatchewan, Canada, 13% of samples were >20 µg/L and one sample exceeded 100 µg/L (Thompson et al. 1999). It was noted that the samples with high arsenic levels were derived from sites that were in near proximity to each other, indicating the presence of 'hot spots' with similar geological characteristics. The Lower Rio Grande Valley Environmental Study (LRGVES), conducted during the spring and summer of 1993, was designed to evaluate multiple forms of exposure to environmental contaminants by Valley residents (Berry et al. 1997). As a part of the study, drinking and household water samples were collected from nine residences and analyzed for contaminants including arsenic. The sources of water available in the residences were public treatment facilities, vended water machines, and a private well. Levels of arsenic ranged from 1.1 to 4.5 µg/L with a median of 3.4 µg/L, and none of the samples exceeded 50 µg/L, which at the time, was the EPA MCL for public drinking water supplies (EPA 1993a). As part of an epidemiological study, Engel and Smith (1994) investigated the levels of arsenic in drinking water throughout the United States between 1968 and 1984. They found that 30 counties in 11 states had mean arsenic levels of >5 µg/L, with a range of 5.4–91.5 µg/L; 15 counties had mean levels from 5 to 10 µg/L; 10 counties had mean levels from 10 to 20 µg/L; and 5 counties had levels >20 µg/L. The highest levels were found in Churchill County, Nevada, where 89% of the population were exposed to a mean arsenic concentration of 100 µg/L and 11% to a mean of 27 µg/L.

Many communities have high levels of arsenic in their drinking water because of contamination or as a result of the geology of the area. In Millard County, Utah, seven towns had median and maximum arsenic levels of 18.1–190.7 and 125–620 µg/L, respectively, in their drinking water (Lewis et al. 1999). The mean arsenic concentration in tap water from homes in Ajo, Arizona, about 2 miles from an open pit copper mine and smelter was 90 µg/L (Morse et al. 1979). The town's water was supplied from five deep wells. A municipal water supply system in the vicinity of a former copper smelter in Anaconda, Montana, had an arsenic level of 1.36 µg/L (Hwang et al. 1997a). Most of the private wells that were sampled in the area had arsenic levels below 5 µg/L, with an average of 2.5 µg/L. In New Hampshire, 992 randomly selected household water samples were analyzed for arsenic levels and the results for domestic well users were compared with those for users of municipal water supplies (Peters et al. 1999). The concentrations ranged from <0.0003 to 180 µg/L with water from domestic wells containing significantly more arsenic than water from municipal supplies; the median concentration of the former was about 0.5 µg/L and the latter was 0.2 µg/L. None of the municipal supplies exceeded an arsenic concentration of 50 µg/L, and 2% of the domestic wells were found to have arsenic concentrations that exceeded 50 µg/L. Approximately 2% of the municipal water users have water with arsenic levels exceeding 10 µg/L compared with 13% of domestic wells. Twenty-five percent of domestic wells and 5% of municipal supplies were found to have arsenic concentrations exceeding 2 µg/L.

Durant et al. (1995) hypothesized that due to a previously unrecognized mobilization of toxic metals from a waste disposal site, residents of Woburn, Massachusetts, may have been exposed to arsenic at levels of 70 µg/L between 1966 and 1986. However, the same investigators working with others (Rogers et al. 1997) later found that the arsenic levels in hair samples donated by Woburn residents were not consistent with the hypothesized arsenic level and suggested that the water arsenic levels were lower than first estimated.

Some developing countries, such as Mexico, Bangladesh, India, and Vietnam have highly elevated levels of arsenic in drinking water in some regions (Bagla and Kaiser 1996; Berg et al. 2001; Tondel et al. 1999; Wyatt et al. 1998a, 1998b). In Bangladesh and West Bengal, the soil naturally contains high levels of arsenic, which leaches into the shallow groundwater that is tapped for drinking water. In West Bengal, India, it is estimated that more than one million Indians are drinking arsenic-laced water and tens of millions more could be at risk in areas that have not been tested for contamination. Analysis of 20,000 tube-well waters revealed that 62% have arsenic at levels above the World Health Organization (WHO) permissible exposure limit (PEL) in drinking water of 10 µg/L, with some as high as 3,700 µg/L

(Bagla and Kaiser 1996). Analysis of 10,991 and 58,166 groundwater samples from 42 and 9 arsenic-affected districts in Bangladesh and West Bengal were found to have arsenic levels that were 59 and 34%, respectively, above 50 µg/L (Chowdhury et al. 2000). Berg et al. (2001), studied the arsenic contamination of the Red River alluvial tract in Hanoi, Vietnam and the surrounding rural areas. Arsenic concentrations in groundwater from private small-scale tube-wells averaged 159 µg/L, ranging from 1 to 3,050 µg/L. Arsenic concentrations ranged from 37 to 320 µg/L in raw groundwater pumped from the lower aquifer for the Hanoi water supply (Berg et al. 2001). Several investigators have noticed a correlation between high levels of arsenic and fluoride in drinking water (Wyatt et al. 1998a, 1998b).

6.4.3 Sediment and Soil

Arsenic is widely distributed in the Earth's crust, which contains about 3.4 ppm arsenic (Wedepohl 1991). It is mostly found in nature minerals, such as realgar (As_4S_4), orpiment (As_2S_3), and arsenolite (As_2O_3), and only found in its elemental form to a small extent. There are over 150 arsenic-bearing minerals (Budavari et al 2001; Carapella 1992). Arsenic concentrations in soils from various countries can range from 0.1 to 50 µg/g and can vary widely among geographic regions. Typical arsenic concentrations for uncontaminated soils range from 1 to 40 µg/g, with the lowest concentrations in sandy soils and soils derived from granites. Higher arsenic concentrations are found in alluvial soils and soils with high organic content (Mandal and Suzuki 2002). Arsenic in soil may originate from the parent materials that form the soil, industrial wastes, or use of arsenical pesticides. Geological processes that may lead to high arsenic concentrations in rock and subsequently the surrounding soil include hydrothermic activity and pegmatite formation (Peters et al. 1999). In the first case, thermal activity results in the dissolution and transport of metals, such as arsenic, which are precipitated in fractures in rocks. In the second process, cooling magmas may concentrate metals that are injected into rocks, crystallizing as pegmatites. Areas of volcanic activity include large areas of California, Hawaii, Alaska, Iceland, and New Zealand.

The U.S. Geological Survey reports the mean and range of arsenic in soil and other surficial materials as 7.2 and <0.1–97 µg/g, respectively (USGS 1984). The concentrations of arsenic in 445 Florida surface soils ranged from 0.01 to 50.6 µg/g (Chen et al. 1999a). The median, arithmetic mean, and geometric mean were 0.35, 1.34±3.77, and 0.42±4.10 µg/g, respectively. Chirenje et al. (2003b) reported a geometric mean arsenic concentrations of 0.40 (0.21–660) and 2.81 (0.32–110) µg/g in surface soil samples (0–20 cm) collected in May–June 2000 from Gainesville and Miami, Florida, respectively. The geometric mean arsenic concentration in 50 California soils was 2.8 µg/g (Chen et al. 1999a). In the Florida surface soils, arsenic was highly correlated (α=0.0001) with the soil content of clay, organic

carbon, CEC, total iron, and total aluminum. Arsenic tends to be associated with clay fractions and iron and manganese oxyhydroxides. Soils of granitic origin are generally low in arsenic, about 4 µg/g, whereas arsenic in soils derived from sedimentary rocks may be as high as 20–30 µg/g (Yan-Chu 1994). Soils overlying arsenic-rich geologic deposits, such as sulfide ores, may have soil concentrations two orders of magnitude higher (NAS 1977a).

Soils in mining areas or near smelters may contain high levels of arsenic. Arsenic concentrations up to 27,000 µg/g were reported in soils contaminated with mine or smelter wastes (EPA 1982b). Soils at an abandoned mining site in the Tamar Valley in southwest England have arsenic concentrations that may exceed 50,000 µg/g (Erry et al. 1999). The average arsenic levels in the top 2 cm of different soil types in the vicinity of a former copper smelter in Anaconda, Montana, ranged from 121 to 236 µg/g; levels were significantly related to proximity and wind direction to the smelter site (Hwang et al. 1997a). Smelter fallout can contaminate land miles from the source. Elevated soil arsenic has been found in spills from the downwind plume over 10 miles from the ASARCO smelter in Tacoma, Washington (WSDOE 2005). The source of elevated arsenic levels in soil in the Mexican community of Anapra in Ciudad Juarez, Chihuahua, was a lead smelter in El Paso, Texas, which ceased operation in 1985. Three geographical locations varying in distance from the smelter source were evaluated for arsenic levels in the soil. Mean arsenic levels of the three sectors at increasing distance from the source were 25.2 µg/g (n=8), 21.4 µg/g (n=7), and 19.5 µg/g (n=4). Soil from a control area located 25 km away from the smelter had a mean concentration of 8.6 µg/g (n=3) (Diaz-Barriga et al. 1997).

Soil on agricultural lands treated with arsenical pesticides may retain substantial amounts of arsenic. One study reported an arsenic concentration of 22 µg/g in treated soil compared to 2 µg/g for nearby untreated soil (EPA 1982b). Arsenic was measured in soil samples taken from 10 potato fields in Suffolk County on Long Island, New York, where sodium arsenite had been used for vine control and fall weed control for many years. Lead arsenate also may have been used as an insecticide in certain areas. The mean arsenic levels taken at a depth of 0–18 cm from each of the 10 fields ranged from 27.8±5.44 µg/g dry weight (n=10) to 51.0±7.40 µg/g dry weight (n=10). These levels were markedly higher than the level of 2.26±0.33 µg/g (n=10) for untreated control soils (Sanok et al. 1995). A survey was conducted in 1993 to determine the concentrations of arsenic and lead in soil samples from 13 old orchards in New York State. Lead arsenate was used for pest control in fruit orchards for many years, mainly from the 1930s to 1960s, and residues remain in the soil. Concentrations of arsenic ranged from 1.60 to 141 µg/g dry weight (Merwin et al. 1994). Arsenic and lead concentrations were also measured in former orchard soils contaminated by lead arsenate from the Hanford site in Washington State. The mean arsenic

concentration in surface (5–10 cm) and subsurface (10–50 cm) soils were 30 (2.9–270) and 74 (32–180) µg/g dry weight, respectively (Yokel and Delistraty 2003). Average arsenic concentration of 5.728, 5.614, and 6.746 µg/g were reported in soils, lake sediments, and wetland sediments, respectively, from Moon Lake, a Mississippi River alluvial floodplain in northwest Mississippi. Intensive cultivation has occurred in this area, including cotton, soybeans, and rice (Cooper and Gillespie 2001).

Contamination by heavy metals is a serious problem in some developing countries. Sepetiba Bay, a semi-enclosed coastal lagoon in Brazil, had sediment arsenic concentrations up to 80,000 µg/g in an area adjacent to a plant that produced zinc and cadmium (Moreira 1996). The plant uses ~1,500 tons of arsenic per year to purify the electrolytic solution used in the production of these metals. In Zimbabwe, surface soil (~10 cm depth) at abandoned mine dumps contained arsenic at an average concentration of 9,530±250 µg/g. Soil near a river stream about 400 m from the mine dumps contained 550±40 µg/g of arsenic (Jonnalagadda and Nenzou 1996).

Natural concentrations of arsenic in sediments are usually <10 µg/g dry weight, but can vary widely around the world (Mandal and Suzuki 2002). Sediment arsenic concentrations reported for U.S. rivers, lakes, and streams range from about 0.1 to 4,000 µg/g (Eisler 1994; Heit et al. 1984; NAS 1977a; Welch et al. 1988). During August through November 1992 and August 1993, bed sediment in the South Platte River Basin (Colorado, Nebraska, and Wyoming) was sampled and analyzed for 45 elements, including arsenic. The range of arsenic found was 2.8–31 µg/g dry weight and the geometric mean (n=23) was 5.7 µg/g (Heiny and Tate 1997). The arsenic concentration in surface sediment (0–2 cm) at 43 sites in the Indian River Lagoon System in Florida ranged from 0.6 to 15 µg/g dry weight with a mean of 5.0±3.9 µg/g (Trocine and Trefry 1996). Arsenic levels were well correlated with those of aluminum. Correlation with aluminum levels is used to normalize sediment level concentrations to natural levels in Florida estuaries. Surficial sediments collected from 18 locations in 3 major tributaries to Newark Bay, New Jersey, were analyzed for 7 toxic metals, including arsenic (Bonnevie et al. 1994). The highest concentrations of arsenic were found in the Rahway River adjacent to a chemical plant, 58 µg/g dry weight, and in the Hackensack River adjacent to a coal-fired power plant, 49 µg/g. The average arsenic concentration for all sediments was 17±16 µg/g. Sediments collected from seven sites in Baltimore Harbor, Maryland, at five seasonal periods between June 1987 and June 1988 had a geometric mean maximum of 7.29 µg/g dry weight and a geometric mean minimum of 1.25 µg/g (Miles and Tome 1997). This harbor is one of two sub-tributaries of the Chesapeake Bay where contaminants have been discharged on a large scale. Metal concentrations have been measured in sediments from the Times

Beach Confined Disposal Facility, an area of documented chemical contamination in Buffalo, New York (Roper et al. 1996); arsenic concentrations ranged from 27.5 to 54.0 µg/g dry weight.

The upper Clark Fork River basin in western Montana is widely contaminated by metals from past mining, milling, and smelting activities. In a 1991 study, arsenic levels were determined in sediment along the river and in a reservoir 205 km downstream. Total arsenic in sediments from Clark Fork River decreased from 404 µg/g dry weight at the farthest upstream sampling station to 11 µg/g, 201 km downstream. Sediment samples from the Milltown Reservoir had arsenic concentrations ranging from 6 to 56 µg/g (Brumbaugh et al. 1994). Total recoverable arsenic in nonfiltered pore water from the Clark Fork River decreased from 1,740 µg/L at the farthest upstream sampling station to 31 µg/L at the 201 km station (Brumbaugh et al. 1994). The Coeur d'Alene river basin in northern Idaho has been contaminated with heavy metals from mining and smelting operations since 1885 (Farag et al. 1998). A 1994 study determined the metal content of sediment, biofilm, and invertebrates at 13 sites in the basin, 10 with historic mining activity and 3 reference sites. The mean arsenic levels in sediment at the mining sites ranged from 8.3 to 179.0 µg/g dry weight, compared to 2.4–13.1 µg/g dry weight at the reference sites. The mean arsenic levels in biofilm adhering to rock in the water at the mining sites ranged from 7.5 to 155.8 µg/g dry weight, compared to 7.2–27.3 µg/g dry weight at the reference sites. In Whitewood Creek, South Dakota, where as much as 100 million tons of mining and milling waste derived from gold mining activities were discharged between 1876 and 1977, mean and maximum sediment arsenic concentrations were 1,920 and 11,000 µg/g, respectively (Goddard 1987). Uncontaminated sediment had mean arsenic levels of 9.2 µg/g. Arsenic concentrations in surface (0–5 cm) sediments from watersheds in Black Hills, South Dakota, an area impacted by gold mining activities, ranged from 23 to 1,951 µg/g dry weight; concentrations from reference areas ranged from 10 to 58 µg/g dry weight (May et al. 2001). Swan Lake, a sub-bay of Galveston Bay in Texas is a highly industrial area that received runoff from a tin smelter in the 1940s and 1950s. Surface sediments at 17 sites where oysters and mussels were collected ranged from 4.53 to 103 µg/g (Park and Presley 1997). A site in the channel leading from the old smelter had arsenic levels of 568 µg/g. Surface sediment was less contaminated than deeper sediment, indicating less arsenic input recently than in the past as a result of the smelter closing.

It has recently been suggested that the wood preservative most commonly used in dock pilings and bulkheads, CCA, can be toxic to estuarine organisms. Wendt et al. (1996) measured arsenic in surface sediments and oysters from creeks with high densities of docks and from nearby reference creeks with no docks. The average concentrations in the sediments ranged from 14 to 17 µg/g throughout the study area, which is within the range of natural background levels.

6.4.4 Other Environmental Media

Background arsenic levels in living organisms are usually <1 µg/g wet weight (Eisler 1994). Levels are higher in areas with mining and smelting activity or where arsenical pesticides were used. Eisler (1994) has an extensive listing of arsenic levels in terrestrial and aquatic flora and fauna from literature sources to about 1990. The U.S. Fish and Wildlife Service's national Contaminant Biomonitoring Program have analyzed contaminants in fish at 116 stations (rivers and the Great Lakes) across the United States. The geometric mean concentration of arsenic for the five collection periods starting in 1976 were (period, concentration wet weight basis): 1976–1977, 0.199 µg/g; 1978–1979, 0.129 µg/g; 1980–1981, 0.119 µg/g; 1984, 0.106 µg/g; and 1986, 0.083 µg/g (Schmitt et al. 1999). In 1986, the maximum and 85th percentile arsenic levels were 1.53 and 0.24 µg/g, respectively. The highest concentrations of arsenic for all five collection periods were in bloaters from Lake Michigan at Sheboygan, Wisconsin. Arsenic levels declined by 50% at this site between 1976–1997 and 1984. The major source of arsenic into Lake Michigan was a facility at Marinette, Wisconsin, which manufactured arsenic herbicides. Table 6-4 contains arsenic levels in aquatic organisms from more recent studies. The Coeur d'Alene river basin in northern Idaho has been contaminated with heavy metals from mining and smelting operations since 1885 (Farag et al. 1998). A 1994 study determined the metal content of sediment, biofilm, and invertebrates at 13 sites in the basin, 10 with historic mining activity and 3 reference sites. The mean arsenic levels in benthic macroinvertebrates at the mining sites ranged from 2.2 to 97.0 µg/g dry weight, compared to 2.1–2.4 µg/g dry weight at the reference sites. A study of aquatic organism in Swan Lake, a highly polluted sub-bay of Galveston Bay, Texas showed that arsenic concentrations were in the order snail>oyster>crab>shrimp>fish (Park and Presley 1997). In contrast to metals like silver, cadmium, copper, and zinc, arsenic concentrations in oysters and mussels were less than in the sediment from which they were collected. No significant correlation was found between levels of arsenic in clams in the Indian River Lagoon in Florida with those found in sediment or water samples (Trocine and Trefry 1996). Small animals living at mining sites ingest more arsenic in their diet and have higher arsenic levels in their bodies than those living on uncontaminated sites (Erry et al. 1999). Seasonal variations in both arsenic intake and dietary composition may affect the amount of arsenic taken up by the body and transferred to predator animals. Tissue arsenic content of wood mice and bank voles living on both arsenic-contaminated mining sites and uncontaminated sites were greater in autumn than spring. The lower tissue arsenic levels in spring of rodents living on contaminated sites suggest that there is no progressive accumulation of arsenic in overwintering animals.

Table 6-4. Levels of Arsenic in Fish and Shellfish—Recent Studies

Sample	Arsenic (µg/g)[a]	Comments	Reference
Finfish		Samples collected from Northwest Atlantic Ocean	
Mean	7.8		
Limit of detection	0.6		
Range	0.2		
Mixed species		Bluefish, striped bass, weakfish, and spot collected from Chesapeake Bay	Blue Crab Advisory Committee
Rockfish	6.8		
Croaker	7.4		
Perch	0.9		
Striped bass	5.5		
Striped bass	2.2		
Mean	5.5		
Bluefin tuna (*Thunnus thynus*)	2.3		
Fish		Samples collected from Chesapeake Bay	
Bottom feeders			
Perch			
Other		Samples collected from Chesapeake Bay	
Rockfish			
Catfish	2.2	Samples collected from Lake Michigan	
Mixed species		Samples collected from Chesapeake Bay	
Shad			
Bluefish	0.6		
Fish	0.0		
Shrimp			
Crab	2.3		
Other			
Mean			
Mixed species		Samples collected from Chesapeake Bay	
Bluefish	2.1		
Fish	0.0		
Other		Samples collected from Chesapeake Bay	

Table 6-4. Levels of Arsenic in Fish and Shellfish—Recent Studies

Sp	Ar (µg/g)[a]	Co	Re
Ma			
Parapenaeus longirostris		Co	Sh
			Ma
Aristeus antennatus			
Plesionika martia			
Nephrops norvegicus			
Fi			
Sh (*Brycon melanopterus*)		Fi	
Hoplias malabaricus)			
Ba (*Pimelodus ornatus*)			
Bi (*Prochilodus nigricans*)			
Da (*Pseudo-platystoma sp.*)			
Fi			
Br		Sa	Ba
Ba			
Ch		Ea	
		(S	
Ch			
Bl			
An			
Sh			
Bl			
Re			

Table 6-4. Levels of Arsenic in Fish and Shellfish—Recent Studies

Sample	Arsenic (µg/g)	Comment[a]	Reference
Sample			
Apple		Obtained from	
Egg			
Leaf			
Apple		Obtained from	
Egg			
Leaf			

[a]Comment

Low levels of arsenic are commonly found in food; the highest levels are found in seafood, meats, and grains. Typical U.S. dietary levels of arsenic in these foods range from 0.02 mg/kg in grains and cereals to 0.14 mg/kg in meat, fish, and poultry (Gartrell et al. 1986). Shellfish and other marine foods contain the highest arsenic concentrations and are the largest dietary source of arsenic (Gunderson 1995a; Jelinek and Corneliussen 1977; Tao and Bolger 1999). Marine organisms appear to have the ability to accumulate arsenic naturally present in seawater and food, rather than due to local pollution (Eisler 1994). Arsenic levels in fish and seafood are usually about 4–5 mg/kg (Bennett 1986; Schroeder and Balassa 1966), but may be as high as 170 mg/kg (NAS 1977b). High arsenic levels can be found in seaweeds. For example arsenic concentrations ranging from 17 to 88 mg/kg dry weight were found in commercially available seaweeds (van Netten et al. 2000). In the U.S. Food and Drug Administration (FDA) Total Diet Study, 1991–1997, seafood contained the highest levels of arsenic, followed by rice/rice cereal, mushrooms, and poultry. Concentrations in canned tuna (in oil), fish sticks, haddock (pan-cooked), and boiled shrimp were 0.609–1.470, 0.380–2.792, 0.510–10.430, and 0.290–2.681 mg/kg, respectively (Tao and Bolger 1999). Typically, arsenic levels in foods in the Total Diet Study, 1991–1996 were low, <0.03 mg/kg; only 63 of the 264 foods contained arsenic above this level. Similar results were reported in the Total Diet Study, 1991–1997, where the mean arsenic concentration in all foods was 0.036 mg/kg dry weight and arsenic was not detectable in about 88% of the foods and was detected at trace levels in another 7.8% of foods. The foods with the highest mean arsenic levels were haddock, canned tuna, fish sticks, shrimp, and fish sandwiches, with arsenic concentrations ranging from 5.33 to 0.568 mg/kg dry weight (Capar and Cunningham 2000).

It is important to bear in mind that much of the arsenic in fish and shellfish is usually present as the organic arsenic compound, arsenobetaine, which does not appear to be harmful to humans and is excreted, rapidly and unchanged, in urine (Cullen 1998; Dabeka et al. 1993; Eisler 1994; Gebel et al. 1998b). Arsenosugars, arsenic-containing ribose derivatives, are the common organoarsenicals found in marine algae; they are also found in mussels, oysters, and clams (Le et al. 2004). In some foods, arsenic is found in its inorganic form, and the percent that is in an inorganic form can be highly variable. For example, a recent study in the Netherlands reported that inorganic arsenic comprised 0.1–41% of the total arsenic in seafood (Vaessen and van Ooik 1989). Buchet et al. (1994) found that, on the average, 3% of the total arsenic in mussels was inorganic in form. Based upon data in the literature, MacIntosh et al. (1997) estimated that inorganic arsenic accounts for 1.5% of total arsenic in fish and 20% of total arsenic in shellfish. Some commercially available seaweeds, especially brown algae varieties, may have high percentages of the total arsenic present as inorganic arsenic (>50%) (Almela et al. 2002; Laparra et al.

2003). Schoof et al. (1998) found considerable variability in the total arsenic and inorganic arsenic content of Taiwanese rice and yams. Roughly three quarters of the arsenic in the samples were inorganic arsenic.

In the Lower Rio Grande Valley Environmental Study, 6 of 30 local food items and replicates collected in the spring of 1993 had arsenic concentrations above the detection limit, ranging from 0.032 to 2.65 µg/g (Berry et al. 1997). MacIntosh et al. (1997) estimated dietary intake of inorganic arsenic and found that 91 food items each contributed at least 0.05% to the intake of total inorganic arsenic. The 35 food items with the highest inorganic arsenic concentrations accounted for 90% of the estimated inorganic arsenic consumption. White rice and shrimp accounted for approximately 15 and 11%, respectively. Nriagu and Lin (1995) analyzed 26 brands of wild rice sold in the United States and found arsenic levels ranging from 0.006 to 0.142 µg/g dry weight.

During a comprehensive total diet study extending from 1985 to 1988, foods were collected in six Canadian cities and processed into 112 composite food samples (Dabeka et al. 1993). The mean, median, and range of total arsenic in all samples were 0.0732, 0.0051, and <0.0001–4.840 µg/g, respectively. Food groups containing the highest mean arsenic levels were fish (1.662 µg/g), meat and poultry (0.0243 µg/g), bakery goods and cereals (0.0245 µg/g), and fats and oils (0.0190 µg/g). Of the individual samples, marine fish had the highest arsenic levels, with a mean of 3.048 µg/g for the cooked composites and 2.466 µg/g for the raw samples. Canned fish (1.201 µg/g) and shellfish (2.041 µg/g) also contained high means. Cooked poultry, raw mushrooms, and chocolate bars contained 0.100, 0.084, and 0.105 µg/g, respectively.

A Danish study (Pedersen et al. 1994) reports the arsenic levels in beverages as the mean (range) in µg/L as follows: red wine, 9 (<2–25); white wine, 11 (<2–33); fortified wine, 5 (<2–11); beer, 7 (4–11); soft drinks, 3 (<2–8); miscellaneous juices, 8 (3–13); instant coffee, 4 (0.7–7); and instant cocoa, 5.6 (1.6–12.8).

In a study of dietary arsenic exposure in the Indigenous Peoples of the western Northwest Territories, Canada, fish contained the highest arsenic concentrations in foods consumed by the Dene and Métis populations with the highest concentration, 1.960 µg/g, found in smoked/dried cisco (fish). Other foods derived from land mammals, birds, and plants contained lower arsenic concentrations. A mean arsenic intake of <1.0 µg/kg/day was reported for this population (Berti et al. 1998).

Schoof et al. (1999a) reported on the analysis of 40 commodities anticipated to account for 90% of dietary inorganic arsenic intake. Consistent with earlier studies, total arsenic concentrations were highest in the seafood sampled (ranging from 160 ng/g in freshwater fish to 2,360 ng/g in marine fish). In contrast, average inorganic arsenic in seafood ranged from <1 to 2 ng/g. The highest inorganic arsenic concentrations were found in raw rice (74 ng/g), followed by flour (11 ng/g), grape juice (9 ng/g), and cooked spinach (6 ng/g). Schoof et al. (1999b) estimated that intake of inorganic arsenic in the U.S. diet ranges from 1 to 20 µg/day, with a mean of 3.2 µg/day.

National monitoring data from the Food Safety and Inspection Service National Residue Program (NRP) (1994–2000) found that the mean arsenic concentration in livers of young chickens ranged from 0.33 to 0.43 µg/g, with an overall mean of 0.39 µg/g (Laskey et al. 2004). The mean arsenic concentrations in liver for mature chickens, turkeys, hogs, and all other species over the same time period ranged from 0.10 to 0.16 µg/g. Laskey et al. (2004) used the NRP arsenic data in livers of young chickens to estimate the concentrations of arsenic in muscle tissue, which is the most commonly consumed part. Based on their calculations, at a mean level of chicken consumption of 60 g/person/day, people may ingest 1.38–5.24 µg/day of inorganic arsenic from chicken.

Tobacco contains an average arsenic concentration of 1.5 ppm, or about 1.5 µg per cigarette (EPA 1998j). Before arsenical pesticides were banned, tobacco contained up to 52 mg As/kg, whereas after the ban, maximum arsenic levels were reduced to 3 µg/g (Kraus et al. 2000). An international literature survey reports arsenic yields of 0–1.4 µg/cigarette for mainstream (inhaled) cigarette smoke (Smith et al. 1997). The wide range of arsenic yields for flue-cured cigarettes suggests that the field history, soil, and fertilizer conditions under which the tobacco is grown will affect the arsenic concentration (Smith et al. 1997). Arsenic emission factors of 0.015–0.023 µg/cigarette (mean 0.018±0.003 µg/cigarette) have been measured for sidestream smoke from a burning cigarette (Landsberger and Wu 1995).

Arsenic concentrations ranged from 0.001 to 0.19 µg/cm^{2}and from not detected to 0.0058 µg/cm^2 in indoor house dust sampled at the doorways and kitchen floors, respectively, of 15 homes in the three communities (Whitney Pier, Ashby, and North End) surrounding the Sydney, Nova Scotia tar ponds, an area that is considered Canada's worst contaminated site (Lambert and Lane 2004). Mean arsenic concentrations of 12.6 (2.6–57) and 10.8 (1.0–49) µg/g were reported in house dust collected from the entryway and child play areas, respectively, from homes in a community in Washington State with a history of lead arsenate use (Wolz et al. 2003). Dust sampling was performed between October 1993 and August 1994 in the homes of 593 children in Hettstedt, a city in eastern Germany with a long history of

mining and smelting of nonferrous ores. A surface loading rate for arsenic was found to be 0.023 μg/m^2/day (Meyer et al. 1999). A median arsenic concentration of 2.1 μg/g and a deposition rate of 0.008 μg/m^2/day was reported in house dust in homes evaluated as part of the German Environmental Survey in 1990–1992. A mean arsenic concentration of 7.3 μg/g was reported in house dust from residences in Ottawa, Canada (Butte and Heinzow 2002). Arsenic was detected in all indoor floor dust samples collected as part of the National Human Exposure Assessment Survey (NHAXES) in Arizona, ranging from 0.3–50.6 μg/g, (O'Rourke et al. 1999).

Arsenic has also been detected in several homeopathic medicines at concentrations up to 650 μg/g (Kerr and Saryan 1986). Some Asian proprietary medicines that are manufactured in China, Hong Kong, and other Asian countries have been reported to contain levels of inorganic arsenic ranging from 25 to 107,000 μg/g (Chan 1994). Fifty medicinally important leafy samples that were analyzed for elemental concentrations contained arsenic at levels ranging from 0.12 to 7.36 μg/g, with a mean of 2.38±1.2 μg/g (Reddy and Reddy 1997). Arsenic concentrations ranged from 0.005 to 3.77 μg/g in 95 dietary supplements purchased from retail stores in the Washington, DC area in 1999 (Dolan et al. 2003). Commercially available samples of Valarian, St. John's Wort, Passion Flower, and Echinacea were purchased in the United States and analyzed for various contaminants; arsenic concentrations were 0.0016–0.0085, 0.0065–0.017.8, 0.0024–0.0124, and 0.0021–0.0102 μg/g, respectively, in these samples (Huggett et al. 2001). Concentrations of heavy metals including arsenic were evaluated in 54 samples of Asian remedies that were purchased in stores in Vietnam and Hong Kong that would be easily accessible to travelers, as well as in health food and Asian groceries in Florida, New York, and New Jersey. Four remedies were found to contain daily doses exceeding 0.1 mg. Two of these contained what would have been a potentially significant arsenic dose, with daily doses of 16 and 7.4 mg of arsenic (Garvey et al. 2001).

The possible presence of toxic compounds in waste materials has raised concerns about the fate of these compounds either during the composting process or when the composted product is applied to soils. Three waste compost products generated at the Connecticut Agricultural Experiment Station had arsenic levels of 12.8, 9.8, and 13 μg/g dry weight, respectively (Eitzer et al. 1997). The arsenic levels in municipal solid waste composts from 10 facilities across the United States ranged from 0.9 to 15.6 μg/g dry weight with a mean of 6.7 μg/g (He et al. 1995). These are lower than the EPA 503 regulatory limit for arsenic of 41 μg/g for agricultural use of sewage sludge (EPA 1993b). Concentrations of arsenic in U.S. sewage sludges, which are sometimes spread on soil, were <1 μg/g. Arsenic is a common impurity in minerals used in fertilizers. A comprehensive Italian study found that the arsenic content in a number

of mineral and synthetic fertilizers ranged from 2.2 to 322 mg/kg with a sample of triple superphosphate having the highest level (Senesi et al. 1999). Arsenic naturally occurs in coal and crude oil at levels of 0.34–130 and 0.0024–1.63 ppm, respectively, which would account for its presence in flue gas, fly ash, and bottom ash from power plants (Pacyna 1987).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure to arsenic may include exposure to the more toxic inorganic forms of arsenic, organic forms of arsenic, or both. While many studies do not indicate the forms of arsenic to which people are exposed, this information may often be inferred from the source of exposure (e.g., fish generally contain arsenic as arsenobetaine). Environment Canada (1993) estimated the intake of the more toxic inorganic arsenic from air, water, food, and ingesting dirt for various age groups of the general population and for those living near point sources. Their results are shown in Table 6-5. For the general population, food is usually the greatest source of arsenic exposure. For inorganic arsenic, food also represents the principal route of intake for all age groups (<0.02–2.0 µg/kg-body weight per day), followed by ingesting dirt for infants and children (0.02–0.08 µg/kg-body weight per day), and water and air for all age groups. Based on limited data, the average daily intake of inorganic arsenic from surface water supplies of drinking water by all age groups is generally <0.5 µg/kg-body weight per day. Intake may be higher from some groundwater supplies. Average daily intakes from ambient air is estimated to range from 0.0003 to 0.0004 µg/kg-body weight per day bringing the range of total daily exposure to inorganic arsenic to 0.1–2.6 µg/kg-body weight per day (Environment Canada 1993). Yost et al. (1998) reported that the estimated daily dietary intake of inorganic arsenic for various age groups ranged from 8.3 to 14 µg/day and from 4.8 to 12.7 µg/day in the United States and Canada, respectively, with 21–40% of the total dietary arsenic occurring in inorganic forms.

Drinking water may also be a significant source of arsenic exposure in areas where arsenic is naturally present in groundwater. While estimates of arsenic intake for typical adults drinking 2 L of water per day average about 5 µg/day (Environment Canada 1993; EPA 1982c), intake can be much higher (10–100 µg/day) in geographical areas with high levels of arsenic in soil or groundwater (see Figure 6-2). It is assumed that nearly all arsenic in drinking water is inorganic (EPA 1984a).

In the United States, food intake of arsenic has been estimated to range from 2 µg/day in infants to 92 µg/day in 60–65-year-old men (see Table 6-6) (Tao and Bolger 1999). The average intake of inorganic arsenic ranges from 1.34 µg/day in infants to 12.54 µg/day in 60–65-year-old men. The greatest

Table 6-5. Estimated Mean Daily Intake of Inorganic Arsenic

Medium	Estimated [illegible]				µg/[illegible]	
	[a]	[b]	[c]	[d]	Adult	[e]
Urban						
Water [f]	0	0	0	0	0	
Food [g]	0	0	0	0	0	
Air [h]	0	0	0	0	0	
Soil [i]	0	0	0	0	0	
Total	0	0	0	0	0	
Rural						
Water [f]	0	0	0	0	0	
Food [g]	0	0	0	0	0	
Air	0	0	0	0	0	
Soil [i]	0	0	0	0	0	
Total	0	0	0	0	0	

See Text for Calculations

[a] [illegible] [3] [illegible]
[b] [illegible] [3] [illegible]
[c] [illegible] [3] [illegible]
[d] [illegible] [3] [illegible]
[e] [illegible] [3] [illegible]
[f] Adults [illegible] µg/[illegible]
[g] Estimated [illegible] Using [illegible]
[h] Adults [illegible] µg/m [3] [illegible]
[i] Regional Cancer [illegible]

Table 6-6. Mean Daily Dietary Intake of Arsenic for Selected U.S. Population Groups

Meal/Item	[illegible]	[illegible]	Dietary [illegible]		
			[illegible]	[illegible] [a]	[illegible] [b] [illegible] [c]
Provisional tolerable daily intake (PTDI)		[d]	2	2	2
[illegible]			[illegible]	[illegible]	[illegible]
[illegible]			[illegible]	[illegible]	[illegible]
[illegible]			[illegible]	[illegible]	[illegible]
[illegible]			[illegible]	[illegible]	[illegible]
[illegible]			[illegible]	[illegible]	[illegible]
[illegible]			[illegible]	[illegible]	[illegible]
[illegible]			[illegible]	[illegible]	[illegible]
[illegible]			[illegible]	[illegible]	[illegible]

[a] [illegible]
[b] [illegible]
[c] Table B-9
[d] No [illegible] PTDI [illegible] [illegible] FAO/WHO [illegible] FDA [illegible] FDA [illegible]

dietary contribution to total arsenic was seafood (76–96%) for all age groups, except infants. For infants, seafood and rice products contributed 42 and 31%, respectively. Adult dietary arsenic intakes reported for other countries range from 11.7 to 280 µg/day (Tao and Bolger 1999). For seafood, it is important to consider the form of arsenic present. Arsenic in fish and shellfish is estimated to be mostly (80–90%) present as arsenobetaine, a nontoxic organic form of arsenic. However, some commercially available seaweeds, especially brown algae varieties, may have high percentages of the total arsenic present as inorganic arsenic (>50%) (Almela et al. 2002; Laparra et al. 2003).

The FDA conducted earlier Total Diet Studies in 1984–1986 and 1986–1991. For the sampling period of June 1984 to April 1986, the total daily intake of arsenic from foods was 58.1 µg for a 25–30-year-old male with seafood contributing 87% of the total (Gunderson 1995a). For the sampling period from July 1986 to April 1991, the total daily intake of arsenic from foods was lower, 38.6 µg for a 25–30-year-old male. Seafood again was the major source of arsenic, contributing 88% of the total (Gunderson 1995b). Results of the two Total Diet Studies for selected population groups are shown in Table 6-6. The Total Diet Study for the sampling period from September 1991 to December 1996, shows that arsenic, at ≥0.03 µg/g, was found in 55 (21%) of the 261–264 foods/mixed dishes analyzed. The highest concentrations again were found in seafood, followed by rice/rice cereal, mushrooms, and poultry. The estimated total daily intake of arsenic from foods was 56.6 µg for a 25–30-year-old male. Seafood was the major contributor, accounting for 88–96% of the estimated total arsenic intake of adults. The dietary intake of inorganic arsenic is estimated to range from 8.3 to 14 µg per day (NRC 1999).

Average daily dietary exposures to arsenic were estimated for approximately 120,000 U.S. adults by combining data on annual diet, as measured by a food frequency questionnaire, with residue data for table-ready foods that were collected for the annual FDA Total Diet Study. Dietary exposures to arsenic were highly variable, with a mean of 50.6 µg/day (range, 1.01–1,081 µg/day) for females and 58.5 µg/day (range, 0.21–1,276 µg/day) for males (MacIntosh et al. 1997). Inorganic arsenic intake in 969 men and women was assessed by a semi-quantitative food frequency questionnaire in combination with a database for arsenic content in foods and by toenail concentrations of arsenic. The mean estimated average daily consumption of inorganic arsenic was 10.22 µg/day, with a standard deviation of 6.26 µg/day and a range of 0.93–104.89 µg/day (MacIntosh et al. 1997).

During a comprehensive total diet study extending from 1985 to 1988, the estimated daily dietary ingestion of total arsenic by the average Canadian was 38.1 µg and varied from 14.9 µg for the 1–4 year-old-age group to 59.2 µg for 20–39-year-old males (Dabeka et al. 1993). Daily intakes of arsenic from

food by women in the Shiga Prefecture, Japan, were investigated by the duplicate portion method and by the market basket method. In 1991 and 1992, the daily intakes determined by the duplicate portion method were 206 and 210 µg, respectively. Those determined by the market basket method were 160 and 280 µg, respectively (Tsuda et al. 1995b).

Arsenic concentrations in human breast milk have been reported to range from 4 to <10 µg/L in pooled human milk samples from Scotland and Finland to 200 µg/L in samples from Antofagasta, Chile, where there is a high natural environmental concentration of arsenic (Broomhill and Kovar 1986). The arsenic concentration in the breast milk of 35 women in Ismir, Turkey, a volcanic area with high thermal activity ranged from 3.24 to 5.41 µg/L, with a median of 4.22 µg/L (Ulman et al. 1998). Sternowsky et al. (2002) analyzed breast milk from 36 women from three different regions in Germany. These regions included the city of Hamburg, a rural area, Soltau, Lower Saxony, and Munster, the potentially contaminated area. Arsenic was not detected (<0.3 µg/L) in 154 of 187 samples, with the highest concentration, 2.8 µg/L, found in a sample from the rural area. The geometric means from the three areas were comparable.

The mean arsenic levels in three groups of cows in the region that grazed on land impacted by lava and thermal activity were 4.71, 4.46, and 4.93 µg/L, compared to 5.25 µg/L for cows kept in sheds and fed commercial pellet feed and municipal water (Ulman et al. 1998). Mean arsenic concentrations in cow's milk ranging from 18.6 to 17.1 µg/L and from 16.7 to 18.0 µg/L were reported for cow's grazing in non-industrial and an industrial regions, respectively, in Turkey (Erdogan et al. 2004).

A Danish study found that carrots grown in soil containing 30 µg/g of arsenic, which is somewhat above the 20 µg/g limit for total arsenic set by Denmark for growing produce, contained 0.014 µg/g fresh weight of arsenic, all in the form of inorganic As(III) and As(V) (Helgesen and Larsen 1998). An adult consuming 376 grams of vegetables a day (90^{th} percentile) represented solely by carrots would consume 5.3 µg of arsenic a day. The study concluded that the estimated intake of arsenic from produce grown in soil meeting regulatory limits was low compared with other food sources and water.

If vegetables are grown in planters made of wood treated with CCA, arsenic may leach out of the wood and be taken up by the vegetables. In a study by Rahman et al. (2004), arsenic was found to diffuse into the soil from the CCA-treated wood, with the highest concentrations found at 0–2 cm from the CCA-treated wood and a steady decline in concentration with increased distance from the wood. Crops grown within 0–2 cm of the CCA-treated wood contained higher concentrations of arsenic than those grown at 1.5 m from the treated wood. However, the concentrations are below U.S. FDA tolerance limits that have

been set for arsenic in select food items. In addition, food grown in this manner is unlikely to constitute a significant part of a person's diet.

In 2003, U.S. manufacturers of arsenical wood preservatives began a voluntary transition from CCA to other wood preservatives in wood products for certain residential uses, such as play structures, picnic tables, decks, fencing, and boardwalks. This phase out was completed on December 31, 2003; wood treated prior to this date could still be used and structures made with CCA-treated wood would not be affected. CCA-treated wood products continue to be used in industrial applications (Brooks 2003, 2005).

The arsenic content in the human body is 3–4 mg and tends to increase with age. Arsenic concentrations in most tissues of the human body are <0.3 to 147 µg/g dry weight, excluding hair, nails, and teeth. Mammals tend to accumulate arsenic in keratin-rich tissues such as hair and nails. The normal concentrations of arsenic range from about 0.08 to 0.25 µg/g in hair, and 0.34 µg/g in nails. The normal concentration of arsenic in urine can range from 5 to 40 µg per day (total) (Mandal and Suzuki 2002). Table 6-7 contains arsenic levels in various human tissues.

A German study investigated the transfer of arsenic from the environment to humans in the northern Palatine region, a former mining area characterized by high soil levels of arsenic (<2–605 µg/g) in residential areas compared to a region in southern lower Saxony with nonelevated levels of arsenic in soil (Gebel et al. 1998a). None of the residents were occupationally exposed to arsenic and the arsenic levels in drinking water were generally below 0.015 mg/L. Therefore, increased exposure to arsenic would only be caused by the soil and home-grown produce. The mean levels of arsenic in urine and hair were lower in the reference area than in the former mining area (see Table 6-7), although within the mining area, there was a slight increase in arsenic levels in hair and arsenic excreted in urine with increasing arsenic content in soil. Children in the Palatine region did not have higher contents of arsenic in their hair or urine. The most significant factor contributing to elevated levels of arsenic in hair and urine was seafood consumption. In the combined population of people living in mining areas containing high levels of arsenic in soil and other areas, the level of arsenic in urine was positively associated with the extent of seafood consumption. However, the study also showed that seafood consumption does not lead to an extreme increase in excretion of arsenic in the urine. There are apparently other, unidentified factors affecting the urine levels. Only arsenic in urine, not in hair, was significantly correlated with age. The level of arsenic in urine was very slightly, but significantly correlated with the consumption of home-grown produce. Tobacco smoking had no correlation with the arsenic content of either hair or urine (Gebel et al. 1998a).

Table 6-7. Levels of Arsenic in Human Tissue and Urine—Recent Studies

Site	Population	Sample	Method	Concentration[a]	Region	Units	Reference
Fish and Shellfish							
		Urine				µg/L	
		Urine				µg/L	
		Hair				µg/g	
		Fish				µg/g	
Soil and Mine							
	Children	Urine					
						µg/g	
						µg/g	
						µg/g	
Soil							
	Atlantic					µg/g	Rao
	Atlantic	Liver				µg/g	
	Inland	Liver				µg/g	
	Atlantic	Lung				µg/g	
	Inland	Lung				µg/g	
	Atlantic	Spleen				µg/g	
	Inland	Spleen				µg/g	
Pulp and Paper Mill Workers			[b]				
	Retired	Urine				µg/g	
	Retired	Hair				µg/g	
Smelter Workers			[b]				
	Retired	Urine				µg/g	
	Retired	Hair				µg/g	
Industrial Workers							
	Nonsmoking	Blood				µg/L	Ulm
Environmental							
	Nonsmoking	Lung		5			
						w	
						w	
Tumor Cases							
	Nonsmoking	Lung				µg/g	
						w	
		Bone					
		Kidney					

Table 6-7. Levels of Arsenic in Human Tissue and Urine—Recent Studies

Site	Population	Specimen	Media	Concentration[a]	Range	Units	Reference
		Liver	6				
		Lung	6				
[illegible]							
	Residents [illegible]	Fingernail	2	6		µg	Mabe [illegible]
		[illegible]	6	6			
	Residents [illegible]	Fingernail	0	0			
		[illegible]	0	0			

[a]Median [illegible]
[b]Sample [illegible]
[illegible]

A study was performed to look at the arsenic levels, as well as the arsenic species present, in hair and nail samples from individuals in an arsenic-affected area in West Bengal, India. Mean arsenic concentrations in hair and fingernails of the chronically arsenic exposed population were 4.46 and 7.32 µg/g, respectively and were 0.07 and 0.19 µg/g in a control population. Fingernail samples were found to contain mostly inorganic arsenic (>80%) as a mixture of As(III) and As(V), as well as DMA(III) and DMA(V). Hair samples also mostly contained inorganic arsenic (>90%), as well as MMA(V) and DMA(V) (Mandal et al. 2003).

Arsenic in soil in communities surrounding former smelters is a public health concern, especially for infants and children who may consume significant quantities of soil. Since lead arsenate was used in apple and other fruit orchards, often at very high application rates, and this compound would be expected to accumulate and persist in surface soil, there are concerns to human health when these when old orchards are converted into subdivisions or when they are used to grow food crops or forage. However, arsenic in soil may be imbedded in minerals or occur as insoluble compounds such as sulfides and therefore, not be taken up by the body from the gastrointestinal tract. In addition, oxidation of mineral surfaces may result in armoring the primary mineral grain by a secondary reaction product. Arsenic-bearing solids are often encapsulated in insoluble matrices such as silica, further diminishing arsenic availability (Davis et al. 1992). In a study of the bioavailability of arsenic in soils from the Butte, Montana, mining district, Davis et al. (1992) prepared a soil that was representative of a mine waste site minimally impacted by smelting activity by blending five separate Butte soils to achieve an arsenic concentration of 13,800 µg/g. Based on *in vitro* results, the arsenic in the soil was demonstrated to be one-fifth as bioavailable as arsenic from sodium arsenate (Na_2HAsO_4). The low bioavailability factors observed for arsenic-bearing soils from a former smelting site in Anaconda, Montana, were explained by the sparingly soluble nature of the arsenic-bearing phases, the presence of authigenic carbonate and silicate rinds, the kinetic hindrance to dissolution, and the inaccessibility of encapsulated arsenic (Davis et al. 1996). Data from another study of arsenic in soils and sediments at the Milltown Reservoir Sediments Superfund site in Montana, which contained mining wastes from the Butte and Anaconda sites indicated that the bioavailabilities of arsenic and other metals studied were ≤0.2% for internal organs and 0.1% for carcasses on a µg/g tissue wet weight basis. These results suggest that the bioavailable fraction of mining waste metals in riparian wetland soils may be quite small (Pascoe et al. 1994).

Sarkar and Datta (2004) examined the bioavailability of arsenic from two soils with different arsenic retention capacities. In this study, Immokalee (Florida) and Orelia (Texas) soils were incubated after

spiking with sodium arsenate for 4 months. The Immokalee soil is a sandy spodosol with low Fe/Al, Ca/Mg, and P contents and is likely to have minimal arsenic retention capacity. The Orelia soil is a sandy clay that is expected to have strong arsenic retention capacity. Arsenic speciation and bioavailability were studied immediately after spiking and after 4 months of incubation. Approximately 85% of the total arsenic (soluble and exchangeable fractions) was considered bioavailable and phytoavailable immediately after pesticide application for the Immokalee soil; after 4 months of incubation, this decreased to approximately 46%. Immediately after pesticide application, the amounts of arsenic extracted in the soluble/exchangeable and Fe/Al-bound fractions were similar that of the Immokalee soil. After 4 months, the soluble arsenic decreased to approximately 45% and the Fe/Al-bound arsenic increased to about 40%. Experiments looking at the bioavailability of arsenic from these two soils indicated that the potentially irreversible adsorption of arsenic by the Orelia soil rendered a significant portion of the total arsenic unavailable for absorption by the human gastrointestinal system. Initially after pesticide application, 100% of the arsenic was bioavailable; after 4 months, the bioavailable fraction was found to decrease to 88 and 69% in the Immokalee and Orelia soils, respectively (Sarkar and Datta 2004).

Hamel et al. (1998) used synthetic gastric juice to estimate the bioaccessible fraction of metals in the stomach with varying liquid to solid ratios. They found that the bioaccessibility may vary in different soils and with varying liquid to solid ratios. Bioaccessibility was defined as the amount of metal that is soluble in synthetic gastric juice and therefore, potentially available for uptake across the intestinal lumen, while bioavailability was defined as the amount that was actually taken across the cell membranes. Arsenic bioaccessibility for National Institute of Standards and Technology (NIST) Montana Soil SRM 2710, with a certified arsenic concentration of 626 µg/g, was fairly consistent across the liquid-to-solid ratios and ranged from 41.8±18 to 56±21%. The extractability of a hazardous waste contaminated soil from Jersey City, New Jersey, was different than that observed for the Montana NIST soil. For the Jersey City soil, which had an arsenic concentration of 1,120 µg/g, there was an increase in the bioaccessible arsenic as the liquid-to-solid ratio increased. Bioaccessible arsenic ranged from 4.5±0.8 (at a liquid-to-solid ratio of 100:1) to 25±9% (at a ratio of 5,000:1). Similarly, smelter impacted soils from Anaconda, Montana contain metal-arsenic oxides and phosphates whose bioaccessibility is limited by solubility restraints for residence times typical of the gastrointestinal tract (Davis et al. 1992, 1996).

Inhalation of arsenic from ambient air is usually a minor exposure route for the general population. For example, the dose to a person who breathes 20 m^3/day of air containing 20–30 ng/m^3 (see Section 6.4.1) would be about 0.4–0.6 µg/day. However, smokers may be exposed to arsenic by inhalation of mainstream smoke. Assuming that 20% of the arsenic in cigarettes is present in smoke, an individual

smoking two packs of cigarettes per day would inhale about 12 µg of arsenic (EPA 1984a). However, a recent German study of the arsenic levels in lung tissue of 50 unexposed deceased people (see Table 6-7) found no significant difference in lung arsenic concentrations of smokers versus nonsmokers, nor were there any significant age- or sex-related differences (Kraus et al. 2000). Before arsenical pesticides were banned, tobacco contained up to 52 µg As/g, whereas after the ban, maximum arsenic levels were reduced to 3 µg/g.

Occupational exposure to arsenic may be significant in several industries, mainly nonferrous smelting, arsenic production, wood preservation, glass manufacturing, and arsenical pesticide production and application. Since arsenic compounds are used as a desiccant for cotton, workers involved in harvesting and ginning cotton may be exposed to arsenic. Occupational exposure would be via inhalation and dermal contact. Should any arsenic be retained in the cotton, workers handling the fabric and the general public would be exposed. The electronics industry is expanding the use of gallium arsenide in the production of electro-optical devices and integrated circuits, and workers in the industry where gallium arsenide is used may be exposed to hazardous substances such as arsenic, arsine, and various acids (Sheehy and Jones 1993). Occupational exposure to arsenic is generally assessed by measuring urinary excretion of arsenic. Past exposure is commonly assessed by arsenic levels in hair. Different types of occupational exposures may result in different uptakes of arsenic because of the bioavailability of the form of arsenic to which workers are exposed. For example, maintenance workers at a Slovak coal-fired power plant exposed to 8-hour TWA arsenic air concentrations of 48.3 µg/m^3 (range, 0.17–375.2) had urinary total arsenic levels of 16.9 µg As/g creatinine (range, 2.6–50.8), suggesting that bioavailability of arsenic from airborne coal fly ash is about one-third that from in copper smelters and similar settings (Yager et al. 1997). Approximately 90% of the arsenic-containing particulates were ≥3.5 µm. Apostoli et al. (1999) monitored 51 glass workers exposed to arsenic trioxide by measuring dust in the breathing zone. The mean concentration of arsenic in air was 82.9 µg/m^3 (1.5–312 µg/m^3); exposure was higher for workers involved in handling the particulate matter. The occupation exposures to principal contaminants, including arsenic, at five coal-fired power plants were evaluated during June–August 2002. Eight air samples were collected per similar exposure group at four of the five facilities; inorganic arsenic concentrations in all samples were below the limit of detection (0.37–0.72 µg/m^3), as well as being below the OSHA permissible exposure limit (PEL) of 10 µg/m^3 (Bird et al. 2004).

NIOSH researchers conducted a study of arsenic exposures and control systems for gallium arsenide operations at three microelectronics facilities during 1986–1987 (Sheehy and Jones 1993). Results at one plant showed that in all processes evaluated but one, the average arsenic exposures were at or above the

OSHA action level of 5 $\mu g/m^3$, with a maximum exposure of 8.2 $\mu g/m^3$. While cleaning the Liquid Encapsulated Czochralski (LEC) pullers, the average potential arsenic exposure of the cleaning operators was 100 times the OSHA PEL of 10 $\mu g/m^3$. Area arsenic samples collected at the plant in break-rooms and offices, 20–60 feet from the process rooms, had average arsenic concentrations of 1.4 $\mu g/m^3$. At the other two plants, personal exposures to arsenic were well controlled for all processes evaluated.

A study has been conducted to examine the relationship between total arsenic levels in hair of employees in a semiconductor fabrication facility and job responsibility, a surrogate variable for arsenic exposure (de Peyster and Silvers 1995). Airborne arsenic was found in areas where equipment was cleaned but not in administrative areas. The highest airborne arsenic level found in the study, 15 $\mu g/m^3$, was collected from the breathing zone of a maintenance employee who was cleaning a source housing over a period of 2 hours in an area with local exhaust ventilation. A concentration of 2 $\mu g/m^3$ was found during the remainder of the cleaning period (~53 minutes). Workers in maintenance who were regularly assigned to cleaning equipment, and therefore presumed to have the highest exposure potential, had a mean hair arsenic level of 0.042 $\mu g/g$. This was higher than the mean of 0.033 $\mu g/g$ observed in administrative controls, but the difference was not significant. Maintenance workers who only occasionally cleaned and maintained arsenic-contaminated equipment had a mean hair arsenic level of 0.034 $\mu g/g$, which was comparable to the controls. The highest group mean hair arsenic level of 0.044 $\mu g/g$, surprisingly, was found in supervisors and engineers who were presumed to have the lowest exposure potential of all workers in the process areas. However, the highest concentrations of hair arsenic in engineers, 0.076 and 0.106 $\mu g/g$, were observed in two heavy smokers who smoked 1–2 packs of cigarettes per day. A 2-way analysis of variance indicated that smoking appeared to be a significant contributing factor whereas occupational exposure was not.

Hwang and Chen (2000) evaluated arsenic exposure in 21 maintenance engineers (exposed group) and 10 computer programmers (control group) at 3 semiconductor manufacturing facilities. Samples of air, wipe, and urine, as well as used cleaning cloths and gloves were collected to determine arsenic exposure. Arsenic was undetectable in 46 of the 93 air samples, and most samples were generally below the recommended occupational exposure limit (10 $\mu g/m^3$) in work areas during ion implanter maintenance. Arsine was detectable in 22 of the 45 area air samples and in 15 of the 35 personal air samples; however, all concentrations were well below the occupational exposure limit of 50 ppb (160 $\mu g/m^3$). Mean arsine concentrations ranged from not detected to 4.0 ppb (15 $\mu g/m^3$) in area air samples, and the mean arsine concentration of personal air for maintenance engineers was 4.3 ppb (14 $\mu g/m^3$). Arsenic concentrations in wipe samples, used cleaning cloths, and gloves, varied from not detected to 146 $\mu g/cm^2$. During ion

implanter maintenance, urinary arsenic levels were found to increase (1.0–7.8 μg/g creatinine) in the maintenance engineers, from a mean baseline concentration of 3.6 μg/g creatinine. The average urinary arsenic level for the computer programmers was 3.8 μg/g creatinine (Hwang and Chen 2000). Mean arsenic concentrations in blood of 103 workers in the optoelectronic industry and 67 controls were 8.58 and 7.85 μg/L, respectively (Liao et al. 2004a).

Concentrations of various metals, including arsenic, were measured in autopsy tissues (liver, lung, kidney, brain, and bone) collected from 78 non-occupationally exposed subjects from Tarragona County, Spain between 1997 and 1999. In general, arsenic concentrations were under the analytical detection limit (0.05 μg/g wet weight) in all tissues (Garcia et al. 2001). A mean arsenic concentrations of 0.035 μg/g wet weight was reported in lung tissue of deceased smelter workers in Sweden, compared with mean arsenic concentration of 7 and 5 μg/g wet weight in lung tissue from rural and urban controls, respectively (Gerhardsson et al. 1988).

CCA preservatives are commonly used for treating timber used in constructions in marine and other humid environments or in contact with the ground. Exposure to CCA compounds may occur through dermal contact and inhalation of dust while working with the treated timber. Nygren et al. (1992) investigated the occupational exposure to airborne dust, chromium, copper, and arsenic in six joinery shops in Sweden where impregnated wood was used for most of their production. The mean airborne concentration of arsenic around various types of joinery machines ranged from 0.54 to 3.1 $\mu g/m^3$. No increased concentrations of arsenic were found in the workers' urine. A study was carried out in Denmark to evaluate arsenic exposure in taxidermists, workers impregnating wood with CCA solutions, fence builders, construction workers, and workers impregnating electric pylons with arsenic solution (Jensen and Olsen 1995). Airborne arsenic exposure was documented in 19 of 27 individuals working with products containing arsenic. The maximum exposure concentration was 17.3 $\mu g/m^3$, found for a single worker who was filling an impregnation container with CCA paste. Median exposures for indoor workers producing garden fences and weekend cottages were 3.7 and 0.9 $\mu g/m^3$, respectively. The maximum urine concentration reported in the study was 294.5 nanomoles arsenic per millimole creatinine (195 μg As/g creatinine) and was from the injector impregnating electric pylons. The median concentration in workers on electric pylons was 80 nanomoles arsenic per millimole creatinine (53 μg As/g creatinine), which was 6 times the concentration in reference individuals. Urine arsenic levels in workers producing garden fences and in taxidermists were 2.9 and 1.8 times the reference level, respectively.

The NIOSH National Occupational Exposure Survey (NOES) conducted in 1981–1983 estimated that about 55,000 workers were potentially exposed to arsenic (NOES 1990). The NOES was based on field surveys of 4,490 facilities that included virtually all workplace environments, except mining and agriculture, where eight or more persons are employed. The principal exposure pathway is probably inhalation of arsenic adsorbed to particulates, but ingestion and possibly dermal exposure may also be common. Since arsenic is no longer produced in the United States (see Section 5.1) and many arsenical pesticide uses have recently been banned (see Chapter 8), it is likely that the number of workers occupationally exposed to arsenic has decreased markedly in recent years.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

As with adults, most children are exposed to arsenic largely through their diet. Since the greatest dietary intake of arsenic is from fish and seafood, infants and young children for whom a substantial part of their food is milk, would not be exposed to arsenic from dietary sources as much as older children. Even when mothers consumer large amounts of seafood, there does not appear to be any major transfer of arsenobetaine, the major form of arsenic in seafood, from seafood to milk (Grandjean et al. 1995). Arsenic concentrations were very low in human milk sampled from 88 mothers in the Faroe Islands, where the seafood diet includes pilot whale meat and blubber. The total arsenic concentrations ranged from 0.1 to 4.4 µg/kg, with a median of 1.6 µg/kg (Grandjean et al. 1995). The arsenic concentration in the breast milk of 35 women in Ismir, Turkey, a volcanic area with high thermal activity ranged from 3.24 to 5.41 µg/L, with a median of 4.22 µg/L (Ulman et al. 1998). The mean arsenic levels in three groups of cows in the region that grazed on land impacted by lava and thermal activity were 4.71, 4.46,

and 4.93 µg/L, compared to 5.25 µg/L for cows kept in sheds and fed commercial pellet feed and municipal water. The arsenic levels in the urine of pregnant women and the cord blood of their infants were 0.625±0.027 and 0.825±0.079 µg/L, respectively. The authors concluded that there was no harmful exposure to arsenic in volcanic areas with high arsenic levels from suckling infants or feeding them local cow's milk, nor was there harm to the newborns from their mother's diet. Sternowsky et al. (2002) analyzed breast milk from 36 women from three different regions in Germany. These regions included the city of Hamburg, a rural area, Soltau, Lower Saxony, and Munster, the potentially contaminated area. Arsenic was not detected (<0.3 µg/L) in 154 of 187 samples, with the highest concentration, 2.8 µg/L, found in a sample from the rural area. The geometric mean arsenic concentrations from the three areas were comparable. Calculated oral intakes of arsenic were between 0.12 and 0.37 µg/day for an infant at 3 months of age and weighing 6 kg.

According to the FDA study of 1986–1991, the mean daily intakes of arsenic are 0.5 and 0.81 µg/kg body weight per day for a 6–11-month-old infant and 2-year-old child, respectively (Gunderson 1995b). This can be compared to a mean daily intake of 0.51 µg/kg-body weight per day for a 25–30-year-old male (see Table 6-6). A more recent Total Diet Study, from September 1991 to December 1996, estimated that the average inorganic arsenic intake for children of various age/sex groups were (age-sex group, total arsenic intake in µg/day, inorganic arsenic intake in µg/day): 6–11 months, 2.15, 1.35; 2 years, 23.4, 4.41; 6 years, 30.3, 4.64; 10 years, 13.3, 4.21; and 14–16 years (females), 21.8, 5.15; 14–16 years (males), 15.4, 4.51 (Tao and Bolger 1999). The greatest dietary contribution (76–96%) of total arsenic intake for all age groups other than infants was seafood. For infants, 41 and 34% of the estimated total arsenic intakes are from seafood and rice/rice cereals, respectively (Tao and Bolger 1999). Only for toddlers does the intake approach the World Health Organization's (WHO) provisional tolerable daily intake (PTDI) for inorganic arsenic (see Table 6-6). Environment Canada (1993) estimated the daily intake of inorganic arsenic from food as <0.04–2.4, <0.05–2.0, <0.03–1.9, and <0.02–1.2 µg/kg body weight per day for 0–0.5, 0.5–4, 5–11, and 12–19-year-old children, respectively (see Table 6-5). A 1985–1988 Canadian total diet study estimated that 1–4-year-olds ingested 14.9 µg of total arsenic per day compared with 38.1 µg by the average Canadian and 59.2 µg for 20–39-year-old males (Dabeka et al. 1993). Total arsenic and arsenobentaine concentrations were measured in 16 baby food samples obtained from manufactures in Spain; total arsenic concentrations ranged from 2.042 to 0.270 µg/g in plaice with vegetables and sole with white sauce, respectively. Arsenobetaine, which is the arsenical commonly found in fish, accounted for essentially 100% of the arsenic present in the samples (Vinas et al. 2003).

Arsenic exposure from drinking water, while generally low compared with that from food, may be elevated especially in groundwater from areas where arsenic occurs naturally in soil such as the western and north central sections of the United States (see Table 6-3 and Figure 6-2). Environment Canada (1993) estimated arsenic intakes from drinking water for infants and children in the general population and those living near point sources (see Table 6-5). Intake from water in the unexposed population was 0.08 µg/kg body weight per day for infants 0–0.5 years old and 0.1–0.3 µg/kg body weight per day for older children. For those living near point sources, arsenic intake from water reached highs of 8.3 µg/kg body weight per day for infants 0–0.5 years old and 10–31 µg/kg body weight per day for older children. Exposure from air was much lower than from other sources even for those living in polluted areas (Environment Canada 1993).

Arsenic exposure in communities near mining and smelting facilities or where arsenic had formerly been applied to agricultural land are a public health concern, especially for infants and children. Since arsenic remains in the surface soil indefinitely and long past land uses may be forgotten, people may not realize that they are living in areas where high levels of arsenic may occur in soil. Contaminated soils pose a particular hazard to children because of both hand-to-mouth behavior and intentional ingestion of soil (pica) that contains metals and other contaminants (Hamel et al. 1998). In these communities, arsenic may contaminate carpeting or may have been tracked in from outside. Children may be exposed to this arsenic while crawling around or playing on contaminated carpeting. Exposure may also result from dermal contact with the soil, or by inhaling the dust and then swallowing it after mucociliary transport up out of the lungs. Because much of the arsenic in soil is embedded in or adsorbed to soil particles or insoluble, it may not be in a form accessible for uptake by the body. Environment Canada (1993) estimated arsenic intakes from soil and dirt for infants and children in the general population and those living near point sources (see Table 6-5). Intake from soil and dirt in the unexposed population was 0.03–0.08 µg/kg body weight per day for infants 0–0.5 years old and 0.02–0.05 µg/kg body weight per day for children 0.5–4 years old. For those living near point sources, arsenic intake from soil and reached highs of 3.0 µg/kg body weight per day for infants 0–0.5 years old and 1.9 µg/kg body weight per day for children 0.5–4 years old.

Hwang et al. (1997b) studied the arsenic exposure of children in Anaconda, Montana, in the vicinity of a former copper smelter from the summer of 1992 through the summer of 1993. Environmental samples and first morning voided urine samples from 414 children <72 months old were collected. Attention was focused on that fraction of the environmental source that was thought to be of the greatest risk to the child (i.e., arsenic in small particles [<250 µm]) that could most readily adhere to hands and toys and could be

inadvertently ingested. Average arsenic levels in different types of soil ranged from 121 to 236 µg/g. Several studies have reported mean soil ingestion values for children ranging from 9 to 1,834 µg /day. Assuming that high arsenic exposure areas have average arsenic levels in soil from 60 to 150 µg/g, the resulting daily arsenic intake from soil could range from 1 to 275 µg/day per child. The geometric mean of speciated urinary arsenic (combined As(III), As(V), MMA and DMA) was 8.6±1.7 µg/L (n=289) in the Hwang study. The mean total urinary arsenic level was 19.1 µg/L, which was 11–22 µg lower than those reported in two previous studies in Anaconda (Baker et al. 1977; Hartwell et al. 1983) and only slightly higher the value of 17.7 µg/L that was found in a survey conducted in Anaconda in 1985, when the smelter had already been shut down (Binder et al. 1987). A nationwide survey on arsenic exposure in the vicinity of smelter sites revealed that children without excess arsenic exposure had average total urinary arsenic levels ranging from 5 to 10 µg/L (Hwang et al. 1997a). Compared to these values, the mean total urinary arsenic values found in the Hwang study were markedly higher, but they were still well below the WHO-recommended maximum excretion level for total arsenic of 100 µg/L as an action level for intervention. The investigators hypothesized that the relatively low urinary arsenic levels found in the study were probably a reflection of the low bioavailability of some forms of arsenic in contaminated soil. Hwang et al. (1997a) stated that arsenic intake through skin contact is insignificant and may be neglected in the assessment of childhood arsenic exposure. They recommend that parents or guardians pay more attention to their children's activity, especially hand-to-mouth behavior, even though the environmental contaminants might be elevated only slightly. Children in the northern Palatine region of German study, a former mining area characterized by high levels of arsenic (<2–605 µg/g) in residential areas did not show higher arsenic levels in their hair or urine than children from a reference area of Germany (Gebel et al. 1998a).

Based on a review of existing studies, Hemond and Solo-Gabriele (2004) estimated that children with contact with CCA-treated wood may be subjected to doses in the range of tens of micrograms of arsenic per day. The most important route of exposure appeared to be by hand-to-mouth activities after contact with the CCA-treated wood.

Concentrations of several toxic metals were measured in the placentas of 200 women in two urban cities in Ukraine, Kyiv and Dniprodzerzhinsk. Arsenic was detected in only 5% of the samples with concentrations ranging from <0.156 to 0.378 µg/g. In a study in Bulgaria, placental arsenic concentrations of 7 and 23 µg/g were reported in a control and smelter area, respectively. A placental arsenic concentration of 34 µg/g was reported in a region of Argentina with high concentrations of arsenic in drinking water (Zadorozhnaja et al. 2000).

Parents can inadvertently carry hazardous materials home from work on their clothes, skin, hair, and tools, and in their vehicles (DHHS 1995). Falk et al. (1981b) reported a case of hepatic angiosarcoma in a child that could be associated with arsenic contamination of a parent's clothing, the water supply, and the environment. The father worked in a copper mine and smelter area where his clothing was contaminated with dust containing arsenic. His daughter, who exhibited a high degree of pica, ate dirt from the yard, and licked dirt off her father's shoes. In a study of arsenic levels in homes in Hawaii, Klemmer et al. (1975) found higher levels in homes of employees of firms that used arsenic for pesticides or wood preservation, compared to homes where residents' work did not involve arsenic. The concentration of arsenic in dust from the homes of workers exposed to arsenic ranged from 5.2 to 1,080 µg/g, compared to concentrations of 1.1–31 µg/g in dust from control homes.

While the harmful effects of many components of tobacco smoke are well known, those due to heavy metals in the smoke have not been sufficiently emphasized. The adverse health effects of these toxic metals on the fetus through maternal smoking are of special concern (Chiba and Masironi 1992). The concentration of arsenic in tobacco is relatively low, usually below detectable limits (<1 µg/g). Although the concentrations of inorganic and organic arsenic in the urine of adults do not appear to be influenced by smoking, a positive association was found between urinary arsenic levels in children and parental smoking habits. As detailed in a WHO report, the mean arsenic level in the urine of children of nonsmoking parents was 4.2 µg/g creatinine, in children with one smoking parent, it was 5.5 µg/g, and in children with both parents smoking, it was 13 µg/g (Chiba and Maseroni 1992).

The use of Chinese herbal medicines (CHM) appears to be common among Chinese women. Both CHM and Chinese proprietary medicines (CPM) are used for treatment of minor ailments in babies and children. Herbal medicines are available in capsule or tablet form in drug stores, supermarkets, and by mail. The CPM "Sin Lak Pill," "Lu Shen Wan," and other anti-asthma preparations have been found to contain inorganic arsenic levels ranging from 25 to 107,000 µg/g, and cases of acute arsenic poisoning have been found in children and adults using these CPM (Chan 1994). Babies and children are particularly at risk because they may be given higher doses of these preparations per kg of body weight than adults would normally consume. They may also lack the hepatic enzymes responsible for drug biotransformation and detoxification (Chan 1994). Concentrations of heavy metals, including arsenic, were evaluated in 54 samples of Asian remedies that were purchased in stores in Vietnam and Hong Kong that would be easily accessible to travelers, as well as in health food and Asian groceries in Florida, New York, and New Jersey. One remedy that was recommended to treat children's fever would expose a

15 kg child to approximately 5.0 mg of arsenic per day (Garvey et al. 2001). A folk remedy, purchased in California, for the treatment of chicken pox, flu-like symptoms, and nasal congestion, which had been given to two children in Wisconsin, was found to contain 36% arsenic acid. One-half teaspoon of this powder (about 500 mg of arsenic) was dissolved in hot water and taken 2–3 times per day (Werner et al. 2001).

Various metallic pigments and colors in the form of salts or lakes are used in toy production. Therefore, children may be exposed to toxic metals while playing with toys, especially when they lick, suck, or swallow a toy or a piece of a toy. Toys produced in European Union Markets must conform to restrictions concerning the bioavailability of toxic metals, including arsenic. The maximum limit for bioavailability of arsenic from the accessible parts of a toy is set to 0.1 μg/day. This corresponds to an arsenic migration limit of 25 μg/g for all toy material, including modeling clay and paints (Rastogi and Pritzl 1996). A study was carried out to determine whether crayons, water colors, and water-based paints conform with the migration limits for toxic metals (Rastogi and Pritzl 1996). For the analysis, 94 samples representing 48 products were obtained from China, Taiwan, Japan, the United States, and European countries. Fifty-two samples showed migration of arsenic, ranging from 0.01 to 3.75 μg/g.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to arsenic (see Section 6.5), there are several groups within the general population that have potentially high exposures (higher than background levels) to arsenic. These populations include individuals living in proximity to sites where arsenic was produced, used (e.g., as a pesticide), or disposed, and individuals living near one of the 1,662 NPL hazardous waste sites where arsenic has been found at elevated levels in some environmental media (HazDat 2005). It also includes point sources such as smelters, coal-fired power plants, and municipal incinerators. People living in areas of volcanic activity may be exposed to higher levels of arsenic since high levels are more likely to be present in the environment. Other populations at risk of potentially high levels of exposure include those whose water supply contains high levels of arsenic and those consuming large amounts of seafood or seaweed. However, as pointed out previously (see Section 6.4.4), arsenic in fish and shellfish, is largely in the form of the less harmful organic arsenical, arseonbetaine.; however, some commercially available seaweeds, especially brown algae varieties, may have high percentages of the total arsenic present as inorganic arsenic (>50%) (Almela et al. 2002; Laparra et al. 2003). While elevated urinary arsenic excretion levels have been associated with the consumption of fish and seafood, in a recent study of 32 sport fish consumers from Lakes Erie, Huron, and Michigan, only 6 (19%) had detectable urine

arsenic concentrations, >4 µg/L, and 5 of these consumed fish from Lake Huron (Anderson et al. 1998). Exposure of high levels of arsenic in drinking water is more apt to be absorbed by the body and be harmful than exposure to arsenic in seafood. For example, a group of 36 people in Zimapán, Mexico who consumed water from an aquifer with 1.0 mg As/L had hair arsenic levels of 2.6–14.1 µg/g (10 µg/g average), compared with 2.4–13.9 µg/g (6.19 µg/g average) for a reference population that consumed bottled water with <0.014 mg/L arsenic (Armienta et al. 1997).

A study was conducted to determine if significant arsenic exposure was occurring at a Superfund site in Fort Valley, Georgia (Hewitt et al. 1995). Random urine, 24-hour urine, hair, and fingernail samples were collected at the end of the workweek from 40 employees at an active pesticide manufacturing facility where arsenical pesticides had been produced for over 50 years prior to the mid-1970s. Measurement of arsenic in the urine is considered to be the best method for monitoring recent exposure in industrial populations. Hair and fingernail analyses may provide an indication of exposures that occurred up to several months prior to testing, but both can adsorb and strongly retain arsenic from external sources. Since arsenic is rapidly cleared from the blood (half-life of 3–4 hours), blood arsenic levels are not considered suitable for monitoring populations for chronic low-level arsenic exposure. Results of the Hewitt study are summarized in Table 6-7. Urinary arsenic levels for all workers were well within the commonly accepted normal range of <100 µg/L.

As noted above, workers in a number of industries may have high exposures to arsenic, especially if proper safety procedures are not followed. For members of the general population, above-average exposure to arsenic from drinking water is possible in areas of high natural arsenic levels in groundwater or elevated arsenic levels in drinking water due to industrial discharges, pesticide applications, or leaching from hazardous waste facilities. Individuals living in the vicinity of large smelters and other industrial emitters of arsenic may be exposed to above-average arsenic levels both in the air, and as a result of atmospheric deposition, in water and soil and subsequent uptake into crops.

People sawing or drilling arsenic-treated wood without protective masks or burning this wood may be exposed to elevated levels of arsenic in air.

Recreational and subsistence fishers who consume appreciably higher amounts of locally caught fish from contaminated bodies of water may be exposed to higher levels of arsenic associated with dietary intake. Arsenic contamination has triggered the issuance of several human health advisories (EPA 1998g). As of December 1997, arsenic was identified as the causative pollutant in a restricted consumption advisory for

the general population for all fish in a 7-mile area including Devil's Swamp Lake and Bayou Baton Rouge in Louisiana. A public health advisory has been issued for consumption of fish and shellfish from the Duwamish River, Seattle, Washington due to arsenic and other chemicals (WSDOE 2005).

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 arsenic 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 arsenic.

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

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The chemical and physical properties of the arsenic species of chief toxicological and environmental concern are sufficiently well characterized to allow estimation of the environmental fates of these compounds. However, more information regarding the K_{ow} and K_{oc} values of the organic arsenicals would help predict the fate of these compounds in the environment.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2002, became available in May of 2004. This database is updated yearly and should provide a list of industrial production facilities and emissions.

While arsenic has not been produced in the United States since 1985, the United States is the largest consumer of arsenic and substantial quantities of arsenic are imported, primarily as arsenic trioxide (Brooks 2003). The agricultural use of inorganic arsenic pesticides have been discontinued in the United States. However, some organic arsenicals still may be used in agriculture. Current production and use data for individual arsenical pesticides and other arsenic compounds would help to estimate human exposure to the various arsenic species. Because arsenical pesticides are so persistent, a more complete picture of past use of these products would enable us to predict what areas may contain high levels of arsenic in soil.

Comprehensive estimates on emissions of arsenic date to the early 1980s (Nriagu and Pacyna 1988). The industrial picture has changed considerably since then and emission controls are being mandated more and more. For example, emission factors for Canadian smelters calculated in 1993 were grossly lower than those estimated in 1983 (Skeaff and Dubreuil 1997). There is a need for accurate and up-to-date measurements of atmospheric arsenic releases from both natural and anthropogenic sources to better assess human exposure to arsenic and guide environmental protection measures.

Environmental Fate. The interconversion of the various arsenic species and transport among the environmental media is complex and not all aspects are well-studied. Additional quantitative data on the rates of oxidation, reduction, and biotransformation reactions of arsenic compounds, and how these depend on environmental conditions would be useful in evaluating and predicting the fate and transport of arsenic at hazardous waste sites and other areas.

Bioavailability from Environmental Media. Toxicokinetic and toxicity studies establish that bioaccessible (e.g., soluble, not strongly adsorbed to soil or embedded in minerals) arsenic is highly absorbed following inhalation and oral exposure (see Sections 3.4.1.2 and 3.4.1.1). Some work has been done on the effect of environmental matrix (soil, food) on accessibility and absorption of arsenic (Davis et al. 1992, 1996; Hamel et al. 1998), but additional data would be valuable. Limited data suggests that dermal absorption of arsenic is very low (see Section 3.4.1.3), further data would be useful to establish whether arsenic uptake occurs from contact with contaminated soil or water, since humans may be exposed by these routes near hazardous waste sites.

Food Chain Bioaccumulation. Bioconcentration factors have been measured for several freshwater and marine species. While some species (mainly marine algae and shellfish) tend to bioconcentrate arsenic (EPA 1980a; Roper et al. 1996), it is not biomagnified through the food chain (Eisler 1994; EPA

1979, 1982b, 1983e). In addition, arsenic in marine biota primarily occurs as arsenobetaine which poses little risk for consumers (Eisler 1994). Carrots growing on land containing somewhat more than the permissible of arsenic in crop land did not contain levels of arsenic that were harmful (Helgesen and Larsen 1998). However, further research on the uptake of arsenic by a variety of plants in a wide range of arsenic polluted sites (e.g., mining area, orchards previously treated with lead arsenate) would be valuable in assessing human exposure near such sites through the consumption of vegetables from home gardens.

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

Extensive monitoring data are available for total arsenic in all environmental media. However, few studies have monitored individual arsenic species in air, water, soil, and biological matrices. Additional monitoring studies that include identification of arsenic species would allow more precise estimation of current exposure levels and possible human health risks.

Exposure Levels in Humans. Arsenic has been detected in human tissues, including blood, urine, hair, nails, and internal organs. Data are available for populations exposed in the workplace and for the general population (de Peyster and Silvers 1995; Jensen and Olsen 1995; Nygren et al. 1992), and some studies have been published on exposures near waste sites (Davis et al. 1992, 1996; Hwang et al. 1997a). Additional biomonitoring studies of residents near waste sites that contain arsenic would be helpful in evaluating the likely human health risks from these sites. This information is necessary for assessing the need to conduct health studies on these populations.

Determination of the particular species of arsenic, rather than just the total arsenic concentration, present in foods, especially seafood, is needed to better estimate the potential hazards to human health by the consumption of these foods (Ryan et al. 2001).

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

Exposures of Children. Contaminated soils pose a particular hazard to children because of pica and hand-to-mouth activities. Some studies have been performed on exposure and body burden (Hamel et al. 1998; Hwang et al. 1997a), but additional studies, including investigations of unique pathways for

exposures of children and the amount of soil a child ingests, would provide valuable data. Based on a review of existing studies, Hemond and Solo-Gabriele (2004) estimated that children with contact with CCA-treated wood may be subjected to doses in the range of tens of micrograms of arsenic per day and suggested that exposure by this route warrants further study. The PTDI assigned by the Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO) applies to adults. Studies are needed to assess whether children are different in their weight adjusted intake of arsenic. No childhood-specific means for reducing exposure were identified.

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 arsenic 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 2005) 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. These studies are summarized in Table 6-8.

The U.S. Geological Survey, along with other federal and state agencies, industry, and academia, is conducting the National Geochemical Survey (NGS) in order to produce a body of geochemical data for the United States based primarily on stream sediments that have been analyzed using a consistent set of analytical methods. The goal of the NGS is to analyze at least one stream sediment sample in every 289 km^2 area by a single analytical method across the entire United States (USGS 2005b).

EPA is conducting a 4-year (2000–2003) national screening-level study of contaminants in freshwater fish, referred to as the National Fish Tissue Study (EPA 2004c). This study will allow the EPA to develop national estimates of the mean concentrations of 268 chemicals in tissues of fish from lakes and reservoirs of the coterminous United States. EPA analysis of the data from this study was scheduled to

Table 6-8. Ongoing Studies on the Environmental Fate and Exposure of Humans to Arsenic

Ite	Affiliation	Research	Sponsor
Bio	St Ne Re Ch Ho		USDA
Bio CB	Ch Un Sig Ne Ke Ve	Bi in	NIEHS
Bio D	Dr Cl He Ne	Sp in	NIEHS
Cl AC; Pl AL Un	Ei Sc Ri Cl	Cl ge	USDA
Dr	Un Cl Ei Sc By Cl	Fi de ge ty	USDA
ED C Un	St Ne Re Li Ne	St ex in	USDA
He W Dr Cl	He Ne	Ti in	NIEHS
Pr U	Nu	Mi pr in co	NIEHS
Ph W Mi St Un	Le Re Ei Sc Ba Ma	Ei ex th ex in	USDA
Ma K Al RO	Th Un Ag He Em Th Al n	Bi ge in ge ge in fu ge ge	USDA
Ho, te Ig St	Un Ph Re Ei Ch Pl Ig	Cl in ex ge	USDA

Table 6-8. Ongoing Studies on the Environmental Fate and Exposure of Humans to Arsenic

Location	Affiliation	Research	Sponsor
Logan, UT	Utah State University, Department of Soil and Water Sciences	Irrigation practices effect on arsenic concentrations in soil and water	USDA
Parlier, CA	University of California, Kearney Agricultural Center	Arsenic uptake by plants	USDA
Statewide	Agricultural Experiment Station, University of Hawaii at Manoa	Forage production and arsenic uptake by plants	USDA
Statewide	Agricultural Experiment Station, University of Hawaii at Manoa	Arsenic uptake by plants	USDA
Statewide	Cooperative Extension Service

begin in January 2005, with the final report to be released in 2006. Interim raw data have been released each year, and are available from EPA. Fish samples have been analyzed for total inorganic arsenic (As(III) and As(V) combined), arsenic(III), arsenic(V), MMA(V), and DMA(V). Analysis for total arsenic was not performed as part of this study.

The American Water Works Association Research Foundation (AWWARF) supports research on arsenic in drinking water.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring arsenic, its metabolites, and other biomarkers of exposure and effect to arsenic. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Atomic absorption spectrophotometry (AAS) is the most common analytical procedure for measuring arsenic in biological materials (Curatola et al. 1978; Foà et al. 1984; Johnson and Farmer 1989; Mushak et al. 1977; Norin and Vahter 1981; Sotera et al. 1988). In AAS analysis, the sample is heated in a flame or in a graphite furnace until the element atomizes. The ground-state atomic vapor absorbs mono-chromatic radiation from a source and a photoelectric detector measures the intensity of transmitted radiation (APHA 1989b). Inductively-coupled plasma atomic emission spectrometry (ICP-AES) and ICP-mass spectrometry (ICP-MS) are increasingly common techniques for the analysis of arsenic; both methods can generally provide lower detection limits than absorbance detection methods.

Samples may be prepared for AAS in a variety of ways. Most often, the gaseous hydride procedure is employed (Curatola et al. 1978; Foà et al. 1984; Johnson and Farmer 1989; Norin and Vahter 1981). In this procedure, arsenic in the sample is reduced to arsine (AsH_3), a gas that is then trapped and introduced into the flame. This approach measures total inorganic arsenic, but may not detect all organic forms unless preceded by a digestion step. Digestion or wet-ashing with nitric, sulfuric, and/or perchloric acids degrades the organic arsenic species to inorganic arsenic so that recovery of total arsenic from biological materials can be achieved (Maher 1989; Mushak et al. 1977; Versieck et al. 1983). For accurate results, it is important to check the completeness of the oxidation; however, this is seldom done (WHO 1981).

The arsenic concentration in biological fluids and tissues may also be determined by neutron activation analysis (NAA) (Landsberger and Simsons 1987; Versieck et al. 1983). In this approach, the sample is irradiated with a source of neutrons that converts a portion of the arsenic atoms to radioactive isotopes, which can be quantified after separation from radioisotopes of other chemicals. Neutron activation has limited use because of the limited number of nuclear reactors in the United States providing this service and the need to dispose of radioactive waste. X-ray fluorescence is also capable of measuring arsenic in biological materials (Bloch and Shapiro 1986; Clyne et al. 1989; Nielson and Sanders 1983) and environmental samples (see Section 7.2). This method has the advantage that no sample digestion or separation steps are required. Hydride generation combined with atomic fluorescence spectroscopy (HG-AFS) is a relatively new technique that provides freedom from interference offered by hydride generation with sensitivity better than to 20 parts per trillion and linearity up to 10 ppm (PSA 2000).

Speciation of arsenic (i.e., analysis of organic arsenic compounds or different inorganic species, rather than total arsenic) is usually accomplished by employing separation procedures prior to introduction of the sample material into a detection system. Various types of chromatography or chelation-extraction techniques are most commonly used in combination with AAS, ICP-AES, or ICP-MS detection methods (Dix et al. 1987; Foà et al. 1984; Johnson and Farmer 1989; Mushak et al. 1977; Norin et al. 1987; Thomas and Sniatecki 1995). In one method, high performance liquid chromatography (HPLC) is combined with HG-AFS to quantify As(III), dimethylarsinic acid (DMA), momomethyl arsonic acid (MMA), and As(V) (PSA 2000). Another approach involves selective reduction of arsenate and arsenite (permitting quantification of individual inorganic arsenic species), and selective distillation of methyl arsines to quantify MMA and DMA (Andreae 1977; Braman et al. 1977; Crecelius 1978). Most methods for measuring arsenic in biological samples are unable to measure arsenobetaine with any accuracy because it does not form a hydride and it gives a different response from inorganic arsenic in electrothermal AAS. Ebdon et al. (1999) successfully employed HPLC coupled with ICP-MS to determine arsenic speciation in blood plasma, which was entirely arsenobetaine. Øygard et al. (1999) developed a simple method to determine inorganic arsenic in biological samples. Their method, which involves initially distilling inorganic arsenic from the sample as $AsCl_3$ using HCl, avoids separating and quantifying all of the different arsenic species, which is both costly and time-consuming.

Table 7-1 summarizes a variety of methods for measuring total arsenic and individual arsenic species in biological materials. None of these methods have been standardized by EPA or other federal agencies. Detection limits in blood and urine are about 0.1–1 ppb for most techniques; limits for hair and tissues are usually somewhat higher.

Table 7-1. Analytical Methods for Determining Arsenic in Biological Samples

Specimen type	Preparation	Analysis method	Sample detection limit	Percent recovery	Reference
Methods for total arsenic:					
Blood	Digestion with nitric acid, hydrogen peroxide, and perchloric acid	GFAAS	6 µg/L	80 For	à tal80
Blood	Dilution with nitric acid, hydrogen peroxide, and perchloric acid	GFAAS	10 µg/L [a]	80 Data	9
Serum	Dilution with nitric acid, hydrogen peroxide, and perchloric acid	NAA	6µg/L	[a] 80 Data	80
Urine	Dilution	NAA	6µg/L 80 Lead		Sie
Urine	Digestion with nitric acid, hydrogen peroxide, and perchloric acid SDDC	Colorimetry	6 µg/L 80 Pitt		
Urine	Preparation by dilution	Flow injection GFAAS	10 µg/L	80 Good	
Urine	Digestion with nitric acid, hydrogen peroxide, and perchloric acid	RF	20 µg/L [a]	80 Cited	
Hair	Washing with nitric acid, hydrogen peroxide, and perchloric acid	GFAAS	6 µg/g	90 Data	9
Soft tissue	Digestion with nitric acid, hydrogen peroxide, and perchloric acid DDDC	ETAAS	20µg/L	90 Mean	9
Nails	Digestion with nitric acid, hydrogen peroxide, and perchloric acid	GFAAS	5 µg/g	Not Applicable	80
Methods for arsenic speciation:					
Urine	Separation of As^{3}, As^{5}, MMA, DMA	IEC-GFAAS	6 µg/L	80 Data	Fa
Urine	Reduction of As^{3}, As^{5}, MMA, DMA	GFAAS	6 µg/L	80 Not Applicable	80

Table 7-1. Analytical Methods for Determining Arsenic in Biological Samples

Specimen type	Preparation	Analysis method	Specimen volume	Percent recovery	Reference
Urine	Reduction of As^{3}, As^{5}, MMA, and DMA to arsines	AAS/TLC/RMS	≤1 g	Not Reported	9
Urine	Extraction with [illegible]	AAS/TLC/RMS	[illegible]	Not Reported	[illegible]
Blood	Acidification; [illegible]	GC/ECD	[illegible]	Not Reported	
Blood plasma	Spotting on TLC	HPLC/ICP-MS	[illegible]	[illegible]	9
Urine	Separation by [illegible]	IEC/ICP-MS	[illegible]	Not Reported	
Major tissues	Extraction with [illegible]	HPLC/ICP-MS	[illegible]	[illegible] (using CRM)	Single 9
Major tissues	Separation by [illegible] HPLC; [illegible]	HPLC/AAS	[illegible]	[illegible]	Large [illegible] 9
Biological samples-Liquid	Digestion with [illegible]	Flame AAS	[illegible]	Not Reported	9

[a] Liquid

CRM = certified reference material; DDDC = diethyldithiocarbamate; DMA = dimethylarsinic acid; ECD = electron capture detector; GC = gas chromatography; HPLC = high performance liquid chromatography; ICPMS = inductively coupled plasma mass spectrometry; IEC = ion exchange chromatography; MMA = monomethylarsonic acid; NAA = neutron activation analysis; RF = radio frequency; RMS = reduction/mass spectrometry; SDDC = sodium diethyldithiocarbamate; TLC = thin layer chromatography; TOF = time-of-flight

7.2 ENVIRONMENTAL SAMPLES

Arsenic in environmental samples is also measured most often by AAS techniques, with samples prepared by digestion with nitric, sulfuric, and/or perchloric acids (Dabeka and Lacroix 1987; EPA 1983b, 1994a, 1994b; Hershey et al. 1988). Other methods employed include a spectrophotometric technique in which a soluble red complex of arsine and silver diethyldithiocarbamate (SDDC) is formed (APHA 1977; EPA 1983c), ICP-AES (EPA 1982b, 1996a), graphite furnace AAS (EPA 1994b), ICP-MS (EPA 1998j), and X-ray fluorescence (Khan et al. 1989; Nielson and Sanders 1983).

HPLC is currently the most common technique for separation of the species of arsenic found in seafood (Benramdane et al. 1999b; Guerin et al. 1999; Kumaresan and Riyazuddin 2001). An advantage of HPLC over other separation methods (e.g., gas chromatography [GC]) is that the arsenic species do not need to be derivatized prior to separation, avoiding concerns over complete conversion to the derivative for detection.

Since arsenic in air is usually associated with particulate matter, standard methods involve collection of air samples on glass fiber or membrane filters, acid extraction of the filters, arsine generation, and analysis by SDDC spectrophotometry or AAS (APHA 1977; NIOSH 1984).

Methods standardized by the EPA for measuring total arsenic in water and waste water, solid wastes, soil, and sediments include: ICP-MS (EPA 1998j, 1994a, 1991), ICP-AES (EPA 1996d), graphite furnace AAS (EPA 1994b), quartz furnace hydride generation AAS (EPA 1996h), and an electrochemical method using anodic stripping voltammetry (ASV) (EPA 1996e). A modification using cryogenic GC to EPA Method 1632 (HG/AAS) allows the technique to be adopted for the species As(III), As(V), MMA, and DMA to the 0.003 ppb level (1996f). Similar methods are recommended by APHA for water using AAS/hydride generation (APHA 1989c), AAS/graphite furnace technique (APHA 1989b), ICP (APHA 1989d), or SDDC spectrophotometry (APHA 1989a). The AAS/hydride generation method is generally resistant to matrix and chemical interferences (APHA 1989a). Techniques to compensate for these interferences have been described by EPA (1982b).

Analysis for arsenic in foods is also most frequently accomplished by AAS techniques (Arenas et al. 1988; Dabeka and Lacroix 1987; Hershey et al. 1988; Tam and Lacroix 1982). Hydride generation is the

sample preparation method most often employed (Arenas et al. 1988; Hershey et al. 1988), but interferences must be evaluated and minimized.

Speciation of inorganic arsenic in environmental samples is usually accomplished by chromatographic separation, chelation-extraction or elution of As(III), and then reduction of As(V) with subsequent similar treatment (Butler 1988; López-Gonzálvez et al. 1994; Mok et al. 1988; Rabano et al. 1989).

Methods are also available for quantifying organic arsenicals in environmental media, including arsenobetaine in fish (Beauchemin et al. 1988; Cannon et al. 1983) and other organic forms of arsenic in water, soil, and foods using hyphenated methods of separation and detection (HPLC/ICP-MS, HPLC/HGAAS, IC/ICP-MS) (Andreae 1977; Braman et al. 1977; Comber and Howard 1989; Crecelius 1978; Heitkemper et al. 1994; López-Gonzálvez et al. 1994; Odanaka et al. 1983; Teräsahde et al. 1996).

Methods have been developed for extraction of arsenic species from solid seafood samples that included treatment of the sample with mixtures of organic solvents (alcohols or chloroform) and water to extract the arsenic compounds that are soluble in water or polar organic solvents. These extracts can be subsequently analyzed by HPLC. Enzymatic digestion using trypsin has also been used to extract arsenic compounds from seafood samples (Benramdane et al. 1999b). These extraction techniques are used in place of digestion when speciated data are needed.

A summary of selected methods for analysis of total arsenic and individual inorganic and organic arsenic species in environmental samples is presented in Table 7-2.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of arsenic 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 arsenic.

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

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Methods for total arsenic:					
Air particulate	Cellulose ester membrane filter, digestion with concentrated nitric acid, hydrochloric acid	NIOSH Method 7900 GFAAS	2 µg/sample	Not reported	NIOSH 1994
Air particulate	Cellulose ester membrane filter, ashing, fusion with Na_2CO_3, dissolution with H_2O_2	NIOSH Method 7901 GFAAS	6 µg/sample	Not reported	NIOSH 1994
Air particulate	Cellulose ester membrane filter, digestion with concentrated nitric acid, hydrochloric acid	NIOSH Method 7300 ICP-AES	0.1 µg/sample	Not reported	NIOSH 1994
Water, soil, sediment	Acid digestion	EPA Method 6010; ICP-AES	53 µg/L	86	EPA 1994a
Water, soil, sediment	Digestion with nitric acid	EPA Method 7060; GFAAS	8 µg/L	85	EPA 1994b
Water, soil, sediment	Digestion with nitric acid	EPA Method 7062; ICP-AES	1 µg/L	85	EPA 1994c
Water, soil, sediment	Digestion with nitric acid	EPA Method 7062; GFAAS using $Ni(NO_3)_2$ as matrix modifier	0.1 µg/L	85	EPA 1994c
Water, soil, sediment	Digestion with nitric acid	EPA Method 6020; ICP-MS	0.4 µg/L	85	EPA 1994d
Water, soil, sediment	Digestion with nitric acid; As extracted into BH_3 in THF	EPA Method 7063	2 µg/L	85	EPA 1994e
Water	Reduction with sodium borohydride, extraction with SDDC	EPA Method 7061; GFAAS using SDDC as matrix modifier	10 µg/L	100	EPA 1994f
Water	Digestion with Method 3010	EPA Method 7060; GFAAS	2 µg/L	Not reported	EPA 1994b

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food	Digestion with nitric acid, hydrochloric acid, and hydrogen peroxide; reduction with potassium iodide; extraction with APDC into methyl isobutyl ketone	GFAAS	0.01 µg	80	Dasgupta et al. 1995
Food	Digestion with nitric acid, perchloric acid, and sulfuric acid; reduction with potassium iodide; extraction with APDC into methyl isobutyl ketone	HGAAS	0.01 µg	80	Dasgupta et al. 1995
Soil, ash	Preparation not specified; NAA		4 ng	SRM	Nielsen and Steinnes 1991
Methods for species of arsenic:					
Air	Cellulose ester membrane filter, NIOSH Method 7900		2 µg	Not specified	NIOSH 1994
Air	Cellulose ester membrane filter, NIOSH Method 7900	NIOSH Method 7900 (GFAAS)	0.01 µg/sample	Not specified	NIOSH 1994
Air	Cellulose ester membrane filter, 0.1 M KOH/0.3 M KI solution	HGAAS	1 ng As^{3+}	95% (As^{3+})	Reeves and Hieftje 1985
Water	Strong anion exchange resin column to separate As^{3+} and As^{5+}; As^{3+} oxidized to As^{5+} with potassium permanganate; As^{5+} reduced to As^{3+} with potassium iodide	IEC system with HGAAS	0.1 µg/L	95%	Braman et al. 1977
Water	Strong anion exchange resin column to separate As^{3+} and As^{5+}; As^{5+} reduced to As^{3+} with sodium borohydride	Cathodic stripping voltammetry	Not specified	Not specified	Brezonik and Brezonik 1979

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Solvent extraction of As(III) with APDC	NAA	0.1 ppb	Not reported	Braman and Foreback 1973
Food, feces, urine	Extraction with nitric acid	HPLC/ICP-MS	0.1 ng	90	Branch et al. 1994
Water	Addition of sodium borohydride	EPA Method 7062, ASV	10 µg/L	90	EPA 1994
Water	Coprecipitation with ferric hydroxide	EPA Method 7060, GFAAS	3 µg/L	Not reported	EPA 1994
Water	Reduction of As(V) to As(III) with sodium borohydride	AAS	2 µg/L	90	Aggett and Aspell 1976
Water	Reduction of MMA, DMA with sodium borohydride; As(III) extracted with APDC	GFAAS	0.1 µg/L	Not reported	Chau and Cheung 1977
Biological tissue	Digestion with nitric acid, perchloric acid, and sulfuric acid; reduction of MMA and DMA with sodium borohydride	GC-MID	2 µg/L	95	Ostapczuk et al. 1988

AAS = atomic absorption spectrometry; APDC = ammonium pyrrolidine dithiocarbamate; ASV = anodic stripping voltammetry; DMA = dimethylarsinic acid; EPA = Environmental Protection Agency; GC = gas chromatography; GFAAS = graphite furnace atomic absorption spectrometry; HPLC = high performance liquid chromatography; ICP-AES = inductively coupled plasma atomic emission spectrometry; ICP-MS = inductively coupled plasma mass spectrometry; MID = microwave induced digestion; MMA = monomethylarsonic acid; NAA = neutron activation analysis; NIOSH = National Institute for Occupational Safety and Health; PEC = preconcentration; PTFE = polytetrafluoroethylene; SDDC = sodium diethyldithiocarbamate; SRM = standard reference material; TF = trifluoroacetic acid

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. The most useful biomarkers of exposure to arsenic are levels of arsenic in urine, hair, or nails. Existing methods are sufficiently sensitive to measure background levels of arsenic in these tissues for average persons, and to detect increases as a result of above-average exposure (Agahian et al. 1990; Clyne et al. 1989; Curatola et al. 1978; Foà et al. 1984; Gebel et al. 1998b; Landsberger and Simsons 1987; Mushak et al. 1977; Pinto et al. 1976; Valentine et al. 1979; Versieck et al. 1983). The precision and accuracy of these methods are documented. Methods are also available that can distinguish nontoxic forms of arsenic (arsenobetaine) from inorganic and organic derivatives that are of health concern (Braman et al. 1977; Dix et al. 1987; Johnson and Farmer 1989; Norin and Vahter 1981; Tam et al. 1982). Further efforts to improve accuracy, reduce interferences, and detect multiple species using a single analysis would be valuable. Arsenic is believed to act by inhibition of numerous cellular and molecular processes. However, these effects are not specific to arsenic, and most can only be measured in tissue extracts.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Arsenic is ubiquitous in the environment. It is found in air, water, soil, sediments, and food in several inorganic and organic forms. Analytical methods exist for the analysis of arsenic species in all of these environmental media, and these methods have the sensitivity to measure background levels and to detect elevated concentrations due to emissions from sources such as smelters, chemical plants, or hazardous waste sites (APHA 1977, 1989c; EPA 1982b, 1983a, 1983b, 1983c, 1991, 1994b, 1996a, 1996f). However, further research to reduce chemical and matrix interferences may improve the speed and accuracy of the analyses.

Le et al. (2004) pointed out that there is a need for the development of certified reference materials (CRMs) for speciation analysis. A shortcoming of many CRMs is that they are only certified for the total concentration of arsenic, and only limited information is available on the identity and concentrations of specific arsenic species in some CRMs.

Continued improvement of the methods for determination of the particular species of arsenic, rather than just the total arsenic concentration, present in foods, especially seafood, is needed since different arsenic species poses different hazards to individuals consuming these foods.

7.3.2 Ongoing Studies

The information in Table 7-3 was found as a result of a search of the Federal Research in Progress database (FEDRIP 2005).

Table 7-3. Ongoing Studies on Analytical Methods for Arsenic in Environmental and Biological Samples

Matrix	Affiliation	Research	Sponsor
Soil	Univ of North Carolina at Chapel Hill	Optimization of digestion procedures	National Institutes of Health
Clay	Univ of Texas	Preconcentration of arsenic species	National Institutes of Health
Biological; Plant; Animal	Univ of Missouri-Columbia	Arsenic speciation	US. Department of Agriculture

Source: FEDRIP 2000

8. REGULATIONS AND ADVISORIES

The international and national regulations and guidelines pertaining to arsenic and its metabolites in air, water, and other media are summarized in Table 8-1.

ATSDR has not derived inhalation MRLs or an intermediate-duration oral MRL for inorganic arsenic, or any MRLs for organic arsenic, due to lack of suitable data.

ATSDR has derived a provisional acute-duration oral MRL for inorganic arsenic of 0.005 mg As/kg/day based on a LOAEL of 0.05 mg As/kg/day for gastrointestinal effects and facial edema in Japanese people who ingested arsenic-contaminated soy sauce for 2–3 weeks (Mizuta et al. 1956). An uncertainty factor of 10 (10 for use of a LOAEL and 1 for human variability) was applied. The MRL is considered provisional because the effects were serious.

ATSDR has derived a chronic-duration oral MRL of 0.0003 mg/kg/day for inorganic arsenic based on a NOAEL of 0.0008 mg As/kg/day for dermal effects in a Taiwanese farming population exposed to arsenic in well water (Tseng 1977; Tseng et al. 1968). An uncertainty factor of 3 (for human variability) was applied.

EPA (IRIS 2005) has derived a chronic oral reference dose (RfD) of 0.0003 mg As/kg/day for inorganic arsenic, based on a NOAEL of 0.0008 mg As/kg/day for dermal effects and possible vascular complications in a Taiwanese farming population exposed to arsenic in well water (Tseng 1977; Tseng et al. 1968). An uncertainty factor of 3 (to account for the lack of reproductive data and uncertainty in whether the NOAEL accounts for all sensitive individuals) was applied. No reference concentration (RfC) for chronic inhalation exposures to arsenic was reported. EPA is currently revising the assessment for inorganic arsenic.

The Department of Health and Human Services (DHHS) has determined that inorganic arsenic is known to be a human carcinogen (NTP 2005). The EPA has determined that inorganic arsenic is a human carcinogen and has assigned it the cancer classification, Group A (IRIS 2005). EPA's quantitative estimates of carcinogenic risk from oral exposures include a cancer slope factor of 1.5 mg/kg/day and a drinking water unit risk of $5x10^{-5}$ µg/L. The inhalation unit risk for cancer is 0.0043 µg/m^3 (IRIS 2005). EPA is currently revising the assessment for inorganic arsenic. The International Agency for Research on Cancer (IARC) cites sufficient evidence of a relationship between exposure to arsenic and human cancer.

Table 8-1. Regulations and Guidelines Applicable to Arsenic and Arsenic Compounds

Agency	Description	Information	Reference
INTERNATIONAL			
IARC	Carcinogenicity classification	Group 1 [a]	IARC 1987
WHO	Air quality guideline	No level recommended	WHO 1987
	Drinking water guideline	0.01 mg/L [b]	WHO 1993
NATIONAL			
Regulations and Guidelines			
a. Air			
ACGIH	TLV-TWA for soluble inorganic compounds	0.01 mg/m³ [3]	ACGIH 1991
EPA	Hazardous air pollutant under the Clean Air Act	Yes	EPA 1990a, 42 USC 7412
NIOSH	REL for inorganic compounds [c]	0.002 mg/m³ [3]	NIOSH 1992
	IDLH for inorganic compounds [c]	5 mg/m³ [3]	
OSHA	PEL (8-hr TWA) for organic compounds	0.5 mg/m³ [3]	OSHA 1989, 29 CFR 1910
	PEL (8-hr TWA) for inorganic compounds	0.01 mg/m³ [3]	OSHA 1989, 29 CFR 1910
	PEL (8-hr TWA) for cotton dust containing arsenic	0.2 mg/m³ [3]	OSHA 1989, 29 CFR 1910
	PEL (8-hr TWA) for pesticides containing arsenic	0.5 mg/m³ [3]	OSHA 1989, 29 CFR 1910
b. Water			
EPA	Designation under the Safe Drinking Water Act	Yes	EPA 1991, 40 CFR 141
	Air emissions standard under the Clean Air Act		EPA 1989
	DWEL	0.05 mg/L	
	Non-zero MCLG under the Safe Drinking Water Act		EPA 1991
	MCLG	0	
	MCL	0.05 mg/L [d]	

Table 8-1. Regulations and Guidelines Applicable to Arsenic and Arsenic Compounds

Agency	Description			Value		Reference
NATIONAL *(cont.)*						
EPA	Regulations for Hazardous Substances and Hazardous Wastes					EPA 40 CFR 302
	Air emissions from arsenic trioxide and metallic arsenic production facilities			1 µg/m³		
	Air emissions from glass manufacturing plants					EPA 40
	Water Quality Criteria			50 µg/L	[e]	
	Drinking Water			50 µg/L	[e]	
cFd						
EPA	Toxic Substances					
	Discharge of arsenic from electrolytic copper refining subcategory					EPA 40 CFR 66
	Copper smelting subcategory			204 mg/L		
	Metallurgical acid plant subcategory					EPA 40 CFR 80
	Copper smelting subcategory			77 mg/L		
	Copper refining subcategory			99 mg/L		
	Primary lead subcategory			65 mg/L		
FDA	Bottled water			10 µg/L		FDA 21 CFR 165
USDA	National Organic Program			Asc		USDA 7 CFR 205
dOe						
ACGIH	Carcinogenic effects			A1 [f]		ACGIH
	Biological exposure indices for inorganic arsenic			35 µg/g creatinine		
EPA	Carcinogenic effects	Oral	Cancer		A [g]	IRIS
	Oral			3 × 10⁻⁴ mg/kg/day	[3]	
	Inhalation			2 × 10⁻³ µg/m³	[3]	
	RfC			Not listed		
	RfD			3 × 10⁻⁴ mg/kg/day	[4]	

Table 8-1. Regulations and Guidelines Applicable to Arsenic and Arsenic Compounds

Ag	Dip	Ifn	Rfe
NATIONAL *(cont.)*			
EPA	S Dig CERCLA Ra R Ai Ai E R Ai S T Ai Ch	Nt 1 0 1 0 0	EPA EPA 9CFR EPA 9CFR EPA 9CFR A
NTP	Cig		NTP

[a] C
[b] P
li
[c] NIOSH
[d] MCL
[e] Th
[f] A.1
[g] A:
[h] I

ACD
RpC
E
fR
MCL =
O
A
PEL =
R =
St
USDA =

CERCLA =
FR
DA =
ARC =
RIS =
NIOSH =
SA =
RC =
USC =

*** DRAFT FOR PUBLIC COMMENT***

IARC classification of arsenic is Group 1 (IARC 2004). The American Conference of Governmental Industrial Hygienists (ACGIH) classifies arsenic (elemental and inorganic compound) as a confirmed human carcinogen, cancer category A1 (ACGIH 2004).

Several arsenic compounds have been designated as "extremely hazardous substances" or "hazardous substances" pursuant to the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980 (EPA 2005c, 2005d). The owner or operator of any facility that produces, uses, or stores any extremely hazardous substance or CERCLA hazardous substance in an amount exceeding the "threshold planning quantity" is required to immediately report any release to any environmental media, if the amount released is equal to or exceeds the specified "reportable quantity" assigned to the substance. As extremely hazardous substances, when arsenic compounds are formulated as solids, they are subject to either of two threshold planning quantities (EPA 2005d). If the solid exists in powdered form and has a particle size less than 100 microns, then it is subject to the lower number. If the solid does not meet this criteria, then it is subject to the higher number. Approximately 11 arsenic compounds are designated as "hazardous substances" under Sections 101(14) and 102(a) of CERCLA and must meet the requirements for reporting releases to the environment in accordance with 40 CFR 302.4. The reportable quantity for each of these three compounds is 1 pound (0.454 kg) (EPA 2005c). The statutory sources for this designation include Sections 307(a) and 311(b) (4) of the Clean Water Act (CWA), Section 3001 of the Resource Conservation and Recovery Act (RCRA), and Section 112 of the Clean Air Act (CAA) (EPA 2005c). The reportable quantities for these compounds are given in Table 8-1.

The statutory requirements of the CAA also contain a mandate for EPA to evaluate and control emissions of hazardous air pollutants (HAPs). Section 112(b) (1) of the Act includes a list of substances that have been designated as HAPs. The mandate requires EPA to identify specific categories of sources (new and existing) that emit or have the potential to emit these substances to the environment and to promulgate emissions standards for each source. Inorganic arsenic compounds have been identified and listed as HAPs (U.S. Congress 1990). Arsenic also appears on the list of toxic chemicals subject to Section 313 of the "Emergency Planning and Community Right-to-Know-Act of 1986" (EPA 2005c).

The EPA has a current maximum contaminant level (MCL) of 0.01 mg/L for arsenic in drinking water (EPA 2002a). The World Health Organization (WHO) has established a provisional guideline value of 0.01 mg/L for arsenic in drinking water (WHO 2004).

8REGULATIONS AND ADVISORIES

The Occupational Safety and Health Administration (OSHA) sets permissible exposure limits (PELs) to protect workers against adverse health effects resulting from exposure to hazardous substances. The PELs determined for hazardous substances are enforceable, regulatory limits on allowable indoor air concentrations. OSHA requires employers of workers who are occupationally exposed to these hazardous substances to institute engineering controls and work practices to reduce and maintain employee exposure to at or below the PEL. An employer must ensure that no employee's exposure to inorganic arsenic is >10 $\mu g/m^3$ when averaged over any 8-hour work shift (OSHA 2005c). OSHA also specifies conditions under which employees must be provided with respirators that reduce their exposure to arsenic and arsenicals (e.g., arsenic trichloride and arsenic phosphide) to below the PEL. The concentrations of inorganic arsenic or conditions of use, and the required respirator type are given in 29 CFR 1910.1018. The requirements applicable to exposures to inorganic arsenic during construction work and for shipyard personnel are identical to those given above (OSHA 2005a, 2005b). However, for exposures to organic arsenic compounds, employers must meet the requirements that OSHA provides for occupational health and environmental controls. ACGIH limits exposure to organic arsenic compounds to 0.01 mg/m^3 (ACGIH 2004). For biological monitoring of exposures occurring in the workplace, ACGIH provides a biological exposure index (BEI) of 35 $\mu g/g$ creatinine. The BEI for a substance applies to 8-hour exposures for 5 days/week (ACGIH 2004). The National Institute for Occupational Safety and Health (NIOSH) has established a recommended exposure level (REL) of 0.002 mg/m^3 (NIOSH 2005).

9. REFERENCES

*Abdo KM, Elwell MR, Montgomery CA, et al. 1989. Toxic responses in F344 rats and B6C3F$_1$ mice given roxarsone in their diets for up to 13 weeks. Toxicol Lett 45:55-56.

Abedin MJ, Cotter-Howells J, Meharg AA. 2002. Arsenic uptake and accumulation in rice (*Oryza sativa* L.) irrigated with contaminated water. Plant Soil 240:311-319.

*Abernathy CO, Chappell WR, Meek ME, et al. 1996. Is ingested inorganic arsenic a "threshold" carcinogen? Fundam Appl Toxicol 29(2):168-175.

Abernathy CO, Liu Y-P, Longfellow D, et al. 1999. Arsenic: Health effects, mechanisms of actions, and research issues. Environ Health Perspect 107(7):593-597.

*Abernathy CO, Marcus W, Chen C, et al. 1989. Report on arsenic (As) work group meetings. Memo from CO Abernathy et al. to Peter Cook and Peter Preuss, U.S. EPA dated 02/23/89.

ACGIH. 1990. Arsenic and soluble compounds. 1990-1991 threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

ACGIH. 1997. 1997 threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

ACGIH. 1998. 1998 threshold limit values for chemical substances and physical agents. Biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

ACGIH. 1999. Arsenic. Documentation of the threshold limit values and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

*ACGIH. 2004. Arsenic. Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

Acharyya SK, Chakraborty P, Lahiri S, et al. 1999. Arsenic poisoning in the Ganges delta. Nature 401(6753):545-547.

Ademuyiwa O, Elsenhans B, Nguyen PT, et al. 1996. Arsenic-copper interaction in the kidney of the rat: Influence of arsenic metabolites. Pharmacol Toxicol 78(3):154-160.

*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 text

9REFERENCES

*Agahian B, Lee JS, Nelson JH, et al. 1990. Arsenic levels in fingernails as a biological indicator of exposure to arsenic. Am Ind Hyg Assoc J 51(12):646-651.

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

*Agency for Toxic Substances and Disease Registry. 1990a. Arsenic toxicity. Case studies in environmental medicine. Atlanta, GA: Agency for Toxic Substances and Disease Registry, U.S. Department of Health & Human Services, Public Health Services. HE20.7917:5 504-U.

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

*Aguilar MV, Martínez-Para MC, Gonzalez MJ. 1997. Effects of arsenic (V)-chromium (III) interaction on plasma glucose and cholesterol levels in growing rats. Ann Nutr Metab 41(3):189-195.

*Ahmad S, Anderson WL, Kitchin KT. 1999a. Dimethylarsinic acid effects on DNA damage and oxidative stress related biochemical parameters in B6C3F1 mice. Cancer Lett 139(2):129-135.

*Ahmad SA, Bandaranayake D, Khan AW, et al. 1997. Arsenic contamination in ground water and arsenicosis in Bangladesh. Int J Environ Health Res 7:271-276.

*Ahmad SA, Sayed MH, Barua S, et al. 2001. Arsenic in drinking water and pregnancy outcomes. Environ Health Perspect 109(6):629-631.

*Ahmad SKA, Sayed MHSU, Hadi SA, et al. 1999b. Arsenicosis in a village in Bangladesh. Int J Environ Health Res 9(3):187-195.

Ahmann D, Krumholz LR, Hemond HF, et al. 1997. Microbial mobilization of arsenic from sediments of the Aberjona Watershed. Environ Sci Technol 31:2923-2930.

Ahsan H, Chen Y, Parvez F, et al. 2004. Association between arsenic exposure from drinking water and premalignant skin lesions in Bangladesh. Am J Epidemiol 159(11 Suppl):S28.

*Ahsan H, Chen Y, Wang Q, et al. 2003. DNA repair gene *XPD* and susceptibility to arsenic-induced hyperkeratosis. Toxicol Lett 143:123-131.

*Ahsan H, Perrin M, Rahman A, et al. 2000. Associations between drinking water and urinary arsenic levels and skin lesions in Bangladesh. J Occup Environ Med 42(12):1195-1205.

Aizawa Y, Takata T, Kurihara M, et al. 1988. Biological monitoring of arsenic in semiconductor workers. Appl Organomet Chem 2:395-398.

*Akao Y, Mizoguchi H, Kojima S, et al. 1998. Arsenic induces apoptosis in B-cell leukaemic cell lines in vitro: Activation of caspases and down-regulation of Bcl-2 protein. Br J Haematol 102:1055-1060.

Akkari KH, Frans RE, Lavy TL. 1986. Factors affecting degradation of MSMA in soil. Weed Sci 34:781-787.

9REFERENCES

Akland G. 1983. Written communication (February 23) to D. Sivulka. Available from: U.S. Environmental Protection Agency, Research Triangle Park, NC. Project file no. ECAO-HA-79-5.

*Alain G, Tousignant J, Rozenfarb E. 1993. Chronic arsenic toxicity. Int J Dermatol 32(12):899-901.

Alam MG, Allinson G, Stagnitti F, et al. 2002. Arsenic contamination in Bangladesh groundwater: A major environmental and social disaster. Int J Environ Health Res 12(3):235-253.

Alam MG, Snow ET, Tanaka A. 2003. Arsenic and heavy metal contamination of vegetables grown in Samta village, Bangladesh. Sci Total Environ 308(1-3):83-96.

Alauddin M, Alauddin ST, Bhattacharjee M, et al. 2003. Speciation of arsenic metabolite intermediates in human urine by ion-exchange chromatography and flow injection hydride generation atomic absorption spectrometry. J Environ Sci Health A Tox Hazard Subst Environ Eng 38(1):115-128.

*Albores A, Cebrian ME, Bach PH, et al. 1989. Sodium arsenite induced alterations in bilirubin excretion and heme metabolism. J Biochem Toxicol 4(2):73-78.

*Albores A, Koropatnick J, Cherian MG, et al. 1992. Arsenic induces and enhances rat hepatic metallothionein production in vivo. Chem Biol Interact 85:127-140.

Ali I, Aboul-Enein HY. 2002. Speciation of arsenic and chromium metal ions by reversed phase high perfomance liquid chromoatography. Chemosphere 48(3):275-278.

Alimonti A, Caroli S, Musmeci L, et al. 1988. Determination of heavy metals in samples in urban solid wastes by means of the ICP atomic spectrometry technique. Sci Total Environ 71:495-500.

Allen T, Rana SV. 2003. Oxidative stress by inorganic arsenic: Modulation by thyroid hormones in rat. Comp Biochem Physiol C 135(2):157-162.

Allen GT, Blackford SH, Tabor VM, et al. 2001. Metals, boron, and selenium in Neosho madtom habitats in the Neosho River in Kansas, USA. Environ Monit Assess 66(1):1-21.

Almela C, Algora S, Benito V, et al. 2003. Heavy metal, total arsenic, and inorganic arsenic contents of algae food products. J Agric Food Chem 50:918-923.

Altamirano-Lozano M, Roldán E, Bonilla E, et al. 1998. Effect of metal compounds on boar sperm motility *in vitro*. Adv Exp Med Biol 444:105-111.

*Altman PK, Dittmer DS. 1974. In: Biological handbooks: Biology data book. Vol. III, 2nd ed. Bethesda, MD: Federation of American Societies for Experimental Biology, 1987-2008, 2041.

Alvarez-Barrera L, Corona-Martinez A, Rodriguez-Aguilera E, et al. 2000. DNA damage in leukocytes and testicular cells in male mice after chronic or acute treatments with sodium arsenate. Environ Mol Mutagen 35(Suppl 31):10.

Alvim-Ferraz MC, Afonso SA. 2003. Incineration of different types of medical wastes: Emission factors for particulate matter and heavy metals. Environ Sci Technol 37(14):3152-3157.

*Amacher DE, Paillet SC. 1980. Induction of trifluorothymidine-resistant mutants by metal ions in L5178Y/TK$^{+/-}$ cells. Mutat Res 78:279-288.

9REFERENCES

*American Wood Preservers Association. 2000. FAQ's: Treated wood uses. American Wood Preserver's Association. http://www.awpa.com/references/faq.asp#uses. July 29, 2005.

Amundsen CE, Hanssen JE, Semb A, et al. 1992. Long-range atmospheric transport of trace elements to Southern Norway. Atmos Environ 26A(7):1309-1324.

Anawar HM, Akai J, Mostofa KM, et al. 2002. Arsenic poisoning in groundwater: Health risk and geochemicals sources in Bangladesh. Environ Int 27(7):597-604.

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

Andersen KJ, Leighty EG, Takahashi MT. 1972. Evaluation of herbicides for possible mutagenic properties. J Agric Food Chem 20:649-656.

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

*Anderson LCD, Bruland KW. 1991. Biogeochemistry of arsenic in natural waters: The importance of methylated species. Environ Sci Technol 25:420-427.

Anderson G, Ratliff L, Smith B. 1996. Exposure to metals at a scrap recycling firm. Appl Occup Environ Hyg 11:160-162.

*Anderson HA, Falk C, Hanrahan L, et al. 1998. Profiles of Great Lakes critical pollutants: A sentenial analysis of human blood and urine. Environ Health Perspect 106(5):279-289.

*Andreae MO. 1977. Determination of arsenic species in natural waters. Anal Chem 49(6):820-823.

Andreae MO. 1980. Arsenic in rain and the atmospheric mass balance of arsenic. J Geophys Res 85:4512-4518.

Andreae MO. 1983. Biotransformation of arsenic in the marine environment. In: Lederer W, Fensterheim R, eds. Arsenic: Industrial, biomedical and environmental perspectives. New York, NY: Van Nostrand Reinhold.

Andren P, Schutz A, Vahter M, et al. 1988. Environmental exposure to lead and arsenic among children living near a glassworks. Sci Total Environ 77:25-34.

Andrew AS, Karagas MR, Hamilton JW. 2003a. Decreased DNA repair gene expression among individuals exposed to arsenic in United States drinking water. Int J Cancer 104(3):263-268.

Andrew AS, Karagas MR, Klei L, et al. 2003b. Drinking water arsenic exposure is associated with decreased DNA repair gene expression. Toxicol Sci 72(S-1):184.

Andrew AS, Karagas MR, Schned A, et al. 2002. Decreased expression of DNA repair genes ERCC1, XPF, and XPB, but not XPG of XPA among individuals exposed to arsenic in drinking water. Proc Am Assoc Cancer Res 43:1029.

9REFERENCES

*Anke M, Grün M, Partschefeld M, et al. 1976. The essentiality of arsenic for animals. Trace Subst Environ Health 10:403-409.

*Anke M, Grün M, Partschefeld M, et al. 1978. Essentiality and function of arsenic. In: Kirchgessner M, ed. Trace element metabolism in man and animals-3. Munich: Freising-Weihenstephen Tech University, 248-252.

Anonymous. 2001. Arsenic in drinking water. J Environ Health 64(2):36, 44.

*APHA. 1977. Tentative method of analysis for arsenic content of atmospheric particulate matter. In: Kate M, ed. Methods of air sampling and analysis. Washington, DC: American Public Health Association, 435-438.

*APHA. 1989a. Arsenic. In: Clesceri LS, Greenberg AE, Trussell RR, eds. Standard methods for the examination of water and wastewater. 17th ed. Washington, DC: American Public Health Association, 3-74-3-78.

*APHA. 1989b. Metals by electrothermal atomic absorption spectrometry. In: Clesceri LS, Greenberg AE, Trussell RR, eds. Standard methods for the examination of water and wastewater. 17th ed. Washington, DC: American Public Health Association, 3-32-3-50.

*APHA. 1989c. Metals by hydride generation/atomic absorption spectrometry. In: Clesceri LS, Greenberg AE, Trussell RR, eds. Standard methods for the examination of water and wastewater. 17th ed. Washington, DC: American Public Health Association, 3-43-3-50.

*APHA. 1989d. Metals by plasma emission spectrometry. In: Clesceri LS, Greenberg AE, Trussell RR, eds. Standard methods for the examination of water and wastewater. 17th ed. Washington, DC: American Public Health Association, 3-53-3-78.

Apodaca LE, Driver NE, Bails JB. 2000. Occurrence, transport, and fate of trace elements, Blue River Basin, Summit County, Colorado: An integrated approach. Environ Geol 39(8):901-913.

Aposhian HV. 1989. Biochemical toxicology of arsenic. Rev Biochem Toxicol 10:265-299.

Aposhian HV. 1998. Mobilization of mercury and arsenic in humans by sodium 2,3-dimercapto-1-propane sulfonate (DMPS). Environ Health Perspect Suppl 106(4):1017-1025.

*Aposhian HV, Aposhian MM. 1989. Newer developments in arsenic toxicity. J Am Coll Toxicol 8:(7)1297-1305.

*Aposhian HV, Arroyo A, Cebrian ME, et al. 1997. DMPS-arsenic challenge test. I: Increased urinary excretion of monomethylarsonic acid in humans given dimercaptopropane sulfonate. J Pharmacol Exp Ther 282(1):192-200.

Aposhian HV, Gurzau ES, Le XC, et al. 2000a. Occurrence of monomethylarsonous acid in urine of humans exposed to inorganic arsenic. Chem Res Toxicol 13(8):693-697.

Aposhian HV, Zakharyan RA, Avram MD, et al. 2003. Oxidation and detoxification of trivalent arsenic species. Toxicol Appl Pharmacol 193(1):1-8.

9REFERENCES

Aposhian HV, Zakharyan RA, Healy SM, et al. 1998. Biodiversity of inorganic arsenite methyltransferases. Toxicologist. Abstracts of the 37th Annual Meeting 42(1-S):353.

Aposhian HV, Zheng B, Aposhian MM, et al. 2000b. DMPS-arsenic challenge test. 11. Modulation of arsenic species, including monomethylarsonous acid (MMA)(111), excreted in human urine. Toxicol Appl Pharmacol 165(1):74-83.

Apostoli P, Alessio L, Romeo L, et al. 1997. Metabolism of arsenic after acute occupational arsine intoxication. J Toxicol Environ Health 52(4):331-342.

*Apostoli P, Bartoli D, Alessio L, et al. 1999. Biological monitoring of occupational exposure to inorganic arsenic. Occup Environ Med 56(12):825-832.

Arai Y, Sparks DL, Davis JA. 2004. Effects of dissolved carbonate on arsenate adsorption and surface speciation at the hematite–water interface. Environ Sci Technol 38(3):817-824.

*Aranyi C, Bradof JN, O'Shea WJ, et al. 1985. Effects of arsenic trioxide inhalation exposure on pulmonary antibacterial defenses in mice. J Toxicol Environ Health 15:163-172.

Arbouine MW, Wilson HK. 1992. The effect of seafood consumption on the assessment of occupational exposure to arsenic by urinary arsenic speciation measurements. J Trace Elem Electrolytes Health Dis 6(3):153-160.

*Arenas V, Stoeppler M, Bergerhoff G. 1988. Arsenic determination in the ultratrace range by atomic absorption spectrometry after preconcentration of the hydride. Fresenius Z Anal Chem 332:447-452.

Argos M, Ahsan H, Parvez F, et al. 2004. The association between arsenic exposure and premalignant skin lesions in modified by socioeconomic status in Bangladesh population. Am J Epidemiol 159(11 Suppl):S21.

Ariyoshi T, Ikeda T. 1974. On the tissue distribution and the excretion of arsenic in rats and rabbits of administration with arsenical compounds. J Hyg Chem 20:290-295.

Armbrust KL, Bridges DC. 2002. Dissipation of monosodium methane arsonate (MSMA) on peanuts. J Agric Food Chem 50(7):1959-1963

*Armienta MA, Rodríguez, Cruz O. 1997. Arsenic content in the hair of people exposed to natural arsenic polluted groundwater a Zimapán, México. Bull Environ Contam Toxicol 59:583-589.

*Armstrong CW, Stroube RB, Rubio T, et al. 1984. Outbreak of fatal arsenic poisoning caused by contaminated drinking water. Arch Environ Health 39(4):276-279.

*Arnold LL, Cano M, St. John M, et al. 1999. Effects of dietary dimethylarsinic acid on the urine and urothelium of rats. Carcinogenesis 20(11):2171-2179.

*Arnold LL, Eldan M, van Gemert M, et al. 2003. Chronic studies evaluating the carcinogenicity of monomethylarsonic acid in rats and mice. Toxicology 190:197-219.

*Aschengrau A, Zierler S, Cohen A. 1989. Quality of community drinking water and the occurrence of spontaneous abortion. Arch Environ Health 44(5):283-290.

9REFERENCES

Ashraf W, Jaffar M, Mohammad D. 1994. Trace metal contamination study on scalp hair of occupationally exposed workers. Bull Environ Contam Toxicol 53:516-523.

Attrep M, Anirudhan M. 1977. Atmospheric inorganic and organic arsenic. Trace Subst Environ Health 11:365-369.

*Aurillo AC, Mason RP, Hemond HF. 1994. Speciation and fate of arsenic in three lakes of the Aberjona Watershed. Environ Sci Tech 28(4):577-585.

*Axelson O, Dahlgren E, Jansson C-D, et al. 1978. Arsenic exposure and mortality: A case referent study from a Swedish copper smelter. Br J Ind Med 35:8-15.

Ayala-Fierro F, Carter DE. 1998. Arsine vs arsenite toxicity in different cell types. Toxicologist 42(1-S):322.

Ayala-Fierro F, Barber DS, Rael LT, et al. 1999. *In vitro* tissue specificity for arsine and arsenite toxicity in the rat. Toxicol Sci 52:122-129.

*Azcue JM, Nriagu JO. 1994. Arsenic: Historical perspectives. In: Nriagu JO, ed. Arsenic in the Environment, part 1: Cycling and characterization. New York, NY: John Wiley and Sons, Inc., 1-15.

Azpiazu MN, Romero F, Diaz JM. 1987. [Potentially toxic metallic components distribution in plants.] Afinidad 44:385-389. (Spanish)

*Babich H, Martin-Alguacil N, Borenfreund E. 1989. Arsenic-selenium interactions determined with cultured fish cells. Toxicol Lett 45:157-164.

Baetjer AM, Lilienfeld AM, Levin ML. 1975. Cancer and occupational exposure to inorganic arsenic. In: Abstracts: 18th International Congress on Occupational Health, Brighton, England, September 14-19, 1975. Brighton, England: International Congress on Occupational Health, Organizing Committee, 393.

*Bagla P, Kaiser J. 1996. India's spreading health crisis draws global arsenic experts. Science 274(5285):174-175.

Bahlis NJ, Jordan-McMurry I, Grad JM, et al. 2001. Phase I results from a phase I/II study of arsenic trioxide (As^2O^3) and ascorbic acid (AA) in relapsed and chemorefractory multiple myeloma. Blood 98(11 Part 1):375a.

*Baj G, Arnulfo A, Deaglio S, et al. 2002. Arsenic trioxide and breast cancer: analysis of the apoptic, differentiative and immunomodulatory effects. Breast Cancer Res Treat 73(1):61-73.

Bajenova OV, Lariviere JP, Oh J, et al. 1998. Effects of the heavy metals chromium and arsenic on hormone-inducible expression of PEPCK/Luciferase genetic constructs. Toxicologist 42(1-S):320-321.

*Baker EL, Hayes CG, Landrigan PJ, et al. 1977. A nationwide survey of heavy metal absorption in children living near primary copper, lead, and zinc smelters. Am J Epidemiol 106(4):261-273.

*Baker LW, Fitzell DL, Seiber JN, et al. 1996. Ambient air concentrations of pesticides in California. Environ Sci Tech 30(4):1365-1368.

9REFERENCES

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 280:239-255.

Ball J. 1987. Soil and groundwater contamination at wood preserving plants. Proc Ind Waste Conf 41:347-351.

Banu BS, Danadevi K, Jamil K, et al. 2001. In vivo genotoxic effect of arsenic trioxide in mice using comet assay. Toxicology 162(3):171-177.

Baptiste P. 2000. Arsenic exposures during burning activities in battery assembly. Appl Occup Environ Hyg 15(9):664-666.

Bara M, Guiet-Bara A, Durlach J. 1987. Toxic metals and human amniotic ion permeability. I. Effects on the total transamniotic transfer. Trace Elem Med 4:154-159.

Barbaud A, Mougeolle JM, Schmutz JL. 1995. Contact hypersensitivity to arsenic in a crystal factory worker. Contact Dermatitis 33(4):272-273.

Barber DS. 1997. Correlation of pulmonary arsenic metabolism and toxicity. Diss Abstr Int B 58(11):153.

Barbey JT. 2001. Cardiac toxicity of arsenic trioxide. Blood 98(5):1632-1634.

Barbey JT, Soignet S. 2001. Prolongation of the QT interval and ventricular tachycardia in patients treated with arsenic trioxide for acute promyelocytic leukemia. Comment on Ann Intern Med 133(11):881-885. Ann Intern Med 135(9):842-843.

*Barbey JT, Pezzullo JC, Soignet SL. 2003. Effect of arsenic trioxide on QT interval in patients with advanced malignancies. J Clin Oncol 21(19):3609-15.

Barchowsky A, Klei LR, Ihnat M, et al. 2003. Signaling pathways involved in arsenic-induced vascular disease. Toxicol Sci 72(S-1):167.

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

Barnes JA, Collins BW, Dix DJ, et al. 2001. Effect of exposure protocol and heat shock protein expression on arsenite induced genotoxicity in MCF-7 breast cancer cells. Environ Mol Mutagen 37(Suppl. 32):20.

Baron P, Schweinsberg F. 1988. A literature review on concentrations of arsenic cadmium, lead, and mercury in human body fluids and tissues to localize normal levels and to detect expositions. 1. Communication: Descriptions of analytical procedures: Arsenic. Zentralbl Bakteriol Mikrobiol Hyg [B] 186:289-310. (German)

*Baroni C, van Esch GJ, Saffiotti U. 1963. Carcinogenic tests of two inorganic arsenicals. Arch Environ Health 7:668-674.

Barrett JC, Oshimura M, Tsutsui T, et al. 1988. Mutation and neoplastic transformation: Correlations and dissociations. Ann N Y Acad Sci 534:95-98.

9REFERENCES

Barrett JC, Shelby MD. 1986. Mechanisms of multistep carcinogenesis: Keys to developing *in vitro* approaches for assessing the carcinogenicity of chemicals. Food Chem Toxicol 24:657-661.

*Bartolome B, Cordoba S, Nieto S, et al. 1999. Acute arsenic poisoning: Clinical and histopathological features. Br J Dermatol 141:1106-1109.

*Barton EN, Gilbert DT, Raju K, et al. 1992. Arsenic: The forgotten poison? West Indian Med J 41(1):36-38.

Basavaraju SR, Jones TD. 1998. Atherosclerotic risks from chemicals: Part I. Toxicological observations and mechanisms of atherosclerosis. Arch Environ Contam Toxicol 35:152-164.

Bass DA, Yaeger JS, Crain JS, et al. 1996. Arsenic speciation using high performance liquid chromatography-inductively coupled plasma-mass spectrometry. Argonne, IL: Argonne National Library, Energy Systems Division. ANL/CMT-ACL/VU-8636. DE95015641.

*Basu A, Ghosh P, Das JK, et al. 2004. Micronuclei as biomarkers of carcinogen exposure in populations exposed to arsenic through drinking water in West Bengal, India: A comparative study in three cell types. Cancer Epidemiol Biomarkers Prev 13(5):820-827.

*Bates MN, Rey OA, Biggs ML, et al. 2004. Case-control study of bladder cancer and exposure to arsenic in Argentina. Am J Epidemiol 159(4):381-389.

Bates MN, Smith AH, Cantor KP. 1995. Case-control study of bladder cancer and arsenic in drinking water. Am J Epidemiol 141(6):523-530.

*Battista G, Bartoli D, Iaia TE, et al. 1996. Art glassware and sinonasal cancer: Report of three cases. Am J Ind Med 30(1):31-35.

Bau DT, Wang TS, Chung CH, et al. 2002. Oxidative DNA adducts and DNA-protein cross-links are the major DNA lesions induced by arsenite. Environ Health Perspect Suppl 110:753-756.

Bauman PF, Smith TK, Bray TM. 1988. The effect of dietary protein and sulfur amino acids on hepatic glutathione concentration and glutathione-dependent enzyme activities in the rat. Can J Physiol Pharmacol 66:1048-1052.

*Baxley MN, Hood RD, Vedel GC, et al. 1981. Prenatal toxicity of orally administered sodium arsenite in mice. Bull Environ Contam Toxicol 26:749-756.

*Bazarbachi A, El-Sabban ME, Nasr R, et al. 1999. Arsenic trioxide and interferon-α synergize to induce cell cycle arrest and apoptosis in human t-cell lymphotropic virus I-transformed cells. Blood 93(1):278-283.

*Beane Freeman LE, Dennis LK, Lynch CF, et al. 2004. Toenail arsenic content and cutaneous melanoma in Iowa. Am J Epidemiol 160(7):679-687.

*Beauchemin D, Bednas ME, Berman SS, et al. 1988. Identification and quantitation of arsenic species in a dogfish muscle reference material for trace elements. Anal Chem 60:2209-2212.

*Beaudoin AR. 1974. Teratogenicity of sodium arsenate in rats. Teratology 10:153-158.

9REFERENCES

Beck BD, Slayton TM. 1998. Impact of arsenic (As_i) metabolism on human populations: Dose-response relationships in arsenic-induced cancers. Toxicologist 42(1-S):354.

*Beck BD, Boardman PD, Hook GC, et al. 1995. Response to Smith et al. Arsenic risk assessment. Environ Health Perspect 103:15-17.

Becker PR. 2000. Concentration of chlorinated hydrocarbons and heavy metals in Alaska Arctic marine mammals. Mar Pollut Bull 40(10):819-829.

*Beckett WS, Moore JL, Keogh JP, et al. 1986. Acute encephalopathy due to occupational exposure to arsenic. Br J Ind Med 43:66-67.

Beckman L. 1978. The Ronnskar smelter - occupational and environmental effects in and around a polluting industry in northern Sweden. Ambio 7:226-231.

*Beckman L, Nordenson I. 1986. Interaction between some common genotoxic agents. Hum Hered 36:397-401.

*Beckman G, Beckman L, Nordenson I. 1977. Chromosome aberrations in workers exposed to arsenic. Environ Health Perspect 19(5-6):145-146.

Bednar AJ, Garbarino JR, Burkhardt MR, et al. 2004. Field and laboratory arsenic speciation methods and their application to natural-water analysis. Water Res 38(2):355-364.

Bednar AJ, Garbarino JR, Ranville JF, et al. 2002a. Presence of organoarsenicals used in cotton production in agricultural water and soil of the southern United States. J Agric Food Chem 50(25):7340-7344.

Bednar AJ, Garbarino JR, Ranville JF, et al. 2002b. Preserving the distribution of inorganic arsenic species in groundwater and acid mine drainage samples. Environ Sci Technol 36:2213-2218.

*Beerman DH. 1994. Growth regulators (animal). In: Kroschwitz JI, Howe-Grant M, eds. Kirk-Othmer encyclopedia of chemical technology. Vol. 12. New York, NY: John Wiley and Sons, 795-815.

*Bekemeier H, Hirschelmann R. 1989. Reactivity of resistance blood vessels ex vivo after administration of toxic chemicals to laboratory animals: Arteriolotoxicity. Toxicol Lett 49:49-54.

Beliaeff B, O'Connor TP, Daskalakis DK, et al. 1997. U.S. mussel watch data from 1986 to 1994: temporal trend detection at large spatial scales. Environ Sci Technol 31:1411-1415.

Benbrahim-Tallaa L, Achanzar WE, Brambila EM, et al. 2003. Altered gene expression associated with arsenite-induced malignant transformation of human prostate epithelial cells. Toxicol Sci 72(S-1):215.

Bencko V. 1987. Arsenic. Adv Mod Environ Toxicol 11:1-30.

Bencko V. 1997. Contribution to neurotoxicity of arsenic in environmental settings. Neurotoxicol 18(3):871.

*Bencko V, Geist T, Arbetová D, et al. 1986. Biological monitoring of environmental pollution and human exposure to some trace elements. J Hyg Epidemiol Microbiol Immunol 30(1):1-10.

9REFERENCES

*Bencko V, Wagner V, Wagnerová M, et al. 1988. Immunological profiles in workers of a power plant burning coal rich in arsenic content. J Hyg Epidemiol Microbiol Immunol 32:137-146.

*Bennett BG. 1986. Exposure assessment for metals involved in carcinogenesis. IARC Sci Publ 71(8):115-127.

*Benramdane L, Accominotti M, Fanton L, et al. 1999a. Arsenic speciation in human organs following fatal arsenic trioxide poisoning--a case report. Clin Chem 45(2):301-306.

*Benramdane L, Bressolle F, Vallon J-J. 1999b. Arsenic speciation in humans and food products: A review. J Chromatogr Sci 37:330-344.

*Benson AA. 1989. Arsonium compounds in algae. Proc Natl Acad Sci USA 86:6131-6132.

*Berg M, Tran HC, Nguyen TC, et al. 2001. Arsenic contamination of groundwater and drinking water in Vietnam: A human health threat. Environ Sci Technol 35(13):2621-2626.

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

*Bergstrom SK, Gillan E, Quinn JJ, et al. 1998. Arsenic trioxide in the treatment of a patient with multiply recurrent, ATRA-resistant promyelocytic leukemia: A case report. J Pediatric Hematol Oncol 20(6):545-547.

*Bernstam L, Nriagu J. 2000. Molecular aspects of arsenic stress. J Toxicol Environ Health Part B Crit Rev 3(4):293-322.

Bernstam L, Lan CH, Lee J, et al. 2002. Effects of arsenic on human keratinocytes: Morphological, physiological, and precursor incorporation studies. Environ Res 89(3):220-235.

*Berry MR, Johnson LS, Jones JW, et al. 1997. Dietary characterizations in a study of human exposures in the lower Rio Grande Valley: I. Foods and beverages. Environ Int 23(5):675-692.

Berteau PE, Flom JO, Dommick RL, et al. 1978. Long-term study of potential carcinogenicity of inorganic arsenic aerosols to mice [Abstract]. Toxicol Appl Pharmacol 45:323.

*Berti PR, Receveur O, Chan HM, et al. 1998. Dietary exposure to chemical contaminants from traditional food among adult dene/métis in the western Northwest territories, Canada. Environ Res A76:131-142.

Bertolero F, Marafante E, Edel Rade J, et al. 1981. Biotransformation and intracellular binding of arsenic in tissues of rabbits after intraperitoneal administration of As-74 labelled arsenite. Toxicology 20:35-44.

Bertolero F, Pozzi G, Sabbioni E, et al. 1987. Cellular uptake and metabolic reduction of pentavalent to trivalent arsenic as determinants of cytotoxicity and morphological transformation. Carcinogenesis 8:803-808.

*Bettley FR, O'Shea JA. 1975. The absorption of arsenic and its relation to carcinoma. Br J Dermatol 92:563-568.

9REFERENCES

*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.

Bhattacharya P, Jacks G, Ahmed KM, et al. 2002. Arsenic in groundwater of the Bengal Delta Plain aquifers in Bangladesh. Bull Environ Contam Toxicol 69:538-545.

*Bhumbla DK, Keefer RF. 1994. Arsenic mobilization and bioavailability in soils. In: Nriagu JO, ed. Arsenic in the environment, part 1: Cycling and characterization. New York, NY: John Wiley & Sons, Inc., 51-82.

*Bickley LK, Papa CM. 1989. Chronic arsenicism with vitiligo, hyperthyroidism, and cancer. N J Med 86(5):377-380.

Biggs ML, Kalman DA, Moore LE, et al. 1997. Relationship of urinary arsenic to intake estimates and a biomarker of effect, bladder cell micronuclei. Mutat Res 386(3):185-195.

Binder S. 1988. The case for the NEDEL (no epidemiologically detectable exposure level). Am J Public Health 78:589-590.

*Binder S, Forney D, Kaye W, et al. 1987. Arsenic exposure in children living near a former copper smelter. Bull Environ Contam Toxicol 39:114-121.

Binder S, Sokal D, Maughan D. 1986. Estimating soil ingestion: The use of tracer elements in estimating the amount of soil ingested by young children. Arch Environ Health 41(6):341-345.

*Bird MJ, MacIntosh DL, Williams PL. 2004. Occupational exposures during routine activities in coal-fueled power plants. J Occup Environ Hyg 1:403-413.

Birmingham DJ, Key MM, Holaday DA, et al. 1965. An outbreak of arsenical dermatoses in a mining community. Arch Dermatol 91:457-464.

Bissen M, Frimmel FH. 2000. Speciation of As(III), As(V), MMA and DMA in contaminated soil extracts by HPLC-ICP/MS. Fresenius J Anal Chem 367:51-55.

*Biswas BK, Dhar RK, Samanta G, et al. 1998. Detailed study report of Samta, one of the arsenic-affected villages of Jessore District, Bangladesh. Curr Sci 74(2):134-145.

*Biswas S, Talukder G, Sharma A. 1999. Prevention of cytotoxic effects of arsenic by short-term dietary supplementation with selenium in mice in vivo. Mutat Res 441:155-160.

Blackwell RQ. 1961a. Estimated total arsenic ingested by residents in the endemic blackfoot area. J Formosan Med Assoc 60:1143-1144.

Blackwell RQ. 1961b. Speculations on the etiology of blackfoot disease. J Formosan Med Assoc 60:460-471.

*Blakley BR. 1987. Alterations in urethan-induced adenoma formation in mice exposed to selenium and arsenic. Drug Nutr Interact 5:97-102.

Blejer HP, Wagner W. 1976. Case study 4: Inorganic arsenic-ambient level approach to the control of occupational cancerigenic exposures. Ann N Y Acad Sci 271:179-186.

9REFERENCES

*Bloch P, Shapiro IM. 1986. An X-ray fluorescence technique to measure in situ the heavy metal burdens of persons exposed to these elements in the workplace. J Occup Med 28(8):609-614.

*Blom S, Lagerkvist B, Linderholm H. 1985. Arsenic exposure to smelter workers: Clinical and neurophysiological studies. Scand J Work Environ Health 11:265-269.

Blythe D, Joyce DA. 2001. Clearance of arsenic by heamodialysis after acute poisoning with arsenic trioxide. Intensive Care Med 27(1):334.

Bode AM, Dong Z. 2002. The paradox of arsenic: Molecular mechanisms of cell transformation and chemotherapeutic effects. Crit Rev Oncol Hematol 42(1):5-24.

*Bolla-Wilson K, Bleecker ML. 1987. Neuropsychological impairment following inorganic arsenic exposure. J Occup Med 29(6):500-503.

*Bollinger CT, van Zijl P, Louw JA. 1992. Multiple organ failure with the adult respiratory distress syndrome in homicidal arsenic poisoning. Respiration 59(1):57-61.

*Bonnevie NL, Huntley SL, Found BW, et al. 1994. Trace metal contamination in surficial sediments from Newark Bay, New Jersey. Sci Total Environ 144:1-16.

Bordajandi LR, Gomez G, Abad E, et al. 2004. Survey of persistent organochlorine contaminants (PCBs, PCDD/Fs, and PAHs), heavy metals (Cu, Cd, Zn, Pb, and Hg), and arsenic in food samples from Huelva (Spain): Levels and health implications. J Agric Food Chem 52(4):992-1001.

*Borgono JM, Greiber R. 1972. Epidemiological study of arsenicism in the city of Antofagasta. Trace Subst Environ Health 5:13-24.

*Borgoño JM, Venturino H, Vicent P. 1980. [Clinical and epidemiological study of arsenism in northern Chile.] Rev Med Chile 108:1039-1048. (Spanish).

Borgoño JM, Vicent P, Venturino H, et al. 1977. Arsenic in the drinking water of the city of Antofagasta: Epidemiological and clinical study before and after installation of a treatment plant. Environ Health Perspect 19:103-105.

Börzsönyi M, Bereczky A, Rudnai P, et al. 1992. Epidemiological studies on human subjects exposed to arsenic in drinking water in southeast Hungary [letter]. Arch Toxicol 66(1):77-78.

*Bourrain JL, Morin C, Béani JC, et al. 1998. Airborne contact dermatitis from cacodylic acid. Contact Dermatitis 38(6):364-365.

*Boutwell RK. 1963. A carcinogenicity evaluation of potassium arsenite and arsanilic acid. Agric Food Chem 11:381-385.

Bradley LJ, Magee BH, Allen SL. 1994. Background levels of polycyclic aromatic hydrocarbons (PAH) and selected metals in New England urban soils. J Soil Contam 3:349-361.

*Braman RS, Foreback CC. 1973. Methylated forms of arsenic in the environment. Science 182:1247-1249.

9REFERENCES

*Braman RS, Johnson DL, Foreback CC, et al. 1977. Separation and determination of nanogram amounts of inorganic arsenic and methylarsenic compounds. Anal Chem 49(4):621-625.

Braun W. 1958. Carcinoma of the skin and the internal organs caused by arsenic. German Med Monthly 3:321-324.

Braune B, Muir D, DeMarch B, et al. 1999. Spatial and temporal trends of contaminants in Canadian Arctic freshwater and terrestrial ecosystems: A review. Sci Total Environ 230:145-207.

Breckenridge RP, Crockett AB. 1995. Determination of background concentrations of inorganics in soil and sediments at hazardous waste sites. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA540S96500.

Brenard R, Laterre P-F, Reynaert M, et al. 1996. Increased hepatocytic mitotic activity as a diagnostic marker of acute arsenic intoxication: A report of two cases. J Hepato 25(2):218-220.

Bronstein AC, Currance PL. 1988. Emergency care for hazardous materials exposure. St. Louis, MO: The C.V. Mosby Company, 123-124.

Brook EJ, Moore JN. 1988. Particle-size and chemical control of As, Cd, Cu, Fe, Mn, Ni, Pb, and Zn in bed sediment from the Clark Fork River, Montana (USA). Sci Total Environ 76:247-266.

*Brooks WE. 2003. Arsenic. U.S. Geological Survey minerals yearbook. USGS, 7.1-7.4, tables 1-3. http://minerals.usgs.gov/minerals/pubs/commodity/arsenic/arsenmyb03.pdf. February 14, 2005.

*Brooks WE. 2005. Arsenic. U.S. Geological Survey, mineral commodity studies, 24-25. http://minerals.usgs.gov/minerals/pubs/commodity/arsenic/arsenmcs05.pdf. February 14, 2005.

*Broomhall J, Kovar IZ. 1986. Environmental pollutants in breast milk. Rev Environ Health 6(1-4):311-337.

*Brouwer OF, Onkenhout W, Edelbroek PM, et al. 1992. Increased neurotoxicity of arsenic in methylenetetrahydrofolate reductase deficiency. Clin Neurol Neurosurg 94(4):307-310.

Brown KG. 1998. Assessing the risk of inorganic arsenic in drinking water in the United States. Hum Ecol Risk Assess 4(5):1061-1070.

*Brown CC, Chu KC. 1982. Environmental epidemiology: Risk assessment: Proceedings of a conference. In: Prentice RL, Whittemore AS, eds. Philadelphia, PA: Society for Industrial and Applied Mathematics, 94-106.

*Brown CC, Chu KC. 1983a. A new method for the analysis of cohort studies: Implications of the multistage theory of carcinogenesis applied to occupational arsenic exposure. Environ Health Perspect 50:293-308.

*Brown CC, Chu KC. 1983b. Implications of the multistage theory of carcinogenesis applied to occupational arsenic exposure. J Natl Cancer Inst 70(3):455-463.

*Brown EJ, Button DK. 1979. A simple method of arsenic speciation. Bull Environ Contam Toxicol 21:37-42.

9REFERENCES

Brown JL, Kitchin KT. 1996. Arsenite, but not cadmium, induces ornithine decarboxylase and heme oxygenase activity in rat liver: Relevance to arsenic carcinogenesis. Cancer Lett 98:227-231.

Brown JL, Kitchin KT. 1998. Arsenic carcinogenesis: Dimethylarsinic acid causes rat pulmonary DNA damage. Toxicologist 42(1-S):322.

Brown KG, Ross GL. 2002. Arsenic, drinking water, and health: A position paper of the American Council on Science and Health. Regul Toxicol Pharmacol 36:162-174.

Brown KG, Boyle KE, Chen CW, et al. 1989. A dose-response analysis of skin cancer from inorganic arsenic in drinking water. Risk Anal 9:519-528.

*Brown KG, Guo H-R, Greene HL. 1997a. Uncertainty in cancer risk at low doses of inorganic arsenic. Hum Ecol Risk Assess 3(3):351-362.

*Brown KG, Guo H-R, Kuo T-L, et al. 1997b. Skin cancer and inorganic arsenic: Uncertainty-status of risk. Risk Anal 17(1):37-42.

*Brown JL, Kitchin KT, George M. 1997c. Dimethylarsinic acid treatment alters six different rat biochemical parameters: Relevance to arsenic carcinogenesis. Teratog Carcinog Mutagen 17:71-84.

*Brown LM, Pottern LM, Blot WJ. 1984. Lung cancer in relation to environmental pollutants emitted from industrial sources. Environ Res 34:250-261.

*Brown MM, Rhyne BC, Goyer RA, et al. 1976. Intracellular effects of chronic arsenic administration on renal proximal tubule cells. J Toxicol Environ Health 1:505-514.

*Brown RM, Newton D, Pickford CJ, et al. 1990. Human metabolism of arsenobetaine ingested with fish. Hum Exp Toxicol 9:41-46.

*Bruce BW, McMahon PB. 1996. Shallow ground-water quality beneath a major urban center: Denver, Colorado, USA. J Hydrol 186:129-151.

*Brumbaugh WG, Ingersoll CG, Kemble NE, et al. 1994. Chemical characterization of sediments and pore water from the upper Clark Fork River and Milltown Reservoir, Montana. Environ Toxicol Chem 13(12):1971-1983.

Brune O, Nordberg G, Wester PO. 1980. Distribution of 23 elements in kidney, liver and lung of a control group in Northern Sweden and of exposed workers from a smelter and refinery. Sci Total Environ 16:13-35.

Buat-Ménard P, Peterson PJ, Havas M, et al. 1987. Group report: Arsenic. In: Hutchinson TC, Meema KM, ed. Lead, mercury, cadmium, and arsenic in the environment. New York, NY: John Wiley & Sons Ltd., 43-48.

Buchancova J, Klimentova G, Knizkova M, et al. 1998. Health status of workers of a thermal power station exposed for prolonged periods to arsenic and other elements from fuel. Cent Eur J Public Health 6(1):29-36.

*Buchet JP, Lauwerys R. 1985. Study of inorganic arsenic methylation by rat liver in vitro: Relevance for the interpretation of observations in man. Arch Toxicol 57:125-129.

9REFERENCES

*Buchet JP, Lauwerys R. 1987. Study of factors influencing the *in vivo* methylation of inorganic arsenic in rats. Toxicol Appl Pharmacol 91:65-74.

*Buchet JP, Lauwerys R. 1988. Role of thiols in the *in vitro* methylation of inorganic arsenic by rat liver cytosol. Biochem Pharmacol 37(16):3149-3153.

*Buchet JP, Lison D. 1998. Mortality by cancer in groups of the Belgian population with a moderately increased intake of arsenic. Int Arch Occup Environ Health 71(2):125-130.

*Buchet JP, Lauwerys R, Mahieu P, et al. 1982. Inorganic arsenic metabolism in man. Arch Toxicol Suppl 5:326-327.

Buchet JP, Lauwerys R, Roels H. 1980. Comparison of several methods for the determination of arsenic compounds in water and in urine. Int Arch Occup Environ Health 46:11-29.

*Buchet JP, Lauwerys R, Roels H. 1981a. Comparison of the urinary excretion of arsenic metabolites after a single oral dose of sodium arsenite, monomethylarsonate or dimethylarsinate in man. Int Arch Occup Environ Health 48:71-79.

*Buchet JP, Lauwerys R, Roels H. 1981b. Urinary excretion of inorganic arsenic and its metabolites after repeated ingestion of sodium metaarsenite by volunteers. Int Arch Occup Environ Health 48:111-118.

Buchet JP, Lison D, Ruggeri M, et al. 1996b. Assessment of exposure to inorganic arsenic, a human carcinogen, due to the consumption of seafood. Arch Toxicol 70(11):773-778.

*Buchet JP, Pauwels J, Lauwerys R. 1994. Assessment of exposure to inorganic arsenic following ingestion of marine organisms by volunteers. Environ Res 66(1):44-51.

Buchet JP, Staessen J, Roels H, et al. 1996a. Geographical and temporal differences in the urinary excretion of inorganic arsenic: A Belgian population study. Occup Environ Med 53(5):320-327.

Buck WB. 1969. Untoward reactions encountered with medicated feeds. In: The use of drugs in animal feeds. Proceedings of a symposium. Washington, DC: National Academy of Sciences. NAS Publishing no. 1679, 196-217.

*Budavari S, O'Neil MJ, Smith A, et al., eds. 2001. The Merck index an encyclopedia of chemicals, drugs and biologicals. 13th ed. Whitehouse Station, NJ: Merck & Co., Inc., 440, 462.

*Bulbulyan MA, Jourenkova NJ, Boffetta P, et al. 1996. Mortality in a cohort of Russian fertilizer workers. Scand J Work Environ Health 22(1):27-33.

*Burgdorf W, Kurvink K, Cervenka J. 1977. Elevated sister chromatid exchange rate in lymphocytes of subjects treated with arsenic. Hum Genet 36:69-72.

Burger J, Gochfeld M. 1999. Heavy metals in Franklin's gull tissues: Age and tissue differences. Environ Toxicol Chem 18(4):673-678.

Burger J, Gochfeld M. 2000. Metals in laysan albatrosses from midway atoll. Arch Environ Contam Toxicol 38:254-259.

9REFERENCES

*Burger J, Dixon C, Shukla T, et al. 2003. Metals in horseshoe crabs from Delaware Bay. Arch Environ Contam Toxicol 44:36-42.

*Burger J, Gaines KF, Boring CS, et al. 2002. Metal levels in fish from the Savannah River: Potential hazards to fish and other receptors. Environ Res 89:85-97.

Burger J, Gochfeld M, Rooney AA, et al. 2000. Metals and metalloids in tissues of American alligators in three Florida lakes. Arch Environ Contam Toxicol 38:501-508.

Burger J, Woolfenden GE, Gochfeld M. 1999. Metal concentrations in the eggs of endangered Florida scrub-jays from central Florida. Arch Environ Contam Toxicol 37:385-388.

Burk D, Beaudoin AR. 1977. Arsenate-induced renal agenesis in rats. Teratology 16:247-260.

*Burkhard EG, Dutkiewicz VA, Husain L. 1994a. A study of SO_2, SO_4^2 and trace elements in clear air and clouds above the midwestern United States. Atmos Environ 28(8):1521-1533.

Burkhard EG, Dutkieewicz VA, Husain L. 1994b. Atmospheric wet deposition of trace elements to Chesapeake Bay: CBAD study year 1 results. Atmos Environ 28(8):1487-1498.

Burns LA. 1998. Arsenic. In: Immunotoxicology of environmental and occupational metals. Midland: Dow Corning Corporation, 1-26.

*Burns LA, Munson AE. 1993. Gallium arsenide selectively inhibits T cell proliferation and alters expression of CD25 (IL-2R/P55). J Pharmacol Exp Ther 265(1):178-186.

*Burns FJ, Uddin AN, Wu F, et al. 2004. Arsenic-induced enhancement of ultraviolet radiation carcinogenesis in mouse skin: A dose-response study. Environ Health Perspect 112(5):599-603.

Burton GA, Lazorchak JN, Waller WT, et al. 1987. Arsenic toxicity changes in the presence of sediment. Bull Environ Contam Toxicol 38:491-499.

*Butler ECV. 1988. Determination of inorganic arsenic species in aqueous samples by ion-exclusion chromatography with electrochemical detection. J Chromatogr 450:353-360.

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

Bye T, Romundstad PR, Rφnneberg A, et al. 1998. Health survey of former workers in a Norwegian coke plant: Part 2. Cancer incidence and cause specific mortality. Occup Environ Med 55:622-626.

*Byrd DM, Roegner ML, Griffiths JC, et al. 1996. Carcinogenic risks of inorganic arsenic in perspective. Int Arch Occup Environ Health 68(6):484-494.

*Byron WR, Bierbower GW, Brouwer JB, et al. 1967. Pathologic changes in rats and dogs from two-year feeding of sodium arsenite or sodium arsenate. Toxicol Appl Pharmacol 10:132-147.

Cabe PA, Carmichael NG, Tilson HA. 1979. Effects of selenium, alone and in combination with silver or arsenic, in rats. Neurobehav Toxicol 1:275-278.

9REFERENCES

Cabon JY, Cabon N. 2000. Speciation of major arsenic species in seawater by flow injection hydride generation atomic absorption spectrometry. Fresenius J Anal Chem 368:484-489.

*Caffery-Nolan RE, McCoy KL. 1998. Direct exposure to gallium arsenide upregulates costimulatory activity of murine macrophages. Toxicol Appl Pharmacol 151:330-339.

Calabrese EJ, Stanek EJ. 1995. Resolving intertracer inconsistencies in soil ingestion estimation. Environ Health Perspect 103:454-457.

Calabrese EJ, Kostecki PT, Gilbert CE. 1987. How much soil do children eat? An emerging consideration for environmental health risk assessment. Comments Toxicol 1:229-241.

*Calderon J, Navarro ME, Jimenez-Capdeville ME, et al. 2001. Exposure to arsenic and lead an neuropsychological development in Mexican children. Environ Res 85(Section A):69-76.

*Calderon RL, Abernathy CO, Thomas DJ. 2004. Consequences of acute and chronic exposure to arsenic in children.33(7):461-466.

*Calderon RL, Hudgens E, Le CX, et al. 1999. Excretion of arsenic in urine as a function of exposure to arsenic in drinking water. Environ Health Perspect 107:663-667.

Caldwell BK, Caldwell JC, Mitra SN, et al. 2003. Searching for an optimum solution to the Bangladesh arsenic crisis. Soc Sci Med 56(10):2089-2096.

Calesnick B, Wase A, Overby LR. 1966. Availability during human consumption of the arsenic in tissue of chicks fed arsanilic-74As acid. Toxicol Appl Pharmacol 9:27-30.

Calleja E, König A, Warrell R JR, et al. 1997. Arsenic trioxide induces apoptosis in K562 chronic myelogenous leukemia (CML) cells. Blood 90(10 Suppl. 1 Part 2):202b.

Cambell BG. 1999. Broadsheet number 48: Mercury, cadmium and arsenic: Toxicology and laboratory investigation. Pathology 31(1):17-22.

*Campbell JP, Alvarez JA. 1989. Acute arsenic intoxication. Am Fam Physician 40(6):93-97.

Cannon JR, Edmonds JS, Francesconi KA, et al. 1981. Isolation, crystal structure and synthesis of arsenobetaine, a constituent of the western rock lobster, the dusty shark, and some samples of human urine. Aust J Chem 34:787-798.

*Cannon JR, Saunders JB, Toia RF. 1983. Isolation and preliminary toxicological evaluation of arsenobetaine- the water-soluble arsenical constituent from the hepatopancreas of the western rock lobster. Sci Total Environ 31:181-185.

*Capar SG, Cunningham WC. 2000. Element and radionuclide concentrations in food: FDA Total Diet Study 1991-1996. J AOAC Int 83:157-177.

*Carapella SC. 1992. Arsenic and arsenic alloys. In: Kroschwitz JI, Howe-Grant M, eds. Kirk-Othmer encyclopedia of chemical technology. New York, NY: John Wiley and Sons, 3:624-633.

*Carbonell-Barrachina AA, Burló F, Valero D, et al. 1999. Arsenic toxicity and accumulation in turnip as affected by arsenic chemical speciation. J Agric Food Chem 47:2288-2294.

9REFERENCES

Carbonell-Barrachina AA, Jugsujinda A, Burlo F, et al. 2000. Arsenic chemistry in municipal sewage sludge as affected by redox potential and pH. Water Res 34:216-224.

*Carlson-Lynch H, Beck BD, Boardman PD. 1994. Arsenic risk assessment. Environ Health Perspect 102(4):354-356.

*Carpenter SJ. 1987. Developmental analysis of cephalic axial dysraphic disorders in arsenic-treated hamster embryos. Anat Embryol 176:345-365.

Carter DE, Aposhian HV, Gandolfi AJ. 2003. The metabolism of inorganic arsenic oxides, gallium arsenide, and arsine: A toxicochemical review. Toxicol Appl Pharmacol 193(3):309-334.

Castlehouse H, Smith C, Raab A, et al. 2003. Biotransformation and accumulation of arsenic in soil amended with seaweed. Environ Sci Technol 37(5):951-957.

*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.

Cazin JC, Cazin M, Gaborit JL, et al. 1987. A study of the effect of decimal and centesimal dilutions of arsenic on the retention and mobilization of arsenic in the rat. Hum Toxicol 6:315-320.

*Cebrián ME, Albores A, Aguilar M, et al. 1983. Chronic arsenic poisoning in the north of Mexico. Hum Toxicol 2:121-133.

Cebrian ME, Albores A, Connelly JC, et al. 1988. Assessment of arsenic effects on cytosolic heme status using tryptophan pyrrolase as an index. J Biochem Toxicol 3:77-86.

Centeno JA, Mullick FG, Finkelman RB, et al. 1999. The etiology of arsenicism in Huizhou Province. Mod Pathol 12(1):174A.

Centeno JA, Mullick FG, Martinez L, et al. 2002. Pathology related to chronic arsenic exposure. Environ Health Perspect Suppl 110:883-886.

*Chaineau E, Binet S, Pol D, et al. 1990. Embryotoxic effects of sodium arsenite and sodium arsenate on mouse embryos in culture. Teratology 41:105-112.

*Chakraborti D, Hussam A, Alauddin M. 2003b. Arsenic: Environmental health aspects with special reference to groundwater in South Asia. J Environ Sci Health Part A 38(1):xi-xv.

*Chakraborti D, Mukherjee SC, Pati S, et al. 2003c. Arsenic groundwater contamination in Middle Ganga Plain, Bihar, India: A future danger? Environ Health Perspect 111:1194-1201.

*Chakraborti D, Mukherjee SC, Saha KC, et al. 2003a. Arsenic toxicity from homeopathic treatment. J Toxicol Clin Toxicol 41(7):963-967.

Chakraborti D, Rahman MM, Paul K, et al. 2002. Arsenic calamity in the Indian subcontinent: What lessons have been learned? Talanta 58:3-22.

*Chakraborti D, Sengupta MK, Rahman MM, et al. 2004. Groundwater arsenic contamination and its health effects in the Ganga-Meghna-Bramaputra plain. J Environ Monit 6(6):74N-83N.

9REFERENCES

*Chakraborty AK, Saha KC. 1987. Arsenical dermatosis from tubewell water in west Bengal. Indian J Med Res 85:326-334.

*Chan PC, Huff J. 1997. Arsenic carcinogenesis in animals and in humans: Mechanistic, experimental, and epidemiological evidence. J Environ Health Sci, C15(2):83-122.

*Chan TYK. 1994. The prevalence use and harmful potential of some Chinese herbal medicines in babies and children. Vet Hum Toxicol 36(3):238-240.

Chang MJW. 1987. Toxic effects of arsenic compounds on culture human fibroblasts. In Vitro Toxicology 1:103-110.

*Chang CC, Ho SC, Tsai SS, et al. 2004. Ischemic heart disease mortality reduction in an arseniasis-endemic area in southwestern Taiwan after a switch in the tap-water supply system. J Toxicol Environ Health A 67(17):1353-1361.

Chang H-R, Yu H-S, Chai C-Y, et al. 1998. Arsenic induces decreased expression of β2-adrenergic receptors in cultured keratinocytes. Arch Dermatol Res 290:402-404.

*Chao CC-K. 1996. Inhibition by arsenite of anticancer drug *cis*-diamminedichloroplatinum(II) induced DNA repair and drug resistance in HeLa cells. Environ Toxicol Pharmacol 1(3):199-205.

*Chappell WR, Beck BD, Brown KG, et al. 1997. Inorganic arsenic: A need and an opportunity to improve risk assessment. Environ Health Perspect 105(10):1060-1067.

Charbonneau SM, Hollins JG, Tam GKH, et al. 1980. Whole body retention, excretion and metabolism of As-75 arsenic acid in the hamster. Toxicol Lett 5:175-182.

*Charbonneau SM, Spencer K, Bryce F, et al. 1978a. Arsenic excretion by monkeys dosed with arsenic-containing fish or with inorganic arsenic. Bull Environ Contam Toxicol 20:470-477.

Charbonneau SM, Tam GKH, Bryce F, et al. 1978b. Pharmacokinetics and metabolism of inorganic arsenic in the dog. Trace Subst Environ Health 12:276-283.

Chattopadhyay S, Bhaumik S, Nag Chaudhury A, et al. 2002a. Arsenic induced changes in growth development and apoptosis in neonatal and adult brain cells in vivo and in tissue culture. Toxicol Lett 128:73-84.

Chattopadhyay S, Bhaumik S, Purkayastha M, et al. 2002b. Apoptosis and necrosis in developing brain cells due to arsenic toxicity and protection with antioxidants. Toxicol Lett 136(1):65-76.

*Chattopadhyay S, Ghosh S, Debnath J, et al. 2001. Protection of sodium arsenite-induced ovarian toxicity by coadministration of L-ascorbate (vitamin C) in mature wistar strain rat. Arch Environ Contam Toxicol 41(1):83-89.

Chattopadhyay S, Misro M, Ghosh S, et al. 2000. Supplementary effect of alpha-tocopherol succinate (vitamin E) on sodium arsenite-induced ovarian steroidogenic function and plasma levels of goonadotrophins in mature albino rats. Toxic Subst Mech 19(3):137-150.

9REFERENCES

Chattopadhyay S, Pal Ghosh S, Ghosh D, et al. 2003. Effect of dietary co-administration of sodium selenite on sodium arsenite-induced ovarian and uterine disorders in mature albino rats. Toxicol Sci 75(2):412-422.

Chen CJ, Chiou HY. 2001. Chen and Chiou respond to "Arsenic and cancer of the urinary tract" by Cantor. Am J Epidemiol 153(5):422-423.

Chen CY, Folt CL. 2000. Bioaccumulation and diminution of arsenic and lead in a freshwater food web. Environ Sci Technol 34:3878-3884.

*Chen C-J, Wang C-J. 1990. Ecological correlation between arsenic level in well water and age-adjusted mortality from malignant neoplasms. Cancer Res 50:5470-5474.

Chen CL, Whanger PD. 1994. Interaction of selenium and arsenic with metallothionein: Effect of vitamin B_{12}. J Inorg Biochem 54(4):267-276.

Chen W, Chen J. 2002. Nested case-control study of lung cancer in four Chinese tin mines. Occup Environ Med 59(2):113-118.

Chen Y, Ahsan H. 2002. Lifetime excess risk of internal cancers due to arsenic exposure among Bangladesh population. Am J Epidemiol 155(11 Suppl):S19.

Chen Y, Ahsan H. 2004. Cancer burden from arsenic in drinking water in Bangladesh. Am J Public Health 94(5):741-744.

*Chen C-J, Chen CW, Wu M-M, et al. 1992. Cancer potential in liver, lung, bladder and kidney due to ingested inorganic arsenic in drinking water. Br J Cancer 66(5):888-892.

*Chen C-J, Chiou H-Y, Chiang M-H, et al. 1996. Dose-response relationship between ischemic heart disease mortality and long-term arsenic exposure. Arterioscler Thromb Vasc Biol 16(4):504-510.

*Chen C-J, Chuang Y-C, Lin T-M, et al. 1985. Malignant neoplasms among residents of a blackfoot disease-endemic area in Taiwan: High-arsenic artesian well water and cancers. Cancer Res 45:5895-5899.

*Chen C-J, Chuang Y-C, You SL, et al. 1986. A retrospective study on malignant neoplasms of bladder, lung and liver in blackfoot disease endemic area in Taiwan. Br J Cancer 53:399-405.

Chen C-J, Hsueh Y-M, Lai M-S, et al. 1995. Increased prevalence of hypertension and long-term arsenic exposure. Hypertension 25(1):53-60.

*Chen C-J, Kuo T-L, Wu M-M. 1988a. Arsenic and cancers [Letter]. Lancet (February 20):414-415.

*Chen C-J, Wu M-M, Lee S-S, et al. 1988b. Atherogenicity and carcinogenicity of high-arsenic artesian well water: Multiple risk factors and related malignant neoplasms of blackfoot disease. Arteriosclerosis 8:452-460.

Chen G-Q, Shi X-G, Tang W, et al. 1997b. Use of arsenic trioxide As_2O_3 in the treatment of acute promyelocytic leukemia (APL): I. As_2O_3 exerts dose-dependent dual effects on APL cells. Blood 89(9):3345-3353.

9REFERENCES

Chen KS, Huang CC, Liaw CC, et al. 1988c. [Multiple primary cancers in blackfoot endemic area: Report of a case.] J Formosan Med Assoc 87:1125-1128. (Chinese)

*Chen M, Ma LQ, Harris WG. 1999a. Baseline concentrations of 15 trace elements in Florida surface soils. J Environ Qual 28:1173-81.

Chen T, Na Y, Wanibuchi H, et al. 1999b. Loss of heterozygosity in (Lewis XF344)F1 rat urinary bladder tumors induced with N-butyl-N-(4-hydroxybutyl)nitrosamine followed by dimethylarsinic acid or sodium L-ascorbate. Jpn J Cancer Res 90:818-823.

Chen Y, Ahsan H, Parvez F, et al. 2004. Validity of a food-frequency questionnaire for a large prospective cohort study in Bangladesh. Br J Nutr 92(5):851-859.

Chen YC, Amarasiriwardena CJ, Hsueh YM, et al. 2002. Stability of arsenic species and insoluble arsenic in human urine. Cancer Epidemiol Biomarkers Prev 11(11):1427-1433.

*Chen YC, Guo YL, Su HJ, et al. 2003a. Arsenic methylation and skin cancer risk in southwestern Taiwan. J Occup Environ Med 45(3):241-248.

*Chen YC, Su HJJ, Guo YLL, et al. 2003b. Arsenic methylation and bladder cancer risk in Taiwan. Cancer Causes Control 14:303-310.

*Chen Z, Chen GQ, Zhu J, et al. 1997a. Use of arsenic compounds in the treatment of acute promyelocytic leukemia (APL). Anticancer Research 17(5c):3937.

*Chhuttani PN, Chawla LS, Sharma TD. 1967. Arsenical neuropathy. Neurology 17:269-274.

*Ch'i I-C, Blackwell RQ. 1968. A controlled retrospective study of blackfoot disease, an endemic peripheral gangrene disease in Taiwan. Am J Epidemiol 88(1):7-24.

*Chiang CE, Luk HN, Wang TM, et al. 2002. Prolongation of cardiac repolarization by arsenic trioxide. Blood 100(6):2249-2252.

*Chiang H-S, Hong C-L, Guo H-R, et al. 1988. Comparative study on the high prevalence of bladder cancer in the blackfoot disease endemic area in Taiwan. J Formosan Med Assoc 87(11):1074-1080.

*Chiba M, Masironi R. 1992. Toxic and trace elements in tobacco and tobacco smoke. Bull WHO 70(2):269-275.

*Chicago Flameproof. 2000. Pressure-treated Supatimber. Montgomery, IL: Chicago Flameproof. http://www.chicagoflameproof.com/supratimber.html. July 29, 2005.

*Chilvers DC, Peterson PJ. 1987. Global cycling of arsenic. In: Hutchinson TC, Meema KM, eds. Lead, mercury, cadmium and arsenic in the environment. New York, NY: John Wiley & Sons, 279-301.

Chiou HY, Chien YH, Chen-Wu C, et al. 1999. A study on the association between sister chromatid exchange and arsenic exposure among residents of Lanyang Basin. Proc Am Assoc Cancer Res 40:613.

*Chiou HY, Chiou ST, Hsu YH, et al. 2001. Incidence of transitional cell carcinoma and arsenic in drinking water: A follow-up study of 8,102 residents in an arseniasis-endemic area in northeastern Taiwan. Am J Epidemiol 153(5):411-418.

9REFERENCES

*Chiou H-Y, Hsueh Y-M, Liaw K-F, et al. 1995. Incidence of internal cancers and ingested inorganic arsenic: A seven-year follow-up study in Taiwan. Cancer Res 55(6):1296-1300.

*Chiou H-Y, Huang W-I, Su C-L, et al. 1997. Dose-response relationship between prevalence of cerebrovascular disease and ingested inorganic arsenic. Stroke 28(9):1717-1723.

*Chirenje T, Ma LQ, Clark C, et al. 2003a. Cu, Cr and As distribution in soils adjacent to pressure-treated decks, fences and poles. Environ Pollut 124(3):407-417.

*Chirenje T, Ma LQ, Szulczewski M, et al. 2003b. Arsenic distribution in Florida urban soils: Comparison between Gainsville and Miami. J Environ Qual 32:109-119.

Chiu HF, Ho SC, Wang LY, et al. 2004. Does arsenic exposure increase the risk for liver cancer? J Toxicol Environ Health A 67(19):1491-1500.

Chou IN. 1989. Distinct cytoskeletal injuries induced by As, Cd, Co, Cr, and Ni compounds. Biomed Environ Sci 2:358-365.

*Choucair AK, Ajax ET. 1988. Hair and nails in arsenical neuropathy. Ann Neurol 23(6):628-629.

Chouchane S, Snow ET. 2001. In vitro effect of arsenical compounds on gluthathione-related enzymes. Chem Res Toxicol 14(5):517-522.

*Chow N-H, Guo YL, Lin JS-N, et al. 1997. Clinicopathological features of bladder cancer associated with chronic exposure to arsenic. Br J Cancer 75(11):1708-1710.

*Chowdhury UK, Biswas BK, Chowdhury TR, et al. 2000. Groundwater arsenic contamination in Bangladesh and West Bengel, India. Environ Health Perspect 108(5):393-397.

Christen K. 2001. Chickens, manure, and arsenic. Environ Sci Technol 35(9):184A-185A.

Chu W, Chan KH. 2000. The predication of partitioning coefficients for chemicals causing environmental concern. Sci Total Environ 248:1-10.

*Chung JS, Kalman DA, Moore LE, et al. 2002. Family correlations of arsenic methylation patterns in children and parents exposed to high concentrations of arsenic in drinking water. Environ Health Perspect 110(7):729-733.

*Cikrt M, Mravcová A, Malátová I, et al. 1988. Distribution and excretion of ^{74}As and ^{75}Se in rats after their simultaneous administration: The effect of arsenic, selenium and combined pretreatment. J Hyg Epidemiol Microbiol Immunol 32(1):17-29.

Cikrt MV, Bencko V, Tich M, et al. 1980. Biliary excretion of 74As and its distribution in the golden hamster after administration of 74As (III) and 74As (V). J Hyg Epidemiol Microbiol 24:384-388.

*Civantos DP, Rodríguez AL, Aguado-Borruey JM, et al. 1995. Fuminant malignant arrhythmia and multiorgan failure in acute arsenic poisoning. Chest 108(6):1774-1775.

Clark DR, Bickham JW, Baker DL, et al. 2000. Environmental contaminants in Texas, USA, wetland reptiles: Evaluation using blood samples. Environ Toxicol Chem 19(9):2259-2265.

Clayton CA, Pellizzari ED, Quackenboss JJ. 2002. National Human Exposure Assessment Survey: Analysis of exposure pathways and routes for arsenic and lead in EPA Region 5. J Expo Anal Environ Epidemiol 12:29-43.

Clayton CA, Pellizzari ED, Whitmore RW, et al. 1999. National Human Exposure Assessment Survey (NHEXAS): Distributions and associations of lead, arsenic and volatile organic compounds in EPA Region 5. J Expo Anal Environ Epidemiol 9:381-392.

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

Clewell H, Crump K, Covington T, et al. 2003. A risk assessment for inhaled arsenic based on urinary arsenic concentration using a pharmacokinetic model. Toxicol Sci 72(S-1):139.

Clewell HJ, Gentry PR, Barton HA, et al. 1999. Requirements for a biologically realistic cancer risk assessment for inorganic arsenic. Int J Toxicol 18(2):131-147.

Clowes LA, Francesconi KA. 2004. Uptake and elimination of arsenobetaine by the mussel *Mytilus edulis* is related to salinity. Comp Biochem Physiol C 137:35-42.

*Clyne N, Ericsson F, Lins L-E, et al. 1989. Plasma trace elements in pre-dialytic uremic patients determined by energy dispersive X-ray fluorescence. Trace Elem Med 6(1):37-40.

Coddington K. 1986. A review of arsenicals in biology. Toxicol Environ Chem 11:281-290.

Cohen JT, Beck BD, Bowers TS, et al. 1998. An arsenic exposure model: Probabilistic validation using empirical data. Hum Ecol Risk Assess 4(2):341-377.

Cohen SM, Arnold LL, Uzvolgyi E, et al. 2002. Possible role of dimethylarsinous acid in dimethylarsinic acid-induced urothelial toxicity and regeneration in the rat. Chem Res Toxicol 15(9):1150-1157.

*Cohen SM, Yamamoto S, Cano M, et al. 2001. Urothelial cytotoxicity and regeneration induced by dimethylarsinic acid in rats. Toxicol Sci 59(1):68-74.

*Çöl M, Çöl C, Soran A, et al. 1999. Arsenic-related Bowen's disease, Palmer keratosis, and skin cancer. Environ Health Perspect 107(8):687-689.

*Colborn T, Clement C. 1992. Chemically induced alterations in sexual and functional development. The Wildlife/Human Connection. In: Advances in modern environmental toxicology. Volume XXI. Princeton, NJ: Princeton Scientific Publishing Co.

*Colborn T, vom Saal F, Soto A. 1993. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ Health Perspect 101(5):378-384.

Cole HN. 1916. A study of sodium cacodylate in the treatment of syphilis. JAMA 67:2012-2013.

*Cole RH, Frederick RE, Healy RP, et al. 1984. Preliminary findings of the priority pollutant monitoring project of the nationwide urban runoff program. J Water Pollut Control Fed 56:898-908.

9REFERENCES

*Coles DG, Ragaini RC, Ondov JM, et al. 1979. Chemical studies of stack fly ash from a coal-fired power plant. Environ Sci Tech 13(4):455-459.

Collechi P, Esposito M, Brera S, et al. 1986. The distribution of arsenic and cobalt in patients with laryngeal carcinoma. J Appl Toxicol 6:287-289.

Colt JS, Baris D, Clark SF, et al. 2002. Sampling private wells at past homes to estimate arsenic exposure: A methodologic study in New England. J Expo Anal Environ Epidemiol 12(5):329-334.

*Comber SDW, Howard AG. 1989. Arsenic speciation by hydride generation atomic absorption spectrometry and its application to the study of biological cycling in the coastal environment. Anal Proc 26:20-22.

*Concha G, Nermell B, Vahter M. 1998a. Metabolism of inorganic arsenic in children with chronic high arsenic exposure in northern Argentina. Environ Health Perspect 106(6):355.

*Concha G, Vogler G, Lezcano D, et al. 1999. Exposure to inorganic arsenic metabolites during early human development. Toxicol Sci 44:185-190.

*Concha G, Vogler G, Nermell B, et al. 1998b. Low-level arsenic excretion in breast milk of native Andean women exposed to high levels of arsenic in the drinking water. Int Arch Occup Environ Health 71(1):42-46.

*Concha G, Vogler G, Nermell B, et al. 2002. Intra-individual variation in the metabolism of inorganic arsenic. Int Arch Occup Environ Health 75:576-580.

Consigli JE, Maldonado SM, Morsino R, et al. 1997. [Regionally endemic chronic hydroarsenicism: Clinical cutaneous.] Rev Argent Dermatol 78(4):230-235. (Spanish)

*Cooper CM, Gillespie WB. 2001. Arsenic and mercury concentrations in major landscape components of an intensively cultivated watershed. Environ Pollut 111:67-74.

Cooper H, Paden WR, Hall EE, et al. 1932. Soils differ markedly in their response to addictions of calcium arsenate. South Carolina Agric Exp Stat Ann Rep 45:23-27.

*Cordier S, Thériault G, Iturra H. 1983. Mortality patterns in a population living near a copper smelter. Environ Res 31:311-322.

*Costa M. 1995. Model for the epigenetic mechanism of action of nongenotoxic carcinogens. Am J Clin Nutr 61(Suppl 3):666S-669S.

Costa M, Heck JD. 1986. Metal ion carcinogenesis: Mechanistic aspects. In: Sigel H, ed. Metal ions in biological systems. Vol. 20. Concepts on metal ion toxicity. New York, NY: Marcel Dekker, 259-278.

*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.

Cotton FA, Wilkinson G. 1972. Advanced inorganic chemistry: A comprehensive text. New York, NY: Interscience Publishers, 382-383.

9REFERENCES

Coupe RH, Thurman EM, Zimmerman LR. 1998. Relation of usage to the occurrence of cotton and rice herbicides in three streams of the Mississippi delta. Environ Sci Technol 32:3673-3680.

*Crecelius EA. 1977. Changes in the chemical speciation of arsenic following ingestion by man. Environ Health Perspect 19:147-150.

*Crecelius EA. 1978. Modification of the arsenic speciation technique using hydride generation. Anal Chem 50(6):826-827.

Creekmore TE, Whittaker DG, Roy RR, et al. 1999. Health status and relative exposure of mule deer and white-tailed deer to soil contaminants at the rocky mountain arsenal. Environ Toxicol Chem 18(2):272-278.

Crema A. 1955. Distribution et elimination de l'arsenic 76 chez la souris normale et cancereuse. Arch Int Pharmacodyn 103:57-70.

*CRIS. 2005. Current Research Information Systems Database. March 31, 2005.

Cristau B, Chabas ME, Placidi M. 1975. [Is p-arsanilic acid biotransformed in the rat and guinea pig?] Ann Pharm Fr 33(1):37-41. (French)

*Csanaky I, Gregus Z. 2002. Species variations in the biliary and urinary excretion of arsenate, arsenite and their metabolites. Comp Biochem Physiol C 131(3):355-365.

*Cullen WR. 1998. Arsenic in the environment. In: Bunnett JF, Mikolajczyk M, eds. Arsenic and old mustard: Chemical problems in the destruction of old arsenical and 'mustard' munitions. Netherlands: Kluwer Academic Publishers, 123-134.

*Cullen NM, Wolf LR, St Clair D. 1995. Pediatric arsenic ingestion. Am J Emerg Med 13(4):432-435.

Cuppit LT. 1980. Fate of toxic and hazardous materials in the air environment. Research Triangle Park, NC: U.S. Environmental Sciences Research Lab. PB80221948.

*Curatola CJ, Grunder FI, Moffitt AE. 1978. Hydride generation atomic absorption spectrophotometry for determination of arsenic in hair. Am Ind Hyg Assoc Journal 39:933-938.

Curnow A, Kendall F, Gould DJ, et al. 2000. Arsenic inhibits single strand DNA repair in cultured human cells. Br J Dermatol 142(3):614.

Custer TW, Custer CM, Larson S, et al. 2002. Arsenic concentrations in house wrens from Whitewood Creek, South Dakota, USA. Bull Environ Contam Toxicol 68:517-524.

Cuzick J, Evans S, Gillman M, et al. 1982. Medicinal arsenic and internal malignancies. Br J Cancer 45:904-911.

*Cuzick J, Sasieni P, Evans S. 1992. Ingested arsenic, keratoses, and bladder cancer. Am J Epidemiol 136(4):417-421.

Czarnecki GL, Baker DH. 1984. Feed additive interactions in the chicken: Reduction of tissue copper deposition by dietary roxarsone in healthy and in Eimeria acervalina-infected or Eimeria teneela-infected chicks. Poult Sci 63:1412-1418.

9REFERENCES

Czarnecki GL, Baker DH, Garst JE. 1984a. Arsenic-sulfur amino acid interactions in the chick. J Anim Sci 59:1573-1581.

Czarnecki GL, Edmonds MS, Izquierdo OA, et al. 1984b. Effect of 3-nitro-4-hydroxylphenylarsonic acid on copper utilization by the pig, rat and chick. J Anim Sci 59:997-1002.

Da D, Chatterjee A, Mandal BK, et al. 2005. Arsenic in ground water in six districts of West Bengal, India: The biggest arsenic calamity in the world. Part 2. Arsenic concentration in drinking water, hair, nails, urine, skin-scale and liver tissue (biopsy) of the affected people. Analyst 120:917-924.

*Dabeka RW, Lacroix GMA. 1987. Total arsenic in foods after sequential wet digestion, dry ashing, coprecipitation with ammonium pyrrolidine dithiocarbamate, and graphite-furnace atomic absorption spectrometry. J Assoc Off Anal Chem 70(5):866-870.

Dabeka RW, Conacher HBS, Salminen J, et al. 1992. Survey of bottled drinking water sold in Canada. Part 1. Lead, cadmium, arsenic, aluminum, and fluoride. J AOAC Int 75(6):949-953.

*Dabeka RW, McKenzie AD, Lacroix GM, et al. 1993. Survey of arsenic in total diet food composites and estimation of the dietary intake of arsenic by Canadian adults and children. J AOAC Int 76(1):14-25.

Dai J, Hellinger N, Waxman S. 1997. Induction of apoptosis by the combined activity of arsenic trioxide (As_2O_3) and ascorbic acid (AA) in t(14;18) B-cell lymphoma. Blood 90(10 Suppl 1 Part1):325a.

*Dai J, Weinberg RS, Waxman S, et al. 1999. Malignant cells can be sensitized to undergo inhibition and apoptosis by arsenic trioxide through modulation of the glutathione redox system. Blood 93(1):268-277.

*Dallaire L, Béliveau R. 1992. Phosphate transport by capillaries of the blood-brain barrier. J Bio Chem 267(31):22323-22327.

*Danaee H, Nelson HH, Liber H, et al. 2004. Low dose exposure to sodium arsenite synergistically interacts with UV radiation to induce mutations and alter DNA repair in human cells. Mutagenesis 19(2):143-148.

*Danan M, Dally S, Conso F. 1984. Arsenic-induced encephalopathy. Neurology 34:1524.

Dang TMN, Tran QT, Vu KV. 1999. Determination of arsenic in urine by atomic absorption spectrophotometry for biological monitoring of occupational exposure to arsenic. Toxicol Lett 108:179-183.

*Darland JE, Inskeep WP. 1997. Effects of pH and phosphate competition on the transport of arsenate. J Environ Qual 26(4):1133-1139.

DART. 1990. Developmental and Reproductive Teratology. National Library of Medicine, Bethesda, MD.

*Das T, Roychoudhury A, Sharma A, et al. 1993. Modification of clastogenicity of three known clastogens by garlic extract in mice in vivo. Environ Mol Mutagen 21(4):383-388.

9REFERENCES

Das T, Roychoudhury A, Sharma A. 1997. Bio-anticlastogenic effects of mustard oil and garlic in the first-generation offsprings of sodium arsenite treated mice. Mutat Res 379(1 Suppl. 1):S89.

Datta DV. 1976. Arsenic and non-cirrhotic portal hypertension. Lancet 1:433.

*Datta S, Talukder G, Sharma A. 1986. Cytotoxic effects of arsenic in dietary oil primed rats. Sci Cult 52(6):196-198.

*Davidson CI, Goold WD, Mathison TP, et al. 1985. Airborne trace elements in Great Smoky Mountains, Olympic, and Glacier National Parks. Environ Sci Technol 19:27-35.

*Davis A, Ruby MV, Bergstrom PD. 1992. Bioavailability of arsenic and lead in soils from the Butte, Montana, mining district. Environ Sci Technol 26(3):461-468.

*Davis A, Ruby MV, Bloom M, et al. 1996. Mineralogic constraints on the bioavailability of arsenic in smelter-impacted soils. Environ Sci Technol 30(2):392-399.

*Davison K, Cote S, Mader S, et al. 2003. Glutathione depletion overcomes resistance to arsenic trioxide in arsenic-resistant cell lines. Leukemia 17(5):931-940.

Davison K, Mann KK, Miller WH Jr. 2002. Arsenic trioxide: Mechanisms of action. Semin Hematol 39:3-7.

Day JA, Montes-Bayon M, Vonderheide AP, et al. 2002. A study of method robustness for arsenic speciation in drinking water samples by anion exchange HPLC-ICP-MS. Anal Bioanal Chem 373(7):664-668.

De Gieter M, Leermakers M, Ryssen RV, et al. 2002. Total and toxic arsenic levels in North Sea fish. Arch Environ Contam Toxicol 43:406-417.

*Deknudt G, Léonard A, Arany J, et al. 1986. *In vivo* studies in male mice on the mutagenic effects of inorganic arsenic. Mutagenesis 1(1):33-34.

*de la Rosa ME, Magnusson J, Ramel C, et al. 1994. Modulating influence of inorganic arsenic on the recombinogenic and mutagenic action of ionizing radiation and alkylating agents in *Drosophila melanogaster*. Mutat Res 318(1):65-71.

Del Razo LM, Aguilar C, Sierra-Santoyo A, et al. 1999. Interference in the quantitation of methylated arsenic species in human urine. J Anal Toxicol 23(2):103-107.

Del Razo LM, García-Vargas GG, Albores A, et al. 1998. Impact of arsenic metabolism on human populations: Metabolism of arsenic and sensitivity to carcinogenesis in humans. Toxicologist 42(1-S):353-354.

Demirozu-Erdinc B, Saldamli I. 2001. Variation of heavy metal contents in frozen vegetable products. Bull Environ Contam Toxicol 67:416-422.

*de Peyster A, Silvers JA. 1995. Arsenic levels in hair of workers in a semiconductor fabrication facility. Am Ind Hyg Assoc J 56(4):377-383.

DeSesso JM. 2001. Teratogen update: Inorganic arsenic. Teratology 64(3):170-173.

9REFERENCES

DeSesso JM, Jacobsen CF, Scialli AR, et al. 1998a. Inorganic arsenic is not likely to be a developmental toxicant at environmental relevant exposures. Teratology 57(4-5):216.

DeSesso JM, Jacobson CF, Scailli AR, et al. 1998b. An assessment of the developmental toxicity of inorganic arsenic. Reprod Toxicol 12(4):385-433.

Deverel SJ, Millard SP. 1988. Distribution and mobility of selenium and other trace elements in shallow groundwater of the western San Joaquin valley, California. Environ Sci Technol 22:697-702.

Devesa V, Martinez A, Suner MA, et al. 2001. Kinetic study of transformations of arsenic species during heat treatment. J Agric Food Chem 49(5):2267-2271.

De Zeeuw RA, Franke JP, Stamm D. 1986. Interlaboratory survey of the quality of urinary arsenic and thallium assays in the European Community. J Clin Chem Clin Biochem 25:351-355.

Dhar P, Mohari N, Mehra RD. 2004. Arsenic administration during rapid brain growth period affects the morphogenesis in rat cerebellum. J Neurochem 88(1):68.

*DHHS. 1995. Report to Congress on workers' home contamination study conducted under the workers' family protection act (29 U.S.C. 671a). Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. September 1995. Pub no. 95-123. PB96192000.

*Díaz-Barriga F, Batres L, Calderón J, et al. 1997. The El Paso smelter 20 years later: Residual impact on Mexican children. Environ Res 74(1):11-16.

Dickinson JO. 1975. Toxicity of cacodylic acid silvicide in cattle. West Vet 3:1-4.

*Dieke SH, Richter CP. 1946. Comparative assays of rodenticides on wild Norway rats. Public Health Rep 61:672-679.

Di Noto R, Boccuni P, LoParodo C, et al. 1997. *In vitro* treatment of APL cells with arsenic trioxide (As_2O_3) results in a highly specific induction of solitary CD66c display. Blood 90(10 Suppl 1 Part 1):326a.

*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.

Diwan A, Ward JM, Waalkes MP. 2002. Multiorgan transplacental carcinogenesis by arsenic in mice. Proc Am Assoc Cancer Res 43:1032.

Diwan BA, Anver M, Waalkes MP. 2000. Induction of hyperplastic lesions of uterus, testes, and liver in mice given repeated injections of arsenic. Proc Am Assoc Cancer Res 41:506.

*Dix K, Cappon CJ, Toribara TY. 1987. Arsenic speciation by capillary gas-liquid chromatography. J Chromatogr Sci 25:164-169.

Dobson RL, Young MR, Pinto JS. 1965. Palmar keratoses and cancer. Arch Dermatol 92:553-556.

9REFERENCES

*Dolan SP, Nortrup DA, Bolger PM, et al. 2003. Analysis of dietary supplements for arsenic, cadmium, mercury, and lead using inductively coupled plasma mass spectrometry. J Agric Food Chem 51(5):1307-1312.

Domingo JL, Bosque MA, Piera V. 1991. *meso*-2,3-Dimercaptosuccinic acid and prevention of arsenite embryotoxicity and teratogenicity in the mouse. Fundam Appl Toxicol 17:314-320.

Donaldson EM. 1988. Determination of arsenic in ores, concentrates and related materials by graphite-furnace atomic-absorption spectrometry after separation by xanthate extraction. Talanta 35:47-54.

*Dong Z. 2002. The molecular mechanisms of arsenic-induced cell transformation and apoptosis. Environ Health Perspect Suppl 110:757-759.

*Dong JT, Luo XM. 1993. Arsenic-induced DNA-strand breaks associated with DNA-protein crosslinks in human fetal lung fibroblasts. Mutat Res 302(2):97-102.

*Dong JT, Luo XM. 1994. Effects of arsenic on DNA damage and repair in human fetal lung fibroblasts. Mutat Res 315(1):11-15.

Donofrio PD, Wilbourn AJ. 1985. Subacute arsenic toxicity presenting on clinical and electromyographic examination as Guillain-Barre syndrome. Ann Neurol 18:156-157.

Donofrio PD, Wilbourn AJ, Albers JW, et al. 1987. Acute arsenic intoxication presenting as Guillain-Barré-like syndrome. Muscle Nerve 10:114-120.

Donoghue DJ, Hairston H, Bartholomew MJ, et al. 1993. Arsenic residues in chicken eggs from laying hens administered feed containing arsanilic acid and roxarsone. Residues of veterinary drugs in food: Proceedings of the Euroresidue II conference, Veldhoven, Netherlands, May 3-5, 1993. Beltsville, MD: Food and Drug Administration, 276-279.

*DPR. 2005. USEPA/OPP Pesticide related database queries. Chemical ingredient database. http://www.cdpr.ca.gov/docs/epa/epamenu.htm. February 25, 2005.

*Driesback RH, ed. 1980. Arsenic and arsine. In: Handbook of poisoning: Prevention, diagnosis and treatment. 11th ed. Los Altos, CA: Lange Medical Publications:241-245.

Dubey NP, Maheshwari HS, Jain SK. 2003. Studies of As2O3 poisoning on protein, RNA and glycogen contents of albino rats. Forensic Sci Int 136(Suppl 1):328.

Ducoff HS, Neal WB, Straube RL, et al. 1948. Biological studies with arsenic 76: II. Excretion and tissue localization. Proc Soc Exp Biol Med 69:548-554.

Dudka S, Miller WP. 1999. Accumulation of potentially toxic elements in plants and their transfer to human food chain. J Environ Sci Health B B34:681-708.

*Dueñas C, Pérez-Alvarez JC, Busteros JI, et al. 1998. Idiopatic portal hypertension and angiosarcoma associated with arsenical salts therapy. J Clin Gastroenterol 26(4):303-305.

Dulout FN, Grillo CA, Seoane AI, et al. 1996. Chromosomal aberrations in peripheral blood lymphocytes from native Andean women and children from northwestern Argentina exposed to arsenic in drinking water. Mutat Res 370(3-4):151-158.

9REFERENCES

Dumas RP. 1990. Written communication (December 12) to Betty Neustadter, Life Systems, Inc., regarding arsenic usage. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances.

Duncan RF, Hershey JW. 1987. Translational repression by chemical inducers of the stress response occurs by different pathways. Arch Biochem Biophys 256:651-661.

*Dunlap LG. 1921. Perforations of the nasal septum due to inhalation of arsenous oxide. JAMA 76(9):568-569.

*Durant JL, Chen J, Hemond HF, et al. 1995. Elevated incidence of childhood leukemia in Woburn, Massachusetts: NIEHS Superfund basic research program searches for causes. Environ Health Perspect 103(Suppl 6):93-98.

*Dutkiewicz T. 1977. Experimental studies on arsenic absorption routes in rats. Environ Health Perspect 19:173-177.

Easterling MR, Styblo M, Evans MV, et al. 2002. Pharmacokinetic modeling of arsenite uptake and metabolism in hepatocytes-mechanistic insights and implications for further experiments. J Pharmacokinet Pharmacodyn 29(3):207-234.

Ebdon L, Sparkes ST. 1987. Determination of arsenic and selenium in environmental samples by hydride generation-direct current plasma-atomic emission spectrometry. Microchem J 36:198-206.

*Ebdon L, Fisher A, Roberts NB, et al. 1999. Determination of organoarsenic species in blood plasma by HPLC-ICP MS. Appl Organomet Chem 13:183-187.

*Eckel WP, Langley WD. 1988. A background-based ranking technique for assessment of elemental enrichment in soils at hazardous waste sites. In: Superfund '88: Proceedings of the 9th National Conference, November 28-30, 1988, Washington, DC. Silver Spring, MD: The Hazardous Materials Control Research Institute, 282-286.

*Edelman GM. 1992. Morphoregulation. Dev Dynamics 193:2-10.

*Edmonds JS, Francesconi KA. 1987. Transformations of arsenic in the marine environment. Experientia 43:553-557.

*Edmonds MS, Baker DH. 1986. Toxic effects of supplemental copper and roxarsone when fed alone or in combination to young pigs. J Anim Sci 63:533-537.

Edmonds JS, Francesconi KA, Cannon JR, et al. 1977. Isolation, crystal structure and synthesis of arsenobetaine, the arsenical constituent of the Western rock lobster Panulirus longipes cygnus George. Tetrahedron Lett 18:1543-1546.

Edwards T, Merilees HL, McBride BC. 1975. Rapid, sensitive method for the separation and detection of arsenic compounds in biological systems. J Chromatogr 106:210-212.

*Eguchi N, Kuroda K, Endo G. 1997. Metabolites of arsenic induced tetraploids and mitotic arrest in cultured cells. Arch Environ Contam Toxicol 32(2):141-145.

9REFERENCES

Eikmann T, Einbrodt HJ. 1987. The arsenic excretion in urine as biological monitoring parameter in normal population collectives [Abstract]. Zentralbl Bakteriol Mikrobiol Hyg B 184:442.

*Eisler R. 1994. A review of arsenic hazards to plants and animals with emphasis on fishery and wildlife. In: Nriagu JO, ed. Arsenic in the environment: Part II: Human health and ecosystem effects. New York, NY: John Wiley & Sons, Inc, 185-259.

Eisler R. 2004. Arsenic hazards to humans, plants, and animals from gold mining. Rev Environ Contam Toxicol 180:133-165.

*Eitzer BD, Iannucci-Berger WA, Mark G, et al. 1997. Fate of toxic compounds during composting. Bull Environ Contam Toxicol 58(6):953-960.

Elfving DC, Wilson KR, Ebel JG, et al. 1994. Migration of lead an arsenic in old orchard soils in the Georgian Bay region of Ontario. Chemosphere 29(2):407-413.

*Ellenhorn MJ. 1997. Ellenhorn's medical toxicology. Diagnosis and treatment of human poisoning. Baltimore, MD: Williams & Wilkins, 1538-1542.

Elliot JE, Scheuhammer AM, Leighton FA, et al. 1992. Heavy metal metallothionein concentrations in Atlantic Canadian Seabirds. Arch Environ Contam Toxicol 22:63-73.

Elsenhans B, Schmolke G, Kolb K, et al. 1987. Metal-metal interactions among dietary toxic and essential trace metals in the rat. Ecotoxicol Environ Safety 14:275-287.

*EMMI. 1997. Environmental Monitoring Methods Index. Version 1.1. PC#4082. Rockville, MD: U.S. Environmental Protection Agency, Government Institutes.

*Endo G, Kuroda K, Okamoto A, et al. 1992. Dimethylarsenic acid induces tetraploids in Chinese hamster cells. Bull Environ Contam Toxicol 48(1):131-137.

*Engel RR, Receveur O. 1993. Re: "Arsenic ingestion and internal cancers: A review". Am J Epidemiol 138(10):896-897.

*Engel RR, Smith AH. 1994. Arsenic in drinking water and mortality from vascular disease: An ecologic analysis in 30 counties in the United States. Arch Environ Health 49(5):418-427.

Englyst V, Lundstrom NG, Gerhardsson L, et al. 2001. Lung cancer risks among lead smelter workers also exposed to arsenic. Sci Total Environ 273(1-3):77-82.

*Enterline PE, Marsh GM. 1982. Cancer among workers exposed to arsenic and other substances in a copper smelter. Am J Epidemiol 116(6):895-911.

*Enterline PE, Day R, Marsh GM. 1995. Cancers related to exposure to arsenic at a copper smelter. Occup Environ Med 52(1):28-32.

*Enterline PE, Henderson VL, Marsh GM. 1987a. Exposure to arsenic and respiratory cancer: A reanalysis. Am J Epidemiol 125(6):929-938.

*Enterline PE, Marsh GM, Esmen NA, et al. 1987b. Some effects of cigarette smoking, arsenic, and SO_2 on mortality among U.S. copper smelter workers. J Occup Med 29(10):831-838.

9REFERENCES

*Environment Canada. 1993. Canadian environmental protection act priority substances list assessment report: Arsenic and its compounds. Ottawa, Canada: Canada Communication Group.

EPA. 1978. Designation of hazardous substances. List of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 116.4.

*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, Office of Water Planning and Standard. EPA440479029a.

*EPA. 1980a. Ambient water quality criteria for arsenic. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. EPA440580021.

EPA. 1980b. Lung cancer/mortality in proximity to a pesticide plant. Washington, DC: U.S. Environmental Protection Agency. PB80207376.

EPA. 1980c. STORET. Washington, DC: U.S. Environmental Protection Agency, Monitoring and Data Support Division.

EPA. 1980d. U.S. Environmental Protection Agency. Fed Regist 45:33132-33133.

EPA. 1980e. U.S. Environmental Protection Agency: Part V. Fed Regist 45:79325-79327.

*EPA. 1980f. Failure to produce arsenic neurotoxicity in the rat. An experimental study. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA5601180022.

EPA. 1981a. Effluent guidelines and standards. Toxic pollutants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 401.

EPA. 1981b. Effluent guidelines and standards. Timber products processing point source category. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 429.

*EPA. 1981c. The carcinogen assessment group's final risk assessment on arsenic. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA600681002. PB81206013.

EPA. 1981d. Assessment of exposure to arsenic from CCA-treated wood: Final report. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment.

EPA. 1982a. Effluent guidelines and standards. Inorganic chemicals manufacturing point source category. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 415.

*EPA. 1982b. Exposure and risk assessment for arsenic. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. PB85221711. EPA440485005. 1.1-4.68.

*EPA. 1982c. Inductively coupled plasma-atomic emission spectrometric method for trace element analysis of water and wastes - method 200.7. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory.

9REFERENCES

EPA. 1982d. Arsenic. In: Intermedia priority pollutant guidance documents. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances.

EPA. 1983a. Effluent guidelines and standards. Electrical and electronic components point source category. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 469.

*EPA. 1983b. Method 206.2 (atomic absorption, furnace technique). In: Methods for chemical analysis of water and wastes. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory. EPA600479020.

*EPA. 1983c. Method 206.3 (atomic absorption-gaseous hydride). In: Methods for chemical analysis of water and wastes. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory. EPA600479020.

*EPA. 1983d. Method 206.4 (spectrophotometric - SDDC). In: Methods for chemical analysis of water and wastes. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory. EPA600479020.

*EPA. 1983e. Method 206.5 (sample digestion prior to total arsenic analysis by silver diethyldithiocarbamate or hydride procedures). In: Methods for chemical analysis of water and wastes. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory. EPA600479020.

EPA. 1983f. Treatability manual: Vol. I: Treatability data. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development, I.4.2.1-I.4.2.6. EPA600282001a.

*EPA. 1983g. Feasibility study to resolve questions on the relationship of arsenic in drinking water to skin cancer. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development.

*EPA. 1984a. Health Assessment Document for Arsenic. Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA 600823021F.

EPA. 1984b. Health assessment document for inorganic arsenic. Final report. Research Triangle Park, NC: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. EPA600883021F. 2-1-3-22, 9-1-9-4.

EPA. 1984c. Health effects assessment for arsenic. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. EPA540186020.

EPA. 1984d. Occurrence of arsenic in drinking water, food and air. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards.

EPA. 1985a. Health advisory for arsenic. Draft. Washington, DC: U.S. Environmental Protection Agency, Office of Drinking Water.

EPA. 1985b. Summary of environmental profiles and hazard indices for constituents of municipal sludge. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards.

EPA. 1985c. U.S. Environmental Protection Agency: Part IV. Fed Regist 50(219):46959-46961.

9REFERENCES

EPA. 1986a. Evaluation of the potential carcinogenicity of arsenic (7940-38-2) in support of reportable quantity adjustments pursuant to CERCLA Section 102. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. OHEA C-073-5.

EPA. 1986b. Inorganic arsenic risk assessment for primary and secondary zinc smelters, primary lead smelters, zinc oxide plants, cotton gins, and arsenic chemical plants. Research Triangle Park, NC: U.S. Environmental Protection Agency, Strategies and Air Standards Division. PB86245255.

EPA. 1986c. Method 7060 - Arsenic (atomic absorption, furnace technique). In: Test methods for evaluating solid waste. 3rd ed. SW-846. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response. .

EPA. 1986d. National emission standard for inorganic arsenic emissions from arsenic trioxide and metallic arsenic production facilities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61, Subpart P.

EPA. 1986e. Creosote, pentachlorophenol, and inorganic arsenicals: Amendment of notice to cancel registrations. U.S. Environmental Protection Agency. Fed Regist 51(7):1334-1348.

*EPA. 1986f. National emission standards for household air pollutants; Standards for inorganic arsenic. U.S. Environmental Protection Agency: Part II. Fed Regist 51(149):27956-27960.

EPA. 1986g. National emission standard for inorganic arsenic emissions from primary copper smelters. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61, Subpart O.

EPA. 1987a. U.S. Environmental Protection Agency. Fed Regist 52:12278.

EPA. 1987b. U.S. Environmental Protection Agency: Part II. Fed Regist 52(77):13396-13398, 13402.

EPA. 1987c. List (phase 1) of hazardous constituents for ground-water monitoring. U.S. Environmental Protection Agency: Part II. Fed Regist 52(131):25942-25953.

EPA. 1987d. Land disposal restrictions for certain "California list" hazardous wastes and modifications to the framework. U.S. Environmental Protection Agency: Part V. Fed Regist 52(130):25760-25763.

*EPA. 1987e. The risk assessment guidelines of 1986. Washington, DC: U.S. Environmental Protection Agency. EPA600887045.

EPA. 1987f. Carcinogenic effects of arsenic compounds in drinking water. Cincinnati, OH: U.S. Environmental Protection Agency, Health Effects Research Laboratory. PB87232542. EPA 600187007.

EPA. 1988a. Inorganic arsenicals; Intent to cancel registrations for pesticide products registered for non-wood preservative use; conclusion of special review. U.S. Environmental Protection Agency. Fed Regist 53(126):24787-24796.

EPA. 1988b. U.S. Environmental Protection Agency: Part II. Fed Regist 53:31138-31222.

EPA. 1988c. U.S. Environmental Protection Agency: Part II. Fed Regist 53:4500-4501.

*EPA. 1988d. Special report on ingested inorganic arsenic: Skin cancer; nutritional essentiality. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. EPA625387013F. PB89125975

*EPA. 1988e. Reference physiological parameters in pharmacokinetic modeling. Washington, DC: U.S. Environmental Protection Agency. EPA600688004. PB88196019.

EPA. 1989a. Guidance for the reregistration of wood preservative pesticide products containing arsenic, chromium, and chromated arsenical compounds as the active ingredient. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticide Programs. PB89102842.

*EPA. 1989b. Interim methods for development of inhalation reference doses. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA600888066F. PB90145723.

EPA. 1989c. U.S. Environmental Protection Agency: Part II. Fed Regist 54:35988-35992.

EPA. 1989d. Reportable quantity adjustments; Digesting of ammonium trisulfate. U.S. Environmental Protection Agency: Part V. Fed Regist 54(155):33426, 33450, 33453-33454, 33456, 33463-33465, 33470.

*EPA. 1989e. Recognition and management of pesticide poisonings, U.S. Environmental Protection Agency. EPA540988001. PB 91145656, 54-62

EPA. 1990a. Effluent guidelines and standards. Nonferrous metals manufacturing point source category. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 421.

EPA. 1990b. Calcium arsenate; Revocation of tolerances. U.S. Environmental Protection Agency. Fed Regist 55(158):33332-33335.

EPA. 1990c. Land disposal restrictions for third scheduled wastes. U.S. Environmental Protection Agency: Part II. Fed Regist 55(106):22520-22536, 22683-22714.

EPA. 1990d. Notice of intent to remove certain active ingredients from list B and to those pesticides containing those ingredients. U.S. Environmental Protection Agency: Part V. Fed Regist 55(147):31164-31174.

*EPA. 1990e. Pollutant concentration estimates from the National Sewage Sludge Survey: Arsenic. U.S. Environmental Protection Agency: Part III. Fed Regist 55(218):47229.

EPA. 1990f. Toxics in the community: 1988: National and local perspectives. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances.

EPA. 1990g. National emissions standard for inorganic arsenic emissions from glass manufacturing plants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61. Subpart N.

EPA. 1990h. Standards of performance for volatile organic compounds (VOC) emissions from synthetic organic chemical manufacturing industry (SOCMI) distillation operation. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 60.667.

9REFERENCES

*EPA. 1990i. 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. 1991. Method 200.8 - Determination of trace elements in waters and wastes by inductively coupled plasma - mass spectrometry. Cincinnati, OH: U.S. Environmental Protection Agency, EPA monitoring and support laboratory.

EPA. 1992. Method 7061A - Arsenic (atomic absorption, gaseous hydride). In: Test methods for evaluating solid waste. 3rd ed. SW-846. Washington, DC: Office of Solid Waste and Emergency Response. U.S. Environmental Protection Agency.

*EPA. 1993a. Arsenic: Supply, demand, and the environment. In: Mercury and arsenic wastes: removal, recovery, treatment, and disposal. U.S. Environmental Protection Agency Pollution Technology Review No. 214, 67-71.

EPA. 1993b. Standards for the management of hazardous waste and specific types of hazardous waste facilities. Health-based limits for exclusion of waste-dericed residues. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 266; Subpart H; Appendix VII.

*EPA. 1994a. Method 6020 - Inductively coupled plasma - mass spectrometry. In: Test methods for evaluating sold waste. 3rd ed. SW-846. Washington DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

*EPA. 1994b. Method 7060A- Arsenic (atomic absorption, furnace technique). In: Test methods for evaluating sold waste. 3rd ed. SW-846. Washington DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

*EPA. 1994c. Method 200.7 - Inductively coupled plasma-atomic emission spectrometric method for trace element analysis of water and wastes. Revision 4.4, EMMC version. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory. http://www.nemi.gov/. April 6, 2005.

EPA. 1995a. Designation, reportable quantities, and notification. List of hazardous substance and reportable quantities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4.

EPA. 1995b. Determination of reportable quantities for hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 117.

*EPA. 1995c. Effluent guidelines and standards. Pesticide chemicals. Metallo-organic pesticide chemicals manufacturing subcategory. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 455, Subpart B.

EPA. 1995d. Toxic chemical release reporting: Community right-to-know. Specific toxic chemical listings. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65.

EPA. 1995e. Maximum contaminant levels for inorganic chemicals. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141, Subpart B.

9REFERENCES

EPA. 1996a. Effluent guidelines and standards. Pesticide chemicals. List of appropriate pollution control technologies. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 455, Table 10.

EPA. 1996b. Proposed guidelines for carcinogen risk assessment. U.S. Environmental Protection Agency. Fed Regist 61(79):17960-18011.

EPA. 1996c. Superfund, emergency planning, and community right-to-know programs. Designation, reportable quantities, and notification. Emergency planning and notification. 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.

*EPA. 1996d. Method 6010B- Inductively coupled plasma-atomic emission spectrometry. In: Test methods for evaluating sold waste. 3rd ed. SW-846. Washington DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

*EPA. 1996e. Method 7063- Arsenic in aqueous samples and extracts by anodic stripping voltammetry (ASV). In: Test methods for evaluating solid waste. 3rd ed. SW-846. Washington DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

*EPA. 1996f. Land disposal restrictions. Prohibitions on storage. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268, Subpart E.

*EPA. 1996g. Land disposal restrictions. Metal bearing wastes prohibited from dilution in a combustion unit according to 40 CFR 268.3(c). U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268, Appendix XI.

*EPA. 1996h. Method 1632: Inorganic arsenic in water by hydride generation quartz furnace atomic absorption. U.S. Environmental Protection Agency, Office of Water, Engineering and Analysis Division.

EPA. 1997a. Identification and listing of hazardous waste. Hazardous constituents. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.

EPA. 1997b. Standards for owners and operators of hazardous waste treatment, storage, and disposal facilities. Ground-water monitoring list. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 264, Appendix IX.

EPA. 1997c. National emission standards for wood furniture manufacturing operations. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 63, Subpart JJ.

EPA. 1997d. Land disposal restrictions Phase IV: Treatment standards for wood preserving wastes, paperwork reduction and streamlining, exemptions from RCRA for certain processed materials; and miscellaneous hazardous waste provision. U.S. Environmental Protection Agency. Fed Regist 62(91)25998.

*EPA. 1997e. Fish and wildlife advisory database. U.S. Environmental Protection Agency. http://www.epa.gov/ost/fishadvice/. March 31, 2005.

EPA. 1997f. Addition of facilities in certain industry sectors; Revised interpretation of otherwise use; Toxic release inventory reporting; Community right-to-know. Fed Regist 62(84):23834.

9REFERENCES

*EPA. 1997g. Relative bioavailability of arsenic in mining wastes. Denver, CO: U.S. Environmental Protection Agency. Document control no. 4500-88-AORH.

*EPA. 1997h. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. EPA630R96012.

*EPA. 1998a. List of pesticides banned and severely restricted in the U.S. U.S. Environmental Protection Agency. http://www.epa.gov.oppfead1/international/piclist.htm. March 31, 2005.

*EPA. 1998b. Effluent limitations guidelines, pretreatment standards and new source performance standards for the industrial waste combustor subcategory of the waste combustors point source category. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 444. Fed Regist 63(25)6392.

*EPA. 1998c. National emission standards for hazardous air pollutants; proposed standards for hazardous air pollutants emissions for the Portland cement manufacturing industry. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 63. Fed Regist 63(56)14182.

*EPA. 1998d. National emissions standards for hazardous air pollutants for primary lead smelters. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 63. Fed Regist 63(74)19200.

*EPA. 1998e. National emission standards for hazardous air pollutants for source categories: national emission standards for primary copper smelters. U.S. Environmental Protection Agency. Fed Regist 63(75)19582.

EPA. 1998f. Land disposal restrictions phase IV: final rule promulgating treatment standards for metal wastes and mineral processing wastes; mineral processing secondary materials and bevill exclusion issues; treatment standards for hazardous soils, and exclusion of recycled wood preserving wastewaters. U.S. Environmental Protection Agency. Fed Regist 63(100)28556.

*EPA. 1998g. Listing of fish and wildlife advisories - 1997. Washington, DC: U.S. Environmental Protection Agency, Office of Water/Office of Science and Technology. EPA823C98001, version 3.

*EPA. 1998h. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 116.4.

*EPA. 1998i. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 401.15.

*EPA. 1998j. Method 6020A- Inductively coupled plasma - mass spectrometry. In: Test methods for evaluating solid waste. 3rd ed. SW-846. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

*EPA. 1998k. U.S. Environmental Protection Agency. Fed Regist 63:40273-40279.

*EPA. 1999a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65.

*EPA. 1999b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.11.

*EPA. 1999c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4.

*EPA. 1999d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.33.

9REFERENCES

*EPA. 1999e. National Recommended Water Quality Criteria-Correction. U.S. Environmental Protection Agency, Office of Water. EPA822Z99001.

EPA. 1999f. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.180.

EPA. 1999g. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.3.

*EPA. 1999h. International Pesticide Notice: EPA cancels the last agricultural use of arsenic acid in the United States. U.S. Environmental Protection Agency. http://www.epa.gov/oppfead1/17b/arsenic.htm. November 3, 1999.

EPA. 1999i. Pesticide chemicals classified as known, probable or possible human carcinogens. http://www.epa.gov/pesticides/carlist/table.htm. November 3, 1999.

*EPA. 2000c. Method 6010C - Inductively coupled plasma-atomic emission spectrometry. U.S. Environmental Protection Agency Office of Solid Waste. http://www.nemi.gov/. April 6, 2005.

*EPA. 2000b. National primary drinking water regulations; Arsenic and clarifications to compliance and new source contaminants monitoring; Proposed rule. U.S. Environmental Protection Agency. Fed Regist 65:38888.

*EPA. 2000a. NCOD query results. Arsenic. Drinking water data. National Contaminant Occurrence Database. Public Water Systems. U.S. Environmental Protection Agency. http://www.epa.gov/ncod/. March 31, 2005.

EPA. 2001a. U.S. Environmental Protection Agency. Fed Regist 66:6976-7066.

*EPA. 2002a. National primary drinking water regulations. Washington, DC: Office of Ground Water and Drinking Water, U.S. Environmental Protection Agency. EPA816F02013. http://www.epa.gov/safewater/mcl.html. February 15, 2005.

*EPA. 2002b. National recommended water quality criteria. Washington, DC: Office of Water, Office of Science and Technology, U.S. Environmental Protection Agency. EPA822R02047. http://www.epa.gov/waterscience/pc/revcom.pdf. February 15, 2005.

*EPA. 2004a. Drinking water standards and health advisories. Washington, DC: Office of Water, U.S. Environmental Protection Agency. EPA822R04005. http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf. February 15, 2005.

*EPA. 2004b. Hazardous air pollutants. Washington, DC: U.S. Environmental Protection Agency. United States Code 42 USC 7412. http://www.epa.gov/ttn/atw/orig189.html. February 15, 2005.

EPA. 2004c. National fish tissue study. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/waterscience/fishstudy/. April 1, 2005.

*EPA. 2005b. 1996 Emissions of arsenic compounds. Technology Transfer Network. National Air Toxics Assessment. Pollutant-Specific Data Tables. U.S. Environmental Protection Agency. http://www.epa.gov/ttn/atw/nata/tablemis.html. March 31, 2005.

9REFERENCES

*EPA. 2005a. Chromated copper arsenate (CCA). U.S. Environmental Protection Agency. http://www.epa.gov/oppad001/reregistration/cca/. February 25, 2005.

*EPA. 2005d. Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 116.4. http://www.epa.gov/ttn/atw/orig189.html. February 15, 2005.

*EPA. 2005e. Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act. Code of Federal Regulations 40 CFR 117.3. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. February 16, 2005.

*EPA. 2005c. STORET data warehouse. U.S. Environmental Protection Agency. http://www.epa.gov/storet/dw_home.html. April 8, 2005.

*EPA. 2005f. Superfund, emergency planning, and community right-to-know programs. Designation, reportable quantities, and notifications. Code of Federal Regulations 40 CFR 302.4. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. February 15, 2005.

*EPA. 2005g. Superfund, emergency planning, and community right-to-know programs. Extremely hazardous substances and their threshold planning quantities. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 355, Appendix A. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. February 15, 2005.

*EPA. 2005h. Superfund, emergency planning, and community right-to-know programs. Toxic chemical release reporting. Code of Federal Regulations 40 CFR 372.65. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. February 16, 2005.

*EPA. 2005i. Tolerances and exemptions from tolerances for pesticide chemicals in food. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.311. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. February 15, 2005.

*EPA. 2005j. Tolerances and exemptions from tolerances for pesticide chemicals in food. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.289. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. February 15, 2005.

*EPA. 2005k. 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. 2005l. Guidelines for carcinogen risk assessment. Washington, DC: U.S. Environmental Protection Agency. EPA630P03001F.

*Erdogan S, Celik S, Erdogan Z. 2004. Comparison of selected toxic elements in cow serum and milk samples from industrial and rural regions. Bull Environ Contam Toxicol 72(5):931-936.

*Erry BV, Macnair MR, Meharg AA, et al. 1999. Seasonal variation in dietary and body organ arsenic concentrations in wood mice *Apodemus sylvaticus* and bank voles *Clethrionomys glareolus*. Bull Environ Contam Toxicol 63:567-574.

9REFERENCES

Espinoza EO, Mann M-J. 1995. Arsenic and mercury in traditional Chinese herbal balls. N Eng J Med 333(12):803-804.

Evans CD, LaDow K, Schumann BL, et al. 2004. Effect of arsenic on benzo[a]pyrene DNA adduct levels in mouse skin and lung. Carcinogenesis 25(4):493-497.

Eybel V, Kotyzova D, Koutensky J, et al. 2001. The thyroid status and arsenic, selenium and iodine level in the thyroid of rats after the long-term administration of these elements. Toxicol Lett 123:127.

Falk H, Caldwell GG, Ishak KG, et al. 1981a. Arsenic-related hepatic angiosarcoma. Am J Ind Med 2:43-50.

*Falk H, Herbert JT, Edmonds L, et al. 1981b. Review of four cases of childhood hepatic angiosarcoma–elevated environmental arsenic exposure in one case. Cancer 47:382-391.

*Fan S-R, Ho I-C, Yeoh FL-F, et al. 1996. Squalene inhibits sodium arsenite-induced sister chromatid exchanges and micronuclei in Chinese hamster ovary-K1 cells. Mutat Res 368(3-4):165-169.

*Farag AM, Woodward DF, Goldstein JN, et al. 1998. Concentrations of metal associated with mining waste in sediments, biofilm, benthic macroinvertebrates, and fish from the Coeur d'Alene River basin, Idaho. Arch Environ Contam Toxicol 34:119-127.

*Farago ME. 1997. Arsenic in the marine environment. In: Gianguzza A, Pelizzetti E, Sammartano S, eds. Marine chemistry. Netherlands: Kluwer Academic Publishers, 275-291.

Farago ME, Thornton I, White ND, et al. 1999. Environmental impacts of a secondary lead smelter in Landskrona, southern Sweden. Environ Geochem Health 21:67-82.

Farmer JG, Johnson, LR, Lovell MA. 1989. Urinary arsenic speciation and the assessment of UK dietary, environmental and occupational exposures to arsenic. Environ Geochem Health 11:93.

Fat L, Gyorffy L, Ghita N, et al. 2000. Neurotoxic effect of chronic exposure to arsenic. Neurotoxicology 21(5):903.

Fattorini D, Alonso-Hernandez CM, Diaz-Asencio M, et al. 2004. Chemical speciation of arsenic in different marine organisms: Importance in monitoring studies. Mar Environ Res 58(2-5):845-850.

*FDA. 1999a. Food and Drug Administration. Code of Federal Regulations. 21 CFR 165.110.

*FDA. 1999b. Food and Drug Administration. Code of Federal Regulations. 21 CFR 510.515.

*FDA. 2005. Beverages. Bottled water. Final Rule. Washington, DC: Food and Drug Administration. Code of Federal Regulations. 21 CFR 165.110. Fed Regist 70:33694-33701. http://www.fda.gov/OHRMS/DOCKETS/98fr/05-11406.pdf. September 1, 2005.

*FEDRIP. 2005. Arsenic. Federal Research in Progress. Dialog Information Services, Palo Alto, CA.

*Feldman RG, Niles CA, Kelly-Hayes M, et al. 1979. Peripheral neuropathy in arsenic smelter workers. Neurology 29:939-944.

9REFERENCES

Feldmann J, Lai VWM, Cullen WR, et al. 1999. Sample preparation and storage can change arsenic speciation in human urine. Clin Chem 45(11):1988-1997.

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

Ferm VH. 1977. Arsenic as a teratogenic agent. Environ Health Perspect 19:215-217.

*Ferm VH, Carpenter SJ. 1968. Malformations induced by sodium arsenate. J Reprod Fertil 17:199-201.

Ferm VH, Hanlon DP. 1985. Constant rate exposure of pregnant hamsters to arsenate during early gestation. Environ Res 37:425-432.

Ferm VH, Hanlon DP. 1986. Arsenate-induced neural tube defects not influenced by constant weight administration of folic acid. Pediatr Res 20:761-762.

*Ferm VH, Saxon A, Smith BM. 1971. The teratogenic profile of sodium arsenate in the golden hamster. Arch Environ Health 22:557-560.

Ferreccio CR, Gonzalez CW, Solari JS, et al. 1995. [Lung cancer in workers exposed to arsenic. A case control study.] Rev Med Chil 124:119-123. (Spanish)

*Ferreccio CR, Gonzalez CW, Solari JS, et al. 1996. [Bronchopulmonary cancer in workers exposed to arsenic: A case control study.] Rev Med Chil 124(1):119-123. (Spanish).

*Ferreccio C, Gonzalez Psych C, Milosavjlevic Stat V, et al. 1998. Lung cancer and arsenic exposure in drinking water: A case-control study in northern Chile. Cad Saude Publica 14(Suppl 3):193-198.

*Ferreccio C, Gonzalez C, Milosavjlevic V, et al. 2000. Lung cancer and arsenic concentrations in drinking water in Chile. Erratum in: Epidemiology 12(2):283. Epidemiology 11(6):673-679.

Fertmann R, Schümann M, Karmaus W, et al. 1997. Sex-ratio variation in the Bille settlement. Scand J Work Environ Health 23(4):308-310.

Ficker E, Kuryshev YA, Dennis AT, et al. 2004. Mechanisms of arsenic-induced prolongation of cardiac repolarization. Mol Pharmacol 66(1):33-44.

Fields S. 2001. Caution–children at play: How dangerous is CCA? Environ Health Perspect 109(6):A262-A269.

*Fincher R-M, Koerker RM. 1987. Long-term survival in acute arsenic encephalopathy: Follow-up using newer measures of electrophysiologic parameters. Am J Med 82:549-552.

Finkelman RB, Belkin HE, Zheng B. 1999. Health impacts of domestic coal use in China. Proc Natl Acad Sci U S A 96:3427-3431.

Fischer AB, Buchet JP, Lauwerys RR. 1985. Arsenic uptake, cytotoxicity and detoxification studied in mammalian cells in culture. Arch Toxicol 57:168-172.

9REFERENCES

Fischer AB, Buchet JP, Lauwerys RR. 1989. Cellular metabolism of arsenic studied in mammalian cells *in vitro*. Environ Geochem Health 11:87-92.

Fisher G, Silberman D, Prentice B, et al. 1979. Filtration studies with neutron-activated coal fly ash. Environ Sci Tech 13:689-693.

Fisher GL, McNeill KL, Democko CJ. 1986. Trace element interactions affecting pulmonary macrophage cytotoxicity. Environ Res 39:164-171.

*Flora SJS, Tripathi N. 1998. Hepatic and renal metallothionein induction following single oral administration of gallium arsenide in rats. Biochem Mol Biol Int 45(6):1121-1127.

Flora SJ, Dubey R, Kanna GM, et al. 2002. Meso 2,3-dimercaptosuccinic acid (DMSA) and monoisoamyl DMSA effect on gallium arsenide induced pathological liver injury in rats. Toxicol Lett 132(1):9-17.

Flora SJS, Dube SN, Pant SC, et al. 1994. Effects of multiple gallium arsenide exposure on some biochemical alterations in rat brain [letter]. Ind Health 32(4):247-252.

*Flora SJS, Dube SN, Vijayaraghavan R, et al. 1997a. Changes in certain hemetological and physiological variables following single gallium arsenide exposure in rats. Biol Trace Elem Res 58:197-208.

*Flora SJS, Kumar P, Kannan GM, et al. 1998. Acute oral gallium arsenide exposure and changes in certain hematological, hepatic, renal and immunological indices at different time intervals in male Wistar rats. Toxicol Lett 94:103-113.

*Flora SJS, Pant SC, Malhotra PR, et al. 1997b. Biochemical and histopathological changes in arsenic-intoxicated rats coexposed to ethanol. Alcohol 14(6):563-568.

Foà V, Bertolero F. 1983. Arsines. In: Parmeggiani L, ed. Encyclopedia of occupational health and safety, Vol. 1. Geneva, Switzerland: International Labor Organization, 183-184.

*Foà V, Colombi A, Maroni M, et al. 1984. The speciation of the chemical forms of arsenic in the biological monitoring of exposure to inorganic arsenic. Sci Total Environ 34:241-259.

*Foà V, Colombi A, Maroni M, et al. 1987. Study of kidney function of workers with chronic low level exposure to inorganic arsenic. In: DeRosa E, Bartolucci GB, Foa V, eds. Occupational and environmental chemical hazards: Cellular and biochemical indices for monitoring toxicity. Horwood, NY: Halsted Press, 362-367.

*Foman 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.

*Foman, 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.

Fortoul T, Vega L, Saavedra R, et al. 1998. Ultrastructural changes in human lymphocytes challenged with sodium arsenite. Environ Mole Mutagen 31(suppl. 29):53.

9REFERENCES

*Fowler BA, Woods JS. 1977. The transplacental toxicity of methyl mercury to fetal rat liver mitochondria: Morpho-metric and biochemical studies. Lab Invest 36:122.

Fowler BA, Woods JS. 1979. The effects of prolonged oral arsenate exposure on liver mitochondria of mice: Morphometric and biochemical studies. Toxicol Appl Pharmacol 50:177-187.

Fowler BA, Akkerman M, Madden EF, et al. 2000. Comparative in vitro studies of arsenic and cadmium interactions on cellular viability and stress response in rat renal tubule epithelial cells. Int J Toxicol 19(6):25.

*Fowler BA, Woods JS, Schiller CM. 1977. Ultrastructural and biochemical effects of prolonged oral arsenic exposure on liver mitochondria of rats. Environ Health Perspect 19:197-204.

*Foy HM, Tarmapai S, Eamchan P, et al. 1992. Chronic arsenic poisoning from well water in a mining area in Thailand. Asia Pac J Public Health 6(3):150-152.

Francesconi KA, Kuehnelt D. 2004. Determination of arsenic species: A critical review of methods and applications, 2000-2003. Analyst 129:373-395.

*Francesconi KA, Edmonds JS, Morita M. 1994. Determination of arsenic and arsenic species in marine environmental samples. In: Nriagu JO, ed. Arsenic in the environment: Part II: Human health and ecosystem effects. New York, NY: John Wiley & Sons, Inc., 185-259.

*Francesconi KA, Tanggaar R, McKenzie CJ, et al. 2002. Arsenic metabolites in human urine after ingestion of an arsenosugar. Clin Chem 48(1):92-101.

Francis AJ, Dodge CJ, Rose AW, et al. 1989. Aerobic and anaerobic microbial dissolution of toxic metals from coal wastes: Mechanism of action. Environ Sci Technol 23:435-441.

*Francis CW, White GH. 1987. Leaching of toxic metals from incinerator ashes. J Water Pollut Control Fed 59(11):979-986.

*Franklin M, Bean WB, Harden RC. 1950. Fowler's solution as an etiologic agent in cirrhosis. Am J Med Sci 219:589-596.

*Franzblau A, Lilis R. 1989. Acute arsenic intoxication from environmental arsenic exposure. Arch Environ Health 44(6):385-390.

*Freeman GB, Johnson JD, Killinger JM, et al. 1993. Bioavailability of arsenic in soil impacted by smelter activities following oral administration in rabbits. Fundam Appl Toxicol 21(1):83-88.

*Freeman GB, Schoof RA, Ruby MV, et al. 1995. Bioavailability of arsenic in soil and house dust impacted by smelter activities following oral administration in cynomolgus monkeys. Fundam Appl Toxicol 28(2):215-222.

Frey MM, Edwards MA. 1997. Surveying arsenic occurrence. J Am Water Works Assoc 89(3):105-117.

Friberg L. 1988. The GESAMP evaluation of potentially harmful substances in fish and other seafood with special reference to carcinogenic substances. Aquat Toxicol 11:379-393.

9REFERENCES

Frisbie SH, Ortega R, Maynard DM, et al. 2002. The concentrations of arsenic and other toxic elements in Bangladesh's drinking water. Environ Health Perspect 110(11):1147-1153.

Frost DV. 1987. Interrelationships of selenium and arsenic in biology. In: Combs GF, Levander OA, Spallholz JE, et al., eds. Selenium in biology and medicine: Part A: Proceedings of the Third International Symposium, Beijing, China, May 27-June 1, 1984. New York, NY: Van Nostrand Reinhold Company, 308-323.

Frost F, Craun G, Brown KG. 2002. Detection of excess arsenic-related cancer risks. Environ Health Perspect 110(1):A12-A13.

Frost F, Frank D, Pierson K, et al. 1993. A seasonal study of arsenic in groundwater, Snohomish County, Washington, USA. Environ Geochem Health 15(4):209-214.

*Frost F, Harter L, Milham S, et al. 1987. Lung cancer among women residing close to an arsenic emitting copper smelter. Arch Environ Health 42(2):148-152.

*Frost FJ, Muller T, Petersen HV, et al. 2003. Identifying US populations for the study of health effects related to drinking water arsenic. J Expo Anal Environ Epidemiol 13(3):231-239.

*FSTRAC. 1990. Summary of state and federal drinking water standards and guidelines. Chemical Communications Subcommittee, Federal State Toxicology and Regulatory Alliance Committee. February 1990.

*FSTRAC. 1995. Summary of state and federal drinking water standards and guidelines. 1993-1995. Contaminant Policy and Communications Subcommittee, Federal-State Toxicology and Regulatory Alliance Committee. Cosponsored by: U.S. Environmental Protection Agency, Office of Science and Technology. Office of Water.

Fujihara J, Kunito T, Kubota R, et al. 2004. Arsenic accumulation and distribution in tissues of black-footed albatrosses. Mar Pollut Bull 48:1153-1160.

Fujino Y, Guo X, Liu J, et al. 2004. Mental health burden amongst inhabitants of an arsenic-affected area in Inner Mongolia, China. Soc Sci Med 59(9):1963-1973.

Fuortes L. 1988. Arsenic poisoning. Ongoing diagnostic and social problem. Postgrad Med 83:233-234.

Gabrilove JL, Köning A, Calleja E, et al. 1997. Effects of arsenicals in chronic leukemias. Anticancer Res 17(5c):3981.

Gailer J, Aposhian HV. 1998. The detection of a novel arsenic-selenium compound. Toxicologist 42(1-S):322.

*Gaines TB. 1960. The acute toxicity of pesticides to rats. Toxicol Appl Pharmacol 2:88-99.

Gallagher RE. 1998. Arsenic--new life for old potion. N Engl J Med 339(19):1389-1391.

Galli CL, Marinovich M. 1987. Dermal toxicity of pesticides. In: Costa LG, Galli CL, Murphy SD, eds. NATO ASI (Advance Science Institute) Series, Toxicology of pesticides: Experimental, clinical and regulatory perspectives. Berlin, West Germany: Springer-Verlag, 147-170.

9REFERENCES

Gamberg M, Braune BM. 1999. Contaminant residue levels in artic wolves (*Canis lupus*) from the Yukon Territory, Canada. Sci Total Environ 243/244:329-338.

Gamble BM, Gallagher PA, Shoemaker JA, et al. 2002. An investigation of the chemical stability in simulated gastric juice and acidic environments using IC-ICP-MS and IC-ESI-MS/MS. Analyst 127(6):781-785.

Gamble BM, Gallagher PA, Shoemaker JA, et al. 2003. An investigation of the chemical stability of arsenosugars in basic environments using IC-ICP-MS and IC-ESI-MS/MS. Analyst 128(12):1458-1461.

*Gao S, Burau RG. 1997. Environmental factors affecting rates of arsine evolution from and mineralization of arsenicals in soils. J Environ Qual 26(3):753-763.

*Garbarino JR, Bednar AJ, Rutherford DW, et al. 2003. Environmental fate of roxarsone in poultry litter. I. Degradation of roxarsone during composting. Environ Sci Technol 37:1509-1514.

*Garcia F, Ortega A, Domingo JL, et al. 2001. Accumulation of metals in autopsy tissues of subjects living in Tarragona county, Spain. J Environ Sci Health Part A 36(9):1767-1786.

Garcia-Montalvo EA, Aguilar C, Del Razo LM. 2003. Dose-response alteration in the urinary pattern of trivalent arsenic species in mice exposed to arsenite. Toxicol Sci 72(S-1):403.

*García-Vargas GG, Hernández-Zavala A. 1996. Urinary porphyrins and heme biosynthetic enzyme activities measured by HPLC in arsenic toxicity. Biomed Chromatogr 10(6):278-284.

García-Vargas GG, Del Razo LM, Cebrián ME, et al. 1994. Altered urinary porphyrin excretion in a human population chronically exposed to arsenic in Mexico. Hum Exp Toxicol 13(12):839-847.

Garip H, Salih IM, Sener BC, et al. 2004. Management of arsenic trioxide necrosis in the maxilla. J Endocrinol 30(10):732-736.

Garland M, Morris JS, Rosner BA, et al. 1993. Toenail trace element levels as biomarkers: Reproducibility over a 6-year period. Cancer Epidemiol Biomarkers Prev 2(5):493-497.

*Gartrell MJ, Craun JC, Podrebarac DS, et al. 1986. Pesticides, selected elements, and other chemicals in adult total diet samples, October 1980-March 1982. J Assoc Off Anal Chem 69(1):146-161.

*Garvey GJ, Hahn G, Lee RV, et al. 2001. Heavy metal hazards of Asian traditional remedies. Int J Environ Health Res 11(1):63-71.

Gebel T. 1997. Arsenic and antimony: Comparative approach on mechanistic toxicology. Chem Biol Interact 107:131-144.

Gebel TW. 2001. Unanswered questions in arsenic toxicology. J Environ Pathol Toxicol Oncol 20(4):299-309.

*Gebel T, Birkenkamp P, Luthin S, et al. 1998a. Arsenic(III), but not antimony(III), induces DNA-protein crosslinks. Anticancer Res 18:4253-4258.

9REFERENCES

*Gebel T, Christensen S, Dunkelberg H. 1997. Comparative and environmental genotoxicity of antimony and arsenic. Anticancer Res 17(4a):2603-2607.

*Gebel TW, Suchenwirth RHR, Bolten C, et al. 1998b. Human biomonitoring of arsenic and antimony in case of an elevated geogenic exposure. Environ Health Perspect 106(1):33-39.

Geiszinger A, Goessler W, Francesconi KA. 2002. Biotransformation of arsenate to the tetramethylarsonium ion in the marine polychaetes *Nereis diversicolor* and *Neris virens*. Environ Sci Technol 36:2905-2910.

Geiszinger A, Goessler W, Kuehnelt D, et al. 1998. Determination of arsenic compounds in earthworms. Environ Sci Technol 32:2238-2243.

Geiszinger A, Goessler W, Pedersen SN, et al. 2001. Arsenic biotransformation by the brown macroalga, *Fucus serratus*. Environ Toxicol Chem 20(10):2255-2262.

Gemel TW. 1999. Arsenic and drinking water contamination. Science 283:1458-1459.

*Gentry PR, Covington TR, Mann S, et al. 2004. Physiologically based pharmacokinetic modeling of arsenic in the mouse. J Toxicol Environ Health A 67(1):43-71.

*Gerhardsson L, Brune D, Nordberg IGF, et al. 1985. Protective effect of selenium on lung cancer in smelter workers. Br J Ind Med 42:617-626.

*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.

Gerhardt RE, Hudson JB, Rao RN, et al. 1978. Chronic renal insufficiency from cortical necrosis induced by arsenic poisoning. Arch Intern Med 138:1267-1269.

*Germolec DR, Spalding J, Boorman GA, et al. 1997a. Arsenic can mediate skin neoplasia by chronic stimulation of keratinocyte-derived growth factors. Mutat Res 86(3):209-218.

Germolec D, Spalding J, Yu H, et al. 1997b. Arsenic enhancement of skin neoplasia by chronic stimulation of growth-promoting cytokines. J Leukoc Biol 61(Suppl 1):14.

*Germolec DR, Spalding J, Yu H-S, et al. 1998. Arsenic enhancement of skin neoplasia by chronic stimulation of growth factors. Am J Pathol 153(6):1775-1785.

*Gerr F, Letz R, Ryan PB, et al. 2000. Neurological effects of environmental exposure to arsenic in dust and soil among humans. Neurotoxicology 21(4):475-87.

*Geubel AP, Mairlot MC, Buchet JP, et al. 1988. Abnormal methylation capacity in human liver cirrhosis. Int J Clin Pharmacol Res 8(2):117-122.

Gianessi LP, Anderson JE. 1995a. Cacodylic acid. Pesticide use in U.S. crop production: National data report. Washington DC: National Center for Food and Agricultural Policy.

Gianessi LP, Anderson JE. 1995b. DSMA. Pesticide use in U.S. crop production: National data report. Washington DC: National Center for Food and Agricultural Policy.

9REFERENCES

Gianessi LP, Anderson JE. 1995c. MSMA. In: Pesticide use in U.S. crop production: National data report. Washington DC: National Center for Food and Agricultural Policy.

Gianessi LP, Anderson JE. 1995d. Pesticide use in U.S. crop production. Washington, DC: National Center for Food and Agricultural Policy.

Gibbs PJ, Miskiewicz AG. 1995. Heavy metals in fish near a major primary treatment sewage plant outfall. Mar Pollut Bull 30(10):667-674.

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

Gilani SH. 1997. Teratogenicity of metals in chick embryos. Teratology 56(6):396.

Ginsberg JM, Lotspeich WD. 1963. Interrelations of arsenate and phosphate transport in the dog kidney. Am J Physiol 205:707-714.

Giri AK, Basu A, Mahat J. 2001. Assessment of genetic damage in the symptomatic individuals exposed to arsenic through drinking water in West Bengal, India. Mutat Res 483:S61.

*Giwercman 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.

*Glazener FS, Ellis JG, Johnson PK. 1968. Electrocardiographic findings with arsenic poisoning. Calif Med 109(2):158-162.

*Goddard KE. 1987. Composition, distribution, and hydrologic effects of contaminated sediments resulting from the discharge of gold milling wastes to Whitewood Creek at Lead and Deadwood, South Dakota. Water-Resources Investigation Report 87-4051. U.S. Geological Survey. http://sd.water.usgs.gov/pubs/abstracts/wri87-4051.html. March 31, 2005.

*Goddard MJ, Tanhehco JL, Dau PC. 1992. Chronic arsenic poisoning masquerading as Landry-Guillain-Barre syndrome. Electromyogr Clin Neurophysiol 32(9):419-423.

*Goebel HH, Schmidt PF, Bohl J, et al. 1990. Polyneuropathy due to acute arsenic intoxication: Biopsy studies. J Neuropathol Exp Neurol 49(2):137-149.

Goering PL, Aposhian HV, Mass MJ, et al. 1999. The enigma of arsenic carcinogenesis: Role of metabolism. Toxicol Sci 49(1):5-14.

*Goering PL, Maronpot RR, Fowler BA. 1988. Effect of intratracheal gallium arsenide administration on δ-aminolevulinic acid dehydratase in rats: Relationship to urinary excretion of aminolevulinic acid. Toxicol Appl Pharmacol 92:179-193.

*Goldfrank RL, Flomenbaum NE, Lewin NA, et al., eds. 1998. Goldfrank's toxicologic emergencies. 6th ed. Stamford, CT: Appleton and Lange, 1261-1273.

*Goldsmith JR, Deane M, Thom J, et al. 1972. Evaluation of health implications of elevated arsenic in well water. Water Res 6:1133-1136.

9REFERENCES

*Goldsmith S, From AHL. 1986. Arsenic-induced atypical ventricular tachycardia. N Engl J Med 303:1096-1097.

Goldstein SH, Babich H. 1989. Differential effects of arsenite and arsenate to *Drosophila melanogaster* in a combined adult/developmental toxicity assay. Bull Environ Contam Toxicol 42:276-282.

*Golomb D, Ryan D, Eby N, et al. 1997. Atmospheric deposition of toxics onto Massachusetts Bay-I. Metals. Atmos Environ 31(9):1349-1359.

Golub MS, Macintosh MS, Baumrind N. 1998. Developmental and reproductive toxicity of inorganic arsenic: Animal studies and human concerns. J Toxicol Environ Health 1:199-241.

Gonsebatt ME, Vega L, Salazar AM, et al. 1996. Genotoxicity of arsenic exposure. 27th Annual Scientific Meeting of the Environmental Mutagen Society, Victoria, British Columbia, Canada, March 23-28, 1996. Environ Mol Mutagen 27(suppl 27):26.

Gonsebatt ME, Vega L, Salazar AM, et al. 1997. Cytogenetic effects in human exposure to arsenic. Mutat Res 386(3):219-228.

González MJ, Aguilar MV, Martínez MC. 1997. Mechanisms of absorption of As_2O_5 from rat small intestine: The effect of different parameters. J Trace Elem Med Biol 11:239-247.

*González MJ, Aguilar MV, Martínez Para MC. 1995. Gastrointestinal absorption of inorganic arsenic (V): The effect of concentration and interactions with phosphate and dichromate. Vet Human Toxicol 37:131-136.

Goodell JP, Hanson PC, Hawkins WB. 1944. Methionine protects against mapharsen liver injury in protein-depleted dogs. J Exp Med 79:625-632.

Gorby MS. 1994. Arsenic in human medicine. In: Nriagu JO, ed. Arsenic in the environment, part II: Human health and ecosystem effects. New York, NY: John Wiley & Sons, Inc., 1-16.

Gordon GF. 1985. Sex and age related differences in trace element concentrations in hair. Sci Total Environ 42:133-147.

Gosselin RE, Smith RP, Hodge HC. 1984. Clinical toxicology of commercial products. 5th ed. Baltimore, MD: Williams and Wilkins, II-129.

Graeme KA, Pollack CV. 1998. Heavy metal toxicity, Part I: Arsenic and mercury. J Emerg Med 16(1):45-56.

Grande GA, Rodgers AA, Ling LJ, et al. 1987. Urine spot test as guide to treatment in acute pentavalent arsenic ingestion. Vet Hum Toxicol 29:73-74.

*Grandjean P, Weihe P, Needham LL, et al. 1995. Relation of a seafood diet to mercury, selenium, arsenic, and polychlorinated biphenyl and other organochlorine concentrations in human milk. Environ Res 71(1):29-38.

Grant LD, Mushak P. 1989. Specification of metals and metal compounds: Implications for biological monitoring and development of regulatory approaches. Toxicol Ind Health 5:891-908.

9REFERENCES

Grant WM. 1974. Toxicology of the eye. Springfield, IL: Charles C. Thomas, 51-57.

Greathouse DG, Craun GF. 1978. Cardiovascular disease study--occurrence of inorganics in household tap water and relationships to cardiovascular mortality rates. Trace Subst Environ Health 12:31-39.

Greaves WW, Rom WN, Lyon JL. 1981. Relationship between lung cancer and distance of residence from non-ferrous smelter stack effluent. Am J Ind Med 2:15-23.

Greenberg SA. 1996. Acute demyelinating polyneuropathy with arsenic ingestion. Muscle Nerve 19(12):1611-1613.

Gregson SK, Roberts RD, Roberts JM. 1988. The fate of heavy metals in co-disposed refuse. Environ Technol Lett 9:983-990.

Gregus Z, Klaassen CD. 1986. Disposition of metals in rats: A comparative study of fecal, urinary, and biliary excretion of eighteen metals. Toxicol Appl Pharmacol 85:24-38.

Griepink B, Tolg G. 1989. Sample digestion for the determination of elemental traces in matrices of environmental concern. Pure Appl Chem 61:1139-1146.

*Groen K, Vaessen HAMG, Kliest JJG, et al. 1993. Bioavailability of inorganic arsenic from bog ore-containing soil in the dog. Environ Health Perspect 102(2):182-184.

Groth DH, Stettler LE, Burg JR, et al. 1986. Carcinogenic effects of antimony trioxide and antimony ore concentrate in rats. J Toxicol Environ Health 18:607-626.

*Guerin T, Astruc A, Astruc M. 1999. Speciation of arsenic and selenium compounds by HPLC hyphenated to specific detectors: A review of the main separation techniques. Talanta 50:1-24.

*Guha Mazumder DN. 1996. Treatment of chronic arsenic toxicity as observed in West Bengal. J Indian Med Assoc 94(2):41-42.

*Guha Mazumder DN, Chakraborty AK, Ghose A, et al. 1988. Chronic arsenic toxicity from drinking tubewell water in rural west Bengal. Bull WHO 66(4):499-506.

*Guha Mazumder DN, Das Gupta J, Santra A, et al. 1998a. Chronic arsenic toxicity in west Bengal--the worst calamity in the world. J Indian Med Assoc 96(1):4-7.

*Guha Mazumder DN, Ghoshal UC, Saha J, et al. 1998b. Randomized placebo-controlled trial of 2,3-dimercaptosuccinic acid in therapy of chronic arsenicosis due to drinking arsenic-contaminated subsoil water. Clin Toxicol 36(7):683-690.

*Guha Mazumder DN, Haque R, Ghosh N, et al. 1998c. Arsenic levels in drinking water and the prevalence of skin lesions in West Bengal, India. Int J Epidemiol 27:871-877.

Gulson BL, Davis JJ, Mizon KJ, et al. 1994. Lead bioavailability in the environment of children: Blood lead levels in children can be elevated in a mining community. Arch Environ Health 49(5):326-331.

*Gunderson EL. 1995a. Dietary intake of pesticides, selected elements, and other chemicals: FDA total diet study, June 1984-April 1986. J AOAC Int 78(4):910-921.

9REFERENCES

*Gunderson EL. 1995b. FDA total diet study, July 1986-April 1991, dietary intakes of pesticides, selected elements, and other chemicals. J AOAC Int 78(6):1353-63.

*Gunn TM, Juriloff DM, Harris MJ. 1992. Further genetic studies of the cause of exancephaly in SELH mice. Teratology 45:679-686.

Guo HR. 2003. The lack of a specific association between arsenic in drinking water and hepatocellular carcinoma. J Hepatol 39(3):383-9.

*Guo HR. 2004. Arsenic level in drinking water and mortality of lung cancer (Taiwan). Cancer Causes Control 15:171-177.

Guo H-R, Valberg PA. 1997. Evaluation of the validity of the U.S. EPA's cancer risk assessment of arsenic for low-level exposures: A likelihood ratio approach. Environ Geochem Health 19:133-141.

Guo H-R, Lipsitz SR, Hu H, et al. 1998. Using ecological data to estimate a regression model for individual data: The association between arsenic in drinking water and incidence of skin cancer. Environ Res 79:82-93.

Guo HR, Yu HS, Hu H, et al. 2001b. Arsenic in drinking water and skin cancers: Cell-type specificity (Taiwan, R.O.C.). Cancer Causes Control 12(10):909-916.

*Guo T, Baasner J, Tsalev DL. 1997. Fast automated determination of toxicologically relevant arsenic in urine by flow injection-hydride generation atomic absorption spectrometry. Analytica Chimica Acta 349(1-3):313-318.

*Guo X, Fujino Y, Kaneko S, et al. 2001a. Arsenic contamination of groundwater and prevalence of arsenical dermatosis in the Hetao plain area, Inner Mongolia, China. Mol Cell Biochem 222(1-2):137-140.

Gurley LR, Valdez JG, Miglio JJ, et al. 1986. Biological availability of nickel arsenides: Cellular response to soluble Ni_5As_2. J Toxicol Environ Health 17:101-117.

Gutleb AC, Helsberg A, Mitchell C. 2002. Heavy metal concentrations in fish from a pristine rainforest valley in Peru: A baseline study before the start of oil-drilling activities. Bull Environ Contam Toxicol 69:523-529.

Guyton AC. 1947. Measurement of the respiratory volumes of laboratory animals. Am J Physiol 150:70-77.

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

*Haddad LM, Winchester JF. 1990. Clinical management of poisoning and drug overdose. 2nd ed. Philadelphia, PA: W.B. Saunders Company, 1024-1027, 18, 92, 97, 98.

Hahn I, Kline SA, Howland RS, et al. 2000. Chronic pediatric arsenic poisoning from pressure-treated wood burned in a fireplace. J Toxicol Clin Toxicol 38(5):550-551.

*Hall JC, Harruff R. 1989. Fatal cardiac arrhythmia in a patient with interstitial myocarditis related to chronic arsenic poisoning. South Med J 82(12):1557-1560.

9REFERENCES

Hall GEM, Pelchat JC, Gauthier G. 1999. Stability of inorganic arsenic (III) and arsenic (V) in water samples. J Anal Atom Spectrom 14:205-213.

*Hamadeh H, Lee E, Siengsubcharti Y, et al. 1998. Arsenic species and gene activation in human lymphoblastoid cells. Toxicologist 42(1-S):360.

Hamamoto E. 1955. [Infant arsenic poisoning by powdered milk.] Jpn Med J 1649:3-12. (Japanese)

*Hamel SC, Buckley B, Lioy PJ. 1998. Bioaccessibility of metals in soils for different liquid to solid ratios in synthetic gastric fluid. Environ Sci Tech 32(3):358-362.

Hanaoka K, Gossler W, Irgolic KJ, et al. 1997. Occurrence of arsenobetaine and arsenochline in micro-suspended particles. Chemosphere 35(11):2463-2469.

*Hanlon DP, Ferm VH. 1977. Placental permeability of arsenate ion during early embryogenesis in the hamster. Experientia 33(9):1221-1222.

Hanlon DP, Ferm VH. 1986a. Concentration and chemical status of arsenic in the blood of pregnant hamsters during critical embryogenesis. I. Subchronic exposure to arsenate utilizing constant rate administration. Environ Res 40:372-379.

Hanlon DP, Ferm VH. 1986b. Concentration and chemical status of arsenic in the blood of pregnant hamsters during critical embryogenesis. II. Acute exposure. Environ Res 40:380-390.

*Hanlon DP, Ferm VH. 1986c. Teratogen concentration changes as the basis of the heat stress enhancement of arsenate teratogenesis in hamsters. Teratology 34:189-193.

*Hanlon DP, Ferm VH. 1987. The concentration and chemical status of arsenic in the early placentas of arsenate-dosed hamsters. Environ Res 42:546-552.

*Hanna LA, Peters JM, Wiley LM, et al. 1997. Comparative effects of essential and nonessential metals on preimplantation mouse embryo development in vitro. Toxicology 116(1-3):123-131.

Hantson P, Haufroid V, Buchet JP, et al. 2003. Acute arsenic poisoning treated by intravenous dimercaptosuccinic acid (DMSA) and combined extrarenal epuration techniques. J Toxicol Clin Toxicol 41(1):1-6.

*Hantson P, Verellen-Dumoulin C, Libouton JM, et al. 1996. Sister chromatid exchanges in human peripheral blood lymphocytes after ingestion of high doses of arsenicals. Int Arch Occup Environ Health 68:342-344.

*Hanusch K, Grossmann H, Herbst K-A, et al. 1985. Arsenic and arsenic compounds. In: Gerhartz W, Yamamoto YS, Campbell FT, et al., eds. Ullman's encyclopedia of industrial chemistry. Weinham, Germany: VCH Verlagsgesellschaft, 113-141

*Haque R, Mazumder DN, Samanta S, et al. 2003. Arsenic in drinking water and skin lesions: Dose-response data from West Bengal, India. Epidemiology 14(2):174-182.

Harbut MR, Kamel NS. 2000. Arsenic body burden and morbidity and mortality. Arch Environ Health 55(4):285-286.

Harkins DK, Susten AS. 2003. Hair analysis: Exploring the state of the science. Environ Health Perspect 111(4):576-578.

*Harrington JM, Middaugh JP, Morse DL, et al. 1978. A survey of a population exposed to high concentrations of arsenic in well water in Fairbanks, Alaska. Am J Epidemiol 108(5):377-385.

Harrington-Brock K, Winkfield E, Mass MJ. 2002. Methylation inactivates pentavalent arsenic species but activates trivalent arsenic species to potent genotoxicants. Environ Mol Mutagen 39:31.

Harrington-Brock K, Fuscoe JC, et al. 1998. Biological effects of arsenic exposure: *In vitro* and *in vivo*. Environ Mole Mutagen 31(suppl. 29):70.

Harrison WP, Frazier JC, Mazzanti EM, et al. 1980. Teratogenicity of disodium methanarsonate and sodium dimethylarsinate (sodium cacodylate) in mice [abstract]. Teratology 21:43A.

*Harrisson JWE, Packman EW, Abbott DD. 1958. Acute oral toxicity and chemical and physical properties of arsenic trioxides. Arch Ind Health 17:118-123.

Hart C. 1987. Art hazards: An overview for sanitarians and hygienists. J Environ Health 49(5):282-287.

*Hartmann A, Speit G. 1994. Comparative investigations of the genotoxic effects of metals in the single cell gel (SCG) assay and the sister chromatid exchange (SCE) test. Environ Mole Mutagen 23(4):299-305.

*Hartmann A, Speit G. 1996. Effect of arsenic and cadmium on the persistence of mutagen-induced DNA lesions in human cells. Environ Mol Mutagen 27(2):98-104.

*Hartwell TW, Handy RW, Harris BS, et al. 1983. Heavy metal exposure in populations living around zinc and copper smelters. Arch Environ Health 38(5):284-295.

Hartwig A. 1998. Carcinogenicity of metal compounds: Possible role of DNA repair inhibition. Toxicol Lett 102-103:235-239.

Hartwig A, Blessing H, Schwerdtle T, et al. 2003. Modulation of DNA repair processes by arsenic and selenium compounds. Toxicology 193(1-2):161-169.

*Hartwig A, Gröblinghoff UD, Beyersmann D, et al. 1997. Interaction of arsenic(III) with nucleotide excision repair in UV-irradiated human fibroblasts. Carcinogenesis 18(2):399-405.

*Hartwig A, Mullenders L, Asmuá M, et al. 1998. Disruption of DNA repair process by carcinogenic metal compounds. Fresenius J Anal Chem 361:377-380.

Hartwig A, Schlepegrell R, Dally H, et al. 1996. Interaction of carcinogenic metal compounds with deoxyribonucleic acid repair processes. Ann Clin Lab Sci 26(1):31-38.

Harvey SC. 1970. Heavy metals. In: Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics. Toronto: Collier-Macmillan Co., 958-965.

9REFERENCES

Hasegawa H, Matsui M, Okamura S, et al. 1999. Arsenic speciation including 'hidden' arsenic in natural waters. Appl Organomet Chem 13:113-119.

Hassan MM, Atkins PJ, Dunn CE. 2003. The spatial pattern of risk from arsenic poisoning: A Bangladesh case study. J Environ Health 38(1):1-24.

*Haupert TA, Wiersma JH, Goldring JM. 1996. Health effects of ingesting arsenic-contaminated groundwater. Wis Med J 95(2):100-104.

Hauser TR, Bromberg SM. 1982. EPA's monitoring program at Love Canal 1980. Environ Monit Assess 2:249-271.

Hay R, McCormack JG. 1987. Arsenic poisoning and peripheral neuropathy. Aust Fam Physician 16:287-289.

*Hayashi H, Kanisawa M, Yamanaka K, et al. 1998. Dimethylarsinic acid, a main metabolite of inorganic arsenics, has tumorigenecity and progression effects in the pulmonary tumors of A/J mice. Cancer Lett 125:82-88.

*HazDat. 2005. Arsenic. ATSDR's Hazardous substance release and health effects database. Agency for Toxic Substances and Disease Registry. www.atsdr.cdc.gov/hazdat.html. March 5, 2005.

He LZ, Peruzzi D, Tribioli C, et al. 1997. Therapeutic trials with retinoic acid and arsenic trioxide (AsO-3) in PML-RAR-α and PLZF-RAR-α transgenic mice as models of APL. Blood 90(10 Suppl. 1 Part 1):187a.

*He X-T, Logan TJ, Traina SJ. 1995. Physical and chemical characteristics of selected US municipal solid waste compost. J Environ Qual 24:543-552.

*Healy SM, Casarez EA, Ayala-Fierro F, et al. 1998. Enzymatic methylation of arsenic compounds. V. Arsenite methyltransferase activity in tissues of mice. Toxicol Appl Pharmacol 148(1):65-70.

Healy SM, Zakharyan RA, Aposhian HV. 1997. Enzymatic methylation of arsenic compounds: IV. *In vitro* and *in vivo* deficiency of the methylation of arsenite and monomethylarsonic acid in the guinea pig. Mutat Res 386(3):229-239.

HEAST. 1990. Health Effects Assessment Summary Tables. 3rd Quarter FY-1990. Washington, DC: U.S. Environmental Protection Agency.

*Hei TK, Liu SX, Waldren C. 1998. Mutagenicity of arsenic in mammalian cells: Role of reactive oxygen species. Proc Natl Acad Sci U S A 95:8103-8107.

Heinrich-Ramm R, Mindt-Prufert S, Szadkowski D. 2002. Arsenic species excretion after controlled seafood consumption. J Chromatogr B Analyt Technol Biomed Life Sci 778:263-273.

Heinrich-Ramm R, Schaller H, Horn J, et al. 2003. Arsenic species excretion after dimercaptopropanesulfonic acid (DMPS) treatment of an acute arsenic trioxide poisoning. Arch Toxicol 77(2):63-68.

9REFERENCES

*Heiny JS, Tate CM. 1997. Concentration, distribution, and comparison of selected trace elements in bed sediment and fish tissue in the South Platte River basin, USA, 1992-1993. Arch Environ Contam Toxicol 32(3):246-259.

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

*Heitkemper DT, Kaine LA, Jackson DS, et al. 1994. Practical applications of element-specific detection by inductively coupled plasma atomic emission spectroscopy and inductively coupled plasma mass spectrometry to ion chromatography of foods. J Chromatogr A 671(1-2):101-108.

*Helgesen H, Larsen EH. 1998. Bioavailability and speciation of arsenic in carrots grown in contaminated soil. Analyst 123(5):791-796.

Helleday T, Nilsson R, Jenssen D. 2000. Arsenic [111] and heavy metal ions induce intrachromosomal homologous recombination in the hprt gene V79 Chinese hamster cells. Environ Mol Mutagen 35(2):114-122.

*Hemond HF, Solo-Gabriele HM. 2004. Children's exposure to arsenic from CCA-treated wooden decks and playground structures. Risk Anal 24(1):51-64.

*Hernández-Zavala A, Del Razo LM, Aguilar C, et al. 1998. Alteration in bilirubin excretion in individuals chronically exposed to arsenic in Mexico. Toxicol Lett 99:79-84.

*Hershey JW, Oostdyk TS, Keliher PN. 1988. Determination of arsenic and selenium in environmental and agricultural samples by hydride generation atomic adsorption spectrometry. J Assoc Off Anal Chem 71(6):1090-1093.

*Hertz-Picciotto I, Smith AH. 1993. Observations on the dose-response curve for arsenic exposure and lung cancer. Scand J Work Environ Health 19(4):217-226.

Hessl SM, Berman E. 1982. Severe peripheral neuropathy after exposure to monosodium methyl arsonate. J Toxicol Clin Toxicol 19:281-287.

*Hewitt DJ, Millner GC, Nye AC, et al. 1995. Investigation of arsenic exposure from soil at a Superfund site. Environ Res 68(2):73-81.

*Heydorn K. 1970. Environmental variation of arsenic levels in human blood determined by neutron activation analysis. Clin Chim Acta 28:349-357.

*Heyman A, Pfeiffer JB, Willett RW, et al. 1956. Peripheral neuropathy caused by arsenical intoxication: A study of 41 cases with observations on the effects of BAL (2,3 dimercapto-propanol). N Engl J Med 254(9):401-409.

*Heywood R, Sortwell RJ. 1979. Arsenic intoxication in the Rhesus monkey. Toxicol Lett 3:137-144.

Hickson. 2000. Online consumer information sheet for CCA pressure treated lumber. The Hickson Corporation, Smyrna, Georgia. http://www.hickson.com/consumer2.html.

*Higgins I, Welch K, Burchfield C. 1982. Mortality of Anaconda smelter workers in relation to arsenic and other exposures. Department of Epidemiology, University of Michigan, Ann Arbor, MI.

9REFERENCES

Hill AB, Fanning EL. 1948. Studies on the incidence of cancer in a factory handling inorganic compounds of arsenic. I. Mortality experience in the factory. Br J Ind Med 5:1-6.

*Hill CH. 1975. Interrelationships of selenium with other trace elements. Fed Proc 34(11):2096-2100.

Hindmarsh JT. 1988. Further comments on chronic arsenic poisoning [Editorial]. West J Med 149(4):330-331.

Hindmarsh JT. 2000. Arsenic, its clinical and environmental significance. J Trace Elem Exp Med 13:165-172.

*Hindmarsh JT, McCurdy RF. 1986. Clinical and environmental aspects of arsenic toxicity. CRC Crit Rev Clin Lab Sci 23:315-347.

*Hindmarsh JT, McLetchie OR, Heffernan LPM, et al. 1977. Electromyographic abnormalities in chronic environmental arsenicalism. J Anal Toxicol 1:270-276.

*Hingston JA, Collins CD, Murphy RJ, et al. 2001. Leaching of chromated copper arsenate wood preservatives: A review. Environ Pollut 111(1):53-66.

Hinwood AL, Jolley DJ, Sim MR. 1999. Cancer incidence and high environmental arsenic concentrations in rural populations: Results of an ecological study. Int J Environ Health Res 9(2):131-141.

Hinwood AL, Sim MR, Jolley D, et al. 2003. Hair and toenail arsenic concentrations of residents living in areas with high environmental arsenic concentrations. Environ Health Perspect 112(2):187-193.

Hirano S, Cui X, Li S, et al. 2003. Difference in uptake and toxicity of trivalent and pentavalent inorganic arsenic in rat heart microvessel endothelial cells. Arch Toxicol 77(6):305-312.

*Hirata M, Hisanaga A, Tanaka A, et al. 1988. Glutathione and methylation of inorganic arsenic in hamsters. Appl Organomet Chem 2:315-321.

*Hochadel JF, Waalkes MP. 1997. Sequence of exposure to cadmium and arsenic determines the extent of toxic effects in male Fischer rats. Toxicology 116:89-98.

*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.

*Hoff RM, Strachan WMJ, Sweet CW, et al. 1996. Atmospheric deposition of toxic chemicals to the Great Lakes: A review of data through 1994. Atmos Environ 30(20):3505-3527.

Hohmann N, Koffler K. 2002. Risk of adverse reactions from contaminants in Chinese herbal medicines can be minimized by using quality products and qualified practitioners. Int J Environ Health Res 12:99-100-101.

*Holland JW. 1904. Arsenic. In: Peterson F, Haines WS, eds. A textbook of legal medicine and toxicology. Philadelphia, PA: WB Saunders and Co., 404-433.

9REFERENCES

Holland JW. 1923. Inorganic poisons: Arsenic. In: Peterson F, Haines WS, Webster RW, eds. Legal medicine and toxicology. Philadelphia, PA: W.B. Saunders Company, 207-247.

*Holland RH, McCall MS, Lanz HC. 1959. A study of inhaled arsenic-74 in man. Cancer Res 19:1154-1156.

*Holmberg RE, Ferm VH. 1969. Interrelationships of selenium, cadmium and arsenic in mammalian teratogenesis. Arch Environ Health 18:873-877.

*Holmqvist I. 1951. Occupational arsenical dermatitis: A study among employees at a copper ore smelting work including investigations of skin reactions to contact with arsenic compounds. Acta Derm Venerol 31(suppl 26):26-29, 44-45, 110-112, 195-204.

*Holson JF, Stump DG, Clevidence KJ, et al. 2000. Evaluation of the prenatal developmental toxicity of orally administered arsenic trioxide in rats. Food Chem Toxicol 38:459-466.

*Holson JF, Stump DG, Ulrich CE, et al. 1999. Absence of prenatal developmental toxicity from inhaled arsenic trioxide in rats. Toxicol Sci 51:87-97.

Hood RD. 1972. Effects of sodium arsenite on fetal development. Bull Environ Contam Toxicol 7:216-222.

*Hood RD. 1985. Cacodylic acid: Agricultural uses, biological effects and environmental fate. Washington, DC: Agent Orange Projects Office. Veterans Administration Central Office, 1-2, 22-24, 35-49, 95-106.

*Hood RD. 1998. Developmental effects of methylated arsenic metabolites in mice. Bull Environ Contam Toxicol 61:231-238.

*Hood RD, Bishop SL. 1972. Teratogenic effects of sodium arsenate in mice. Arch Environ Health 24:62-65.

*Hood RD, Harrison WP. 1982. Effects of prenatal arsenite exposure in the hamster. Bull Environ Contam Toxicol 29:671-678.

*Hood RD, Harrison WP, Vedel JC. 1982. Evaluation of arsenic metabolites for prenatal effects in the hamster. Bull Environ Contam Toxicol 29:679-687.

Hood RD, Thacker GT, Patterson BL. 1977. Effects in the mouse and rat of prenatal exposure to arsenic. Environ Health Perspect 19:219-222.

*Hood RD, Thacker GT, Patterson BL, et al. 1978. Prenatal effects of oral versus intraperitoneal sodium arsenate in mice. J Environ Pathol Toxicol 1:857-864.

*Hood RD, Vedel GC, Zaworotko MJ, et al. 1988. Uptake distribution and metabolism of trivalent arsenic in the pregnant mouse. J Toxicol Environ Health 25:423-434.

*Hood RD, Vedel-Macrander GC, Zaworotko MJ, et al. 1987. Distribution, metabolism and fetal uptake of pentavalent arsenic in pregnant mice following oral or intraperitoneal administration. Teratology 35:19-25.

9REFERENCES

Hopenhayn C, Ferreccio C, Browning SR, et al. 2003a. Arsenic exposure from drinking water and birth weight. Epidemiology 14(5):593-602.

Hopenhayn C, Huang B, Christian J, et al. 2003b. Profile of urinary arsenic metabolites during pregnancy. Environ Health Perspect 111(16):1888-1891.

*Hopenhayn-Rich C, Biggs ML, Fuchs A, et al. 1996a. Bladder cancer mortality associated with arsenic in drinking water in Argentina. Epidemiology 7(2):117-124.

Hopenhayn-Rich C, Biggs ML, Smith AH, et al. 1996b. Methylation study of a population environmentally exposed to arsenic in drinking water. Environ Health Perspect 104(6):620-628.

*Hopenhayn-Rich C, Biggs ML, Smith AH. 1998. Lung and kidney cancer mortality associated with arsenic in drinking water in Córdoba, Argentina. Int J Epidemiol 27:561-569.

*Hopenhayn-Rich C, Browning SR, Hertz-Picciotto I, et al. 2000. Chronic arsenic exposure and risk of infant mortality in two areas of Chile. Environ Health Perspect 108(7):667-673.

Hopenhayn-Rich C, Smith AH, Goeden HM. 1993. Human studies do not support the methylation threshold hypothesis for the toxicity of inorganic arsenic. Environ Res 60(2):161-177.

*Howell GO, Hill CH. 1978. Biological interaction of selenium with other trace elements in chicks. Environ Health Perspect 25:147-150.

*HSDB. 1998. Hazardous substance data bank (Arsenic). Bethesda, MD: National Library of Medicine. National Toxicology Program.

Hsieh LL, Chen HJ, Hsieh JT, et al. 1994. Arsenic-related Bowen's disease and paraquat-related skin cancerous lesions show no detectable ras and p53 gene alterations. Cancer Lett 86:59-65.

*Hsu C-H, Yang S-A, Wang J-Y, et al. 1999. Mutational spectrum of p53 gene in arsenic-related skin cancers from the blackfoot disease endemic area of Taiwan. Br J Cancer 80(7):1080-1086.

*Hsu Y-H, Li S-Y, Chiou H-Y, et al. 1997. Spontaneous and induced sister chromatid exchanges and delayed cell proliferation in peripheral lymphocytes of Bowen's disease patients and matched controls of arseniasis-hyperendemic villages in Taiwan. Mutat Res 386(3):241-251.

*Hsueh YM, Cheng GS, Wu MM, et al. 1995. Multiple risk factors associated with arsenic-induced skin cancer: Effects of chronic liver disease and malnutritional status. Br J Cancer 71(1):109-14.

Hsueh YM, Hsu MK, Chiou HY, et al. 2002. Urinary arsenic speciation in subjects with or without restriction from seafood dietary intake. Toxicol Lett 133:83-91.

*Hsueh Y-M, Huang Y-L, Huang C-C, et al. 1998a. Urinary levels of inorganic and organic arsenic metabolites among residents in an arseniasis-hyperendemic area in Taiwan. J Toxicol Environ Health 54(6):431-444.

*Hsueh Y-M, Wu W-L, Huang Y-L, et al. 1998b. Low serum carotene level and increase risk of ischemic heart disease related to long-term arsenic exposure. Atherosclerosis 141:249-257.

9REFERENCES

Hu Y, Snow ET. 1998a. Arsenic-GSH interactions: Modulation of cellular redox levels and signal transduction pathways. Environ Mol Mutagen 31(Suppl 29):53.

Hu Y, Snow ET. 1998b. Effect of arsenic on DNA ligase activity in human cells in culture. Environ Mole Mutagen 31(Suppl 29):53.

Hu Y, Snow ET. 1998c. Modulation of DNA repair and GSH levels in human keratinocytes by sub-micromolar arsenic. Proc Am Assoc Cancer Res 39:243.

*Hu Y, Su L, Snow ET. 1998. Arsenic toxicity is enzyme specific and its effects on ligation are not caused by the direct inhibition of DNA repair enzymes. Mutat Res 408:203-218.

Hu CJ, Zhang AH, Huang HH. 2003. Molecular pathology of skin carcinogenesis due to arsenicalism from coal-burning. Arch Environ Health 58(2):92-96.

Huang C, Ke Q, Costa M, et al. 2004. Molecular mechanisms of arsenic carcinogenesis. Mol Cell Biochem 255(1-2):57-66.

*Huang H, Huang CF, Huang JS, et al. 1992. The transition from late G_1 to early S phase is most vulnerable to the coclastogenic effect of ultraviolet radiation plus arsenite. Int J Radiat Biol 61(1):57-62.

*Huang H, Huang CF, Wu DR, et al. 1993. Glutathione as a cellular defense against arsenite toxicity in cultured Chinese hamster ovary cells. Toxicology 79(3):195-204.

*Huang R-N, Ho I-C, Yih L-H, et al. 1995. Sodium arsenite induces chromosome endoreduplication and inhibits protein phosphatase activity in human fibroblasts. Environ Mol Mutagen 25(3):188-196.

Huang RY, Jan KY, Lee TC. 1987. Posttreatment with sodium arsenite is coclastogenic in log phase but not in stationary phase. Hum Genet 75:159-162.

*Huang S-Y, Chang C-S, Tang J-L, et al. 1998. Acute and chronic arsenic poisoning associated with treatment of acute promyelocytic leukaemia. Br J Haematol 103:1092-1095.

Huang XJ, Wiernik PH, Klein RS, et al. 1997. Potentiation of arsenic trioxide (As_2O_3) induced apoptosis by retinoic acid (RA) in RA-sensitive (S) and RA-resistant (R) HL-60 myeloid leukemia cells. Blood 90(10 Suppl 1 Part 1):329a.

*Huang Y-Z, Qian X-C, Wang G-Q, et al. 1985. Endemic chronic arsenism in Xinjiang. Chin Med J 98(3):219-222.

Huff J, Waalkes M, Chan P. 1998. Arsenic: Evidence of carcinogenicity in animals. Environ Health Perspect 106(12):582.

*Huggett DB, Khan IA, Allgood JC, et al. 2001. Organochlorine pesticides and metals in select botanical dietary supplements. Bull Environ Contam Toxicol 66:150-155.

Hughes MF. 2002. Arsenic toxicity and potential mechanisms of action. Toxicol Lett 133(1):1-16.

*Hughes MF, Del Razo LM, Kenyon EM. 2000. Dose-dependent effects on tissue distribution and metabolism of dimethylarsinic acid in the mouse after intravenous administration. Toxicology 143(2):155-166.

*Hughes MF, Kenyon EM, Edwards BC, et al. 2003. Accumulation and metabolism of arsenic in mice after repeated oral administration of arsenate. Toxicol Appl Pharmacol 191(3):202-210.

Hughes JP, Polissar L, van Belle G. 1988. Evaluation and synthesis of health effects studies of communities surrounding arsenic producing industries. Int J Epidemiol 17:407-413.

Hughes MF, Kenyon EM. 1998. Dose-dependent effects on the disposition of monomethylarsonic acid and dimethylarsinic acid in the mouse after intravenous administration. J Toxicol Environ Health A53(2):95-112.

*Hughes MF, Menache M, Thompson DJ. 1994. Dose-dependent disposition of sodium arsenate in mice following acute oral exposure. Fundam Appl Toxicol 22(1):80-89.

Hugues De The, Zhu J, Koken M, et al. 1997. Arsenic and retinoic acid: Towards rational treatments of acute promyelocytic leukaemia. Exp Hematol 25(8):909.

Hullinger G, Sangster L, Colvin B, et al. 1998. Bovine arsenic toxicosis from ingestion of ashed copper-chrome-arsenate treated timber. Vet Hum Toxicol 40(3):147-148.

Hung DQ, Nekrassova O, Compton RG. 2004. Analytical methods for inorganic arsenic in water: A review. Talanta 64:269-277.

Hunt LE, Howard AG. 1994. Arsenic speciation and distribution in the carnon estuary following the acute discharge of contaminated water from a disused mine. Mar Pollut Bull 28(1):33-38.

Hunt E, Hader SL, Files D, et al. 1999. Arsenic poisoning seen at Duke Hospital, 1965-1998. N C Med J 60(2):70-74.

Hunter ES, Dix D. 1996. Antisense oligonucleotides against *Hsp70-1* and *70-3* increase mouse embryonic sensitivity to arsenite-induced dysmorphogenesis in vitro. Teratology 53(2):86.

Hunter FT, Kip AF, Irvine W. 1942. Radioactive tracer studies on arsenic injected as potassium arsenite. J Pharmacol Exp Ther 76:207.

*Hwang Y-H, Bornschein RL, Grote J, et al. 1997a. Environmental arsenic exposure of children around a former copper smelter site. Environ Res 72(1):72-81.

*Hwang Y-H, Bornschein RL, Grote J, et al. 1997b. Urinary arsenic excretion as a biomarker of arsenic exposure in children. Arch Environ Health 52(2):139-147.

*Hwang YH, Chen SC. 2000. Monitoring of low level arsenic exposure during maintenance of ion implanters. Arch Environ Health 55(5):347-354.

Hwang YH, Lee ZY, Wang JD, et al. 2002. Monitoring of arsenic exposure with speciated urinary inorganic arsenic metabolites for ion implanter maintenance engineers. Environ Res 90:207-216.

Hypertension Study Group. 2001. Prevalence, awareness, treatment and control of hypertension among the elderly in Bangladesh and India: A multicentre study. Bull World Health Organ 79(6):490-500.

9REFERENCES

Hysong TA, Burgess JL, Cebrian Garcia ME, et al. 2003. House dust and inorganic urinary arsenic in two Arizona mining towns. J Expo Anal Environ Epidemiol 13(3):211-218.

*IARC. 1980. Arsenic and arsenic compounds. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 23. Some metals and metallic compounds. Lyon, France: International Agency for Research on Cancer, 39-141.

*IARC. 1987. Arsenic and arsenic compounds. IARC monographs on the evaluation of carcinogenic risk of chemicals to humans. Suppl 7. Overall evaluations of carcinogenicity: Updating of IARC monographs volumes 1-42. World Health Organization, International Agency for Research on Cancer, Lyon, France, 29-33, 57.

*IARC. 2004. Overall evaluations of carcinogenicity to humans: As evaluated in IARC Monographs volumes 1-82 (at total of 900 agents, mixtures and exposures). Lyon, France: International Agency for Research on Cancer. http://www-cie.iarc.fr/monoeval/crthall.html. February 15, 2005.

*Ide CW, Bullough GR. 1988. Arsenic and old glass. J Soc Occup Med 38:85-88.

*Ihrig MM, Shalat SL, Baynes C. 1998. A hospital-based case-control study of stillbirths and environmental exposure to arsenic using and atmospheric dispersion model linked to a geographical information system. Epidemiology 9(3):290-294.

IJC. 1983. An inventory of chemical substances identified in the Great Lakes ecosystem. Vol 1. Summary. Report to the Great Lakes Water Quality Board by the International Joint Commission, Windsor, Ontario.

IJC. 1989. 1989 report on Great Lakes water quality. Presented at Hamilton, Ontario, October 1989. Windsor, Ontario: International Joint Commission, Great Lakes Water Quality Board.

Innes JR, Ulland BM, Valerio MG, et al. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. J Natl Cancer Inst 42:1101-1114.

Inoue Y, Date Y, Yoshida K, et al. 1996. Speciation of arsenic compounds in the urine of rats orally exposed to dimethylarsinic acid ion chromatography with ICP-MS as an element-selective detector. Appl Organomet Chem 10(9):707-711.

*Inoue Y, Kawabata K, Takahashi H, et al. 1994. Determination of arsenic compounds using inductively coupled plasma mass spectrometry with ion chromatography. J Chromatog A675(1-2):149-154.

Irgolic K. 1982. Speciation of arsenic compounds in water supplies. Cincinnati, OH: U.S. Environmental Protection Agency, Health Effects Research Laboratory. EPA6005182010.

*IRIS. 2005. Arsenic. Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/iris/subst/index.html. February 15, 2004.

Ishinishi N, Kodama Y, Nobutomo K, et al. 1977. Preliminary experimental study on carcinogenicity of arsenic trioxide in rat lung. Environ Health Perspect 19:191-196.

*Ishinishi N, Yamamoto A, Hisanaga A, et al. 1983. Tumorigenicity of arsenic trioxide to the lung in Syrian golden hamsters by intermittent instillations. Cancer Lett 21:141-147.

9REFERENCES

Ishitsuka K, Suzuki S, Hanada S, et al. 1997. Arsenic acid as well as retinoic acids have therapeutic potential to adult T cell leukemia. Blood 90(10 Suppl. 1 Part 1):324a-325a.

*ITA. 2005a. U.S. Trade quick-reference tables: December 2003 Imports. 280480: Arsenic. International Trade Administration. http://www.ita.doc.gov/td/industry/otea/Trade-Detail/Latest-December/Imports/28/280480.html. February 14, 2005.

*ITA. 2005b. U.S. Trade quick-reference tables: December 2003 Imports. 281129: Inorganic Oxygen Compounds of Nonmetals, NESOI. International Trade Administration. http://www.ita.doc.gov/td/industry/otea/Trade-Detail/Latest-December/Imports/28/281129.html. February 14, 2005.

Ivankovic S, Eisenbrand G, Preussmann R. 1979. Lung carcinoma induction in BD rats after a single intratracheal instillation of an arsenic-containing pesticide mixture formerly used in vineyards. Int J Cancer 24:786-788.

Jackson BP, Bertsch PM. 2001. Determination of arsenic speciation in poultry wastes by IC-ICP-MS. Environ Sci Technol 35(24):4868-4873.

Jacobsen CF, Colshire D, McLean VA. 1999. Appropriate exposure routes and doses in studies designed to assess developmental toxicity: A case study of inorganic arsenic. Int J Toxicol 18(5):361-368.

*Jacobson-Kram D, Montalbano D. 1985. The reproductive effects assessment group's report on the mutagenicity of inorganic arsenic. Environ Mutagen 7:787-804.

*Jager JW, Ostrosky-Wegman P. 1997. Arsenic: A paradoxical human carcinogen. Mutat Res 386(3):181-184.

*Jaghabir MTW, Abdelghani A, Anderson AC. 1988. Oral and dermal toxicity of MSMA to New Zealand white rabbits, *Oryctalagus cuniculus*. Bull Environ Contam Toxicol 40:119-122.

*Jaghabir MTW, Abdelghani AA, Anderson AC. 1989. Histopathological effects of monosodium methanearsonate (MSMA) on New Zealand white rabbits (*Oryctalagus cuniculus*). Bull Environ Contam Toxicol 42:289-293.

*Jain A, Loeppert RH. 2000. Effect of competing anions on the adsorption of arsenate and arsenite by ferrihydrite. J Environ Qual 29:1422-1430.

*Jain A, Raven KP, Loeppert RH. 1999. Arsenite and arsenate adsorption on ferrihydrite: Surface charge reduction and net OH^- release stoichiometry. Environ Sci Technol 33:1179-1184.

Jakobsson-Lagerkvist B, Soderberg HA, Nordberg GF, et al. 1993. Biological monitoring of arsenic, lead and cadmium in occupationally and environmentally exposed pregnant women. Scand J Work Environ Health 19:50-53.

Jalali N, Pajoomand A, Shadnia S, et al. 2001. The report of acute renal failure due to exposure to arsine. Toxicol Lett 123:91.

James WH. 1998. Sex ratio of offspring of residents of a highly polluted housing site. Scand J Work Environ Health 24(1):74-75.

9REFERENCES

*Jan KY, Huang RY, Lee TC. 1986. Different modes of action of sodium arsenite, 3-aminobenzamide and caffeine on the enhancement of ethyl methanesulfonate clastogenicity. Cytogenet Cell Genet 41:202-208.

Jang YC, Townsend TG, Ward M, et al. 2002. Leaching of arsenic, chromium, and copper in a contaminated soil at a wood preserving site. Bull Environ Contam Toxicol 69:808-816.

*Janssen RPT, Peijnenburg WJGM, Posthuma L, et al. 1997. Equilibrium partitioning of heavy metals in Dutch field soils: I. Relationship between metal partition coefficients and soil characteristics. Environ Toxicol Chem 16(12):2470-2478.

*Järup L, Pershagen G. 1991. Arsenic exposure, smoking, and lung cancer in smelter workers - a case-control study. Am J Epid 134(6):545-551.

*Järup L, Pershagen G, Wall S. 1989. Cumulative arsenic exposure and lung cancer in smelter workers: A dose-response study. Am J Ind Med 15:31-41.

*Jelinek CF, Corneliussen PE. 1977. Levels of arsenic in the United States food supply. Environ Health Perspect 19:83-87.

Jenkins RA. 1986. Occurrence of selected metals in cigarette tobaccos and smoke. IARC Sci Publ 71:129-141.

*Jenkins RB. 1966. Inorganic arsenic and the nervous system. Brain 89:479-498.

Jensen GE. 1987. Measurement of occupational exposure of arsenic: A preliminary study of arsenic in urine. In: Trace elements in human health and disease. Second Nordic Symposium, Odense, Denmark, August 17-21.

*Jensen GE, Hansen ML. 1998. Occupational arsenic exposure and glycosylated haemoglobin. Analyst 123(1):77-80.

*Jensen GE, Olsen ILB. 1995. Occupational exposure to inorganic arsenic in wood workers and taxidermists-air sampling and biological monitoring. J Environ Sci Health A30(4):921-938.

Jensen GE, Christensen JM, Poulsen OM, et al. 1991. Occupational and environmental exposure to arsenic-increased urinary arsenic level in children. Sci Total Environ 107:169-177.

*Jha AN, Noditi M, Nilsson R, et al. 1992. Genotoxic effects of sodium arsenite on human cells. Mutat Res 284(2):215-221.

Jiang JQ. 2001. Removing arsenic from groundwater for the developing world--a review. Water Sci Technol 44(6):89-98.

Jiang G, Gong Z, Li XF, et al. 2003. Interaction of trivalent arsenicals with metallothionein. Chem Res Toxicol 16(7):873-880.

Jiang SJ, Lin TM, Wu HL, et al. 2002. Decrease of fibrinolytic activity in human endothelial cells by arsenite. Thromb Res 105(1):55-62.

9REFERENCES

Jianhua N, Guoqiang C, Zhiziang S, et al. 1998. Pharmacokinetics of intravenous arsenic trioxide in the treatment of acute promyelocytic leukemia. Chin Med J 111(12):1107-1110.

*Jimi S, Uchiyama M, Takaki A, et al. 2004. Mechanisms of cell death induced by cadmium and arsenic. Ann N Y Acad Sci 1011:325-331.

Jin Y, Sun G, Li X, et al. 2004. Study on the toxic effects induced by different arsenicals in primary cultured rat astroglia. Toxicol Appl Pharmacol 196(3):396-403.

*Johansen MG, McGowan JP, Tu SH, et al. 1984. Tumorigenic effect of dimethylarsinic acid in the rat. Proc West Pharmacol Soc 27:289-291.

*Johanson CE. 1980. Permeability and vascularity of the developing brain: Cerebellum vs cerebral cortex. Brain Res 190:3-16.

Johnson DL, Braman RS. 1975. Alkyl-and inorganic arsenic in air samples. Chemosphere 6:333-338.

*Johnson LR, Farmer JG. 1989. Urinary arsenic concentrations and speciation in Cornwall residents. Environ Geochem Health 11:39-44.

Johnson RD, Manske DD, New DH, et al. 1984. Pesticide, heavy metal, and other chemical residues in infant and toddler total diet samples. (III). August 1976-September 1977. J Assoc Off Anal Chem 67:145-154.

*Jones CA, Inskeep WP, Neuman DR. 1997. Arsenic transport in contaminated mine tailings following liming. J Environ Qual 26(2):433-439.

Jongen WM, Cardinaals JM, Bos PM. 1985. Genotoxicity testing of arsenobetaine, the predominant form of arsenic in marine fishery products. Food Chem Toxicol 23:669-673.

*Jonnalagadda SB, Nenzou G. 1996. Studies on arsenic rich mine dumps: III. Effect on the river water. J Environ Sci Health A31(10):2547-2555.

Josephson J. 2002. The slow poisoning of Bangladesh: Metals in drinking water. Environ Health Perspect 110(11):A690-691.

Jun M, Jiwei L, Minghua J, et al. 1997. Clinical observation on arsenic trioxide in the treatment of acute promyelocytic leukemia. Experimental Hematology 25(8):866.

*Kachinskas DJ, Qin Q, Phillips MA, et al. 1997. Arsenate suppression of human keratinocyte programming. Mutat Res 386(3):253-261.

Kahakachchi C, Uden PC, Tyson JF. 2004. Extraction of arsenic species from spiked soils and standard reference materials. Analyst 129(8):714-718.

Kähkönen MA, Suominen KP, Manninen PKG, et al. 1998. 100 years of sediment accumulation history of organic halogens and heavy metals in recipient lakes of pulping industry in Finland. Environ Sci Technol 32(12):1741-1746.

*Kaise T, Watanabe S, Itoh K. 1985. The acute toxicity of arsenobetaine. Chemosphere 14(9):1327-1332.

9REFERENCES

*Kaise T, Yamauchi H, Horiguchi Y, et al. 1989. A comparative study on acute toxicity of methylarsonic acid, dimethylarsinic acid and trimethylarsine oxide in mice. Appl Organomet Chem 3:273-277.

*Kalbitz K, Wennrich R. 1998. Mobilization of heavy metals and arsenic in polluted wetland soils and its dependence on dissolved organic matter. Sci Total Environ 209:27-39.

*Kalman DA. 1987. Dietary contributions to arsenic species in urine. In: Trace elements in human health and disease: Extended abstracts from the second Nordic symposium, Odense, 17-21 August 1987. Copenhagen: World Health Organization, 136-139, 230-233.

Kaltreider RC, Ihnat MA, Andrew AS, et al. 1998. Effects of the heavy metals arsenic and chromium on transcription factor binding and gene expression. Toxicologist 42(1-S):321.

*Kaltreider RC, Pesce CA, Ihnat MA, et al. 1999. Differential effects of arsenic(III) and chromium(VI) on nuclear transcription factor binding. Mol Carcinog 25:219-229.

*Kamijo Y, Soma K, Asari Y, et al. 1998. Survival after massive arsenic poisoning self-treated by high fluid intake. Clin Toxicol 36(1-2):27-29.

Kannan GM, Flora SJ. 2004. Chronic arsenic poisoning in the rat: Treatment with combined administration of succimers and an antioxidant. Ecotoxicol Environ Saf 58(1):37-43.

*Kannan GM, Tripathi N, Dube SN, et al. 2001. Toxic effects of arsenic (III) on some hematopoietic and central nervous system variables in rats and guinea pigs. J Toxicol Clin Toxicol 37(7):675-682.

*Karagas MR, Morris JS, Weiss JE, et al. 1996. Toenail samples as an indicator of drinking water arsenic exposure. Cancer Epidemiol Biomarkers Prev 5(10):849-852.

*Karagas MR, Stukel TA, Morris JS, et al. 2001. Skin cancer risk in relation to toenail arsenic concentrations in a US population-based case-control study. Am J Epidemiol 153(6):559-565.

*Karagas MR, Tosteson TD, Blum J, et al. 1998. Design of an epidemiologic study of drinking water arsenic exposure and skin and bladder cancer risk in a U.S. population. Environ Health Perspect Suppl 106(4):1047-1050.

Karagas MR, Tosteson TD, Blum J, et al. 2000. Measurement of low levels of arsenic exposure: A comparison of water and toenail concentrations. Am J Epidemiol 152(1):84-90.

*Karagas MR, Tosteson TD, Morris JS, et al. 2004. Incidence of transitional cell carcinoma of the bladder and arsenic exposure in New Hampshire. Cancer Causes Control 15:465-472.

Karalliedde L, Wheeler H, Maclehose R, et al. 2000. Possible immediate and long-term health effects following exposure to chemical warfare agents. Public Health 114(4):238-248.

Karim M. 2000. Arsenic in groundwater and health problems in Bangladesh. Water Res 34(1):304-310.

*Kashiwada E, Kuroda K, Endo G. 1998. Aneuploidy induced by dimethylarsinic acid in mouse bone marrow cells. Mutat Res 413:33-38.

9REFERENCES

*Kasper ML, Schoenfield L, Strom RL, et al. 1984. Hepatic angiosarcoma and bronchioloalveolar carcinoma induced by Fowler's solution. JAMA 252(24):3407-3408.

Kato K, Hayashi H, Hasegawa A, et al. 1994. DNA damage induced in cultured human alveolar (L-132) cells by exposure to dimethylarsinic acid. Environ Health Perspect 102(Suppl 3):285-8.

Kato K, Ito H, Okamoto K. 1997. Modulation of the arsenite-induced expression of stress proteins by reducing agents. Cell Stress Chaperones 2(3):199-209.

Katsnelson BA. 1998. Re: Arsenic carcinogenicity testing. Environ Health Perspect 106(12):582.

*Kavanagh PJ, Farago ME, Thornton I, et al. 1997. Bioavailability of arsenic in soil and mine wastes of the Tamar Valley, SW England. Chem Speciat Bioavail 9(3):77-81.

*Kawaguchi K, Oku N, Rin K, et al. 1996. Dimethylarsenics reveal DNA damage induced by superoxide anion radicals. Biol Pharm Bull 19(4):551-553.

Kawata H, Kuroda K, Endo Y, et al. 2001. Dimethylarsenic acid targets tubulin in mitotic cells to induce abnormal spindles. Appl Organomet Chem 15:676-682.

*Kennedy S, Rice DA, Cush PF. 1986. Neuropathology of experimental 3-nitro-4-hydroxyphenylarsonic acid toxicosis in pigs. Vet Pathol 23:454-461.

Kenyon EM, Hughes MF. 2001. A concise review of the toxicity and carcinogenicity of dimethylarsinic acid. Toxicology 160(1-3):227-236.

Kenyon EM, Hughes MF, Levander OA. 1997. Influence of dietary selenium on the disposition of arsenate in the female B6C3F$_1$ mouse. J Toxicol Environ Health 51(3):279-299.

*Kerckaert GA, Brauninger R, LeBoeuf RA, et al. 1996. Use of the Syrian hamster embryo cell transformation assay for carcinogenicity prediction of chemicals currently being tested by the national toxicology program in rodent bioassays. Environ Health Perspect 104(suppl. 5):1075-1084.

*Kerkvliet NI, Steppan LB, Koller LD, et al. 1980. Immunotoxicology studies of sodium arsenate - effects of exposure on tumor growth and cell-mediated tumor immunity. J Environ Pathol Toxicol 4:65-79.

*Kerr HD, Saryan LA. 1986. Arsenic content of homeopathic medicines. Clin Toxicol 24(5):451-459.

*Kerr KB, Cavett JW, Thompson OL. 1963. The toxicity of an organic arsenical, 3-nitro-4-hydroxyl-phenylarsonic acid. I. Acute and subacute toxicity. Toxicol Appl Pharmacol 5:507-525.

*Kersjes MP, Maurer JR, Trestrail JH, et al. 1987. An analysis of arsenic exposures referred to the Blodgett Regional Poison Center. Vet Hum Toxicol 29(1):75-78.

*Kessel M, Liu SX, Xu A, et al. 2002. Arsenic induces oxidative DNA damage in mammalian cells. Mol Cell Biochem 234-235(1-2):301-308.

*Khan AH, Tarafdar SA, Ali M, et al. 1989. The status of trace and minor elements in some Bangladeshi foodstuffs. J Radioanalyt Nuc Chem 134(2):367-381.

9REFERENCES

*Kidwell JM, Phillips LJ, Birchard GF. 1995. Comparative analyses of contaminant levels in bottom feeding and predatory fish using the national contaminant biomonitoring program data. Bull Environ Contam Toxicol 54(6):919-923.

*Kim MJ, Nriagu J, Haack S. 2002. Arsenic species and chemistry in groundwater of southeast Michigan. Environ Pollut 120(2):379-390.

*Kingston RL, Hall S, Sioris L. 1993. Clinical observations and medical outcome in 149 cases of arsenate ant killer ingestion. J Toxicol Clin Toxicol 31(4):581-591.

Kinjo K, Kizaki A, Muto A, et al. 1997. Establishment of a retinoic acid resistant human APL model in hGM-CSF transgenic SCID mice and their application to the *in vivo* study of arsenic trioxide (As_2O_3). Blood 90(10 Suppl. 1 Part 1):332a.

*Kinney PL, Chillrud SN, Ramstrom S, et al. 2002. Exposures to multiple air toxics in New York City. Environ Health Perspect 110(Suppl. 4):539-546.

Kitamura M, Kuroda K, Endo Y, et al. 2002. Cysteine enhances clastogenic activity of dimethylarsinic acid. Appl Organomet Chem 16:391-396.

Kitchin KT. 2001. Recent advances in arsenic carcinogenesis: Modes of action, animal model systems, and methylated arsenic metabolites. Toxicol Appl Pharmacol 172(3):249-261.

*Kitchin KT, Ahmad S. 2003. Oxidative stress as a possible mode of action for arsenic carcinogenesis. Toxicol Lett 137(1-2):3-13.

Kitchin KT, Del Razo LM, Brown JL, et al. 1999. An integrated pharmacokinetic and pharmacodynamic study of arsenite action. 1. Heme oxygenase induction in rats. Teratog Carcinog Mutagen 19(6):385-402.

Kjellstrom T. 1979. Exposure and accumulation of cadmium in populations from Japan, the United States, and Sweden. Environ Health Perspect 28:169-197.

Klaassen CD. 1974. Biliary excretion of arsenic in rats, rabbits and dogs. Toxicol Appl Pharmacol 29:447-457.

Klaue B, Blum JD. 1999. Trace analyses of arsenic in drinking water by inductively coupled plasma mass spectrometry: High resolution versus hydride generation. Anal Chem 71:1408-1414.

*Klemmer HW, Leitis E, Pfenninger K. 1975. Arsenic content of house dusts in Hawaii. Bull Environ Contam Toxicol 14(4):449-452.

Knobeloch L, Korthof S, Anderson H. 1998. Never on a Saturday (or a Sunday): The case against using weekend urine specimens to assess arsenic exposure. Wis Med J 97(9):46-48.

Knowles FC, Benson AA. 1984. The enzyme inhibitory form of inorganic arsenic. Z Gesamte Hyg 30:625-626.

*Ko Y-C. 1986. A critical review of epidemiologic studies on blackfoot disease. J Voeh 8(3)339-353.

9REFERENCES

Koch I, Feldmann J, Wang L, et al. 1999. Arsenic in the Meager Creek hot springs environment, British Columbia, Canada. Sci Total Environ 236:101-117.

*Kochhar TS, Howard W, Hoffman S, et al. 1996. Effect of trivalent and pentavalent arsenic in causing chromosome alterations in cultured Chinese hamster ovary (CHO) cells. Toxicol Lett 84(1):37-42.

*Koh E, Kondoh N, Kaihara H, et al. 1989. Ureteral tumor with multiple Bowen's disease forty-two years after exposure to arsenic. Eur Urol 16:398-400.

Kohlmeyer U, Jantzen E, Kuballa J, et al. 2003. Benefits of high resolution IC-ICP-MS for the routine analysis of inorganic and organic arsenic species in food products of marine and terrestrial origin. Anal Bioanal Chem 377(1):6-13.

Kollmer WE. 1992. Arsenic in induced hair of the rat and its relation to the content in various organs during chronic exposure. J Trace Elem Electrolytes Health Dis 6(1):11-14.

*Komori M, Nishio K, Kitada M et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human livers. Biochemistry 29:4430-4433.

Korte N. 1991. Naturally occurring arsenic in groundwaters of the midwestern United States. Environ Geol Water Sci 18(2):137-141.

Koscieniak P. 2004. On analytical usefulness of the recovery method. Anal Lett 37(12):2625-2640.

*Kraus RJ, Ganther HE. 1989. Synergistic toxicity between arsenic and methylated selenium compounds. Biol Trace Elem Res 20:105-113.

*Kraus T, Quidenus G, Schaller KH. 2000. Normal values for arsenic and selenium concentrations in human lung tissue. Arch Environ Contam Toxicol 38:384-389.

*Kreiss K, Zack MM, Feldman RG, et al. 1983. Neurologic evaluation of a population exposed to arsenic in Alaskan well water. Arch Environ Health 38(2):116-121.

*Kreppel H, Bauman JW, Liu J, et al. 1993. Induction of metallothionein by arsenicals in mice. Fundam Appl Toxicol 20:184-189.

*Kreppel H, Liu J, Liu Y, et al. 1994. Zinc induced arsenite tolerance in mice. Fundam Appl Toxicol 23:32-37.

*Kreppel H, Reichl FX, Kleine A, et al. 1995. Antidotal efficacy of newly synthesized dimercaptosuccinic acid (DMSA) monoesters in experimental arsenic poisoning in mice. Fundam Appl Toxicol 26(2):239-245.

Kresimon J, Gruter UM, Hirner AV. 2001. HG/LT-GC/ICP-MS coupling for identification of metal(loid) species in human urine after fish consumption. Fresenius J Anal Chem 371:586-590.

*Krishnan K, Andersen ME. 1994. Physiologically-based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. Principles and methods of toxicology. 3rd ed. New York, NY: Raven Press, Ltd., 149-188.

9REFERENCES

*Krishnan K, Andersen ME, Clewell HJ III, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures: Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

*Kroemer G, de Thé H. 1999. Arsenic trioxide, a novel mitochondriotoxic anticancer agent? J Natl Cancer Inst 91(9):743-745.

*Kroes R, van Logten MJ, Berkvens JM, et al. 1974. Study on the carcinogenicity of lead arsenate and sodium arsenate and on the possible synergistic effect of diethylnitrosamine. Food Cosmet Toxicol 12(5-6):671-679.

Kubota R, Kunito T, Tanabe S. 2003. Occurrence of several arsenic compounds in the liver of birds, cetaceans, pinnipeds, and sea turtles. Environ Toxicol Chem 22(6):1200-1207.

Kumana CR, Au WY, Lee NSL, et al. 2002. Systemic availability of arsenic from oral arsenic-trioxide used to treat patients with hematological malignancies. Eur J Clin Pharmacol 58:521-526.

Kumar S, Singh A. 2000. Biological monitoring of industrial solvent workers exposed to toluene and xylene. J Environ Biol 21(1):79-84.

*Kumaresan M, Riyazuddin P. 2001. Overview of speciation chemistry of arsenic. Curr Sci 80(7):837-846.

Kuroda K, Yoshida K, Yoshimura M, et al. 2004. Microbial metabolite of dimethylarsinic acid is highly toxic and genotoxic. Toxicol Appl Pharmacol 198(3):345-353.

Kuo TP, Chen MH. 1969. Follow-up study of surgical treatment of endemic spontaneous gangrene in tropical Taiwan. J Formosan Med Assoc 68:275-289.

*Kurokawa Y, Takahashi M, Maekawa A, et al. 1989. Promoting effect of metal compounds on liver, stomach, kidney, pancreas, and skin carcinogenesis. J Am Coll Toxicol 8(7)1235-1239.

*Kurttio P, Komulain H, Hakala E, et al. 1998. Urinary excretion of arsenic species after exposure to arsenic present in drinking water. Arch Environ Contam Toxicol 34:297-305.

*Kurttio P, Pukkala E, Kahelin H, et al. 1999. Arsenic concentrations in well water and risk of bladder and kidney cancer in Finland. Environ Health Perspect 107(9):705-710.

*Kyle RA, Pease GL. 1965. Hematologic aspects of arsenic intoxication. N Engl J Med 273(1):18-23.

*LaForce MJ, Fendorf SE, Li GC, et al. 1998. A laboratory evaluation of trace element mobility from flooding and nutrient loading of Coeur d'Alene River sediments. J Environ Qual 27:318-328.

*Lagerkvist B, Linderholm H, Nordberg GF. 1986. Vasospastic tendency and Raynaud's phenomenon in smelter workers exposed to arsenic. Environ Res 39:465-474.

*Lagerkvist BEA, Linderholm H, Nordberg GF. 1988. Arsenic and Raynaud's phenomenon: Vasospastic tendency and excretion of arsenic in smelter workers before and after the summer vacation. Int Arch Occup Environ Health 60:361-364.

9REFERENCES

*Lagerkvist BJ, Zetterlund B. 1994. Assessment of exposure to arsenic among smelter workers: A five-year follow-up. Am J Ind Med 25(4):477-488.

Lai M-S, Hsueh Y-M, Chen C-J, et al. 1994. Ingested inorganic arsenic and prevalence of diabetes mellitus. Am J Epidemiol 139(5):484-492.

Lai VWM, Sun Y, Ting E, et al. 2004. Arsenic speciation in human urine: Are we all the same? Toxicol Appl Pharmacol 198:297-306.

Lakso JU, Peoples SA. 1975. Methylation of inorganic arsenic by mammals. J Agric Food Chem 23:674-676.

Lam RHF, Brown JP, Fan AM. 1994. Chemicals in California drinking water: Source of contamination, risk assessment, and drinking water standards. In: Wang RGM, ed. Water contamination and health: Integration of exposure assessment, toxicology, and risk assessment. New York: Marcel Dekker, Inc.,15-44.

*Lambert TW, Lane S. 2004. Lead, arsenic, and polycyclic aromatic hydrocarbons in soil and house dust in the communities surrounding the Sydney, Nova Scotia, tar ponds. Environ Health Perspect 112(1):35-41.

*Lamm SH, Engel A, Kruse MB, et al. 2004. Arsenic in drinking water and bladder cancer mortality in the United States: An analysis based on 133 U.S. counties and 30 years of observation. J Occup Environ Med 46(3):298-306.

Lammon CA, Hood RD. 2001. Influence of diet and dietary protein level on the developmental toxicity of inorganic arsenic in mice. Teratology 63(6):289.

*Landau ED, Thompson DJ, Feldman RG, et al. 1977. Selected noncarcinogenic effects of industrial exposure to inorganic arsenic. Washington, DC: U.S. Environmental Protection Agency. EPA560677018.

*Lander JJ, Stanley RJ, Sumner HW, et al. 1975. Angiosarcoma of the liver associated with Fowler's solution (potassium arsenite). Gastroenterology 68(6):1582-1586.

*Landolph JR. 1994. Molecular mechanisms of transformation of C3H/10T1/2 C1 8 mouse embryo cells and diploid human fibroblasts by carcinogenic metal compounds. Environ Health Perspect 102(suppl. 3):119-125.

Landrigan PJ. 1981. Arsenic-state of the art. Am J Ind Med 2:5-14.

*Landsberger S, Simsons A. 1987. Chromium, nickel, and arsenic determinations in human samples by thermal and epithermal neutron activation analyses. Biol Trace Elem Res 13:357-362.

*Landsberger S, Wu D. 1995. The impact of heavy metals from environmental tobacco smoke on indoor air quality as determined by Compton suppression neutron activation analysis. Sci Total Environ 173-174(1-6):323-337.

Langlois C, Langis R. 1995. Presence of airborne contaminants in the wildlife of northern Quebec. Sci Total Environ 160/161:391-402.

9REFERENCES

Lanphear BP, Succop P, Roda S, et al. 2003. The effect of soil abatement on blood lead levels in children living near a former smelting and milling operation. Public Health Rep 118(2):83-91.

*Lantzsch H, Gebel T. 1997. Genotoxicity of selected metal compounds in the SOS chromotest. Mutat Res 389(2-3):191-197.

*Lanz H, Wallace PC, Hamilton JG. 1950. The metabolism of arsenic in laboratory animals using As^{74} as a tracer. Univ California Publ Pharmacol 2(29):263-282.

*Laparra JM, Velez D, Montoro R, et al. 2003. Estimation of arsenic bioaccessibility in edible seaweed by an in vitro digestion method. J Agric Food Chem 51:6080-6085.

*Larochette N, Decaudin D, Jacotot E, et al. 1999. Rapid communication; Arsenite induces apoptosis via a direct effect on the mitochondrial permeability transition pore. Exp Cell Res 249:413-421.

*Larramendy ML, Popescu NC, DiPaolo J. 1981. Induction by inorganic metal salts of sister chromatid exchanges and chromosome aberrations in human and Syrian hamster strains. Environ Mutagen 3:597-606.

*Larsen EH, Moseholm L, Nielsen MM. 1992. Atmospheric deposition of trace elements around point sources and human health risk assessment: II. Uptake of arsenic and chromium by vegetables grown near a wood preservation factory. Sci Total Environ 126(3):263-275.

*Lasky T, Sun W, Kadry A, et al. 2004. Mean total arsenic concentrations in chicken 1989-2000 and estimated exposures for consumers of chicken. Environ Health Perspect 112(1):18-21.

Lau S, Mohamed M, Yen ATC, et al. 1998. Accumulation of heavy metals in freshwater molluscs. Sci Total Environ 214:113-121.

Law RJ, Morris RJ, Allchin CR, et al. 2003. Metals and organochlorines in small cetaceans stranded on the east coast of Australia. Mar Pollut Bull 46:1200-1211.

Lawson NM, Mason RP. 2001. Concentration of mercury, methylmercury, cadmium, lead, arsenic, and selenium in the rain and stream water of two contrasting watersheds in western Maryland. Water Res 35(17):4039-4052.

Le SXC, Cullen WR, Reimer KJ. 1994. Speciation of arsenic compounds in some marine organisms. Environ Sci Technol 28:1598-1604.

*Le XC, Lu X, Li X-F. 2004. Arsenic speciation. Anal Chem 76:27A-33A.

Le XC, Lu X, Ma M, et al. 2000. Speciation of key arsenic metabolic intermediates in human urine. Anal Chem 72(21):5172-5177.

Le Bouil A, Cailleux A, Turcant A, et al. 1999. Determination of monomethylarsonic acid and dimethylarsinic acid in urine by liquid chromotography-tandem mass spectrometry. J Anal Toxicol 23(4):257-261.

*Lebow S, Williams RS, Lebow P. 2003. Effect of simulated rainfall and weathering on release of preservative elements from CCA treated wood. Environ Sci Technol 37:4077-4082.

9REFERENCES

*Lee AM, Fraumeni JF Jr. 1969. Arsenic and respiratory cancer in man: An occupational study. J Natl Cancer Inst 42:1045-1052.

*Lee DC, Roberts JR, Kelly JJ, et al. 1995. Whole-bowel irrigation as an adjunct in the treatment of radiopaque arsenic [letter]. Am J Emerg Med 13(2):244-245.

Lee K, Vallarino J, Dumyahn T, et al. 1999. Ozone decay rates in residences. J Air Waste Manage Assoc 49:1238-1244.

*Lee MY, Bae ON, Chung SM, et al. 2002. Enhancement of platelet aggregation and thrombus formation by arsenic in drinking water: A contributing factor to cardiovascular disease. Toxicol Appl Pharmacol 179(2):83-88.

Lee MY, Jung BI, Chung SM, et al. 2003. Arsenic-induced dysfunction in relaxation of blood vessels. Environ Health Perspect 111(4):513-517.

*Lee T-C, Ho I-C. 1994. Differential cytotoxic effects of arsenic on human and animal cells. Environ Health Perspect 102(Suppl 3):101-105.

Lee TC, Ko JL, Jan KY. 1989a. Differential cytotoxicity of sodium arsenite in human fibroblasts and Chinese hamster ovary cells. Toxicology 56:289-299.

Lee TC, Lee KC, Tzeng YJ, et al. 1986a. Sodium arsenite potentiates the clastogenicity and mutagenicity of DNA crosslinking agents. Environ Mutagen 8:119-128.

*Lee T-C, Oshimura M, Barrett JC. 1985. Comparison of arsenic-induced cell transformation, cytotoxicity, mutation and cytogenetic effects in Syrian hamster embryo cells in culture. Carcinogenesis 6(10):1421-1426.

*Lee T-C, Tanaka N, Lamb PW, et al. 1988. Induction of gene amplification by arsenic. Science 241:79-81.

*Lee T-C, Wang-Wuu S, Huang RY, et al. 1986b. Differential effects of pre- and posttreatment of sodium arsenite on the genotoxicity of methyl methanesulfonate in Chinese hamster ovary cells. Cancer Res 46:1854-1857.

Lee TC, Wei ML, Chang WJ, et al. 1989b. Elevation of glutathione levels and glutathione S-transferase activity in arsenic-resistant Chinese hamster ovary cells. In Vitro Cell Dev Biol 25:442-448.

*Lee-Chen SF, Gurr JR, Lin IB, et al. 1993. Arsenite enhances DNA double-strand breaks and cell killing of methyl methanesulfonate-treated cells by inhibiting the excision of alkali-labile sites. Mutat Res 294(1):21-28.

*Lee-Chen SF, Yu CT, Jan KY. 1992. Effect of arsenite on the DNA repair of UV-irradiated Chinese hamster ovary cells. Mutagenesis 7(1):51-55.

*Lee-Chen SF, Yu CT, Wu DR, et al. 1994. Differential effects of luminol, nickel, and arsenite on the rejoining of ultraviolet light and alkylation-induced DNA breaks. Environ Mol Mutagen 23(2):116-120.

9REFERENCES

*Lee-Feldstein A. 1983. Arsenic and respiratory cancer in man: Follow-up of an occupational study. In: Lederer W, Fensterheim R, eds. Arsenic: Industrial, biomedical and environmental perspectives. New York, NY: Van Nostrand Reinhold, 245-265.

*Lee-Feldstein A. 1986. Cumulative exposure to arsenic and its relationship to respiratory cancer among copper smelter employees. J Occup Med 28(4):296-302.

Lee-Feldstein A. 1989. A comparison of several measures of exposure to arsenic. Matched case-control study of copper smelter employees. Am J Epidemiol 129:112-124.

*Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: Implications for practice. Pediatr Clin North Am 44:55-77.

Lehmann S, Bengtzen S, Paul A, et al. 1997. Arsenic trioxide (As_2O_3) induces apoptosis and cytotoxic effects in blast cells from patients with non-M3 AML. Blood 90(10 Suppl 1 Part 1):325a.

Leivuori M, Vallius H. 1998. A case study of seasonal variation in the chemical composition of accumulating suspended sediments in the central Gulf of Finland. Chemosphere 36(10):2417-2435.

Lemmo NV, Faust SD, Belton T, et al. 1983. Assessment of the chemical and biological significance of arsenical compounds in a heavily contaminated watershed. Part I. The fate and speciation of arsenical compounds in aquatic environments-a literature review. J Environ Sci Health Part A 18(3):335-387.

*Léonard A, Lauwerys RR. 1980. Carcinogenicity, teratogenicity and mutagenicity of arsenic. Mutat Res 75:49-62.

Leong GKP, Stone JL, Farmer ER, et al. 1987. Nonmelanoma skin cancer in Japanese residents of Kauai, Hawaii. J Am Acad Dermatol 17:233-238.

*Le Quesne PM, McLeod JG. 1977. Peripheral neuropathy following a single exposure to arsenic. J Neurol Sci 32:437-451.

*Lerda D. 1994. Sister-chromatid exchange (SCE) among individuals chronically exposed to arsenic in drinking water. Mutat Res 312(2):111-120.

*Lerman BB, Ali N, Green D. 1980. Megaloblastic, dyserythropoietic anemia following arsenic ingestion. Ann Clin Lab Science 10(6):515-517.

Lerman S, Clarkson TW. 1983. The metabolism of arsenite and arsenate by the rat. Fundam Appl Toxicol 3:309-314.

*Lerman S, Clarkson TW, Gerson RJ. 1983. Arsenic uptake and metabolism by liver cells is dependent on arsenic oxidation state. Chem Biol Interact 45:401-406.

*Leung H-W. 1993. Physiologically-based pharmacokinetic modelling. In: Ballantine B, Marro T, Turner P, eds. General and applied toxicology. Vol. 1. New York, NY: Stockton Press, 153-164.

Leung PL, Huang HM. 1997. Analysis of trace elements in the hair of volunteers suffering from naso-pharyngeal cancer. Biol Trace Elem Res 57(1):19-25.

9REFERENCES

*Levander OA. 1977. Metabolic interrelationships between arsenic and selenium. Environ Health Perspect 19:159-164.

*Levander OA, Bauman, CA. 1966. Selenium metabolism: VI. Effect of arsenic on the excretion of selenium in the bile. Toxicol Appl Pharm 9:106-115.

*Levin-Scherz JK, Patrick JD, Weber FH, et al. 1987. Acute arsenic ingestion. Ann Emerg Med 16(6):702-704.

*Lewis DR, Southwick JW, Ouellet-Hellstrom R, et al. 1999. Drinking water in Utah: A cohort mortality study. Environ Health Perspect 107(5):359-365.

*Lewis TA, Hartman CB, McCoy KL. 1998a. Gallium arsenide differentially affects processing of phagolysosmal targeted antigen by macrophages. J Leukoc Biol 63:321-330.

*Lewis TA, Hartmann CB, McCoy KL. 1998b. Gallium arsenide modulates proteolytic cathepsin activities and antigen processing by macrophages. J Immunol 161:2151-2157.

Li F, Sun G, Lu X, et al. 1997. [Studies on influence of arsenic on SSH content in blood and tissues of mice.] Zhonguo Gonggong Weisheng Xuebao 16(6):370-371. (Chinese)

Li F, Sun G, Lui S, et al. 1998a. [Study on the influence of arsenic on GSH-Px activity.] Gongye Weisheng Yu Zhiyebing 24(5):266-268. (Chinese)

*Li J-H, Rossman TG. 1989. Inhibition of DNA ligase activity by arsenite: A possible mechanism of its comutagenesis. Mol Toxicol 2:1-9.

*Li J-H, Rossman TG. 1991. Comutagenesis of sodium arsenite with ultraviolet radiation in Chinese hamster V79 cells. Biol Met 4:197-200.

*Li W, Chou I-N. 1992. Effects of sodium arsenite on the cytoskeleton and cellular glutathione levels in cultured cells. Toxicol Appl Pharmacol 114(1):132-139.

*Li W, Wanibuchi H, Salim EI, et al. 1998b. Promotion of the NCI-Black-Reiter male rat bladder carcinogenesis by dimethylarsinic acid an organic arsenic compound. Cancer Lett 134(1):29-36.

Li W, Wei C, Zhang C, et al. 2003. A survey of arsenic species in Chinese seafood. Food Chem Toxicol 41(8):1103-1110.

Li Y, Yao H, Sun M, et al. 1997. [Pathological observation of arsenic-induced malformation in post-implantation rat embryos cultured in vitro.] Zhonguo Gonggong Weisheng Xuebao 16(4):222-224. (Chinese)

Li Y, Zhu H, Pan Y, et al. 1998c. [Teratogenic effect of arsenic on rats.] Zhong Fan Yixue Yu Fanghu Zazhi 32(1):37-39. (Chinese)

Li YM, Broome JD. 1997a. Apoptosis induced in premyelocytic leukemia cells by arsenic and proteasome inhibitors. Blood 90(10 Suppl. 1 Part 2):203b.

Li YM, Broome JD. 1997b. Differential cytotoxicity of As_2O_3 and arsenic azoproteins on leukemic cells. Blood 90(10 Suppl. 1 Part 2):203b.

9REFERENCES

*Li YM, Broome JD. 1999. Arsenic targets tubulins to induce apoptosis in myeloid leukemia cells. Cancer Res 59:776-780.

*Lianfang W, Jianzhong H. 1994. Chronic arsenism from drinking water in some areas of Xinjiang, China. In: Nriagu JO, ed. Arsenic in the environment: Part II: Human health and ecosystem effects. New York, NY: John Wiley and Sons, Inc., 159-172.

*Liao W-T, Chang K-L, Chen G-S, et al. 2004a. Arsenic induces human keratinocyte apoptosis by the FAS/FAS ligand pathway, which correlates with alterations in nuclear factor-κB and activator protein-1 activity. J Invest Dermatol 122(1):125-129.

Liao YH, Yu HS, Ho CK, et al. 2004b. Biological monitoring of exposures to aluminum, gallium, indium, arsenic, and antimony in optoelectronic industry workers. J Occup Environ Med 46(9):931-936.

Lide DR. 1996. CRC handbook of chemistry and physics, 77th ed. Boca Raton, FL: CRC Press, Inc., 3-15, 4-119.

*Liebscher K, Smith H. 1968. Essential and nonessential trace elements: A method of determining whether an element is essential or nonessential in human tissue. Arch Environ Health 17:881-890.

Lien H-C, Tsai T-F, Lee YY, et al. 1999. Merkel cell carcinoma and chronic arsenicism. J Am Acad Dermatol 41(4):641-3.

Lilienfeld DE. 1988. Arsenic, geographical isolates, environmental epidemiology, and arteriosclerosis. [Editorial]. Arteriosclerosis 8:449-451.

*Lin J-K, Tseng S-F. 1992. Chromosomal aberrations and sister-chromatid exchanges induced by *N*-nitroso-2-acetylaminofluorene and their modifications by arsenite and selenite in Chinese hamster ovary cells. Mutat Res 265(2):203-210.

Lin S-M. 1986. Diagnostic usefulness of trace arsenic in human urine, whole blood, hair, and fingernails. Kaohsiung J Med Sci 2:100-113.

Lin T-H, Huang Y-L, Tseng W-C. 1995. Arsenic and lipid peroxidation in patients with blackfoot disease. Bull Environ Contam Toxicol 54(4):488-493.

*Lindgren A, Danielsson BRG, Dencker L, et al. 1984. Embryotoxicity of arsenite and arsenate: Distribution in pregnant mice and monkeys and effects on embryonic cells *in vitro*. Acta Pharmacol Toxicol 54:311-320.

*Lindgren A, Vahter M, Dencker L. 1982. Autoradiographic studies on the distribution of arsenic in mice and hamsters administered ^{74}As-arsenite or -arsenate. Acta Pharmacol Toxicol 51:253-265.

Lindsay CD, Hambrook JL, Brown RF, et al. 2004. Examination of changes in connective tissue macromolecular components of large white pig skin following application of Lewisite vapour. J Appl Toxicol 24(1):37-46.

*Ling YH, Jiang JD, Holland JF, et al. 2002. Arsenic trioxide produces polymerization of microtubules and mitotic arrest before apoptosis in human tumor cell lines. Mol Pharmacol 62(3):529-538.

9REFERENCES

*Liou SH, Lung JC, Chen YH, et al. 1999. Increased chromosome-type chromosome aberration frequencies as biomarkers of cancer risk in a blackfoot endemic area. Cancer Res 59(7):1481-1484.

Lioy PJ, Freeman NCG, Millette JR. 2002. Dust: A metric for use in residential and building exposure assessment and source characterization. Environ Health Perspect 110(10):969-983.

*Lithner G, Holm K, Borg H. 1995. Bioconcentration factors for metals in humic waters at different pH in the Röbbskär area (N. Sweden). Water, Air and Soil Pollution 85:785-790.

Little JE, Wise SS, Slotnick MJ, et al. 2003. Cytotoxicity and clastogenicity of arsenic, cadmium and chromium in human bronchial cells. Toxicol Sci 72(S-1):219.

*Little RE, Kay GN, Cavender JB, et al. 1990. Torsade de pointes and T-U wave alternans associated with arsenic poisoning. PACE 13:164-170.

Liu P, Han ZC. 2003. Treatment of acute promyelocytic leukemia and other hematologic malignancies with arsenic trioxide: Review of clinical and basic studies. Int J Hematol 78(1):32-39.

*Liu Y-C, Huang H. 1997. Involvement of calcium-dependent protein kinase C in arsenite-induced genotoxicity in Chinese hamster ovary cells. J Cell Biochem 64(3):423-433.

*Liu YT, Chen Z. 1996. A retrospective lung cancer mortality study of people exposed to insoluble arsenic and radon. Lung Cancer 14(Suppl 1):137-148.

*Liu J, Liu Y, Goyer RA, et al. 2000a. Metallothionein-I/II null mice are more sensitive than wild-type mice to the hepatotoxic and nephrotoxic effects of chronic oral or injected inorganic arsenicals. Toxicol Sci 55(2):460-467.

Liu J, Liu Y, Habeebu SM, et al. 2000b. Chronic combined exposure to cadmium and arsenic exacerbates nephrotoxicity, particularly in metallothionein-I/II null mice. Toxicology 147(3):157-166.

Liu J, Liu Y, Powell DA, et al. 2002b. Multidrug-resistance mdr1a/1b double knockout mice are more sensitive than wild type mice to acute arsenic toxicity, with higher arsenic accumulation in tissues. Toxicology 170(1-2):55-62.

Liu J, Xie Y, Ward JM, et al. 2003. Toxicogenomic analysis of aberrant gene expression in liver tumors and nontumorous livers of adult mice exposed in utero to inorganic arsenic. Toxicol Sci 77(2):249-257.

*Liu J, Zheng B, Aposhian HV, et al. 2002a. Chronic arsenic poisoning from burning high-arsenic-containing coal in Guizhou, China. Environ Health Perspect 110(2):119-122.

*Livingston, AL. 1978. Forage plant estrogens. J Toxicol Environ Health 4:301-324.

Lo FB, Arai DK. 1989. Biological monitoring of toxic metals in urine by simultaneous inductively coupled plasma-atomic emission spectrometry. Am Ind Hyg Assoc J 50:245-251.

Lobdell DT, Ning Z, Kwok RK, et al. 2004. Drinking water arsenic and perinatal outcomes. Am J Epidemiol 159(11 Suppl):S87.

*Loebenstein JR. 1994. The materials flow of arsenic in the United States. Washington, DC: Bureau of Mines, Division of Mineral Commodities, United States Department of the Interior. BUMINES-IC-9382.

9REFERENCES

*Loffredo CA, Aposhian HV, Cebrian ME, et al. 2003. Variability in human metabolism of arsenic. Environ Res 92(2):85-91.

*Löfroth G, Ames BN. 1978. Mutagenicity of inorganic compounds in *Salmonella typhimurium*: arsenic, chromium, and selenium. Mutat Res 53:65-66.

Lombeck I, Altenhenne R, Bremer HJ. 1987. Urinary excretion of arsenic in children in relationship to age and diet. Trace Elem Med 4:134-137.

Long ER, Macdonald DD, Smith SL, et al. 1995. Incidence of adverse biological effects within ranges of chemical concentrations in marine and estuarine sediments. Environ Manage 19(1):81-97.

*López-Gonzálvez MA, Gómez MM, Cámara C, et al. 1994. On-line microwave oxidation for the determination of organoarsenic compounds by high-performance liquid chromatography-hydride generation atomic absorption spectrometry. J Anal Atom Spectrom 9(3):291-295.

*Lovell MA, Farmer JG. 1985. Arsenic speciation in urine from humans intoxicated by inorganic arsenic compounds. Hum Toxicol 4:203-214.

*Lu FJ, Shih SR, Liu TM, et al. 1990. The effect of fluorescent humic substances existing in the well water of blackfoot disease endemic areas in Taiwan on prothrombin time and activated partial thromboplastin time in vitro. Thromb Res 57:747-753.

*Lu M, Levin J, Sulpice E, et al. 1999. Effect of arsenic trioxide on viability, proliferation, and apoptosis in human megakaryocytic leukemia cell lines. Exp Hematol 27:845-852.

Lu SN, Chow NH, Wu WC, et al. 2004. Characteristics of hepatocellular carcinoma in a high arsenicism area in Taiwan: A case-control study. J Occup Environ Med 46(5):437-441.

Lubin JH, Fraumeni JF. 2000. Re: "Estimates of the annual number of clinically recognized pregnancies in the United States, 1981-1991". Am J Epidemiol 152(3):297-293.

Lubin JH, Pottern LM, Blot WJ, et al. 1981. Respiratory cancer among copper smelter workers: Recent mortality statistics. J Occup Med 23:779-784.

*Lubin JH, Pottern LM, Stone BJ, et al. 2000. Respiratory cancer in a cohort of copper smelter workers: Results from more than 50 years of follow-up. Am J Epidemiol 151(6):554-565.

*Lüchtrath H. 1983. The consequences of chronic arsenic poisoning among Moselle wine growers: Pathoanatomical investigations of post-mortem examinations performed between 1960 and 1977. J Cancer Res Clin Oncol 105:173-182.

*Lugo G, Cassady G, Palmisano P. 1969. Acute maternal arsenic intoxication with neonatal death. Am J Dis Child 117:328-330.

*Lundgren KD. 1954. Damage to respiratory organs in workers in a smelting plant. Nord Hyg Tidskr 3:66-82.

*Luong KVQ, Nguyen LTH. 1999. Organic arsenic intoxication from bird's nest soup. Am J Med Sci 317(4):269-271.

9REFERENCES

*Luster MI, Simeonova PP. 2004. Arsenic and urinary bladder cell proliferation. Toxicol Appl Pharmacol 198(3):419-423.

Luster MI, Wilmer JL, Germolec DR, et al. 1995. Role of keratinocyte-derived cytokines in chemical toxicity. Toxicol Lett 82/83:471-476.

*Luten JB, Riekwel-Booy G, Rauchbaar A. 1982. Occurrence of arsenic in plaice (*Pleuronectes platessa*), nature of organo-arsenic compound present and its excretion by man. Environ Health Perspect 45:165-170.

Lutter C, Iyengar V, Barnes R, et al. 1998. Breast milk contamination in Kazakhstan: Implications for infant feeding. Chemosphere 37(9-12):1761-1772.

*Lynn S, Gurr JR, Lai HT, et al. 2000. NADH oxidase activation is involved in arsenite-induced oxidative DNA damage in human vascular smooth muscle cells. Circ Res 86(5):514-519.

*Lynn S, Lai H-T, Gurr JR, et al. 1997. Arsenite retards DNA break rejoining by inhibiting DNA ligation. Mutagenesis 12(5):353-358.

Lyytikainen M, Sormunen A, Peraniemi S, et al. 2001. Environmental fate and bioavailability of wood preservatives in freshwater sediments near an old sawmill site. Chemosphere 44:341-350.

Ma LQ, Tan F, Harris WG. 1997. Concentrations and distributions of eleven metals in Florida soils. J Environ Qual 26(3):769-775.

*Mabuchi K, Lilienfeld AM, Snell LM. 1979. Lung cancer among pesticide workers exposed to inorganic arsenicals. Arch Environ Health 34:312-320.

MacDonald R. 2001. Providing clean water: Lessons from Bangladesh. Br Med J 322(7287):626-627.

MacIntosh DL, Spengler JD, Ozkaynak H, et al. 1996. Dietary exposures to selected metals and pesticides. Environ Health Perspect 104:202-209.

*MacIntosh DL, Williams PL, Hunter DJ, et al. 1997. Evaluation of a food frequency questionnaire-food composition approach for estimating dietary intake of inorganic arsenic and methylmercury. Cancer Epidemiol Biomarkers Prev 6(12):1043-1050.

Maeda S, Ohki A, Kusadome K, et al. 1992. Bioaccumulation of arsenic and its fate in a freshwater food chain. Appl Organomet Chem 6:213-219.

*Maehashi H, Murata Y. 1986. Arsenic excretion after treatment of arsenic poisoning with DMSA or DMPS in mice. Jpn J Pharmacol 40:188-190.

*Mahaffey KR, Fowler BA. 1977. Effects of concurrent administration of lead, cadmium, and arsenic in the rat. Environ Health Perspect 19:165-171.

*Mahaffey KR, Capar SG, Gladen BC, et al. 1981. Concurrent exposure to lead, cadmium and arsenic. Effects on toxicity and tissue metal concentrations in the rat. J Lab Clin Med 98(1):463-481.

9REFERENCES

Mahajan SK, Aggarwal HK, Wig N, et al. 1992. Arsenic induced neuropathy. J Assoc Physicians India 40(4):268-269.

*Mahata J, Basu A, Ghosal S, et al. 2003. Chromosomal aberrations and sister chromatid exchanges in individuals exposed to arsenic through drinking water in West Bengel, India. Mutat Res 534(1-2):133-143.

*Maher WA. 1989. Some observations on the determination of total arsenic in biological tissues. Microchem J 40:132-135.

Mahieu P, Buchet JP, Lauwerys R. 1987. [Clinical and biological course of acute oral poisoning by arsenic anhydride with considerations on therapeutic approach.] J Toxicol Clin Exp 7:273-278. (French)

Maier A, Schumann BL, Chang X, et al. 2002. Arsenic co-exposure potentiates benzo[a]pyrene genotoxicity. Mutat Res 517(1-2):101-111.

*Maiorino RM, Aposhian HV. 1985. Dimercaptan metal-binding agents influence the biotransformation of arsenite in the rabbit. Toxicol Appl Phamacol 77:240-250.

*Maitani T, Saito N, Abe M, et al. 1987a. Chemical form-dependent induction of hepatic zinc-thionein by arsenic administration and effect of co-administered selenium in mice. Toxicol Lett 39:63-70.

Maitani T, Uchiyama S, Saito Y. 1987b. Hydride generation-flame atomic-absorption spectrometry as an arsenic detector for high-performance liquid chromatography. J Chromatogr 391:161-168.

Majer BJ, Mersch-Sundermann V, Darroudi F, et al. 2004. Genotoxic effects of dietary and lifestyle related carcinogens in human derived hepatoma (HepG2, Hep3B) cells. Mutat Res 551(1-2):153-166.

*Makkonen N, Hirvonen M-R, Savolainen K, et al. 1995. The effect of free gallium and gallium in liposomes on cytokine and nitric oxide secretion from macrophage like cells in vitro. Inflamm Res 44:523-528.

Man ACK, Zheng YH, Mak PK. 1996. Trace elements in scalp hair of professional drivers and university teachers in Hong Kong. Biol Trace Elem Res 53(1-3):241-247.

*Mandal BK, Suzuki KT. 2002. Arsenic around the world: A review. Talanta 58:201-235.

Mandal BK, Ogra Y, Anzai K, et al. 2004. Speciation of arsenic in biological samples. Toxicol Appl Pharmacol 198(3):307-318.

*Mandal BK, Ogra Y, Suzuki KT. 2001. Identification of dimethylarsinous and monomethylarsonous. Chem Res Toxicol 14(4):371-378.

*Mandal BK, Ogra Y, Suzuki KT. 2003. Speciation of arsenic in human nail and hair from arsenic-affected area by HPLC-inductively coupled argon plasma mass spectrometry. Toxicol Appl Pharmacol 189(2):73-83.

*Mann S, Droz PO, Vahter M. 1996a. A physiologically based pharmacokinetic model for arsenic exposure. I. Development in hamsters and rabbits. Toxicol Appl Pharmacol 137(1):8-22.

*Mann S, Droz PO, Vahter M. 1996b. A physiologically based pharmacokinetic model for arsenic exposure. II. Validation and application in humans. Toxicol Appl Pharmacol 140(2):471-486.

*Mappes R. 1977. [Experiments on excretion of arsenic in urine.] Int Arch Occup Environ Health 40:267-272. (German)

*Marafante E, Vahter M. 1984. The effect of methyltransferase inhibition on the metabolism of [^{74}As] arsenite in mice and rabbits. Chem Biol Interact 50:49-57.

*Marafante E, Vahter M. 1986. The effect of dietary and chemically induced methylation deficiency on the metabolism of arsenate in the rabbit. Acta Pharmacol Toxicol 59(Suppl 7):35-38.

*Marafante E, Vahter M. 1987. Solubility, retention and metabolism of intratracheally and orally administered inorganic arsenic compounds in the hamster. Environ Res 42:72-82.

*Marafante E, Lundborg M, Vahter M, et al. 1987a. Dissolution of two arsenic compounds by rabbit alveolar macrophages *in vitro*. Fundam Appl Toxicol 8:382-388.

Marafante E, Vahter M, Dencker L. 1984. Metabolism of arsenocholine in mice, rats and rabbits. Sci Total Environ 34:223-240.

*Marafante E, Vahter M, Envall J. 1985. The role of the methylation in the detoxication of arsenate in the rabbit. Chem Biol Interact 56:225-238.

*Marafante E, Vahter M, Norin H, et al. 1987b. Biotransformation of dimethylarsinic acid in mouse, hamster and man. J Appl Toxicol 7(2):111-117.

*Marcus WL, Rispin AS. 1988. Threshold carcinogenicity using arsenic as an example. In: Cothern CR, Mehlman MA, Marcus WL, eds. Advances in modern environmental toxicology: Vol. XV: Risk assessment and risk management of industrial and environmental chemicals. Princeton, NJ: Princeton Scientific Publishing Co., 133-158.

Marimuthu P. 2001. Arsenic contamination in West Bengel and Bangladesh: Statistical errors. Environ Health Perspect 109(2):A62-63.

*Mariner PE, Holzmer FJ, Jackson RE, et al. 1996. Effects of high pH on arsenic mobility in a shallow sandy aquifer and on aquifer permeability along the adjacent shoreline, Commencement Bay Superfund Site, Tacoma, Washington. Environ Sci Tech 30(5):1645-1651.

Marlowe M, Cossairt A, Moon C, et al. 1985a. Main and interaction effects of metallic toxins on classroom behavior. J Abnorm Child Psychol 13(2):185-198.

Marlowe M, Stellern J, Moon C, et al. 1985b. Main and interaction effects of metallic toxins on aggressive classroom behavior. Aggressive Behavior 11:41-48.

*Martin DS, Willis SE, Cline DM. 1990. N-Acetylcysteine in the treatment of human arsenic poisoning. J Am Board Fam Pract 3:293-296.

*Martinez V, Creus A, Venegas W, et al. 2004. Evaluation of micronucleus induction in a Chilean population environmentally exposed to arsenic. Mutat Res 564(1):65-74.

9REFERENCES

*Mason RP, Laporte JM, Andres S. 2000. Factors controlling the bioaccumulation of mercury, methylmercury, arsenic, selenium, and cadmium by freshwater invertebrates and fish. Arch Environ Contam Toxicol 38:283-97.

*Mason RW, Edwards IR, Fisher LC. 1989. Teratogenicity of combinations of sodium dichromate, sodium arsenate and copper sulphate in the rat. Comp Biochem Physiol 93(2):407-411.

Mass MJ. 1992. Human carcinogenesis by arsenic. Environ Geochem Health 14(2):49-54.

Mass MJ. 1998. Mechanisms of arsenic induced cancer: A role for hypermethylation. Toxicologist. Abstracts of the 37th Annual Meeting 42(1-S):353.

*Mass MJ, Wang L. 1997. Arsenic alters cytosine methylation patterns of the promoter of the tumor suppressor gene *p*53 in human lung cells: A model for a mechanism of carcinogenesis. Mutat Res 386(3):263-277.

Masscheleyn PH, Deluane RD, Patrick WH. 1991. Heavy metals in the environment: Arsenic and selenium chemistry as affected by sediment redox potential and pH. J Environ Qual 20:522-527.

Masscheleyn PH, Delaune RD, Patrick WH. 1991. Effect of redox potential and pH on arsenic speciation and solubility in a contaminated soil. Environ Sci Technol 25:1414-1419.

Matanoski G, Landau E, Tonascia J, et al. 1980. Lung cancer mortality in proximity to a pesticide plant. Washington, DC: American Public Health Association and U.S. Environmental Protection Agency, Office of Toxic Substances. PB80207376.

*Matanoski G, Landau E, Tonascia J, et al. 1981. Cancer mortality in an industrial area of Baltimore. Environ Res 25:8-28.

Mathias CG. 1988. Occupational dermatoses. J Am Acad Dermatol 19:1107-1114.

Matschullat J, Scharnweber T, Garbe-Schönberg D, et al. 1999. Epilithic lichen--atmospheric deposition monitors of trace elements and organohalogens? J Air Waste Manage Assoc 49:1201-1211.

*Matsui M, Nishigori C, Toyokuni S, et al. 1999. The role of oxidative DNA damage in human arsenic carcinogenesis: Detection of 8-hydroxy-2'-deoxyguanosine in arsenic-related Bowen's disease. J Invest Dermatol 113:26-31.

*Matthews EJ, Spalding JW, Tennant RW. 1993. Transformation of BALB/c-3T3 cells: V. Transformation responses of 168 chemicals compared with mutagenicity in Salmonella and carcinogenicity in rodent bioassays. Environ Health Perspect 101(suppl 2):347-482.

*May TW, Wiedmeyer RH, Gober J, et al. 2001. Influence of mining-related activities on concentrations of metals in water and sediment from streams of the Black Hills, South Dakota. Arch Environ Contam Toxicol 40:1-9.

*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.

*Mazumdar S, Redmond CK, Enterline PE, et al. 1989. Multistage modeling of lung cancer mortality among arsenic-exposed copper-smelter workers. Risk Anal 9(4):551-563.

McCabe LJ, Symons JM, Lee RD, et al. 1970. Survey of community water supply systems. J Am Water Works Assoc 62:670-687.

McCarty KM, Senn DB, Kile ML, et al. 2004. Antimony: An unlikely confounder in the relationship between well water arsenic and health outcomes in Bangladesh. Environ Health Perspect 112(8):809-811.

*McDorman EW, Collins BW, Allen JW. 2002. Dietary folate deficiency enhances induction of micronuclei by arsenic in mice. Environ Mol Mutagen 40(1):71-77.

McDorman EW, Collins BW, Moore T, et al. 1998. Micronucleus analysis in mice chronically exposed to arsenic in drinking water. 29th Annual Meeting of the Environmental Mutagen Society, Anaheim. Environ Mole Mutagen 31(suppl. 29):39

McEntee T. 1995. Industrial antimicrobial agents. In: Kroschwitz JI, Howe-Grant M, eds. Kirk-Othmer encyclopedia of chemical technology. Vol. 14. New York, NY: John Wiley and Sons, 187-189.

*McFall TL, Richards S, Matthews G. 1998. Rehabilitation in an individual with chronic arsenic poisoning: Medical, psychological, and social implications. J Spinal Cord Med 21(2):142-147.

*McGeehan SL. 1996. Arsenic sorption and redox reactions: Relevance to transport and remediation. J Environ Sci Health A31(9):2319-2336.

*McGeehan SL, Fendorf SE, Naylor DV. 1998. Alteration of arsenic sorption in flooded-dried soils. Soil Sci Soc Am J 62:828-833.

McGown EL, van Ravenswaay T, Dumlao CR. 1988. Histologic changes in nude mouse skin and human skin xenografts following exposure to sulfhydryl reagents: Arsenicals. Toxicol Pathol 15:149-156.

McKone TE, Ryan PB. 1989. Human exposures to chemicals through food chains: An uncertainty analysis. Environ Sci Technol 23:1154-1163.

*McLaren RG, Naidu R, Smith J, et al. 1998. Fractionation and distribution of arsenic in soils contaminated by cattle dip. J Environ Qual 27:348-354.

McLellan F. 2002. Arsenic contamination effects millions in Bangladesh. Lancet 359(9312):1127.

Meador JP, Ernest D, Hohn AA, et al. 1999. Comparison of elements in bottlenose dolphins stranded on the beaches of Texas and Florida in the Gulf of Mexico over a one-year period. Arch Environ Contam Toxicol 36:87-98.

Meador JP, Ernest DW, Kagley A. 2004. Bioaccumulation of arsenic in marine fish and invertebrates from Alaska and California. Arch Environ Contam Toxicol 47(2):223-233.

Mealey J, Brownell GL, Sweet WH. 1959. Radioarsenic in plasma, urine, normal tissues, and intracranial neoplasms. Arch Neurol Psychiatr 81:310-320.

Meharg AA, Rahman M. 2003. Arsenic contamination of Bangladesh paddy field soils: Implications fro rice contribution to arsenic consumption. Environ Sci Technol 37:229-234.

9REFERENCES

*Meister RT, ed. 1987. Farm chemicals handbook. Willoughby, OH: Meister Publishing. Section C:21, 46-47, 101, 177-178, 230-231.

Meister RT, ed. 1989. Farm chemicals handbook. Willoughby, OH: Meister Publishing Company.

*Meister RT, ed. 1999. Farm chemicals handbook '99. Willoughby, OH: Meister Publishing Company.

Menendez D, Salazar AM, Miranda E, et al. 1998. Induction of p53 protein expression by sodium arsenite. Environ Mole Mutagen 31(suppl. 29):64.

*Meng Z. 1993a. Effects of arsenic on DNA synthesis in human lymphocytes stimulated by phytohemagglutinin. Biol Trace Elem Res 39(1):73-80.

*Meng Z. 1993b. Effects of arsenic on DNA synthesis in human lymphocytes. Arch Environ Contam Toxicol 25(4)525-528.

*Meng Z. 1994. Effects of arsenic on DNA synthesis in human lymphocytes. In: Nraigu JO, ed. Arsenic in the environment, part II: Human health and ecosystem effects. New York, NY: John Wiley & Sons, Inc., 133-142.

*Meng Z, Hsie AW. 1996. Polymerase chain reaction-based deletion analysis of spontaneous and arsenite-enhanced gpt mutants in CHO-As_{52} cells. Mutat Res 356(2)255-259.

*Menzel DB, Rasmussen RE, Lee E, et al. 1998. Human lymphocyte heme oxygenase 1 as a response biomarker to inorganic arsenic. Biochem Biophys Res Commun 250:653-656.

*Menzel DB, Ross M, Oddo SV, et al. 1994. A physiologically based pharmacokinetic model for ingested arsenic. Environ Geochem Health 16:209-218.

Merck. 1989. The Merck index: An encyclopedia of chemicals, drugs, and biologicals. 11 ed. Rahway NJ: Merck and Company, Inc., 126.

*Merwin I, Pruyne PT, Ebel JG, et al. 1994. Persistence, phytotoxicity, and management of arsenic, lead and mercury residues in old orchard soils of New York State. Chemosphere 29(6):1361-1367.

*Meyer I, Heinrich J, Lippold U. 1999. Factors affecting lead, cadmium, and arsenic levels in house dust in a smelter town in eastern Germany. Environ Res 81:32-44.

*Michaud DS, Wright ME, Cantor KP, et al. 2004. Arsenic concentrations in prediagnostic toenails and the risk of bladder cancer in a cohort study of male smokers. Am J Epidemiol 160(9):853-859.

*Miles AK, Tome MW. 1997. Spatial and temporal heterogeneity in metallic elements in industrialized aquatic bird habitats. Environ Pollut 95(1):75-84.

*Milham S, Strong T. 1974. Human arsenic exposure in relation to a copper smelter. Environ Res 7:176-182.

Miller M. 1998. Scientists explore use of arsenic in therapy. J Natl Cancer Inst 90(24):1866-1867.

Miller-Ihli NJ, Wolf WR. 1986. Characterization of a diet reference material for 17 elements. Anal Chem 58:3225-3231.

9REFERENCES

Miller WH, Schipper HM, Lee JS, et al. 2002. Mechanisms of action of arsenic trioxide. Cancer Res 62(14):3893-3903.

Milstein LS, Essader A, Pellizzari ED, et al. 2002. Selection of a suitable mobile phase for the speciation of four arsenic compounds in drinking water samples using ion-exchange chromatography coupled to inductively coupled plasma mass spectrometry. Environ Int 28(4):277-283.

Milstein LS, Essader A, Pellizzari ED, et al. 2003. Development and application of a robust speciation method for determination of six arsenic compounds present in human urine. Environ Health Perspect 111:293-296.

Milton A, Johnson M. 1999. Arsenic in the food chains of a revegetated metalliferous mine tailings pond. Chemosphere 39(5):765-779.

*Milton AH, Rahman M. 2002. Respiratory effects and arsenic contaminated well water in Bangladesh. Int J Environ Health Res 12(2):175-179.

*Milton AH, Hasan Z, Shahidullah SM, et al. 2004. Association between nutritional status and aresnicosis due to chronic arsenic exposure in Bangladesh. Int J Environ Health Res 14(2):99-108.

Minyard JP & Roberts WE. 1991. Chemical contaminants monitoring. State findings on pesticide residues in foods– 1988 and 1989. J Assoc Off Anal Chem 74:438-452.

*Mirkes PE, Cornel L. 1992. A comparison of sodium arsenite- and hyperthermia-induced stress responses

Mitchell RD, Ayala-Fierro F, Carter DE. 2000. Systemic indicators of inorganic arsenic toxicity in four animal species. J Toxicol Environ Health 59:119-134.

Mitchell-Heggs CAW, Conway M, Cassar J. 1990. Herbal medicine as a cause of combined lead and arsenic poisoning. Hum Exp Toxicol 9:195-196.

Mitra K, Kundu SN, Khuda Bukhsh AR. 1999. Efficacy of a potentized homoeopathic drug (Arsenic Album-30) in reducing toxic effects produced by arsenic trioxide in mice: II. On alterations in body weight and total protein. Complement Ther Med 7:24-34.

*Mitra SR, Mazumder DN, Basu A, et al. 2004. Nutritional factors and susceptibility to arsenic-caused skin lesions in West Bengal, India. Environ Health Perspect 112(10):1104-1109.

*Miyazaki K, Ushijima K, Kadono T, et al. 2003. Negative correlation between urinary selenium and arsenic levels of the residents living in an arsenic-contaminated area in Bangladesh. J Health Sci 49(3):239-242.

*Mizuta N, Mizuta M, Ito F, et al. 1956. An outbreak of acute arsenic poisoning caused by arsenic-contaminated soy-sauce (shōyu): A clinical report of 220 cases. Bull Yamaguchi Med Sch 4(2-3):131-149.

*Mohamed KB. 1998. Occupational contact dermatitis from arsenic in a tin-smelting factory. Contact Dermatitis 38:224-225.

9REFERENCES

*Mok WM, Wai CM. 1988. Determination of arsenic and antimony in biological materials by solvent extraction and neutron activation. Talanta 35:183-186.

*Mok WM, Wai CM. 1994. Mobilization of arsenic in contaminated river waters. In: Nriagu JO, ed. Arsenic in the environment, part 1: Cycling and characterization. New York, NY: John Wiley & Sons, Inc., 99-117.

*Mok WM, Riley JA, Wai CM. 1988. Arsenic speciation and quality of groundwater in a lead-zinc mine, Idaho. Water Res 22(6):769-774.

Moody JP, Williams RT. 1964a. The fate of arsanilic acid and acetylarsanilic acid in hens. Food Cosmet Toxicol 2:687-693.

Moody JP, Williams RT. 1964b. The fate of 4-nitrophenylarsonic acid in hens. Food Cosmet Toxicol 2:695-706.

*Moore DF, O'Callaghan CA, Berlyne G, et al. 1994. Acute arsenic poisoning: Absence of polyneuropathy after treatment with 2,3-dimercaptopropanesulphonate (DMPS). J Neurol Neurosurg Psychiatry 57(9):1133-1135.

*Moore JN, Ficklin WH, Johns C. 1988. Partitioning of arsenic and metals in reducing sulfidic sediments. Environ Sci Technol 22:432-437.

*Moore LE, Lu M, Smith AH. 2002a. Childhood cancer incidence and arsenic exposure in drinking water in Nevada. Arch Environ Health 57(3):201-206.

Moore LE, Smith AH, Eng C, et al. 2002b. Arsenic-related chromosomal alterations in bladder cancer. J Natl Cancer Inst 94(22):1688-1696.

*Moore LE, Smith AH, Hopenhayn-Rich C, et al. 1995. Increased bladder cells micronuclei in two populations environmentally exposed to arsenic in drinking water. Clin Chem 41(12 Part 2)1915-1917.

*Moore LE, Smith AH, Hopenhayn-Rich C, et al. 1997a. Micronuclei in exfoliated bladder cells among individuals chronically exposed to arsenic in drinking water. Cancer Epidemiol Biomarkers Prev 6(1)31-36.

*Moore LE, Warner ML, Smith AH, et al. 1996. Use of the fluorescent micronucleus assay to detect the genotoxic effects of radiation and arsenic exposure in exfoliated human epithelial cells. Environ Mol Mutagen 27(3):176-184.

Moore LO. 1976. Mutagenesis and carcinogenesis tests with monosodium methanearsonate, cacodylic acid and arsenic trioxide by bacteria and cell culture tests. Weslaco, TX: The Ansul Company, Weslaco Technical Center.

*Moore MM, Harrington-Brock K, Doerr CL. 1994. Genotoxicity of arsenic and its methylated metabolites. Environ Geochem Health 16:191-198.

Moore MM, Harrington-Brock K, Doerr CL. 1997b. Relative genotoxic potency of arsenic and its methylated metabolites. Mutat Res 386(3):279-290.

9REFERENCES

Morales KH, Ryan L, Kuo TL, et al. 2000. Risk of internal cancers from arsenic in drinking water. Environ Health Perspect 108(7):655-661.

*Moreira JC. 1996. Threats by heavy metals: Human and environmental contamination in Brazil. Sci Total Environ 188(Suppl 1):S61-S71.

Morikawa T, Wanibuchi H, Morimura K, et al. 2000. Promotion of skin carcinogenesis by dimethylarsinic acid in keratin (K6)/ODC transgenic mice. Jpn J Cancer Res 91(6):579-81.

Morrell JJ, Keefe D, Baileys RT. 2003. Copper, zinc and arsenic in soil surrounding Douglas-fir poles treated with ammoniacal copper zinc arsenate (ACZA). J Environ Qual 32:2095-2099.

*Morris JS, Schmid M, Newman S, et al. 1974. Arsenic and noncirrhotic portal hypertension. Gastroenterology 66(1):86-94.

Morrison PF. 1987. Effects of time-variant exposure on toxic substance response. Environ Health Perspect 76:113-140.

Morrison RJ, Gangaiya P, Naqasima MR, et al. 1997. Trace metal studies in the Great Astrolabe Lagoon, Fiji, a pristine marine environment. Mar Pollut Bull 34(5):353-356.

*Morrissey RE, Mottet NK 1983. Arsenic-induced exencephaly in the mouse and associated lesions occurring during neurulation. Teratology 28:399-411.

*Moriss-Kay GM, Wood H, Chen W. 1994. Normal neurulation in mammals. In: Ciba Foundation Symposium, neural tube defects. New York: John Wiley & Sons, 51-69.

*Morse DL, Harrington JM, Housworth J, et al. 1979. Arsenic exposure in multiple environmental media in children near a smelter. Clin Toxicol 14(4):389-399.

Morselli L, Zappoli S, Tirabassi T. 1992. Characterization of the effluents from a municipal solid waste incinerator plant and of their environmental impact. Chemosphere 24(12):1175-1784.

*Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. Clin Pharmacokin 5:485-527.

Mortelmans KE, Riccio ES, Sheppard GF. 1980. *In vitro* detection of mitotic crossing-over, mitotic gene conversion and reverse mutation with S. cerevisiae D7 for 7 pesticides. EPA Contract No. 68-02-2947.

Mortimer MR. 2000. Pesticide and trace metal concentrations in Queensland estuarine crabs. Mar Pollut Bull 41(7-12):359-366.

*Morton W, Starr G, Pohl D, et al. 1976. Skin cancer and water arsenic in Lane County, Oregon. Cancer 37:2523-2532.

*Morton WE, Caron GA. 1989. Encephalopathy: An uncommon manifestation of workplace arsenic poisoning? Am J Ind Med 15:1-5.

*Mottet NK, Ferm VH. 1983. The congenital teratogenicity and perinatal toxicity of metals. In: Clarkson TW, Nordberg GF, Sager PR, eds. Reproductive and developmental toxicity of metals. New York, NY: Plenum Press, 93-125.

9REFERENCES

Moyer TP. 1999. Seafood recommendation in Knobeloch paper 'inappropriate'. Wis Med J 98(1):5.

*Moxon AL, Paynter CR, Halverson AW. 1945. Effect of route of administration on detoxication of selenium by arsenic. J Pharmacol Exp Ther 84:115-119.

Mudroch A, Clair TA. 1986. Transport of arsenic and mercury from gold mining activities through an aquatic system. Sci Total Environ 57:205-216.

Mudur G. 2000. Half of Bangladesh population at risk of arsenic poisoning. Br Med J 320(7238):822.

Mukherjee AB, Bhattacharya P. 2001. Arsenic in groundwater in the Bengal Delta Plain: Slow poisoning in Bangladesh. Environ Res 9(3):189-220.

Mukherjee S, Das D, Darbar S, et al. 2003. Dietary intervention affects arsenic-generated nitric oxide and reactive oxygen intermediate toxicity in islet cells of rats. Curr Sci 85(6):786-793.

*Mukherjee S, Das D, Darbar S, et al. 2004. Arsenic trioxide generates oxidative stress and islet cell toxicity in rabbit. Curr Sci 86(6):854-857.

Mumford JL, Xia Y, Schmitt MT, et al. 2001. Assessing arsenic exposure and skin hyperkeratosis in inner Mongolia, China. Proc Am Assoc Cancer Res 42:233.

Mumma RO, Raupach DC, Sahadewan K, et al. 1990. National survey of elements and radioactivity in municipal incinerator ashes. Arch Environ Contam Toxicol 19:399-404.

*Mumma RO, Raupach DC, Waldman JP, et al. 1984. National survey of elements and other constituents in municipal sewage sludges. Arch Environ Contam Toxicol 13:75-83.

Munro IC, Charbonneau SM, Sandi E, et al. 1974. Biological availability of arsenic from fish [Abstract]. Toxicol Appl Pharmacol 29:111.

*Murai T, Iwata H, Otoshi T, et al. 1993. Renal lesions induced in F34/DuCrj rats by 4-weeks oral administration of dimethylarsinic acid. Toxicol Lett 66:53-61.

Murata K, Iwazawa T, Takayama T, et al. 1994. Quadruple cancer including Bowen's disease after arsenic injections 40 years earlier: Report of a case. Surg Today 24(12):1115-1118.

*Mure K, Uddin AN, Lopez LC, et al. 2003. Arsenite induces delayed mutagenesis and transformation in human osteosarcoma cells at extremely low concentrations. Environ Mol Mutagen 41:322-331.

Murphy BL, Toole AP, Bergstrom PD. 1989. Health risk assessment for arsenic contaminated soil. Environ Geochem Health 11:163-169.

*Murphy MJ, Lyon LW, Taylor JW. 1981. Subacute arsenic neuropathy: Clinical and electrophysiological observations. J Neurol Neurosurg Psychiatry 44:896-900.

Murshed R, Douglas RM, Ranmuthugala G, et al. 2004. Clinician's roles in management of arsenicos in Bangladesh: Interview study. Br Med Bull 328(7438):493-4.

9REFERENCES

*Mushak P, Crocetti AF. 1995. Risk and revisionism in arsenic cancer risk assessment. Environ Health Perspect 103(7-8):684-689.

Mushak P, Crocetti AF. 1996. Response: Accuracy, arsenic and cancer. Environ Health Perspect 104(10):1014-1018.

*Mushak P, Dessauer K, Walls EL. 1977. Flameless atomic absorption (FAA) and gas-liquid chromatographic studies in arsenic bioanalysis. Environ Health Perspect 19:5-10.

*Muzi G, dell'Omo M, Madeo G, et al. 2001. Arsenic poisoning caused by Indian ethnic remedies. J Pediatr 139(1):169.

Mycyk MB, Crulcich M, Mucha A, et al. 2003. Exposure assessment of children exposed to arsenic in an urban playlot. J Toxicol Clin Toxicol 41(5):737.

Nagai N, Usui T, Asahi A, et al. 1956a. [Comparison of biochemical findings and clinical pictures on subacute or chronic arsenic poisoning of infants due to arsenic containing powdered milk.] Shonika Kiyo 2(2)133-151. (Japanese)

*Nagai N, Usui T, Asahi A, et al. 1956b. Comparison of biochemical findings and clinical pictures on subacute or chronic arsenic poisoning of infants due to arsenic containing powdered milk. NTIS no. PB-258710-T.

*Nagymajtényi L, Selypes A, Berencsi G. 1985. Chromosomal aberrations and fetotoxic effects of atmospheric arsenic exposure in mice. J Appl Toxicol 5(2):61-63.

*Nakadaira H, Endoh K, Katagiri M, et al. 2002. Elevated mortality from lung cancer associated with arsenic exposure for a limited duration. J Occup Environ Med 44(3):291-299.

*Nakamuro K, Sayato Y. 1981. Comparative studies of chromosomal aberrations induced by trivalent and pentavalent arsenic. Mutat Res 88:73-80.

Narang AP. 1987. Arsenicosis in India. J Toxicol Clin Toxicol 25:287-296.

Narasaki H. 1985. Determination of arsenic and selenium in fat materials and petroleum products by oxygen bomb combustion and automated atomic absorption spectrometry with hydride generation. Anal Chem 57:2481-2486.

*NAS. 1977a. Medical and biologic effects of environmental pollutants: Arsenic. Washington, DC: National Academy of Sciences. http://www.nap.edu/books/0309026040/html/index.html. May 12, 2005.

*NAS. 1977b. Arsenic. Drinking water and health. Washington, DC: National Academy of Sciences, 316-344, 428-430.

NAS. 1989. Recommended dietary allowances. 10th ed. Washington, DC: National Academy Press.

*NAS/NRC. 1989. Report of the oversight committee. In: Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press.

NATICH. 1989. National Air Toxics Information Clearing House: NATICH database report on state, local and EPA air toxics activities. Report to U.S. Environmental Protection Agency, Office of Air

9REFERENCES

Quality Planning and Standards. Research Triangle Park, NC, by Radian Corporation, Austin, TX. EPA45038929.

NATICH. 1992. National air toxics information clearinghouse. Report on state, local, and EPA air toxics activities. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. September 1, 1992.

Navarro PA, Liu L, Keefe DL. 2004. In vivo effects of arsenite on meiosis, preimplantation development, and apoptosis in the mouse. Biol Reprod 70(4):980-985.

Neary DG, Bush PB, Michael JL. 1993. Fate, dissipation and environmental effects of pesticides in southern forests: A review of a decade of research progress. Environ Toxicol Chem 12:411-428.

*Neiger RD, Osweiler GD. 1989. Effect of subacute low level dietary sodium arsenite on dogs. Fundam Appl Toxicol 13:439-451.

*Neiger RD, Osweiler GD. 1992. Arsenic concentrations in tissues and body fluids of dogs on chronic low level dietary sodium arsenite. J Vet Diagn Invest 4:334-337.

Nelson WC, Lykins MH, Mackey J, et al. 1973. Mortality among orchard workers exposed to lead arsenate spray: A cohort study. J Chronic Dis 26:105-118.

*Nemec MD, Holson JF, Farr CH, et al. 1998. Developmental toxicity assessment of arsenic acid in mice and rabbits. Reprod Toxicol 12(6):647-658.

*Nesnow S, Roop BC, Lambert G, et al. 2002. DNA damage induced by methylated trivalent aresnicals is mediated by reactive oxygen species. Chem Res Toxicol 15(12):1627-1634.

*Newman JA, Archer VE, Saccomanno G, et al. 1976. Histologic types of bronchogenic carcinoma among members of copper-mining and smelting communities. Ann N Y Acad Sci 271:260-268.

Ng JC, Seawright AA, Chiswell B, et al. 1998. Tumors induced by chronic arsenic exposure in mice. Hum Exp Toxicol 17(9):502.

Ng JC, Seawright AA, Moore MR. 2001. Metallothionen is not protective against the carcinogenic effect of chronic arsenic exposure in mice. Toxicol Lett 123:82.

Nicholas DR, Ramamoorthy S, Palace V, et al. 2003. Biogeochemical transformations of arsenic in circumneutral freshwater sediments. Biodegradation 14(2):123-137.

Nicholson FA, Smith SR, Alloway BJ, et al. 2003. An inventory of heavy metals inputs to agricultural soils in England and Wales. Sci Total Environ 311:205-219.

*Nielsen FH, Hunt CD, Uthus EO. 1980. Interactions between essential trace and ultratrace elements. Ann NY Acad Sci 355:152-164.

*Nielson KK, Sanders RW. 1983. Multielement analysis of unweighed biological and geological samples using backscatter and fundamental parameters. Advances in X-ray Analysis 26:385-390.

Nikolaidis NP, Dobbs GM, Chen J, et al. 2004. Arsenic mobility in contaminated lake sediments. Environ Pollut 129(3):479-487.

9REFERENCES

NIOSH. 1975. Criteria for a recommended standard: Occupational exposure to inorganic arsenic. New Criteria-1975. Washington, DC: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, DHEW Publication no. NIOSH 75-149.

NIOSH. 1979. Arsine (arsenic hydroxide) poisoning in the workplace. Current Intelligence Bulletin 32. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

*NIOSH. 1984. Arsenic trioxide, as As - method 7901. In: NIOSH manual of analytical methods. 3rd ed. Vol. 1. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication no. 84-100. PB85179018.

NIOSH. 1985. Arsenic, organo - method 5022. In: NIOSH manual of analytical methods. 3rd ed. Vol. 2. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication no. 84-100. PB88204722.

NIOSH. 1987. Arsenic and compounds - method 7900. In: NIOSH manual of analytical methods. 3rd ed. Vol. 1. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication no. 84-100.

NIOSH. 1990. NIOSH pocket guide to chemical hazards. Washington, DC: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, 42.

NIOSH. 1994a. Arsenic and compounds, as As (except AsH_3 and As_2O_3) - method 7900. NIOSH Manual of Analytical Methods (NMAM). National Institute for Occupational Safety and Health. August 1994. http://www.cdc.gov/niosh/nmam/pdfs/7900.pdf. April 6, 2005.

NIOSH. 1994b. Arsenic trioxide, as As - method 7901. NIOSH Manual of Analytical Methods (NMAM). National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/nmam/pdfs/7901.pdf. April 6, 2005.

NIOSH. 1994c. Arsenic, organo-method 5022. NIOSH Manual of Analytical Methods (NMAM). National Institute for Occupational Safety and Health. August 1994. http://www.cdc.gov/niosh/nmam/pdfs/5022.pdf. April 6, 2005.

NIOSH. 1994d. Arsine - method 6001. NIOSH Manual of Analytical Methods (NMAM). National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/nmam/pdfs/6001.pdf. April 6, 2005

NIOSH. 1994e. NIOSH Manual of Analytical Methods. 4th ed., August 15, 1994. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, DHHS. Method 7300 - Elements by ICP; Method 7900 - Arsenic; method 5022 - Arsenic, organo; Method 7901 - Arsenic trioxide.

9REFERENCES

NIOSH. 1997. Arsenic. NIOSH Pocket Guide to Chemical Hazards. Washington, DC: U.S. Department of Health and Human Services. National Institute for Occupational Safety and Health. PB97177604.

*NIOSH. 1999. Arsenic. Online pocket guide to chemical hazards. Wysiwyg://58/http://www.cdc.gov/niosh/npg/npg.html. March 20, 2005.

NIOSH. 2003. Elements by ICP (Nitric/perchloric acid ashing) - method 7300. NIOSH Manual of Analytical Methods (NMAM). National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/nmam/pdfs/7300.pdf. April 6, 2005.

*NIOSH. 2005a. Arsenic. 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/npgdname.html. February 15, 2004.

NIOSH. 2005b. International Chemical Safety Cards (ICSCs): U.S. National Version http://www.cdc.gov/niosh/ipcs/nicstart.html. April 7, 2005.

*Nishikawa T, Wanibuchi H, Ogawa M, et al. 2002. Promoting effects of monomethylarsonic acid, dimethylarsinic acid and trimethylarsine oxide on induction of rat liver preneoplastic gluthathione S-transferase placental from positive foci: A possible reactive oxygen species mechanism. Int J Cancer 100(2):136-139.

*Nishioka H. 1975. Mutagenic activities of metal compounds in bacteria. Mutat Res 31:185-189.

NJDEP. 1993. Ground water quality standards. New Jersey Department of Environmental Protection, Division of Water Quality. http://www.nj.gov/dep/wmm/sgwqt/sgwqt.htm January 15, 2001.

*NOES. 1990. National Occupational Exposure Survey, National Institute for Occupational Safety and Health, Cincinnati, OH. July 16, 1990.

Nolte J. 1988. Pollution source analysis of river water and sewage sludge. Environ Technol Lett 9:857-868.

Noort D, Benschop HP, Black RM. 2002. Biomonitoring of exposure to chemical warfare agents: A review. Toxicol Appl Pharmacol 184(2):116-126.

*Nordberg GF, Andersen O. 1981. Metal interactions in carcinogenesis: Enhancement, inhibition. Environ Health Perspect 40:65-81.

*Nordenson I, Beckman G, Beckman L, et al. 1978. Occupational and environmental risks in and around a smelter in northern Sweden: II. Chromosomal aberrations in workers exposed to arsenic. Hereditas 88:47-50.

*Nordenson I, Salmonsson S, Brun E, et al. 1979. Chromosome aberrations in psoriatic patients treated with arsenic. Hum Genet 48:1-6.

*Nordenson I, Sweins A, Beckman L. 1981. Chromosome aberrations in cultured human lymphocytes exposed to trivalent and pentavalent arsenic. Scand J Work Environ Health 7:277-281.

Nordstrom DK. 2002. Public health. Worldwide occurrences of arsenic in ground water. Science 296(5576):2413-2145.

*Nordström S, Beckman L, Nordenson I. 1978a. Occupational and environmental risks in and around a smelter in northern Sweden. I. Variations in birthweight. Hereditas 88:43-46.

*Nordström S, Beckman L, Nordenson I. 1978b. Occupational and environmental risks in and around a smelter in northern Sweden. III. Frequencies of spontaneous abortion. Hereditas 88:51-54.

*Nordström S, Beckman L, Nordenson I. 1979a. Occupational and environmental risks in and around a smelter in northern Sweden. V. Spontaneous abortion among female employees and decreased birth weight in their offspring. Hereditas 90:291-296.

*Nordström S, Beckman L, Nordenson I. 1979b. Occupational and environmental risks in and around a smelter in northern Sweden. VI. Congenital malformations. Hereditas 90:297-302.

*Norin H, Vahter M. 1981. A rapid method for the selective analysis of total urinary metabolites of inorganic arsenic. Scand J Work Environ Health 7:38-44.

Norin H, Christakopoulos A, Rondahl L, et al. 1987. Identification and quantification of arsenocholine and acetylarsenocholine in trace amounts in biological material by use of pyrolysis gas chromatography/mass spectrometry. Biomed Environ Mass Spectrom 14:117-125.

Norman JA, Pickford CJ, Sanders TW, et al. 1987. Human intake of arsenic and iodine from seaweed-based food supplements and health foods available in the UK. Food Addit Contam 5(1):103-109.

*NRC. 1993. Pesticides in the diets of infants and children. National Research Council. Washington, DC: National Academy Press.

*NRC. 1999. Arsenic in drinking water. National Research Council. Washington, DC: National Academy Press.

Nriagu JO. 1988. A silent epidemic of environmental metal poisoning? Environ Pollut 50:139-161.

*Nriagu JO, Lin T-S. 1995. Trace metals in wild rice sold in the United States. Sci Total Environ 172(2-3):223-228.

*Nriagu JO, Pacyna JM. 1988. Quantitative assessment of worldwide contamination of air, water and soils by trace metals. Nature 333:134-139.

NTP. 1989a. National Toxicology Program. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. NTP 89-239.

*NTP. 1989b. National Toxicology Program - technical report series no. 345. Toxicology and carcinogenesis studies of roxarsone (CAS No. 121-19-7) in F344/N rats and B6C3F1 mice (feed studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NTP-TR-345; NIH pub no. 89-2800.

*NTP. 1994. Seventh annual report on carcinogens - 1994. National Toxicology Program. Research Triangle Park, NC: National Institute of Environmental Health Sciences, 21-26.

NTP. 1998a. NTP Chemical Repository. (Radian Corporation, August 29, 1991). Arsenic trioxide National Toxicological Program. National Institute of Environmental Health Sciences. http://ntp-db.niehs.nih.gov/NTP_Reports/NTP_Chem_H&S/NTP_Chem1/Radian327-53-3.txt May 1, 2005.

NTP. 1998b. NTP Chemical Repository. (Radian Corporation, August 29, 1991). Arsenic chloride. National Toxicological Program. National Institute of Environmental Health Sciences. http://ntp-db.niehs.nih.gov/NTP_Reports/NTP_Chem_H&S/NTP_Chem1/Radian327-53-3.txt. May 1, 2005.

*NTP. 2000. Report on carcinogens. 9th ed. U.S. Department of Health and Human Services. Research Triangle Park, NC: National Toxicology Program.

NTP. 2004. Arsenic compounds, inorganic. In: National Toxicology Program, eds. Report on carcinogens. 11th ed. Research Triangle Park, North Carolina: National Institute of Environmental Health Sciences:III18-III21.

*NTP. 2005. Report on carcinogens. 11 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. February 15, 2004.

Nygren O, Nilsson CA. 1993. Determination and speciation of chromium copper and arsenic in wood and dust from CCA-impregnated timber. Analysis 21:83-89.

*Nygren O, Nilsson C-A, Lindahl R. 1992. Occupational exposure to chromium, copper and arsenic during work with impregnated wood in joinery shops. Ann Occup Hyg 36(5)509-517.

*Oberly TJ, Hoffman WP, Garriott ML. 1996. An evaluation of the twofold rule for assessing a positive response in the L5178Y $TK^{+/-}$ mouse lymphoma assay. Mutat Res 369 (3-4):221-232.

*Oberly TJ, Piper CE, McDonald DS. 1982. Mutagenicity of metal salts in the L5178Y mouse lymphoma assay. J Toxicol Environ Health 9:367-376.

*Odanaka Y, Matano O, Goto S. 1980. Biomethylation of inorganic arsenic by the rat and some laboratory animals. Bull Environ Contam Toxicol 24:452-459.

*Odanaka Y, Tsuchiya N, Matano O, et al. 1983. Determination of inorganic arsenic and methylarsenic compounds by gas chromatography and multiple ion detection mass spectrometry after hydride generation-heptane cold trap. Anal Chem 55:929-932.

Odanaka Y, Tsuchiya N, Matano O, et al. 1985. Characterization of arsenic metabolites in rice plant treated with DSMA (disodium methanearsonate). J Agric Food Chem 33:757-763.

O'Day PA, Carroll SA, Waychunas GA. 1998. Rock-water interactions controlling zinc, cadmium, and lead concentrations in surface waters and sediments, U.S. Tri-State Mining District. 1. Molecular identification using x-ray absorption spectroscopy. Environ Sci Technol 32(7):943-955.

*Offergelt JA, Roels H, Buchet JP, et al. 1992. Relation between airborne arsenic trioxide and urinary excretion of inorganic arsenic and its methylated metabolites. Br J Ind Med 49(6)387-393.

O'Flaherty EJ. 1998. Physiologically based models of metal kinetics. Crit Rev Toxicol 28(3):271-317.

9REFERENCES

Ohnishi K, Yoshida H, Shigeno K, et al. 2000. Prolongation of the QT interval and ventricular tachycardia in patients treated with arsenic trioxide for acute promyelocytic leukemia. Ann Intern Med 133(11):881-885.

Ohnishi Y, Murakami S, Ohtsuka H, et al. 1997. Merkel cell carcinoma and multiple Bowen's disease: Incidental association or possible relationship to inorganic arsenic exposure? J Dermatol 24(5):310-316.

*Ohyama S, Ishinishi N, Hisanaga A, et al. 1988. Comparative chronic toxicity, including tumorigenicity, of gallium arsenide and arsenic trioxide intratracheally instilled into hamsters. Appl Organomet Chem 2:333-337.

*Okada S, Yamanaka K. 1994. Induction of lung-specific DNA damage by methylarsenics via the production of free radials. In: Nriagu JO, ed. Arsenic in the environment. New York, NY: John Wiley & Sons, Inc., 143-157.

O'Kamura S, Inoue N. 1999. [Hematological disturbances caused by arsenic poisoning.] Fukuoka Igaku Zasshi 90(2):33-38. (Japanese)

*Okui T, Fujiwara Y. 1986. Inhibition of human excision DNA repair by inorganic arsenic and the co-mutagenic effect in V79 Chinese hamster cells. Mutat Res 172:69-76.

Olmez I, Kotra JP, Lowery S, et al. 1985. Airborne lead and trace elements in an indoor shooting range: A study of the DC National Guard Armory Pistol Range. Environ Toxicol Chem 4:447-452.

Ong E-S, Yong Y-L, Woo S-O. 1999. Determination of arsenic in traditional Chinese medicine by microwave digestion with flow injection-inductively coupled plasma mass spectrometry (FI-ICP-MS). J AOAC Int 82(4):963-967.

*Orosz CG, Wakely E, Sedmak DD, et al. 1997. Prolonged murine cardiac allograft acceptance. Transplantation 63(8)1109-1117.

*O'Rourke MK, Rogan SP, Jin S, et al. 1999. Spatial distributions of arsenic exposure and mining communities from NHEXAS Arizona. National Human Exposure Assessment Survey. J Expo Anal Environ Epidemiol 9(5):446-455.

OSHA. 1983. Occupational Safety and Health Administration. Fed Regist 48:1894.

OSHA. 1989. Air contaminants. Occupational Safety and Health Administration: Part III. Fed Regist 54(12):2332-2335, 2923-2924.

OSHA. 1996a. Occupational safety and health standards. Safety and health regulations for construction. Inorganic arsenic. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.1118.

OSHA. 1996b. Occupational safety and health standards. Toxic and hazardous substances. Inorganic arsenic. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1018.

OSHA. 1996c. Air contaminants. Inorganic arsenic. Occupational Safety and Health Administration. Department of Labor. Code of Federal Regulations. 29 CFR 1915.1018.

9REFERENCES

OSHA. 1997. Occupational health and environmental controls. Threshold limit values of airborne contaminants for construction. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55, Appendix A.

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 1910.1018.

OSHA. 1999c. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000.

OSHA. 1999d. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55.

*OSHA. 2005a. Air contaminants. Occupational safety and health standards for shipyard employment. Washington, DC: Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000. http://www.osha.gov/comp-links.html. February 15, 2005.

*OSHA. 2005b. Gases, vapors, fumes, dusts, and mists. Safety and health regulations for construction. Washington, DC: Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55, Appendix A. http://www.osha.gov/comp-links.html. February 15, 2005.

*OSHA. 2005c. Inorganic arsenic. Occupational safety and health standards. Washington, DC: Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1018. http://www.osha.gov/comp-links.html. March 24, 2005.

*OSHA. 2005d. Limits for air contaminants. Occupational safety and health standards. Washington, DC: Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000. http://www.osha.gov/comp-links.html. February 15, 2005.

O'Shaughnessy E, Kraft GH. 1976. Arsenic poisoning: Long-term follow-up of a nonfatal case. Arch Phys Med Rehabil 57:403-406.

O'Shea TJ, Everette AL, Ellison LE. 2001. Cyclodiene insecticide, DDE, DDT, arsenic, and mercury contamination of big brown bats (*Eptesicus fuscus*) foraging at a Colorado superfund site. Arch Environ Contam Toxicol 40:112-120.

*OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment. OTA-BA-438.

*Ott MG, Holder BB, Gordon HL. 1974. Respiratory cancer and occupational exposure to arsenicals. Arch Environ Health 29:250-255.

*Owen GM, Brozek J. 1966. Influence of age, sex and nutrition on body composition during childhood and adolescence. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 222-238.

*Oya-Ohta Y, Kaise T, Ochi T. 1996. Induction of chromosomal aberrations in cultured human fibroblasts by inorganic and organic arsenic compounds and the different roles of glutathione in such induction. Mutat Res 357(1-2)123-129.

9REFERENCES

*Øygard JK, Lundebye A-K, Julshamin K. 1999. Determination of inorganic arsenic in marine food samples by hydrochloric acid distillation and flow-injection hydride-generation atomic absorption spectrometry. J AOAC Int 82(5):1217-1223.

*Pacyna JM. 1987. Atmospheric emissions of arsenic, cadmium, lead and mercury from high temperature processes in power generation and industry. In: Hutchinson TC, Meema KM, eds. Lead, mercury, cadmium and arsenic in the environment. New York: John Wiley & Sons Ltd., 69-87.

*Pacyna JM, Scholtz MT, Li Y-F. 1995. Global budget of trace metal sources. Environ Rev 3(2):145-159.

*Page BJ, Loar GW. 1993. Chromium compounds. In: Kroschwitz JI, Howe-Grant M, eds. Kirk-Othmer encyclopedia of chemical technology. Vol. 6. New York, NY: John Wiley and Sons, 297-298.

*Page GW. 1981. Comparison of groundwater and surface water for patterns and levels of contamination by toxic substances. Environ Sci Technol 15(12):1475-1481.

Palmer JS. 1972. Toxicity of 45 organic herbicides to cattle, sheep and chickens. Washington, DC: U.S. Department of Agriculture. USDA production research report no. 137.

Pandey PK, Khare RN, Sharma R, et al. 1999. Arsenicosis and deteriorating groundwater quality: Unfolding crisis in central-east Indian region. Curr Sci 77(5):686-693.

Pandey PK, Yadav S, Nair S, et al. 2002. Arsenic contamination of the environment: A new perspective from central-east India. Environ Int 28(4):235-245.

*Pantsar-Kallio M, Manninen PKG. 1997. Speciation of mobile arsenic in soil samples as a function of pH. Sci Total Environ 204(2):193-200.

Parish GG, Glass R, Kimbrough R. 1979. Acute arsine poisoning in two workers cleaning a clogged drain. Arch Environ Health 224-227.

*Park J, Presley BJ. 1997. Trace metal contamination of sediments and organisms from the Swan Lake area of Galveston Bay. Environ Pollut 98(2):209-221.

*Paschal DC, DiPietro ES, Phillips DL, et al. 1989. Age dependence of metals in hair in a selected US population. Environ Res 48:17-28.

*Pascoe GA, Blanchet RJ, Linder G. 1994. Bioavailability of metals and arsenic to small mammals at a mining waste-contaminated wetland. Arch Environ Contam Toxicol 27:44-50.

Patterson R, Vega L, Trouba K, et al. 2004. Arsenic-induced alterations in the contact hypersensitivity response in Balb/c mice. Toxicol Appl Pharmacol 198(3):434-443.

PAX. 1973. PAX Company Arsenic Advisory Committee. Report of the PAX company Advisory Committee to the Environmental Protection Agency. Salt Lake City: PAX Company Arsenic Advisory Committee. PB265964.

*Pedersen GA, Mortensen GK, Larsen EH. 1994. Beverages as a source of toxic trace element intake. Food Addit Contam 11(3):351-363.

9REFERENCES

Pellizzari ED, Smith DJ, Clayton CA, et al. 2001. An assessment of the data quality for NHEXAS-Part I: Exposure to metals and volatile organic chemicals in Region 5. J Expo Anal Environ Epidemiol 11:140-154.

Peoples SA. 1964. Arsenic toxicity in cattle. Ann N Y Acad Sci 111:644-649.

Peoples SA, Maddy KT, Peifer WR, et al. 1979. Occupational exposures to pesticides containing organoarsenicals in California. Vet Hum Toxicol 21:417-421.

Peraza MA, Ayala-Fierro F, Barber DS, et al. 1998. Effects of micronutrients on metal toxicity. Environ Health Perspect Suppl 106(1):203-216.

Peraza MA, Kuester RK, Sipes IG, et al. 1998. Lack of dimethylarsenic hepatotoxicity to six week old male Fischer 344 rats. Toxicologist Abstracts of the 37th Annual Meeting 42(1-S):321-322.

Pereira R, Ribeiro R, Goncalves F. 2004. Scalp hair analysis as a tool in assessing human exposure to heavy metals (S. Domingos mine, Portugal). Sci Total Environ 327(1-3):81-92.

*Permapost 2000. Chromated copper arsenate, CCA-C. Permapost Products Co., Hillsboro, Oregon. http://www.permapost.com/cca.htm.

*Perry K, Bowler RG, Buckell HM, et al. 1948. Studies in the incidence of cancer in a factory handling inorganic compounds of arsenic--II: Clinical and environmental investigations. Br J Ind Med 5:6-15.

*Pershagen G. 1985. Lung cancer mortality among men living near an arsenic-emitting smelter. Am J Epidemiol 122(4):684-694.

Pershagen G. 1986. Sources of exposure and biological effects of arsenic. In: O'Neill IK, Schuller P, Fishbein L, eds. IARC Science Publication no. 71. Environmental carcinogens selected methods of analysis. Lyon, France: International Agency for Research on Cancer, 45-61.

*Pershagen G, Björklund NE. 1985. On the pulmonary tumorigenicity of arsenic trisulfide and calcium arsenate in hamsters. Cancer Lett 27:99-104.

*Pershagen G, Bergman F, Klominek J, et al. 1987. Histological types of lung cancer among smelter workers exposed to arsenic. Br J Ind Med 44:454-458.

Pershagen G, Lind B, Björklund NE. 1982. Lung retention and toxicity of some inorganic arsenic compounds. Environ Res 29:425-434.

*Pershagen G, Nordberg G, Bjorkland NE. 1984a. Carcinomas of the respiratory tract in hamsters given arsenic trioxide and/or benzo[*a*]pyrene by the pulmonary route. Environ Res 34:227-241.

Pershagen G, Nordberg G, Bjorkland NE. 1984b. Experimental evidence on the pulmonary carcinogenicity of arsenic trioxide. Arch Toxicol Suppl 7:403-404.

*Pershagen G, Wall S, Taube A, et al. 1981. On the interaction between occupational arsenic exposure and smoking and its relationship to lung cancer. Scand J Work Environ Health 7:302-309.

9REFERENCES

*Pesch B, Ranft U, Jakubis P, et al. 2002. Environmental arsenic exposure from a coal-burning power plant as a potential risk factor for nonmelanoma skin carcinoma: Results from a case-control study in the district of Prievidza, Slovakia. Am J Epidemiol 155(9):798-809.

Peters HA, Croft WA, Woolson EA, et al. 1984. Seasonal arsenic exposure from burning chromium-copper-arsenate-treated wood. JAMA 251:2393-2396.

Peters HA, Croft WA, Woolson EA, et al. 1986. Hematological, dermal and neuropsychological disease from burning and power sawing chromium-copper-arsenic (CCA)-treated wood. Acta Pharmacol Toxicol (Copenh) 59(Suppl 7):39-43.

Peters JH, Guilbaut M, Eschner T, et al. 1998. Application of in vitro bioaccessibility test data to a public health risk assessment of arsenic-contaminated soils. Toxicologist. Abstracts of the 37th Annual Meeting 42(1-S):229.

Peters RA, Thompson RH, King AJ, et al. 1944. The treatment of post-arsphenamine jaundice with sulphur-containing amino acids. Q J Med 14:35-56.

Peters RA, Thompson RH, King AJ, et al. 1945. Sulphur-containing amino acids and jaundice. Nature 153:773.

*Peters SC, Blum JD, Klaue B, et al. 1999. Arsenic occurrence in New Hampshire drinking water. Environ Sci Technol 33:1328-1333.

*Peterson RG, Rumack BH. 1977. D-penicillamine therapy of acute arsenic poisoning. J Pediatr 91(4):661-666.

*Petres J, Baron D, Hagedorn M. 1977. Effects of arsenic cell metabolism and cell proliferation: Cytogenic and biochemical studies. Environ Health Perspect 19:223-227.

*Petrick JS, Ayala-Fierro F, Cullen WR, et al. 2000. Monomethylarsenous acid (MMA III) is more toxic than arrsenite in Chang human hepatocytes. Toxicol Appl Pharmacol 163:203-207.

*Petrick JS, Jagadish B, Mash EA, et al. 2001. Monomethylarsenous acid (MMA^{III}) and arsenite: LD_{50} in hamsters and in vitro inhibition of pyruvate dehydrogenase. Chem Res Toxicol 14(6):651-656.

Phaneuf D, Cote I, Dumas P, et al. 1999. Evaluation of the contamination of marine algae (seaweed) from the St. Lawrence River and likely to be consumed by humans. Environ Res 80:S175-S182.

Philipp R. 1985. Arsenic exposure: Health effects and the risk of cancer. Rev Environ Health 5:27-57.

*Philp RB, Leung FY, Bradley C. 2003. A comparison of the metal content of some benthic species from coastal waters of the Florida panhandle using high-resolution inductively coupled plasma mass spectrometry (ICP-MS) analysis. Arch Environ Contam Toxicol 44:218-223.

*Pi J, He Y, Bortner C, et al. 2005. Low level, long-term inorganic arsenite exposure causes generalized resistance to apoptosis in cultured human keratinocytes: Potential role in skin co-carcinogenesis. Int J Cancer 116:20-26.

9REFERENCES

*Pi J, Yamauchi H, Kumagai Y, et al. 2002. Evidence for induction of oxidative stress caused by chronic exposure of Chinese residents to arsenic contained in drinking water. Environ Health Perspect 110:331-336.

Piamphongsant T. 1999. Chronic environmental arsenic poisoning. Int J Dermatol 38:401-410.

Pinto SS, Bennett BM. 1963. Effect of arsenic trioxide exposure on mortality. Arch Environ Health 7:583-591.

*Pinto SS, McGill CM. 1953. Arsenic trioxide exposure in industry. Ind Med Surg 22(7):281-287.

*Pinto SS, Enterline PE, Henderson V, et al. 1977. Mortality experience in relation to a measured arsenic trioxide exposure. Environ Health Perspect 19:127-130.

*Pinto SS, Henderson V, Enterline PE. 1978. Mortality experience of arsenic-exposed workers. Arch Environ Health 33:325-331.

*Pinto SS, Varner MO, Nelson KW, et al. 1976. Arsenic trioxide absorption and excretion in industry. J Occup Med 18(10):677-680.

*Piontek M, Hengels KJ, Borchard F, et al. 1989. [Noncirrhotic liver fibrosis after chronic arsenic poisoning.] Dtsch Med Wochenschr 114:1653-1657. (German)

*Pirrone N, Keeler GJ. 1996. A preliminary assessment of the urban pollution in the Great Lakes region. Sci Total Environ 189/190:91-98.

Piscator M. 1986. The dependence of toxic reactions on the chemical species of elements. In: Bernhard M, Brinckman FE, Sadler PJ, eds. The importance of chemical "speciation" in environmental processes. Heidelberg, Germany: Springer-Verlag Berlin, 59-70.

*Pitten F-A, Müller G, König P, et al. 1999. Risk assessment of former military base contaminated with organoarsenic-based warfare agents: Uptake of arsenic by terrestrial plants. Sci Total Environ 226:237-245.

Pizarro I, Gomez M, Palacios MA, et al. 2003. Evaluation of stability of arsenic species in rice. Anal Bioanal Chem 376(1):102-109.

*Poddar S, Mukherjee P, Talukder G, et al. 2000. Dietary protection by iron against clastogenic effects of short-term exposure to arsenic in mice in vivo. Food Chem Toxicol 38(8):735-737.

Polissar AV, Hopke PK, Poirot RL. 2001. Atmospheric aerosol over Vermont: Chemical composition and sources. Environ Sci Technol 35:4604-4621.

*Polissar L, Lowry-Coble K, Kalman DA, et al. 1990. Pathways of human exposure to arsenic in a community surrounding a copper smelter. Environ Res 53:29-47.

*Poma K, Degraeve N, Kirsch-Volders M, et al. 1981. Cytogenetic analysis of bone marrow cells and spermatogonia of male mice after in vivo treatment with arsenic. Experientia 37:129-130.

*Poma K, Degraeve N, Susanne C. 1987. Cytogenetic effects in mice after chronic exposure to arsenic followed by a single dose of ethylmethane sulfonate. Cytologia 52:445-449.

9REFERENCES

*Pomroy C, Charbonnaeu SM, McCullough RS, et al. 1980. Human retention studies with ^{74}As. Toxicol Appl Pharm 53:550-556.

*Pongratz R. 1998. Arsenic speciation in environmental samples of contaminated soil. Sci Total Environ 224:133-141.

Pott WA, Benjamin SA, Yang RS. 2001. Pharmacokinetics, metabolism, and carcinogenicity of arsenic. Rev Environ Toxicol 169:165-214.

Pott WA, Benjamin SA, Yang RSH. 1998. Inhibitory effects of arsenic-containing mixtures in a multiple organ carcinogenicity bioassay. Toxicologist 42(1-S):75.

Potts AM, Gonasun LM. 1980. Toxic responses of the eye. In: Casarett LJ, Doull J, eds. Casarett and Doull's toxicology. The basic science of poisons. New York: Macmillan Publishing Co. Inc., 301-302.

Powell JH, Powell RE. 2001. Trace elements in fish overlying subaqueous tailings in the tropical west Pacific. Water Air Soil Pollut 125:81-104.

*Prasad GVR, Rossi NF. 1995. Arsenic intoxication associated with tubulointerstitial nephritis. Am J Kidney Dis 26(2)373-376.

Pratt S, Gottschalg E, Atmaca M, et al. 2004. Heat shock protein induced by sodium arsenite and cadmium chloride in rat hepatocytes and rat FGC4 hepatoma cells. Toxicology 194(3):235-236.

*Prier RF, Nees PO, Derse PH. 1963. The toxicity of an organic arsenical, 3-nitro-4-hydroxyphenyl-arsonic acid. II. Chronic toxicity. Toxicol Appl Pharmacol 5:526-542.

*Prukop JA, Savage NL. 1986. Some effects of multiple, sublethal doses of monosodium methanearsonate (MSMA) herbicide on hematology, growth, and reproduction of laboratory mice. Bull Environ Contam Toxicol 36:337-341.

Przygoda G, Feldmann J, Cullen WR. 2001. The arsenic eaters of Styria: A different picture of people who were chronically exposed to arsenic. Appl Organomet Chem 15:457-462.

*PSA. 2000. Excalibur atomic fluorescence: Measurements of arsenic, selenium, antimony, bismuth and tellurium. Orpington, England: PS Analytical Ltd. http://www.banian.com. March 31, 2005.

Pulido MD, Parrish AR. 2003. Metal-induced apoptosis: Mechanisms. Mutat Res 533:227-241.

*Qiao Y-L, Taylor PR, Yao S-X, et al. 1997. Risk factors and early detection of lung cancer in a cohort of Chinese tin miners. Ann Epidemiol 7:533-541.

*Quatrehomme G, Ricq O, Lapalus P, et al. 1992. Acute arsenic intoxication: Forensic and toxicologic aspects (an observation). J Forensic Sci 37(4)1163-1171.

Que Hee SS, Boyle JR. 1988. Simultaneous multielemental analysis of some environmental and biological samples by inductively coupled plasma atomic emission spectrometry. Anal Chem 60:1033-1042.

9REFERENCES

*Rabano ES, Castillo NT, Torre KJ, et al. 1989. Speciation of arsenic in ambient aerosols collected in Los Angeles. J Air Pollut Control Assoc 39:76-80.

Raessler M, Michalke B, Schulte-Hostede S, et al. 2000. Long-term monitoring of arsenic and selenium species in contaminated groundwaters by HPLC and HG-AAS. Sci Total Environ 258(3):171-181.

Rahman M. 2002. Arsenic and hypertension in Bangladesh (comment on Bull World Health Organ 79(6):490-500). Bull World Health Organ 80(2):173.

Rahman M, Axelson O. 1995. Diabetes mellitus and arsenic exposure: A second look at case-control data from a Swedish copper smelter. Occup Environ Med 52(11)773-774.

*Rahman FA, Allan DL, Rosen CJ, et al. 2004. Arsenic availability from chromated copper arsenate (CCA)-treated wood. J Environ Qual 33(1):173-180.

Rahman MM, Chowdhury UK, Mukherjee SC, et al. 2001. Chronic arsenic toxicity in Bangladesh and West Bengal, India--a review and commentary. J Toxicol Clin Toxicol 39(7):683-700.

Rahman MM, Mandal BK, Chowdhury TR, et al. 2003. Arsenic groundwater contamination and sufferings of people in North 24-Parganas, one of the nine arsenic affected districts of West Bengal, India. J Environ Sci Health A Tox Hazard Subst Environ Eng 38(1):25-59.

*Rahman M, Tondel M, Ahmad SA, et al. 1998. Diabetes mellitus associated with arsenic exposure in Bangladesh. Am J Epidemiol 148(2):198-203.

*Rahman M, Tondel M, Ahmad SA, et al. 1999a. Hypertension and arsenic exposure in Bangladesh. Hypertension 33:74-78.

Rahman M, Tondel M, Axelson O. 1999b. Chronic arsenicism and squamous cell carcinoma – a case report. Cancer Lett 143(Suppl 1):S38.

Rahman M, Wingren G, Axelson O. 1995 Diabetes mellitus among Swedish art glass workers--an effect of arsenic exposure? Scand J Work Environ Health 22(2):146-149.

Raie RM. 1996. Regional variation in As, Cu, Hg, and Se and interaction between them. Ecotoxicol Environ Saf 35:248-252.

Ramel C, Magnusson J. 1979. Chemical induction of nondisjunction in Drosophila. Environ Health Perspect 31:59-66.

*Ramirez P, Eastmond DA, Laclette JP, et al. 1997. Disruption of microtubule assembly and spindle formation as a mechanism for the induction of aneuploid cells by sodium arsenite and vanadium pentoxide. Mutat Res 386(3):291-298.

*Ramos-Morales P, Rodríguez-Arnaiz R. 1995. Genotoxicity of two arsenic compounds in germ cells and somatic cells of *Drosophila melanogaster*. Environ Mol Mutagen 25(4):288-299.

*Rasmussen RE, Menzel DB. 1997. Variation in arsenic-induced sister chromatid exchange in human lymphocytes and lymphoblastoid cell lines. Mutat Res 386(3)299-306.

9REFERENCES

*Rastogi SC, Pritzl G. 1996. Migration of some toxic metals from crayons and water colors. Bull Environ Contam Toxicol 56(4)527-533.

Ratnaike RN. 2003. Acute and chronic arsenic toxicity. Postgrad Med J 79(933):391-396.

Raven KP, Loeppert RH. 1997. Heavy metals in the environment: Trace element composition of fertilizers and soil amendments. J Environ Qual 26:551-557.

Raven KP, Jain A, Loeppert RH. 1998. Arsenite and arsenate adsorption on ferrihydrite: Kinetics, equilibrium, and adsorption envelopes. Environ Sci Technol 32:344-349.

*Rea MA, Gregg JP, Qin Q, et al. 2003. Global alteration of gene expression in human keratinocytes by inorganic arsenic. Carcinogenesis 24(4):747-756.

*Reddy PRK, Reddy SJ. 1997. Elemental concentrations in medicinally important leafy materials. Chemosphere 34(9-10):2193-2212.

*Redman AD, Macalady DL, Ahmann D. 2002. Natural organic matter affects arsenic speciation and sorption onto hematite. Environ Sci Technol 36:2889-2896.

*Regelson W, Kim U, Ospina J, et al. 1968. Hemangioendothelial sarcoma of liver from chronic arsenic intoxication by Fowler's solution. Cancer 21(3):514-522.

Reichl F-X, Hunder G, Liebl B, et al. 1995. Effect of DMPS and various adsorbents on the arsenic excretion in guinea-pigs after injection with As_2O_3. Arch Toxicol 69(10):712-717.

Reichl FX, Szinicz L, Kreppel H, et al. 1989. Effects on mitochondrial metabolism in livers of guinea pigs after a single or repeated injection of As_2O_3. Arch Toxicol 63:419-422.

*Reimann C, De Caritat P, Halleraker JH, et al. 1997. Rainwater composition in eight arctic catchments in Northern Europe (Finland, Norway and Russia). Atmos Environ 31(2):159-170.

Reimer KJ. 1989. The methylation of arsenic in marine sediments. Appl Organomet Chem 3:475-490.

*Reitz RH, Mendrala AL, Corley RA, et al. 1990. Estimating the risk of liver cancer associated with human exposures to chloroform using physiologically based pharmacokinetic modeling. Toxicol Appl Pharm 105:443-459.

Rencher AC, Carter MW, McKee DW. 1977. A retrospective epidemiological study of mortality at a large western copper smelter. J Occup Med 19:754-758.

*Reymann F, Møller R, Nielsen A. 1978. Relationship between arsenic intake and internal malignant neoplasms. Arch Dermatol 114:378-381.

*Rhoads K, Sanders CL. 1985. Lung clearance, translocation and acute toxicity of arsenic, beryllium, cadmium, cobalt, lead, selenium, vanadium, and ytterbium oxides following deposition in rat lung. Environ Res 36:359-378.

*Rice DA, Kennedy S, McMurray CH, et al. 1985. Experimental 3-nitro-4-hydroxyphenylarsonic acid toxicosis in pigs. Res Vet Sci 39:47-51.

9REFERENCES

Rice KC, Conko KM, Hornberger GM. 2002. Anthropogenic sources of arsenic and copper to sediments in a suburban lake, Northern Virginia. Environ Sci Technol 36:4962-4967.

Riedel GF, Sanders JG, Osman RW. 1987. The effect of biological and physical disturbances on the transport of arsenic from contaminated estuarine sediments. Estuarine Coastal Shelf Sci 25:693-706.

Riediker M, Williams R, Devlin R, et al. 2003. Exposure to particulate matter, volatile organic compounds, and other sir pollutants inside patrol cars. Environ Sci Technol 37:2084-2093.

Riget F, Johansen P, Asmund G. 1997. Baseline levels and natural variability of elements in three seaweed species from west Greenland. Mar Pollut Bull 34(3):171-176.

*Rin K, Kawaguchi K, Yamanaka K, et al. 1995. DNA-strand breaks induced by dimethylarsinic acid, a metabolite of inorganic arsenics, are strongly enhanced by superoxide anion radicals. Biol Pharm Bull 18(1):45-48.

*Rivara MIZ, Cebrián MG, Corey G, et al. 1997. Cancer risk in an arsenic contaminated area of Chile. In: International congress on hazardous waste: Impact on human and ecological health, ed. Hazardous waste, impacts on human ecological health: Proceedings of the 2nd International Congress on Hazardous Waste, Impact on Human and Ecological Health. Princeton, New Jersey: Princeton Scientific Pub. Co., 408-426.

Roat JW, Wald A, Mendelow H, et al. 1982. Hepatic angiosarcoma associated with short-term arsenic ingestion. Am J Med 73:933-936.

*Robertson FN. 1989. Arsenic in ground-water under oxidizing conditions, southwest United States. Environ Geochem Health 11:171-185.

*Rodriguez RR, Basta NT, Casteel SW, et al. 1999. An in vitro gastrointestinal method to estimate bioavailable arsenic in contaminated soils and solid media. Environ Sci Technol 33:642-649.

*Rodriguez VM, Carrizales L, Jimenez-Capdeville ME, et al. 2001. The effects of sodium arsenite exposure on behavioral parameters in the rat. Brain Res Bull 55(2):301-308.

*Rodriguez VM, Carrizales L, Mendoza MS, et al. 2002. Effects of sodium arsenite exposure on development and behavior in the rat. Neurotoxicol Teratol 24(6):743-750.

*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.

*Rogers EH, Chernoff N, Kavlock RJ. 1981. The teratogenic potential of cacodylic acid in the rat and mouse. Drug Chem Toxicol 4(1):49-61.

Rom WN, Varley G, Lyon JL, et al. 1982. Lung cancer among residents living near the El Paso smelter. Br J Ind Med 39:269-272.

Ronquillo D, Stoltzfus RJ, Kordas K. 2004. Arsenic exposure is associated with a decrease in cognitive performance independent of nutritional status. FASEB J 18(4-5):358.11.

9REFERENCES

*Roper JM, Cherry DS, Simmers JW, et al. 1996. Bioaccumulation of toxicants in the zebra mussel, *Dreissena polymorpha*, at the Times Beach confined disposal facility, Buffalo, New York. Environ Pollut 94(2):117-129.

Rosas I, Belmont R, Armienta A, et al. 1999. Arsenic concentrations in water, soil, milk and forage in Comarca Lagunera, Mexico. Water Air Soil Pollut 112:133-149.

*Rosen BP. 2002. Biochemistry of arsenic detoxification. FEBS Lett 529:86-92.

*Rosenbaum AS, Axelrad DA, Woodruff TJ, et al. 1999. National estimates of outdoor air toxics concentrations. J Air Waste Manage Assoc 49:1138-1152.

*Rosenberg HG. 1974. Systemic arterial disease and chronic arsenicism in infants. Arch Pathol 97:360-365.

Rosenberg MJ, Landrigan PJ, Crowley S. 1980. Low-level arsenic exposure in wood processing plants. Am J Ind Med 1:99-107.

Rosner U. 1998. Effects of historical mining activities on surface water and groundwater-an example from northwest Arizona. Environ Geol 33(4):224-230.

Rosner MH, Carter DE. 1987. Metabolism and excretion of gallium arsenide and arsenic oxides by hamsters following intratracheal instillation. Fundam Appl Toxicol 9:730-737.

*Rossman TG. 1981. Enhancement of UV-mutagenesis by low concentrations of arsenite in *E. coli*. Mutat Res 91:207-211.

*Rossman TG. 2003. Mechanism of arsenic carcinogenesis: An integrated approach. Mutat Res 533(1-2):37-65.

*Rossman TG, Stone D, Molina M, et al. 1980. Absence of arsenite mutagenicity in E coli and Chinese hamster cells. Environ Mut 2:371-379.

*Rossman TG, Uddin AN, Burns FJ, et al. 2001. Arsenite is a carcinogen with solar ultraviolet radiation for mouse skin: An animal model for arsenic carcinogenesis. Toxicol Appl Pharmacol 176:64-71.

*Rossman TG, Uddin AN, Burns FJ. 2004. Evidence that arsenite acts as a cocarcinogen in skin cancer. Toxicol Appl Pharmacol 198(3):394-404.

*Rössner P, Bencko V, Havránková H. 1977. Effect of the combined action of selenium and arsenic on suspension culture of mice fibroblasts. Environ Health Perspect 19:235-237.

*Roth F. 1957. The sequelae of chronic arsenic poisoning in Moselle Vintners. Ger Med Mon 2:172-175.

Roussel C, Bril H, Fernandez A. 2000. Arsenic speciation: Involvement in evaluation of environmental impact caused by mine wates. J Environ Qual 29:182-188.

Rousselot P, Labaume S, Larghero J, et al. 1997. Arsenic trioxide (As_2O_3) and melarsoprol induce myeloma cell apoptosis in vitro with a preferential effect on tumoral cells in patients' bone marrow. Blood 90(10 Suppl. 1 Part 1):325a.

9REFERENCES

*Rousselot P, Labaume S, Marolleau J-P, et al. 1999. Arsenic trioxide and melarsoprol induce apoptosis in plasma cell lines and in plasma cells from myeloma patients. Cancer Res 59:1041-1048.

Rowland IR, Davies MJ. 1981. *In vitro* metabolism of inorganic arsenic by the gastro-intestinal microflora of the rat. J Appl Toxicol 1:278-283.

Roy M. 1983. Arsenic and medical surveillance. Occup Health Ontario 4:17-29.

Roy P, Saha A. 2002. Metabolism and toxicity of arsenic: A human carcinogen. Curr Sci 82(1):38-45.

Roychowdhury T, Tokunaga H, Ando M. 2003. Survey of arsenic and other heavy metals in food composites and drinking water and estimations of dietary intake by the villagers from an arsenic-affected area of West Bengal, India. Sci Total Environ 308(1-3):15-35.

Roychowdhury T, Uchino T, Tokunaga H, et al. 2002. Survey of arsenic in food composites from an arsenic-affected area of West Bengal, India. Food Chem Toxicol 40(11):1611-1621.

RTECS database. 2005. Registry of toxic effects of chemical substances. Canadian Centre for Occupational Health and Safety.

Rubin ES. 1999. Toxic releases from power plants. Environ Sci Technol 33:3062-3067.

*Ruby MV, Davis A, Schoof R, et al. 1996. Estimation of lead and arsenic bioavailability using a physiologically based extraction test. Environ Sci Technol 30(2):422-430.

*Ruby MV, Schoof R, Brattin W, et al. 1999. Advances in evaluating the oral bioavailability of inorganics in soil for use in human health risk assessment. Environ Sci Technol 33(21):3697-3704.

Rudnai P, Borzonyi M. 1980. Carcinogenic effect of arsenic trioxide in transplacentally and neonatally treated CFLP mice. Nat Sci 2:11-18.

*Rupa DS, Schuler M, Eastmond DA. 1997. Detection of hyperdiploidy and breakage affecting the 1cen-1q12 region of cultured interphase human lymphocytes treated with various genotoxic agents. Environ Mole Mutagen 29(2):161-167.

Rusyniak DE, Furbee RB, Kirk MA. 2002. Thallium and arsenic poisoning in a small midwestern town. Ann Emerg Med 39(3):307-311.

Rutherford DW, Bednar AJ, Garbarino JR, et al. 2003. Environmental fate of roxarsone in poultry litter. Part II. Mobility of arsenic in soils amended with poultry litter. Environ Sci Technol 37:1515-1520.

Ryan PB, Huet N, MacIntosh DL. 2000. Longitudinal investigation of exposure to arsenic, cadmium, and lead in drinking water. Environ Health Perspect 108(8):731-735.

*Ryan PB, Scanlon KA, MacIntosh DL. 2001. Analysis of dietary intake of selected metals in the NHEXAS-Maryland investigation. Environ Health Perspect 109(2):121-128.

*Saady JJ, Blanke RV, Poklis A. 1989. Estimation of the body burden of arsenic in a child fatally poisoned by arsenite weedkiller. J Anal Toxicol 13:310-312.

9REFERENCES

Sadiq M. 1997. Arsenic chemistry in soils: An overview of thermodynamic predications and filed observations. Water Air Soil Pollut 93:117-136.

Saha KC. 2001. Cutaneous malignancy in arsenicosis. Br J Dermatol 145(1):185.

Saha JC, Dikshit AK, Bandyopadhyay M, et al. 1999. A review of arsenic poisoning and its effects on human health. Crit Rev Environ Sci 29(3):218-313.

*Saha KC, Poddar D. 1986. Further studies on chronic arsenical dermatosis. Indian J Dermatol 31:29-33.

Sakata M. 1987. Relationship between adsorption of arsenic (III) and boron by soil and soil properties. Environ Sci Technol 21:1126-1130.

Sakurai T, Kaise T, Matsubara C. 1998. Inorganic and methylated arsenic compounds induce cell death in murine macrophages via different mechanisms. Chem Res Toxicol 11:273-283.

*Salazar AM, Calderon-Aranda E, Cebrian ME, et al. 2004. p53 Expression in circulating lymphocytes of non-melanoma skin cancer patients from an arsenic contaminated region in Mexico. A pilot study. Mol Cell Biochem 255(1-2):25-31.

Salcedo JC, Portales A, Landecho E, et al. 1984. Transverse study of a group of patients with vasculopathy from chronic arsenic poisoning in communities of the Francisco de Madero and San Pedro Districts, Coahuila, Mexico. Rev Fac Med Torreon 12:16.

*Salim EI, Wanibuchi H, Morimura K, et al. 2003. Carcinogenicity of dimethylarsinic acid in p53 heterozygous knockout and wild-type C57BL/6J mice. Carcinogenesis 24(2):335-342.

Salnikow K, Cohen MD. 2002. Backing into cancer: Effects of arsenic on cell differentiation. Toxicol Sci 65(2):161-163.

*Samsøe-Petersen L, Larsen EH, Larsen PB, et al. 2002. Uptake of trace elements and PAHs by fruit and vegetables from contaminated soils. Environ Sci Technol 36:3057-3063.

Sandberg GR, Allen IK. 1975. A proposed arsenic cycle in an agronomic ecosystem. In: Woolson EA, ed. Arsenical pesticides. American Chemical Society Symposium Series no. 7. Washington, DC: American Chemical Society, 124-147.

*Sanders JG, Riedel GF, Osmann RW. 1994. Arsenic cycling and its impact in estuarine and coastal marine ecosystems. In: Nriagu JO, ed. Arsenic in the environment, part I: Cycling and characterization. New York, NY: John Wiley & Sons, Inc., 289-308.

Sandhu SS, Ma TH, Peng Y, et al. 1989. Clastogenicity evaluation of seven chemicals commonly found at hazardous industrial waste sites. Mutat Res 224:437-445.

*Sandstrom AIM, Wall SGI, Taube A. 1989. Cancer incidence and mortality among Swedish smelter workers. Br J Ind Med 46:82-89.

*Sanok WJ, Ebel JG, JR, Manzell KL, et al. 1995. Residues of arsenic and lead in potato soils on long island. Chemosphere 30(4):803-806.

9REFERENCES

*Santra A, Maiti A, Das S, et al. 2000. Hepatic damage caused by chronic arsenic toxicity in experimental animals. J Toxicol Clin Toxicol 38(4):395-405.

*Sardana MK, Drummond GS, Sassa S, et al. 1981. The potent heme oxygenase inducing action of arsenic in parasiticidal arsenicals. Pharmacology 23:247-253.

Sarin SK, Sharma G, Banerjee S, et al. 1999. Hepatic fibrogenesis using chronic arsenic ingestion studies in a murine model. Indian J Exp Biol 37:147-151.

*Sarkar D, Datta R. 2004. Arsenic fate and bioavailability in two soils contaminated with sodium arsenate pesticide: An incubation study. Bull Environ Contam Toxicol 72(2):240-247.

Sarkar M, Chaudhuri GR, Chattopadhyay A, et al. 2003. Effect of sodium arsenite on spermatogenesis, plasma gonadotrophins and testosterone in rats. Asian J Androl 5:27-31.

*Sass U, Grosshans E, Simonart JM. 1993. Chronic arsenicism: Criminal poisoning or drug-intoxication? Report of two cases. Dermatology 186(4)303-305.

Sax NI. 1984. Dangerous properties of industrial materials. 6th ed. New York, NY: Van Nostrand Reinhold Company.

Sax NI, Lewis RJ. 1987. Hawley's condensed chemical dictionary. 11th ed. New York, NY: Van Nostrand Reinhold Company, 98-99.

Sax NI, Lewis RJ. 1989. Dangerous properties of industrial materials. 7th ed. New York, NY: Van Nostrand Reinhold Company, 3:297, 299, 304-305.

Schmitt CJ, Brumbaugh WG. 1990. National Contaminant Biomonitoring Program: Concentrations of arsenic, cadmium, copper, lead, mercury, selenium, and zinc in U.S. freshwater fish, 1976-1984. Arch Environ Contam Toxicol 19:731-747.

*Schmitt CJ, Zajicek JL, May TW, et al. 1999. Organochlorine residues and elemental contaminants in U.S. freshwater fish, 1976-1986: National contaminant biomonitoring program. Rev Environ Contam Toxicol 162:43-104.

Schoen A, Beck B, Sharma R, et al. 2004. Arsenic toxicity at low doses: Epidemiological and mode of action considerations. Toxicol Appl Pharmacol 198(3):253-267.

*Schoenwolf GC, Smith JL. 1990. Mechanisms of neurulation: Traditional viewpoint and recent advances. Development 109:243-270.

Schoof RA, Evans CG. 1998. Use of background arsenic exposure data to assess health significance of exposures to arsenic in soil. Toxicologist. Abstracts of the 37th Annual Meeting 42(1-S):229.

*Schoof RA, Eickhoff J, Yost LJ, et al. 1999a. Dietary exposure to inorganic arsenic. In: Chappell WR, Abernathy CO, Calderon RL, eds. Arsenic exposure and health effects. Amsterdam: Elsevier Science, 81-88.

*Schoof RA, Yost LJ, Crecelius K, et al. 1998. Dietary arsenic intake in Taiwanese districts with elevated arsenic in drinking water. Hum Ecol Risk Assess 4(1):117-135.

9REFERENCES

*Schoof RA, Yost LJ, Eickhoff J, et al. 1999b. A market basket survey of inorganic arsenic in food. Food Chem Toxicol 37:839-846.

*Schrauzer GN. 1987. Effects of selenium antagonists on cancer susceptibility: New aspects of chronic heavy metal toxicity. J UOEH 9(Suppl):208-215.

*Schrauzer GN, Ishmael D. 1974. Effects of selenium and of arsenic on the genesis of spontaneous mammary tumors in inbred C_3H mice. Ann Clin Lab Sci 4(6):441-447.

*Schrauzer GN, White DA, McGinness JE, et al. 1978. Arsenic and cancer: Effects of joint administration of arsenite and selenite on the genesis of adenocarcinoma in inbred female C_3H/St mice. Bioinorg Chem 9:245-253.

*Schrauzer GN, White DA, Schneider CJ. 1976. Inhibition of the genesis of spontaneous mammary tumors in C_3H mice: Effects of selenium and of selenium-antagonistic elements and their possible role in human breast cancer. Bioinorg Chem 6:265-270.

*Schroeder HA, Balassa JJ. 1966. Abnormal trace metals in man: Arsenic. J Chron Dis 19:85-106.

*Schroeder HA, Balassa JJ. 1967. Arsenic, germanium, tin and vanadium in mice: Effects on growth, survival and tissue levels. J Nutr 92:245-252.

*Schroeder HA, Mitchener M. 1971. Toxic effects of trace elements on the reproduction of mice and rats. Arch Environ Health 23:102-106.

*Schroeder HA, Kanisawa M, Frost DV, et al. 1968. Germanium, tin and arsenic in rats: Effects on growth, survival, pathological lesions and life span. J Nutr 96:37-45.

*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.

*Schulz H, Nagymajtenyi L, Institoris L, et al. 2002. A study on behavioral, neurotoxicological, and immunotoxicological effects of subchronic arsenic treatment in rats. J Toxicol Environ Health A 65(16):1181-1193.

*Schwartz K. 1977. Essentiality versus toxicity of metals. In: Brown SS, ed. Clinical chemistry and chemical toxicology of metals. Vol. 1. Amsterdam: Elsevier, 3-22.

Schwerdtle T, Walter I, Mackiw I, et al. 2003. Induction of oxidative DNA damage by arsenite and its trivalent and pentavalent methylated metabolites in cultured human cells and isolated DNA. Carcinogenesis 24(5):967-974.

*Scott N, Hatlelid KM, MacKenzie NE, et al. 1993. Reactions of arsenic (III) and arsenic (V) species with glutathione. Chem Res Toxicol 6:102-106.

*Scudlark JR, Church TM. 1988. The atmospheric deposition of arsenic and association with acid precipitation. Atmos Environ 22(5):937-943.

*Scudlark JR, Conko KM, Church TM. 1994. Atmospheric wet deposition of trace elements to Chesapeake Bay: CBAD study year 1 results. Atmos Environ 28(8):1487-1498.

9REFERENCES

Sedman RM, Mahmood RJ. 1994. Soil ingestion by children and adults reconsidered using the results of recent tracer studies. J Air Waste Manage Assoc 44:141-144.

Segura M, Munoz J, Madrid Y, et al. 2002. Stability study of As(III), As(V), MMA and DMA by anion exchange chromatography and HG-AFS in wastewater samples. Anal Bioanal Chem 374(3):513-519.

Seike N, Wanibuchi H, Morimura K, et al. 2002. Lack of promotion effect due to oral administration of dimethylarsinic acid on rat lung carcinogenesis initiated with N-bis (2-hydroxypropyl) nitrosamine. Cancer Lett 175(2):113-119.

Selby LA, Case AA, Osweiler GD, et al. 1977. Epidemiology and toxicology of arsenic poisoning in domestic animals. Environ Health Perspect 19:183-189.

*Senesi GS, Baldassarre G, Senesi N, et al. 1999. Trace element inputs into soils by anthropogenic activities and implications for human health. Chemosphere 39(2):343-377.

Seppalainen AM. 1988. Neurophysiological approaches to the detection of early neurotoxicity in humans. CRC Crit Rev Toxicol 18:245-298.

*Setchell BP, Waites GMH. 1975. The blood-testis barrier. In: Creep RO, Astwood EB, Geiger SR, eds. Handbook of physiology: Endocrinology V. Washington, DC: American Physiological Society.

*Shahin U, Yi SM, Paode RD, et al. 2000. Long-term elemental dry deposition fluxes measured around Lake Michigan with an automated dry deposition sampler. Environ Sci Technol 34:1887-1892.

*Shannon RL, Strayer DS. 1989. Arsenic-induced skin toxicity. Hum Toxicol 8:99-104.

Shao W, Nervi C, Rosenauer A, et al. 1997. An APL subclone with a dominant negative PML-RARA mutation that resists retinoid degradation undergoes loss of PML-RARA protein and apoptosis in response to arsenic. Anticancer Research 17(5c):3934.

Sharpless GR, Metzger M. 1941. Arsenic and goiter. J Nutr 21:341-346.

*Sheehy JW, Jones JH. 1993. Assessment of arsenic exposures and controls in gallium arsenide production. Am Ind Hyg Assoc J 54(2):61-69.

*Shen J, Wanibuchi H, Salim EI, et al. 2003a. Induction of glutathione *S*-transferase placental form positive foci in liver and epithelial hyperplasia in urinary bladder, but no tumor development in male epithelial hyperplasia in urinary bladder, but no tumor development in male Fischer 344 rats treated with monomethylarsonic acid for 104 weeks. Toxicol Appl Pharmacol 193(3):335-345.

Shen J, Wanibuchi H, Salim EI, et al. 2003b. Liver tumorigenicity of trimethylarsine oxide in male Fischer 344 rats--association with oxidative DNA damage and enhanced cell proliferation. Carcinogenesis 24(11):1827-1835.

*Shen Z-X, Chen G-Q, Ni J-H, et al. 1997. Use of arsenic trioxide (As_2O_3) in the treatment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients. Blood 89(9):3354-3360.

*Shi H, Shi X, Liu KJ. 2004. Oxidative mechanism of arsenic toxicity and carcinogenesis. Mol Cell Biochem 255(1-2):67-78.

9REFERENCES

Shibata A, Ohneseit PF, Tsai YC, et al. 1994. Mutational spectrum in the p53 gene in bladder tumors from the endemic area of blackfoot disease in Taiwan. Carcinogenesis 15(6):1085-1087.

Shiomi K, Aoyama M, Yamanaka H, et al. 1988. Chemical forms of arsenic in sponges, sea anemones and sea hare. Comp Biochem Physiol 90c(2):361-365.

Shipp AM, Clewell HJ, Crump KS, et al. 1998. Application of the risk assessment approaches in the USEPA proposed cancer guidelines to arsenic. Toxicologist 42(1-S):229.

*Shirachi DY, Johansen MG, McGowan JP, et al. 1983. Tumorigenic effect of sodium arsenite in rat kidney. Proc West Pharmacol Soc 26:413-415.

Shraim A, Cui X, Li S, et al. 2003. Arsenic speciation in the urine and hair of individuals exposed to airborne arsenic through coal-burning in Guizhou, PR China. Toxicol Lett 137(1-2):35-48.

Shraim A, Sekaran NC, Anuradha CD, et al. 2002. Speciation of arsenic in tube-well water samples collected from West Bengal, India, by high-performance liquid chromatography-induced coupled plasma mass spectrometry. Appl Organomet Chem 16:202-209.

*Shum S, Whitehead J, Vaughn L, et al. 1995. Chelation of organoarsenate with dimercaptosuccinic acid. Vet Hum Toxicol 37(3):239-242.

Siegel FR, Galasso JJ, Kravitz JH. 2001. Geochemistry of thirteen Voronin Trough cores, Kara Sea, European Arctic: Hg and As contaminants at a 1965 timeline. Appl Geochem 16:19-34.

*Siewicki TC. 1981. Tissue retention of arsenic in rats fed witch flounder or cacodylic acid. J Nutr 111:602-609.

*Sikorski EE, McCay JA, White KL Jr, et al. 1989. Immunotoxicity of the semiconductor gallium arsenide in female B6C3F1 mice. Fundam Appl Toxicol 13:843-858.

Silbergeld EK. 2004. Arsenic in food. Comment on Environ Health Perspect 112(1):18-21. Environ Health Perspect 112(6):A338-A339.

*Silver AS, Wainman PL. 1952. Chronic arsenic poisoning following use of an asthma remedy. JAMA 150(6):584-585.

Simmon VF, Mitchell AD, Jorgensen TA. 1977. Evaluation of selected pesticides as chemical mutagens. In vitro and in vivo studies. Palo Alto, CA: Stanford Research Institute.

Simon I. 1932. Studii comparativi fra il dimetilarsinato di sodio ed il manometilarsinato bisodico. I. Tossicita del metilarsinato bisodico (arrhenal o metarsolo) ed alterazioni anatomo-patologiche deliavvelanamento. Arch Int Pharmacodyn Ther 45:142-159.

Singh DB, Prasad G, Rupainwar DC, et al. 1988. Arsenic (III) removal from aqueous solution by adsorption. Water Air Soil Pollut 42:373-386.

*Singh I. 1983. Induction of reverse mutation and mitotic gene conversion by some metal compounds in *Saccharomyces cerevisiae*. Mutat Res 117:149-152.

9REFERENCES

Sittig M, ed. 1980. Pesticide manufacturing and toxic materials control encyclopedia. Park Ridge, NJ: Noyes Data Corporation, 59, 125, 128, 356, 541, 542, 675.

Sittig M. 1985. Handbook of toxic and hazardous chemicals and carcinogens. 2nd ed. Park Ridge, NJ: Noyes Publications.

*Skeaff JM, Dubreuil AA. 1997. Calculated 1993 emission factors of trace metals for Canadian non-ferrous smelters. Atmos Environ 31(10):1449-1457.

Skerfving S, Bencko V, Vahter M, et al. 1999a. Environmental health in the Baltic region - toxic metals. Scand J Work Environ Health 25(Suppl. 3):40-64.

Skurikhin IM. 1989. Methods of analysis for toxic elements in food products. 3. Limit of determination of methods for assuring safety. J Assoc Off Anal Chem 72:294-297.

Sky-Peck HH. 1986. Trace metals and neoplasia. Clin Physiol Biochem 4:99-111.

*Slayton TM, Beck BD, Reynolds KA, et al. 1996. Issues in arsenic cancer risk assessment. Environ Health Perspect 104 (10):1012-1018.

Smedley PL, Kinniburgh DG. 2002. A review of the source, behaviour and distribution of arsenic in natural waters. Appl Geochem 17:517-568.

Smith B, Coulehan B. 2002. Potential exposure to arsenic and other highly toxic chemicals when handling museum artifacts. Appl Occup Environ Hyg 17(11):741-743.

*Smith AH, Goycolea M, Haque R, et al. 1998a. Marked increase in bladder and lung cancer mortality in a region of northern Chile due to arsenic in drinking water. Am J Epidemiol 147(7):660-669.

*Smith AH, Hopenhayn-Rich C, Bates MN, et al. 1992. Cancer risks from arsenic in drinking water. Environ Health Perspect 97:259-267.

*Smith CJ, Livingston SD, Doolittle DJ. 1997. An international literature survey of "IARC group I carcinogens" reported in mainstream cigarette smoke. Food Chem Toxicol 35(10-11):1107-1130.

*Smith E, Naidu R, Alston AM. 1999. Chemistry of arsenic in soils: I. Sorption of arsenate and arsenite by four Australian soils. J Environ Qual 28:1719-1726.

Smith E, Naidu R, Alston AM. 2002. Chemistry of inorganic arsenic in soils: II. Effect of phosphorus, sodium, and calcium on arsenic sorption. J Environ Qual 31(2):557-563.

*Smith RA, Alexander RB, Wolman MG. 1987. Water-quality trends in the nation's rivers. Science 235:1607-1615.

Smith TB, Reardon KF, Gustafson DL, et al. 1998b. The evaluation of carcinogenic potential of chemical mixtures containing arsenic and volatile organics in SHE cells. Toxicologist. Abstracts of the 37th Annual Meeting 42(1-S):75.

*Smith TJ, Crecelius EA, Reading JC. 1977. Airborne arsenic exposure and excretion of methylated arsenic compounds. Environ Health Perspect 19:89-93.

9REFERENCES

Snegireff LS, Lombard OM. 1951. Arsenic and cancer. Observations in the metallurgical industry. Arch Ind Hyg Occup Med 4:199-205.

*Sobel W, Bond GG, Baldwin CL, et al. 1988. An update of respiratory cancer and occupational exposure to arsenicals. Am J Ind Med 13:263-270.

*Sofuni T, Honma M, Hayashi M, et al. 1996. Detection of *in vitro* clastogens and spindle poisons by the mouse lymphoma assay using the microwell method: Interim report of an international collaborative study. Mutagenesis 11(4):349-355.

*Soignet SL, Maslak P, Wang Z-G, et al. 1998. Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. N Engl J Med 339(19):1341-1348.

*Solomons NW. 1984. The other trace minerals: Manganese, molybdenum, vanadium, nickel, silicon, and arsenic. Curr Top Nutr Dis 12:269-295.

*Sommers SC, McManus RG. 1953. Multiple arsenical cancers of the skin and internal organs. Cancer 6:347-359.

*Somogyi A, Beck H. 1993. Nurturing and breast-feeding: Exposure to chemicals in breast milk. Environ Health Perspect 101(suppl. 2):45-52.

*Sotera JJ, Dulude GR, Stux RL. 1988. Determination of toxic elements in biological materials by furnace atomic absorption spectrometry. Sci Total Environ 71:45-48.

Soto G, Luna A, Acosta-Saavedra L, et al. 2003. Alteration on immune cells subpopulations and lymphocyte proliferation by arsenic exposure in infant populations. Toxicol Sci 72(S-1):377.

Souey NV, Klei LR, Ihnat MA. 2002. Mechanisms for arsenite-induced angiogenesis. FASEB J 16(5):A961.

*Southwick JW, Western AE, Beck MM, et al. 1981. Community health associated with arsenic in drinking water in Millard County, Utah. Cincinnati, OH: U.S. Environmental Protection Agency, Health Effects Research Laboratory. EPA600181064. PB82108374.

Spallholz JE, Mallory BL, Rhaman MM. 2004. Environmental hypothesis: Is poor dietary selenium intake and underlying factor for arsenicosis and cancer in Bangladesh and West Bengel, India? Sci Total Environ 323(1-3):21-32.

Spiegelstein O, Lu X, Le XC, et al. 2003. Teratogenicity of arsenate and valproate is enhanced in mice lacking folate binding protein-2 (Folbp2) Birth Defects Res A Clin Mol Teratol 67(5):325.

Spiethoff A, Wiethege T, Hollstein M, et al. 1997. German uranium miners studies: Evaluation of the central archive of the institute of pathology at Stollberg--first results. Appl Occup Environ Hyg 12(12):964-969.

Spliethoff HM, Hemond HF. 1996. History of toxic metals discharge to surface waters of the Aberjona watershed. Environ Sci Technol 30:121-128.

SRI. 1982. Arsenic trioxide-salient statistics. In: Chemical economics handbook. Menlo Park, CA: Stanford Research Institute.

9REFERENCES

SRI. 1987. Directory of chemical producers: United States of America. Menlo Park, CA: SRI International, 474.

SRI. 1988. Directory of chemical producers: United States of America. Menlo Park, CA: SRI International, 469-470.

SRI. 1989. Directory of chemical producers: United States of America. Menlo Park, CA: SRI International, 471.

SRI. 1990. Directory of chemical producers: United States of America. Menlo Park, CA: SRI International, 475.

SRI. 1997. 1997 Directory of chemical producers: United States of America. Menlo Park, CA: Stanford Research Institute International, 462.

SRI. 2004. Directory of chemical producers. Menlo Park, CA: SRI International, 456, 640, 768, 771.

Srivastava AK, Hasan SK, Srivastava RC. 2001. Arsenicism in India: Dermal lesions and hair levels. Arch Environ Health 56(6):562.

Staples CA, Werner AF, Hoogheem TJ. 1985. Assessment of priority pollutant concentrations in the United States using STORET database. Environ Toxicol Chem 4:131-142.

Steinberg ML, Su L, Snow ET. 1997. Low dose chronic treatment of human keratinocytes with inorganic arsenic causes hyperproliferation and altered protein phosphorylation. 28th Annual Meeting of the Environmental Mutagen Society, Minneapolis, Minnesota, USA, April 19-23, 1997. Environ Mol Mutagen 29(suppl 28):48.

Steinhelper ME, Olson MS. 1988. Effects of phenylarsine oxide on agonist-induced hepatic vasoconstriction and glycogenolysis. Biochem Pharmacol 37:1167-1169.

*Steinmaus C, Yuan Y, Bates MN, et al. 2003. Case-control study of bladder cancer and drinking water arsenic in the western United States. Am J Epidemiol 158(12):1193-1201.

*Steinnes E, Rambaek JP, Hanssen JK. 1992. Large scale multi-element survey of atmospheric deposition using naturally growing moss as a biomonitor. Chemosphere 25(5):735-752.

*Sternowsky HJ, Moser B, Szadkowsky D. 2002. Arsenic in breast milk during the first 3 months of lactation. Int J Hyg Environ Health 205(5):405-409.

Stevens JT, DiPasquale LC, Farmer JD, et al. 1977a. The evaluation of the acute inhalation toxicology of technical grade organoarsenical pesticides. Research Triangle Park, NC: U.S. Environmental Protection Agency, Health Effects Research Laboratory.

*Stevens JT, DiPasquale LC, Farmer JD. 1979. The acute inhalation toxicology of the technical grade organoarsenical herbicides, cacodylic acid and disodium methanearsonic acid; a route comparison. Bull Environ Contam Toxicol 21:304-311.

*Stevens JT, Hall LL, Farmer JD, et al. 1977b. Disposition of ^{14}C and/or ^{74}As-cacodylic acid in rats after intravenous, intratracheal or peroral administration. Environ Health Perspect 19:151-157.

9REFERENCES

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.

*Stilwell DE, Graetz TJ. 2001. Copper, chromium, and arsenic levels in soil near highway traffic sound barriers built using CCA pressure-treated wood. Bull Environ Contam Toxicol 67:303-308.

Stohrer G. 2001. Re: Risk assessment of internal cancers from arsenic in drinking water. Environ Health Perspect 109(12):A571.

Stoica A, Pentecost E, Martin MB. 2000. Effects of arsenite on estrogen receptor-alpha expression and activity in MCF-7 breast cancer cells. Endocrinology 141(10):3595-3602.

Stokinger HE. 1981. The metals. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology. 3rd ed. Vol. 2A. Toronto: John Wiley and Sons, 1517-1530.

*Storelli MM, Marcotrigiano GO. 2001. Total, organic, and inorganic arsenic in some commercial species of crustaceans from the Mediterranean Sea (Italy). J Food Prot 64(11):1858-1862.

*Storer RD, McKelvey TW, Kraynak AR, et al. 1996. Revalidation of the in vitro alkaline elution/rat hepatocyte assay for DNA damage: Improved criteria for assessment of cytotoxicity and genotoxicity and results for 81 compounds. Mutat Res 368(2):59-101.

Storm DL. 1994. Chemical monitoring of California's public drinking water sources: Public exposures and health impacts. In: Wang RGM, ed. Water contamination and health: Integration of exposure assessment, toxicology, and risk assessment. New York: Marcel Dekker, Inc., 67-124.

*Stump DG, Holson JF, Fleeman TL, et al. 1999. Comparative effects of single intraperitoneal or oral doses of sodium arsenate or arsenic trioxide during in utero development. Teratology 60:283-291.

*Stutz DR, Janusz SJ. 1988. Hazardous materials injuries: A handbook for pre-hospital care. 2nd ed. Beltsville, MD: Bradford Communications Corporation, 208-209.

*Styblo M, Thomas DJ. 2001. Selenium modifies the metabolism and toxicity of arsenic in primary rat hepatocytes. Toxicol Appl Pharmacol 172(1):52-61.

Styblo M, Del Razo LM, Vega L, et al. 2000. Comparative toxicity of trivalent and pentavalent inorganic and methylated arsenicals in rat and human cells. Arch Toxicol 74(6):289-299.

Su L, Hu Y, Dunlop B, et al. 1997. Arsenic is cytotoxic at micromolar concentration but does not inhibit purified human DNA repair enzymes at less than millimolar concentrations. 28th Annual Meeting of the Environmental Mutagen Society, Minneapolis, Minnesota, USA, April 19-23, 1997. Environ Mole Mutagen 29(suppl 28):49.

Suner MA, Devesa V, Clemente MJ, et al. 2002. Organoarsenical species contents in fresh and processed seafood products. J Agric Food Chem 50(4):924-932.

Susten AS, Grissom RE, Sanderson L, et al. 1998. An integrated approach to estimating total arsenic (As) exposure in humans. Toxicologist. Abstracts of the 37th Annual Meeting 42(1-S):229.

Suzuki KT, Mandal BK, Ogra Y. 2002. Speciation of arsenic in body fluids. Talanta 58(1):111-119.

Swanson SA, Angle CR. 1998. Increased cellular homocysteine (Hcy) as a mechanism for the proliferative responses of cobalamin (B12) dependent human fibroblasts to arsenic (As3+). Toxicologist 42(1-S):323.

*Sweins A. 1983. Protective effect of selenium against arsenic-induced chromosomal damage in cultured human lymphocytes. Hereditas 98:249-252.

*Szinicz L, Forth W. 1988. Effect of As_2O_3 on gluconeogenesis. Arch Toxicol 61:444-449.

*Szuler IM, Williams CN, Hindmarsh JT, et al. 1979. Massive variceal hemorrhage secondary to presinusoidal portal hypertension due to arsenic poisoning. Can Med Assoc J 120:168-171.

*Tabocova S, Hunter ES, Gladen BC. 1996. Developmental toxicity of inorganic arsenic in whole embryo culture: Oxidation state, dose, time, and gestational age dependence. Toxicol Appl Pharmacol 138(2):298-307.

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 41:690-695.

*Takahashi K, Yamauchi H, Yamato N, et al. 1988. Methylation of arsenic trioxide in hamsters with liver damage induced by long-term administration of carbon tetrachloride. Appl Organomet Chem 2:309-314.

Takahashi W, Pfenninger K, Wong L. 1983. Urinary arsenic, chromium, and copper levels in workers exposed to arsenic-based wood preservatives. Arch Environ Health 38:209-214.

*Tam GKH, Lacroix G. 1982. Dry ashing, hydride generation atomic absorption spectrometric determination of arsenic and selenium in foods. J Assoc Off Anal Chem 65(3):647-650.

Tam GK, Charbonneau SM, Bryce F, et al. 1978. Separation of arsenic metabolites in dog plasma and urine following intravenous injection of ^{74}As. Anal Biochem 86:505-511.

Tam GK, Charbonneau SM, Lacroix G, et al. 1979a. Confirmation of inorganic arsenic and dimethylarsenic acid in urine and plasma of dog by ion-exchange and TLC. Bull Environ Contam Toxicol 21:371-374.

*Tam GKH, Charbonneau SM, Bryce F, et al. 1979b. Metabolism of inorganic arsenic (^{74}As) in humans following oral ingestion. Toxicol Appl Pharmacol 50:319-322.

*Tam GKH, Charbonneau SM, Bryce F, et al. 1982. Excretion of a single oral dose of fish-arsenic in man. Bull Environ Contam Toxicol 28:669-673.

*Tamaki S, Frankenberger WT. 1992. Environmental biochemistry of arsenic. Rev Environ Contam Toxicol 124:79-110.

Tamm I, Paternostro G, Zapata JM. 1999. Treatment of acute promyelocytic leukemia with arsenic trioxide. N Engl J Med 340(13):1043-1045.

9REFERENCES

Tanaka A, Hirata M, Omura M. 2003. Pulmonary squamous cyst induced by exposure to indium arsenide in hamsters. J Occup Health 45:405-407.

*Tao SS-H, Bolger PM. 1999. Dietary intakes of arsenic in the United States. Food Addit Contam 16:465-472.

Tatum FM, Hood RD. 1999. Arsenite uptake and metabolism by rat hepatocyte primary cultures in comparison with kidney- and hepatocyte-derived rat cell lines. Toxicol Sci 52:20-25.

*Taubeneck MW, Daston GP, Rogers JM, et al. 1994. Altered maternal zinc metabolism following exposure to diverse developmental toxicants. Reprod Toxicol 8(1):25-40.

*Tay C-H, Seah C-S. 1975. Arsenic poisoning from anti-asthmatic herbal preparations. Med J Aust 2:424-428.

*Taylor HE, Antweiler RC, Roth DA, et al. 2001. The occurrence and distribution of selected trace elements in the upper Rio Grande and tributaries in Colorado and northern New Mexico. Arch Environ Contam Toxicol 41:410-426

*Taylor PR, Qiao YL, Schatzkin A, et al. 1989. Relation of arsenic exposure to lung cancer among tin miners in Yunnan Province. Br J Ind Med 46:881-886.

Tchounwou PB, Centeno JA, Patlolla AK. 2004. Arsenic toxicity, mutagenesis, and carcinogenesis--a health risk assessment and management approach. Mol Cell Biochem 255(1-2):47-55.

*Teräsahde P, Pantsar-Kallio M, Manninen PKG. 1996. Simultaneous determination of arsenic species by ion chromatography-inductively coupled plasma mass spectrometry. J Chromatog A750(1-2):83-88.

*Tezuka M, Hanioka K, Yamanaka K, et al. 1993. Gene damage induced in human alveolar type II (L-132) cells by exposure to dimethylarsinic acid. Biochem Biophys Res Commun 191(3):1178-1183.

Thanabalasingam P, Pickering WF. 1986. Arsenic sorption by humic acids. Environ Pollut Ser B 12:233-246.

*Thomas DC, Whittemore AS. 1988. Methods for testing interactions, with applications to occupational exposures, smoking, and lung cancer. Am J Ind Med 13:131-147.

*Thomas KW, Pellizzari ED, Berry MR. 1999. Population-based dietary intakes and tap water concentrations for selected elements in the EPA Region V National Human Exposure Assessment Survey (NHEXAS). J Expo Anal Environ Epidemiol 9:402-413.

*Thomas P, Sniatecki K. 1995. Inductively coupled plasma mass spectrometry: Application to the determination of arsenic species. Fresenius J Anal Chem 351 (4-5):410-414.

Thomas DJ, Herbin-Davis KM. 1998. Characteristics of the accumulation of arsenic (As) by arsenate (As^V)-exposed rabbit erythrocytes. Toxicologist 42(1-S):322.

Thomas DJ, Styblo M, Lin S. 2001. The cellular metabolism and systemic toxicity of arsenic. Toxicol Appl Pharmacol 176:127-144.

9REFERENCES

*Thomas DJ, Waters SB, Styblo M. 2004. Elucidating the pathway for arsenic methylation. Toxicol Appl Pharmacol 198(3):319-326.

*Thompson TS, Le MD, Kasick AR, et al. 1999. Arsenic in well water supplies in Saskatchewan. Bull Environ Contam Toxicol 63:478-483.

*Tian D, Ma H, Feng Z, et al. 2001. Analyses of micronuclei in exfoliated epithelial cells from individuals chronically exposed to arsenic via drinking water in inner Mongolia, China. J Toxicol Environ Health A 64(6):473-484.

*Tice RR, Yager JW, Andrews P, et al. 1997. Effect of hepatic methyl donor status on urinary excretion and DNA damage in B6C3F1 mice treated with sodium arsenite. Mutat Res 386(3):315-334.

Tilbury KL, Stein JE, Krone CA, et al. 2002. Chemical contaminants in juvenile gray whales (*Eschrichtius robustus*) from a subsistence harvest in Arctic feeding grounds. Chemosphere 47:555-564.

Tinwell H, Stephens SC, Ashby J. 1991. Arsenite as the probable active species in the human carcinogenicity of arsenic: Mouse micronucleus assays on Na and K arsenite, orpiment, and Fowler's solution. Environ Health Perspect 95:205-210.

*Tintinalli JE, Ruiz E, Krone RL, eds. 1996. Emergency medicine. A comprehensive study. American College of Emergency Physicians. 4th ed. New York, NY: The McGraw-Hill Companies, Inc.

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.

*Tokunaga H, Roychowdhury T, Chandraskaran N, et al. 2002. Urinary arsenic species in an arsenic-affected area of West Bengal, India. Appl Organomet Chem 16:406-414.

*Tokunaga H, Roychowdhury T, Uchino T, et al. 2003. Urinary arsenic species in arsenic-affected area of West Bengal, India (Part II) J Health Sci 49(6):464-474.

*Tollestrup K, Daling JR, Allard J. 1995. Mortality in a cohort of orchard workers exposed to lead arsenate pesticide spray. Arch Environ Health 50(3):221-229.

Tollestrup K, Frost FJ, Harter L, et al. 2002. Mortality in children residing near the Asarco Copper Smelter in Ruston, Washington [Abstract]. Am J Epidemiol 155(11):S39.

*Tondel M, Rahman M, Magnuson A, et al. 1999. The relationship of arsenic levels in drinking water and the prevalence rate of skin lesions in Bangladesh. Environ Health Perspect 107(9):727-729.

Tong Y, Xu XY. 1998. Peripheral neuropathy, skin damage and liver abnormalities in miners with long-term exposure to arsenic. Toxicologist 42(1-S):321.

Trepka MJ, Heinrich J, Schulz C, et al. 1996. Arsenic burden among children in industrial areas of eastern Germany. Sci Total Environ 180(2):95-105.

Tretner A, Kofod M, Scholz C, et al. 2000. Arsenic speciation related to arsenic origine and geochemical conditions of the groundwater samples. In: Rosbjerg D, ed. Groundwater research. Rotterdam: Balkema, 199-200.

9REFERENCES

*TRI02. 2005. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Office of Environmental Information. U.S. Environmental Protection Agency. Toxics Release Inventory. http://www.epa.gov/triexplorer/. April 10, 2005.

*Trocine RP, Trefry JH. 1996. Metal concentrations in sediment, water and clams from the Indian River Lagoon, Florida. Mar Pollut Bull 32(10):754-759.

Trouba K, Glanzer J, Vorce RL. 1998. Long-term modulation of mitogen activated protein kinase following sodium arsenite exposure. Toxicologist. Abstracts of the 37th Annual Meeting 42(1-S):323.

*Tsai M-H, Chien R-N, Hsieh S-H, et al. 1998a. Primary hepatic angiosarcoma: Report of a case involving environmental arsenic exposure. Chang Keng I Hsueh Tsa Chih 21(4):469-474.

*Tsai S, Chou H, The H, et al. 2003. The effects of chronic arsenic exposure from drinking water on the neurobehavioral development in adolescence. Neurotoxicology 24:747-753.

Tsai S-M, Wang T-N, Ko Y-C. 1998b. Cancer mortality trends in a blackfoot disease endemic community of Taiwan following water source replacement. J Toxicol Environ Health 55:389-404.

*Tsai SM, Wang TN, Ko YC. 1999. Mortality for certain diseases in areas with high levels of arsenic in drinking water. Arch Environ Health 54(3):186-193.

Tseng CH. 2002. An overview on peripheral vascular disease in blackfoot disease-hyperendemic villages in Taiwan. Angiology 53(5):529-537.

Tseng CH. 2004. The potential biological mechanisms of arsenic-induced diabetes mellitus. Toxicol Appl Pharmacol 197(2):67-83.

*Tseng W-P. 1977. Effects and dose-response relationships of skin cancer and blackfoot disease with arsenic. Environ Health Perspect 19:109-119.

*Tseng W-P. 1989. Blackfoot disease in Taiwan: A 30-year follow-up study. Angiology 40(6):547-558.

*Tseng C-H, Chong C-K, Chen C-J, et al. 1995. Abnormal peripheral microcirculation in seemingly normal subjects living in blackfoot-disease-hyperendemic villages in Taiwan. Int J Microcirc Clin Exp 15(1):21-27.

*Tseng C-H, Chong C-K, Chen C-J, et al. 1996. Dose-response relationship between peripheral vascular disease and ingested inorganic arsenic among residents in blackfoot disease endemic villages in Taiwan. Atherosclerosis 120:125-133.

*Tseng CH, Chong CK, Tseng CP, et al. 2003. Long-term arsenic exposure and ischemic heart disease in arseniasis-hyperendemic villages in Taiwan. Toxicol Lett 137(1-2):15-21.

*Tseng CH, Tai TY, Chong CK, et al. 2000. Long-term arsenic exposure and incidence of non-insulin dependent diabetes mellitus: A cohort study in arseniasis-hyperendemic villages in Taiwan. Environ Health Perspect 108(9):847-851.

9REFERENCES

*Tseng WP, Chu HM, How SW, et al. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J Natl Cancer Inst 40:453-463.

*Tsuda T, Babazono A, Yamamoto E, et al. 1995a. Ingested arsenic and internal cancer: A historical cohort study followed for 33 years. Am J Epidemiol 141(3):198-209.

*Tsuda T, Indue T, Kojima M, et al. 1995b. Market basket and duplicate portion estimation of dietary intakes of cadmium, mercury, arsenic, copper, manganese, and zinc by Japanese adults. J AOAC Int 78(6):1363-1368.

*Tsuda T, Kume Y, Yamamoto M, et al. 1987. An epidemiological study on cancer in certified arsenic poisoning patients in Toroku. Jpn J Ind Health 29:496-497.

Tsuji JS, Benson R, Schoof RA, et al. 2004. Health effect levels for risk assessment of childhood exposure to arsenic. Regul Toxicol Pharmacol 39(2):99-110.

*Tsuruta D, Hamada T, Mochida K, et al. 1998. Merkel cell carcinoma, Bowen's disease and chronic occupational arsenic poisoning. Br J Dermatol 139:291-294.

Turck PA, Eason CT, Wickstrom M. 1998. Assessment of the developmental toxicity of sodium monofluoroacetate (1080) in rats. Toxicologist 42(1-S):258-259.

Turner DR. 1987. Speciation and cycling of arsenic, cadmium, lead and mercury in natural waters. In: Hutchinson TC, Meema KM, eds. Lead, mercury, cadmium and arsenic in the environment. New York, NY: John Wiley & Sons Ltd., 43-48.

Turpeinen R, Pantsar-Kallio M, Haggblom M, et al. 1999. Influence of microbes on the mobilization, toxicity and biomethylation of arsenic in soil. Sci Total Environ 236(1-3):173-180.

Tzeng G, Liou CP, Chang MY. 2003. Genetic imbalances of six urothelial carcinoma cell lines derived from a blackfoot endemic area in Taiwan. Am J Hum Genet 73(5):223.

Uddin AN, Burns FJ, Rossman TG. Vitamin E and organoselenium prevent the carcinogenic activity of arsenite with solar UV in mouse skin. In Press

*Ueda H, Kuroda K, Endo G. 1997. The inhibitory effect of selenium on induction of tetraploidy by dimethylarsinic acid in Chinese hamster cells. Anticancer Res 17(3c):1939-1943.

*Uede K, Furukawa F. 2003. Skin manifestations in acute arsenic poisoning from the Wakayama curry-poisoning incident. Br J Dermatol 149(4):757-762.

*Ulitzer S, Barak M. 1988. Detection of genotoxicity of metallic compounds by the bacterial bioluminescence test. J Biolumin Chemilumin 2:95-99.

*Ulman C, Gezer S, Anal O, et al. 1998. Arsenic in human and cow's milk: A reflection of environmental pollution. Water Air Soil Pollut 101(1-4):411-416.

*Unnikrishnan D, Dutcher JP, Varshneya N, et al. 2001. Torsades de pointes in 3 patients with leukemia treated with arsenic trioxide. Blood 97(5):1514-1516.

9REFERENCES

Urieta I, Jalon M, Eguileor I. 1996. Food surveillance in the Basque Country (Spain). II. Estimation of the dietary intake of organochloride pesticides, heavy metals, arsenic, aflatoxin M_1, iron and zinc through the Total Diet Study, 1990/91. Food Addit Contam 13(1):29-52.

*U.S. Bureau of Mines. 1988. Mineral commodity summaries. Washington, DC: U.S. Bureau of Mines, 14-15.

*U.S. Bureau of Mines. 1990. Mineral commodity summaries. Washington, DC: U.S. Bureau of Mines, 22-23.

*U.S. Congress. 1977. Federal water pollution control act, as amended by the clean water act of 1977. U.S. Congress. Public Law 95-217. December 28, 1977.

*U.S. Congress. 1990. Clean Air Act. Title III. Section 112. National emission standards for hazardous air pollutants. U.S. Congress. 42 USC 7412. Revised by Public Law 101-549. November 15, 1990.

*USC. 1999. United States Code. 42 USC 7412. November 9, 1999. http://www4.law.cornell.edu/uscode/. June 2, 2005.

*USDA. 2004. Nonsynthetic substances prohibited for use in organic crop production. Washington, DC: U.S. Department of Agriculture. Code of Federal Regulations 7 CFR 205.602. http://www.access.gpo.gov/nara/cfr/waisidx_04/7cfr205_04.html. February 15, 2005.

U.S. Fish and Wildlife Service. 1988. Arsenic hazards to fish, wildlife, and invertebrates: A synoptic review. Laurel, MD: U.S. Fish and Wildlife Service. PB88169404.

*USGS. 1984. Element concentrations in soils and other surficial materials on of the conterminous United States. U.S. Geological Survey. Professional Paper 1270.

*USGS. 1998. Arsenic. U.S. Geological Survey – Mineral Information – 1998 by Robert G. Reese, Jr. http://minerals.usgs.gov/minerals/pubs/commodity/arsenic/160498.pdf.

USGS. 1999a. Mineral Commodity Summaries 1999. Arsenic. U.S. Geological Survey. http://minerals.usgs.gov/minerals/pubs/commodity/arsenic/index.html.

*USGS. 1999b. Arsenic in ground water of the Willamette Basin, Oregon. U.S. Geological Survey. http://or.water.usgs.gov/pubs_dir/Online/Pdf/98-4205.pdf. April 7, 2005.

*USGS. 1999c. Arsenic-rich pyrite in the Mississippian Marshall Sandstone: Source of anomalous arsenic in southeastern Michigan ground water. U.S. Geological Survey. http://minerals.usgs.gov/east/midwest/abstract7.html. August 23,1999.

*USGS. 2005a. Arsenic in ground water in the United States. http://water.usgs.gov/nawqa/trace/pubs/arsenic_fig1.htm. April 1, 2005.

*USGS. 2005b. The national geochemical survey – database and documentation. http://tin.er.usgs.gov/geochem/doc/home.htm. April 1, 2005.

*Uthus EO, Cornatzer WE, Nielsen FH. 1983. Consequences of arsenic deprivation in laboratory animals. In: Lederer W, Fensterheim R, eds. Arsenic: Industrial, biomedical and environmental perspectives. New York, NY: Van Nostrand Reinhold, 173-189.

9REFERENCES

*Vaessen HA, van Ooik A. 1989. Speciation of arsenic in Dutch total diets: Methodology and results. Z Lebensm Unters Forsch 189:232-235.

*Vahter M. 1981. Biotransformation of trivalent and pentavalent inorganic arsenic in mice and rats. Environ Res 25:286-293.

*Vahter M. 1983. Metabolism of arsenic. In: Fowler BA, ed. Biological and environmental effects of arsenic. New York, NY: Elsevier Science Publishers, 171-198.

*Vahter M. 1986. Environmental and occupational exposure to inorganic arsenic. Acta Pharmacol Toxicol 59:31-34.

Vahter M. 2000. Genetic polymorphism in the biotransformation of inorganic arsenic and its role in toxicity. Toxicol Lett 112/113:209-217.

Vahter M. 2002. Mechanisms of arsenic biotransformation. Toxicology 181-182:211-217.

Vahter M. 2003. Toxicokinetics of arsenic in experimental animals and humans. Toxicology 191(1):4.

Vahter M, Concha G. 2001. Role of metabolism in arsenic toxicity. Pharmacol Toxicol 89(1):1-5.

*Vahter M, Envall J. 1983. In vivo reduction of arsenate in mice and rabbits. Environ Res 32:14-24.

*Vahter M, Marafante E. 1983. Intracellular interaction and metabolic fate of arsenite and arsenate in mice and rabbits. Chem Biol Interact 47:29-44.

*Vahter M, Marafante E. 1985. Reduction and binding of arsenate in Marmoset monkeys. Arch Toxicol 57:119-124.

*Vahter M, Marafante E. 1987. Effects of low dietary intake of methionine, choline or proteins on the biotransformation of arsenite in the rabbit. Toxicol Lett 37:41-46.

Vahter M, Marafante E. 1988. In vivo methylation and detoxication of arsenic. Royal Soc Chem (Spec Publ) 66:105-119.

*Vahter M, Norin H. 1980. Metabolism of ^{74}As-labeled trivalent and pentavalent inorganic arsenic in mice. Environ Res 21:446-457.

Vahter M, Concha G, Nermell B, et al. 1995. A unique metabolism of inorganic arsenic in native Andean women. Eur J Pharmacol 293(4):455-462.

*Vahter M, Friberg L, Rahnster B, et al. 1986. Airborne arsenic and urinary excretion of metabolites of inorganic arsenic among smelter workers. Int Arch Occup Environ Health 57:79-91.

Vahter M, Marafante E, Dencker L. 1983. Metabolism of arsenobetaine in mice, rats and rabbits. Sci Total Environ 30:197-211.

Vahter M, Marafante E, Dencker L. 1984. Tissue distribution and retention of ^{74}As-dimethylarsinic acid in mice and rats. Arch Environ Contam Toxicol 13:259-264.

9REFERENCES

*Vahter M, Marafante E, Lindgren A, et al. 1982. Tissue distribution and subcellular binding of arsenic in Marmoset monkeys after injection of ^{74}As-arsenite. Arch Toxicol 51:65-77.

*Valentine JL, Campion DS, Schluchter MD, et al. 1981. Arsenic effects on human nerve conduction. In: Howell JC, Gawthorne JM, White L, eds. Trace element metabolism in man and animals - TEMA 4. Proceedings of the Fourth International symposium on Trace Elements or Man and Animals. Canberra: Australian Academy of Science, 409-411.

*Valentine JL, He S-Y, Reisbord LS, et al. 1992. Health response by questionnaire in arsenic-exposed populations. J Clin Epidemiol 45(5):487-94.

*Valentine JL, Kang HK, Spivey G. 1979. Arsenic levels in human blood, urine and hair in response to exposure via drinking water. Environ Res 20:24-32.

*Valentine JL, Reisbord LS, Kang HK, et al. 1985. Arsenic effects on population health histories. In: Mills CF, Bremner I, Chesters JK, eds. Trace elements in man and animals - TEMA 5: Proceedings of the Fifth International Symposium on Trace Elements in Man and Animals. Slough, UK: Commonwealth Agricultural Bureaux, 289-294.

*Vallee BL, Ulmer DD, Wacker WE. 1960. Arsenic toxicology and biochemistry. Arch Ind Health 21:132-151.

*van Netten C, Cann SAH, Morley DR, et al. 2000. Elemental and radioactive analysis of commercially available seaweed. Sci Total Environ 255:169-175.

*Vantroyen B, Heilier JF, Meulemans A, et al. 2004. Survival after a lethal dose of arsenic trioxide. J Toxicol Clin Toxicol 42(6):889-895.

Vargas M, Hamadeh H, Lee E, et al. 1998. Activation of transcription factors by sodium arsenite in human lymphocytes. Toxicologist 42(1-S):323-324.

*Vega L, Gonsebatt ME, Ostrosky-Wegman P. 1995. Aneugenic effect of sodium arsenite on human lymphocytes in vitro: An individual susceptibility effect detected. Mutat Res 334(3):365-373.

Vega L, Saavedra R, Ostrosky-Wegman P. 1996. Sodium arsenite effects on interleukin 2 secretion. Environ Mole Mutagen 27(suppl. 27)71. 27th Annual Scientific Meeting of the Environmental Mutagen.

Veinott G, Perroncashman S, Anderson MR. 2001. Baseline metal concentrations in coastal Labrador sediments. Mar Pollut Bull 42:187-192.

*Versieck J, Hoste J, Vanballenberghe L, et al. 1983. Trace element measurements in serum by neutron activation analysis. In: Harling, OK, Clark L, Von der Hardt P, eds. Use and development of low and medium flux research reactors. Proceedings of the International Symposium on the use and development of low and medium flux research reactors, Massachusetts Institute of Technology, Cambridge, Massachusetts, U.S.A., October 16-19, 1983. Munchen: Karl Thiemig, 717-723.

*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.

Vienna A, Capucci E, Wolfsperger M, et al. 1995. Heavy metal concentration in hair of students in Rome. Anthropol Anz 53(1):27-32.

*Vig BK, Figueroa ML, Cornforth MN, et al. 1984. Chromosome studies in human subjects chronically exposed to arsenic in drinking water. Am J Ind Med 6:325-338.

Villanueva C, Kogevinas M. 1999. Comments on "drinking water arsenic in Utah: A cohort mortality study." Environ Health Perspect 107(5):A544.

*Vinas P, Lopez-Garcia I, Merino-Merono B, et al. 2003. Stability of arsenobetaine levels in manufactured baby foods. J Food Prot 66(12):2321-2324.

Viraraghavan T, Subramanian KS, Aruldoss JA. 1999. Arsenic in drinking water. Problems and solutions. Water Sci Technol 40(2):69-76.

*Viren JR, Silvers A. 1994. Unit risk estimates for airborne arsenic exposure: An updated view based on recent data from two copper smelter cohorts. Regul Toxicol Pharmacol 20(2):125-138.

*Viren J, Silvers A. 1999. Nonlinearity in the lung cancer dose-response for airborne arsenic: Apparent confounding by year of hire in evaluating lung cancer risks from arsenic exposure in Tacoma smelter workers. Regul Toxicol Pharmacol 30:117-129.

Vogt BL, Rossman TG. 2001. Effects of arsenite on p53, p21 and cyclin D expression in normal human fibroblasts: A possible mechanism for arsenite's comutagenicity. Mutat Res 478:159-168.

*Von Endt DW, Kearney PC, Kaufman DD. 1968. Degradation of monosodium methanearsonic acid by soil microorganisms. J Agric Food Chem 16(1):17-20.

Waalkes MP, Zhao Z. 1998. The association of arsenic-induced malignant transformation with DNA hypomethylation and aberrant gene expression. Toxicologist 42(1-S):353.

*Waalkes MP, Harvey MJ, Klaassen CD. 1984. Relative in vitro affinity of hepatic metallothionein for metals. Toxicol Lett 20:33-39.

Waalkes MP, Keefer LK, Diwan BA. 2000. Induction of proliferative lesions of the uterus, testes, and liver in Swiss mice given repeated injections of sodium arsenate: Possible estrogenic mode of action. Toxicol Appl Pharmacol 166(1):24-35.

Waalkes MP, Liu J, Chen H, et al. 2003b. Mechanisms underlying arsenic carcinogenesis. Toxicology 191(1):4-5.

Waalkes MP, Liu J, Chen H, et al. 2004d. Estrogen signaling in livers of male mice with hepatocellular carcinoma induced by exposure to arsenic *in utero*. J Natl Cancer Inst 96(6):466-474.

*Waalkes MP, Liu J, Ward JM, et al. 2004a. Mechanisms underlying arsenic carcinogenesis: Hypersensitivity of mice exposed to inorganic arsenic during gestation. Toxicology 198(1-3):31-38.

*Waalkes MP, Liu J, Ward JM, et al. 2004b. Animal models for arsenic carcinogenesis: Inorganic arsenic is a transplacental carcinogen in mice. Toxicol Appl Pharmacol 198(3):377-384.

*Waalkes MP, Ward JM, Diwan BA. 2004c. Induction of tumors of the liver, lung, ovary and adrenal in adult mice after brief maternal gestational exposure to inorganic arsenic: Promotional effects of postnatal phorbol ester exposure on hepatic and pulmonary, but not dermal cancers. Carcinogenesis 25(1):133-141.

*Waalkes MP, Ward JM, Liu J, et al. 2003a. Transplacental carcinogenicity of inorganic arsenic in the drinking water: Induction of hepatic, ovarian, pulmonary, and adrenal tumors in mice. Toxicol Appl Pharmacol 186(1):7-17.

*Wade HJ, Frazer ES. 1953. Toxipathic hepatitis due to Fowler's solution; A case treated with dimercaprol. Lancet (February):269-271.

*Wadge A, Hutton M. 1987. The leachability and chemical speciation of selected trace elements in fly ash from coal combustion and refuse incineration. Environ Pollut 48:85-99.

Wagner SL, Weswig P. 1974. Arsenic in blood and urine of forest workers. Indexes of exposure to cacodylic acid. Arch Environ Health 28:77-79.

*Wagner SL, Maliner JS, Morton WE, et al. 1979. Skin cancer and arsenical intoxication from well water. Arch Dermatol 115:1205-1207.

*Wahlberg JE, Boman A. 1986. Contact sensitivity to arsenical compounds: Clinical and experimental studies. Derm Beruf Umwelt 34:10-12.

Wahlen R. 2004. Fast and accurate determination of arsenobetaine in fish tissues using accelerated solvent extraction and HPLC-ICP-MS determination. J Chromatogr Sci 42:217-222.

*Wakao N, Koyatsu H, Komai Y, et al. 1988. Microbial oxidation of arsenite and occurrence of arsenite-oxidizing bacteria in acid mine water from a sulfur-pyrite mine. Geomicrobiol J 6:11-24.

Wakhlu A, Aggarwal A, Misra R. 2003. Chronic arsenic poisoning mimicking Gottron's rash. J Rheumatol 30(2):415-16.

*Walker S, Griffin S. 1998. Site-specific data confirm arsenic exposure predicted by the U.S. Environmental Protection Agency. Environ Health Perspect 106(3):133-139.

*Wall S. 1980. Survival and mortality pattern among Swedish smelter workers. Int J Epidemiol 9(1):73-87.

Walsh LM, Keeney DR. 1975. Behavior and phytotoxicity of inorganic arsenicals in soils. In: Arsenic Pesticides. ACS Symp Series 7. American Chemical Society, Washington, DC, 35.

Walsh PR, Duce RA, Fasching JL. 1979. Considerations of the enrichment, sources, and flux of arsenic in the troposphere. J Geophys Res 84(C4):1719-1726.

*Walton FS, Waters SB, Jolley SL, et al. 2003. Selenium compounds modulate the activity of recombinant rat As111-methyltransferase and the methylation of arsenite by rat and human hepatocytes. Chem Res Toxicol 16(3):261-265.

*Wan B, Christian RT, Soukup SW. 1982. Studies of cytogenetic effects of sodium arsenicals on mammalian cells in vitro. Environ Mutagen 4:493-498.

*Wang ZY. 2001. Arsenic compounds as anticancer agents. Cancer Chemother Pharmacol 48(Suppl 1):S72-S76.

*Wang TS, Huang H. 1994. Active oxygen species are involved in the induction of micronuclei by arsenite in XRS-5 cells. Mutagenesis 9(3):253-257.

Wang G, Huang Y, Gang J, et al. 2000. Endemic arsenism, fluorosis and arsenic-fluoride poisoning caused by drinking water in Kuitun, Xinjiang. Chin Med J 113(6):524.

*Wang SL, Chiou JM, Chen CJ, et al. 2003. Prevalence of non-insulin-dependent diabetes mellitus and related vascular diseases in southwestern arseniasis-endemic and nonendemic areas in Taiwan. Environ Health Perspect 111(2):155-59.

*Wang TS, Shu YF, Liu YC, et al. 1997a. Glutathione peroxidase and catalase modulate the genotoxicity of arsenite. Toxicology 121(3):229-237.

Wang ZG, Rivi R, Delva L, et al. 1997b. Arsenic trioxide and melarsoprol induce programmed cell death in myeloid leukemia cell lines and function in a PML and PML/RARα independent manner. Blood 90(10 Suppl. 1 Part 1)327a.

*Wanibuchi H, Yamamoto S, Chen H, et al. 1996. Promoting effects of dimethylarsinic acid on N-butyl-N-(4-hydroxybutyl)nitrosamine-induced urinary bladder carcinogenesis in rats. Carcinogenesis 17(11):2435-2439.

Warner KL. 2001. Arsenic in glacial drift aquifers and the implication for drinking water– lower Illinois River Basin. Ground Water 39(3):433-442.

Warner ML, Moore LE, Smith MT, et al. 1994. Increased micronuclei in exfoliated bladder cells of individuals who chronically ingest arsenic-contaminated water in Nevada. Cancer Epidemiol Biomarkers Prev 3(7):583-590.

Warren RL, Weber JB. 1994. Evaluating pesticide movement in North Carolina soils. Soil Science Society of North Carolina Proceedings 37:23-35.

*Wasserman GA, Liu X, Parvez F, et al. 2004. Water arsenic exposure and children's intellectual function in Araihazar, Bangladesh. Environ Health Perspect 112(13):1329-1333.

*Watanabe C, Inaoka T, Kadono T, et al. 2001. Males in rural Bangladeshi communities are more susceptible to chronic arsenic poisoning than females: Analyses based on urinary arsenic. Environ Health Perspect 109(12):1265-1270.

Watanabe C, Kawata A, Sudo N, et al. 2004. Water intake in an Asian population living in arsenic-contaminated area. Toxicol Appl Pharmacol 198(3):272-282.

*Watrous RM, McCaughey MB. 1945. Occupational exposure to arsenic: In the manufacture of arsphenamine and related compounds. Ind Med 14(8):639-646.

Wauchope RD, McDowell LL. 1984. Adsorption of phosphate, arsenate, methanearsonate, and cacodylate by lake and stream sediments: Comparisons with soils. J Environ Qual 13:499-504.

Wax PM, Thornton CA. 2000. Recovery from severe arsenic-induced peripheral neuropathy with 2,3-dimercapto-1-propanesulphonic acid. J Toxicol Clin Toxicol 38(7):777-780.

9REFERENCES

Weast RC, ed. 1985. CRC handbook of chemistry and physics. 66th ed. Boca Raton, FL: CRC Press, Inc., B-74 - B-75.

*Webb DR, Sipes IG, Carter DE. 1984. *In vitro* solubility and *in vivo* toxicity of gallium arsenide. Toxicol Appl Pharmacol 76:96-104.

*Webb DR, Wilson SE, Carter DE. 1986. Comparative pulmonary toxicity of gallium arsenide, gallium (III) oxide, or arsenic (III) oxide intratracheally instilled into rats. Toxicol Appl Pharmacol 82:405-416.

*Webb DR, Wilson SE, Carter DE. 1987. Pulmonary clearance and toxicity of respirable gallium arsenide particulates intratracheally instilled into rats. Am Ind Hyg Assoc J 48(7):660-667.

*Wedepohl KH. 1991. The composition of the upper earth's crust and the natural cycles of selected metals. Metals in natural raw materials. Natural resources. In: Merian E, ed. Metals and their compounds in the environment. Occurrence, analysis, and biological relevance. New York, NY: VCH, 3-17.

Weed Society of America. 1967. Herbicide handbook of the Weed Society of America. Geneva, NY: WF Humphrey, 134-137.

Wei C, Li W, Zhang C, et al. 2003. Safety evaluation of organoarsenical species in edible *Porphyra* from the China Sea. J Agric Food Chem 51(17):5176-5182.

*Wei M, Wanibuchi H, Morimura K, et al. 2002. Carcinogenicity of dimethylarsinic acid in male F344 rats and genetic alterations in induced urinary bladder tumors. Carcinogenesis 23(8):1387-1397.

*Wei M, Wanibuchi H, Yamamoto S, et al. 1999. Urinary bladder carcinogenicity of dimethylarsinic acid in male F344 rats. Carcinogenesis 20(9):1873-1876.

Weinberg C. 2004. Arsenic and drinking water. Epidemiology 15(2):255-256.

Weir E. 2002. Arsenic and drinking water. Can Med Assoc J 166(1):69.

*Weis P, Weis JS, Lores E. 1993. Uptake of metals from chromated-copper-arsenate (CCA)-treated lumber by Epibiota. Mar Pollut Bull 26(8):428-430.

*Welch AH, Lico MS, Hughes JL. 1988. Arsenic in groundwater of the western United States. Ground Water 26(3):333-347.

*Welch K, Higgins I, Oh M, et al. 1982. Arsenic exposure, smoking and respiratory cancer in copper smelter workers. Arch Environ Health 37(6):325-335.

*Wendt PH, Van Dolah RF, Bobo MY, et al. 1996. Wood preservative leachates from docks in an estuarine environment. Arch Environ Contam Toxicol 31(1):24-37.

Wentworth W. 1983. Compliance monitoring data from federal reporting data system. U.S. Environmental Protection Agency, Office of Drinking Water, State Programs Division.

*Werner MA, Knobeloch LM, Erbach T, et al. 2001. Use of imported folk remedies and medications in the Wisconsin Hmong community. Wis Med J 100(7):32-34.

9REFERENCES

*West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J Pediatrics 32:10-18.

*Wester RC, Maibach HI, Sedik L, et al. 1993. *In vivo* and *in vitro* percutaneous absorption and skin decontamination of arsenic from water and soil. Fundam Appl Toxicol 20(3):336-340.

Westervelt P, Pollock J, Haug J, et al. 1997. Response and toxicity associated with dose escalation of arsenic trioxide in the treatment of resistant acute promyelocytic leukemia. Blood 90(10 Suppl 1 Part 2)249b.

*Westhoff DD, Samaha RJ, Barnes A. 1975. Arsenic intoxication as a cause of megaloblastic anemia. Blood 45(2):241-246.

Westoo G, Rydalv M. 1972. [Arsenic levels in foods.] Var Foda 24:21-40. (Swedish)

Whitnack GC, Martens BH. 1971. Arsenic in potable desert ground-water: An analysis problem. Science 171:383-385.

*WHO. 1981. Environmental health criteria 18: Arsenic. IPCS International Programme on Chemical Safety. Geneva, Switzerland: World Health Organization.

WHO. 1984a. Arsenic. Guidelines for drinking-water quality. Vol. 1. Recommendations. Geneva, Switzerland: World Health Organization, 53.

WHO. 1984b. Arsenic. Guidelines for drinking water quality. Vol. 2. Health criteria and other supporting information. World Health Organization: Geneva, Switzerland. 63-67.

WHO. 1986. Diseases caused by arsenic and its toxic compounds. In: Early detection of occupational diseases. Geneva, Switzerland: World Health Organization 74-78.

*WHO. 1996. Guidelines for drinking-water quality: Vol. 2--Health criteria and other supporting information.

*WHO. 2000. Air quality guidelines. 2nd ed. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/air/Activities/20050104_1. February 15, 2005.

*WHO. 2004. Guidelines for drinking-water quality. 3rd ed. Geneva, Switzerland: World Health Organization. http://www.who.int/water_sanitation_health/dwq/gdwq3/en/. February 15, 2005.

Wicklund KG, Daling JR, Allard J, et al. 1988. Respiratory cancer among orchardists in Washington state, 1968-1980. J Occup Med 30:561-564.

*Wicks MJ, Archer VE, Auerbach O, et al. 1981. Arsenic exposure in a copper smelter as related to histological type of lung cancer. Am J Ind Med 2:25-31.

*Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Bronner F, eds. Mineral metabolism: An advanced treatise. Volume II: The elements Part A. New York: Academic Press.

*Wiencke JK, Yager JW. 1992. Specificity of arsenite in potentiating cytogenetic damage induced by the DNA crosslinking agent diepoxybutane. Environ Mol Mutagen 19(3):195-200.

9REFERENCES

*Wiencke JK, Yager JW, Varkonyi A, et al. 1997. Study of arsenic mutagenesis using the plasmid shuttle vector pZ189 propagated in DNA repair proficient human cells. Mutat Res 386(3):335-344.

Wildfang EK, Zakharyan RA, Aposhian HV. 1998. Hamster and rabbit arsenite and MMA methyltransferase kinetics: Comparison of in vitro properties. Toxicologist. Abstracts of the 37th Annual Meeting 42(1-S):283.

*Willhite CC. 1981. Arsenic-induced axial skeletal (dysraphic) disorders. Exp Mol Pathol 34:145-158.

*Willhite CC, Ferm VH. 1984. Prenatal and developmental toxicology of arsenicals. Adv Exp Med Biol 177:205-228.

Williams LE, Barnett MO, Kramer TA, et al. 2003. Adsorption and transport of arsenic (V) in experimental subsurface systems. J Environ Qual 32:841-850.

*Williams TM, Rawlins BG, Smith B, et al. 1998. In-vitro determination of arsenic bioavailability in contaminated soil and mineral beneficiation waste from Ron Phibun, Southern Thailand: A basis for improved human risk assessment. Environ Geochem Health 20(4):169-177.

*Wingren G, Axelson O. 1993. Epidemiologic studies of occupational cancer as related to complex mixtures of trace elements in the art glass industry. Scand J Work Environ Health 19(suppl. 1):95-100.

Winski SL, Carter DE. 1998. Arsenate toxicity in human erythrocytes: characterization of morphologic changes and determination of the mechanism of damage. J Toxicol Environ Health 53:345-355.

*Wlodarczyk BJ, Bennett GD, Calvin JA, et al. 1996. Arsenic-induced neural tube defects in mice: Alterations in cell cycle gene expression. Reprod Toxicol 10(6):447-454.

Wlodarczyk B, Spiegelstein O, Gelineau-van Waes J, et al. 2001. Arsenic-induced congenital malformations in genetically susceptible folate binding protein-2 knockout mice. Toxicol Appl Pharmacol 177(3):238-46.

*Wolz S, Fenske RA, Simcox NJ, et al. 2003. Residential arsenic and lead levels in an agricultural community with a history of lead arsenate use. Environ Res 93:293-300.

*Wong O, Whorton MD, Foliart DE, et al. 1992. An ecologic study of skin cancer and environmental arsenic exposure. Int Arch Occup Environ Health 64(4):235-241.

*Wong SS, Tan KC, Goh CL. 1998a. Cutaneous manifestations of chronic arsenicism: Review of seventeen cases. J Am Acad Dermatol 38:179-185.

*Wong ST, Chan HL, Teo SK. 1998b. The spectrum of cutaneous and internal malignancies in chronic arsenic toxicity. Singapore Med J 39(4):171-173.

Wongphatarakul V, Friedlander SK, Pinto JP. 1998. A comparative study of $PM_{2.5}$ ambient aerosol chemical databases. Environ Sci Technol 32:3926-3934.

Wood JM. 1974. Biological cycles for toxic elements in the environment. Science 188:1049-1052.

9REFERENCES

*Woods JS, Fowler BA. 1977. Effects of chronic arsenic exposure on hematopoietic function in adult mammalian liver. Environ Health Perspect 19:209-213.

*Woods JS, Fowler BA. 1978. Altered regulation of mammalian hepatic heme biosynthesis and urinary porphyrin excretion during prolonged exposure to sodium arsenate. Toxicol Appl Pharmacol 43:361-371.

*Woods JS, Southern MR. 1989. Studies on the etiology of trace metal-induced porphyria: Effects of porphyrinogenic metals on coproporphyrinogen oxidase in rat liver and kidney. Toxicol Appl Pharmacol 97:183-190.

Woollons A, Russel-Jones R. 1998. Chronic endemic hydroarsenicism. Br J Dermatol 139:1092-1096.

Woolson EA. 1976. Generation of dimethyl arsine from soil. Paper presented at 16th meeting, Weed Science Society of America, Paper No. 218.

Woolson EA. 1977. Fate of arsenicals in different environmental substrates. Environ Health Perspect 19:73-81.

Wrobel K, Wrobel K, Parker B, et al. Determination of As(III), As(V), monomethylarsonic acid, dimethylarsinic acid and arsenobetaine by HPLC–ICP–MS: Analysis of reference materials, fish tissues and urine. Talanta 58:899-907.

*WSDOE. 2005. Tacoma Shelter Plume: South King County mainland soil study. Washington State Department of Ecology. http://www.ecy.wa.gov/programs/tcp/sites/tacoma_smelter/soil_study.htm. July 14, 2005.

Wu H, Manonmanii K, Lam PK, et al. 2004. Urinary arsenic speciation and porphyrins in C57Bl/6J mice chronically exposed to low doses of sodium arsenate. Toxicol Lett 154(1-2):149-157.

Wu MM, Chiou HY, Ho IC, et al. 2003. Gene expression of inflammatory molecules in circulating lymphocytes from arsenic-exposed human subjects. Environ Health Perspect 111(11):1429-1438.

*Wu MM, Chiou HY, Wang TW, et al. 2001. Association of blood arsenic levels with increased reactive oxidants and decreased antioxidant capacity in a human population of northeastern Taiwan. Environ Health Perspect 109(10):1011-1017.

*Wu M-M, Kuo T-L, Hwang Y-H, et al. 1989. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. Am J Epidemiol 130(6):1123-1132.

*Wulff M, Högberg U, Sandstrom A. 1996. Cancer incidence for children born in a smelting community. Acta Oncologica (Stockholm) 35(2):179-183.

*Wyatt CJ, Fimbres C, Romo L, et al. 1998b. Incidence of heavy metal contamination in water supplies in Northern Mexico. Environ Res A76:114-119.

*Wyatt CJ, Quiroga VL, Acosta RTO, et al. 1998a. Excretion of arsenic (As) in urine of children, 7-11 years, exposed to elevated levels of As in the city water supply in Hermosillo, Sonora, Mexico. Environ Res A78:19-24.

Xie Y, Liu J, Liu Y, et al. 2003. Toxicokinetic and genomic analysis of chronic arsenic exposure in multidrug-resistance double knockout mice. Toxicol Sci 72(S-1):214.

9REFERENCES

Xie Z, Zhao S, Konopleva M, et al. 1997. Melarsoprol and arsenic trioxide increase cell death on doxorubicin-resistant human leukemia and myeloma cells by regulating expression of BCL-2 apoptosis regulatory family. Blood 90(10 Suppl. 1 Part 1):495a.

Xu H, Allard B, Grimvall A. 1988. Influence of pH and organic substance on the adsorption of arsenic on geologic materials. Water Air Soil Pollut 40:293-306.

*Xuan X-Z, Lubin JH, Li J-Y, et al. 1993. A cohort study in southern China of tin miners exposed to radon and radon decay products. Health Phys 64(2):120-131.

*Yager JW, Wiencke JK. 1993. Enhancement of chromosomal damage by arsenic: Implications for mechanism. Environ Health Perspect 101(Suppl 3):79-82.

*Yager JW, Wiencke JK. 1997. Inhibition of poly(ADP-ribose) polymerase by arsenite. Mutat Res 386(3):345-351.

*Yager JW, Hicks JB, Fabianova E. 1997. Airborne arsenic and urinary excretion of arsenic metabolites during boiler cleaning operations in a Slovak coal-fired power plant. Environ Health Perspect 105(8):836-842.

Yamato N. 1988. Concentrations and chemical species of arsenic in human urine and hair. Bull Environ Contam Toxicol 40:633-640.

*Yamamoto A, Hisanaga A, Ishinishi N. 1987. Tumorigenicity of inorganic arsenic compounds following intratracheal instillations to the lungs of hamsters. Int J Cancer 40:220-223.

*Yamamoto S, Konishi Y, Matsuda T, et al. 1995. Cancer induction by an organic arsenic compound, dimethylarsinic acid (cacodylic acid), in F344/DuCrj rats after pretreatment with five carcinogens. Cancer Res 55(6):1271-1276.

*Yamamoto S, Wanibuchi H, Hori T, et al. 1997. Possible carcinogenic potential of dimethylarsinic acid as assessed in rat in vivo models: A review. Mutat Res 386(3):353-361.

*Yamanaka K, Okada S. 1994. Induction of lung-specific DNA damage by metabolically methylated arsenics via the production of free radicals. Environ Health Perspect 102(Suppl 3)37-40.

*Yamanaka K, Hasegawa A, Sawamura R, et al. 1989a. Dimethylated arsenics induce DNA strand breaks in lung *via* the production of active oxygen in mice. Biochem Biophys Res Commun 165(1):43-50.

*Yamanaka K, Hayashi H, Kato K, et al. 1995. Involvement of preferential formation of apurinic/apyrimidinic sites in dimethylarsenic-induced DNA strand breaks and DNA-protein crosslinks in cultured alveolar epithelial cells. Biochem Biophys Res Commun 207(1):244-249.

*Yamanaka K, Hayashi H, Kato K, et al. 1997. DNA single-strand breaks in L-132 cells resulting from inhibition of repair polymerization shortly after exposure to dimethylarsinic acid. Biol Pharm Bull 20(2):163-167.

9REFERENCES

Yamanaka K, Hoshino M, Okamoto M, et al. 1990. Induction of DNA damage by dimethylarsine, a metabolite of inorganic arsenics, is for the major part likely due to its peroxyl radical. Biochem Biophys Res Commun 168:58-64.

Yamanaka K, Katsumata K, Ikuma K, et al. 2000. The role of orally administered dimethylarsinic acid, a main metabolite of inorganic arsenics, in the promotion and progression of UVB-induced skin tumorigenesis in hairless mice. Cancer Lett 152(1):79-85.

*Yamanaka K, Ohba H, Hasegawa A, et al. 1989b. Mutagenicity of dimethylated metabolites of inorganic arsenics. Chem Pharm Bull 37(10):2753-2756.

Yamanaka K, Ohtsubo K, Hasegawa A, et al. 1996. Exposure to dimethylarsinic acid, a main metabolite of inorganic arsenics, strongly promotes tumorigenesis initiated by 4-nitroquinoline 1-oxide in the lungs of mice. Carcinogenesis 17(4):767-770.

Yamanaka K, Takabayashi F, Mizoi M, et al. 2001. Oral exposure of dimethylarsinic acid, a main metabolite of inorganic arsenics, in mice leads to an increase in 8-oxo-2'-deoxyguanosine level, specifically in the target organs for arsenic carcinogenesis. Biochem Biophys Res Commun 287(1):66-70.

*Yamanaka K, Tezuka M, Kato K, et al. 1993. Crosslink formation between DNA and nuclear proteins by *in vivo* and *in vitro* exposure of cells to dimethylarsinic acid. Biochem Biophys Res Commun 191(3):1184-1191.

*Yamauchi H, Yamamura Y. 1984. Metabolism and excretion of orally administered dimethylarsinic acid in the hamster. Toxicol Appl Pharmacol 74:134-140.

*Yamauchi H, Yamamura Y. 1985. Metabolism and excretion of orally administered arsenic trioxide in the hamster. Toxicology 34:113-121.

Yamauchi H, Aminaka Y, Yoshida K, et al. 2004. Evaluation of DNA damage in patients with arsenic poisoning: Urinary 8-hydroxydeoxyguanine. Toxicol Appl Pharmacol 198(3):291-296.

Yamauchi H, Kaise T, Takahashi K, et al. 1990. Toxicity and metabolism of trimethylarsine in mice and hamsters. Fundam Appl Toxicol 14:399-407.

*Yamauchi H, Kaise T, Yamamura Y. 1986a. Metabolism and excretion of orally administered arsenobetaine in the hamster. Bull Environ Contam Toxicol 36:350-355.

*Yamauchi H, Takahashi K, Mashiko M, et al. 1989. Biological monitoring of arsenic exposure of gallium arsenide- and inorganic arsenic-exposed workers by determination of inorganic arsenic and its metabolites in urine and hair. Am Ind Hyg Assoc J 50(11):606-612.

Yamauchi H, Takahashi K, Yamamura Y. 1986b. Metabolism and excretion of orally and intraperitoneally administered gallium arsenide in the hamster. Toxicology 40:237-246.

*Yamauchi H, Yamato N, Yamamura Y. 1988. Metabolism and excretion of orally and intraperitoneally administered methylarsonic acid in the hamster. Bull Environ Contam Toxicol 40:280-286.

Yamauchi H, Yoshida T, Aikawa H, et al. 1998. Metabolism and biological monitoring of arsenic poisoning following chronic arsenic exposure in Inner Mongolia, China. Toxicologist 42(1-S):321.

*Yan-Chu H. 1994. Arsenic distribution in soils. In: Nriagu JO, ed. Arsenic in the environment, part 1: Cycling and characterization. New York, NY: John Wiley & Sons, Inc., 17-49.

Yanez L, Garcia-Nieto E, Rojas E, et al. 2003. DNA damage in blood cells from children exposed to arsenic and lead in a mining area. Environ Res 93(3):231-240.

*Yang J-L, Chen M-F, Wu C-W, et al. 1992. Posttreatment with sodium arsenite alters the mutational spectrum induced by ultraviolet light irradiation in Chinese hamster ovary cells. Environ Mol Mutagen 20(3)156-164.

Yang T, Blackwell RQ. 1961. Nutritional and environmental conditions in the endemic blackfoot area. Formosan Sci 15:101-129.

Yang TH, Blackwell RQ. 1960. Preliminary results of nutritional surveys of afflicted and nonafflicted families in the endemic blackfoot area. J Formosan Med Assoc 59:24-25.

*Yang CY, Chang CC, Tsai SS, et al. 2003. Arsenic in drinking water and adverse pregnancy outcome in an arseniasis-endemic area in northeastern Taiwan. Environ Res 91(1):29-34.

*Yee-Chien L, Haimei H. 1996. Lowering extracellular calcium content protects cells from arsenite-induced killing and micronuclei formation. Mutagenesis 11(1):75-78.

*Yih L-H, Ho I-C, Lee T-C. 1997. Sodium arsenite disturbs mitosis and induces chromosome loss in human fibroblasts. Cancer Res 57(22):5051-5059.

*Yokel J, Delistraty DA. 2003. Arsenic, lead, and other trace elements in soils contaminated with pesticide residues at the Hanford site (USA). Environ Toxicol 18(2):104-114.

Yong L, Huigang Z, Peiyan K. 1998. [Influence of arsenic on proliferation and differentiation of rat bud cells in vitro.] Wei Sheng Yen Chiu 27(3):161-163. (Chinese)

*Yoshida K, Kuroda K, Inoue Y, et al. 2001. Metabolism of dimethylarsinic acid in rats: Production of unidentified metabolites *in vivo*. Appl Organomet Chem 15:539-547.

Yoshida T, Shimamura T, Shigeta S. 1987. Enhancement of the immune response in vitro by arsenic. Int J Immunopharmacol 9:411-415.

Yoshida T, Shimamura T, Shigeta S. 1990. A rapid microassay for hemolytic antibody--its application to immunotoxicological study. J Toxicol Sci 15:29-37.

*Yost LJ, Schoof RA, Aucoin R. 1998. Intake of inorganic arsenic in the North American diet. Human Ecol Risk Assess 4(1):137-152.

*Yu D. 1998a. A realistic risk assessment of inorganic arsenic. J Environ Sci Health Part A 33(6):1149-1170.

*Yu D. 1998b. Uncertainties in a pharmacokinetic modeling for inorganic arsenic. J Environ Sci Health Part A 33(7):1369-1390.

9REFERENCES

*Yu D. 1999a. A physiologically based pharmacokinetic model of inorganic arsenic. Regul Toxicol Pharmacol 29:128-141.

*Yu D. 1999b. A pharmacokinetic modeling of inorganic arsenic: A short-term oral exposure model for humans. Chemosphere 39(15):2737-2747.

Yu HS. 1984. Blackfoot disease and chronic arsenism in southern Taiwan. Int J Dermatol 23:258-260.

*Yu H-S, Chang K-L, Wang C-M, et al. 1992. Alterations of mitogenic responses of mononuclear cells by arsenic in arsenical skin cancers. J Dermatol 19(11):710-714.

Yu H-S, Chang K-L, Yu C-L, et al. 1998. Defective IL-2 receptor expression in lymphocytes of patients with arsenic-induced Bowen's disease. Arch Dermatol Res 290:681-687.

*Yu H-S, Sheu H-M, Ko S-S, et al. 1984. Studies on blackfoot disease and chronic arsenism in southern Taiwan: With special reference to skin lesions and fluorescent substances. J Dermatol 11:361-370.

*Zadorozhnaja TD, Little RE, Miller RK, et al. 2000. Concentrations of arsenic, cadmium, copper, lead, mercury, and zinc in human placentas from two cities in Ukraine. J Toxicol Environ Health A 61:255-263.

Zagury GJ, Samson R, Deschenes L. 2003. Occurrence of metals in soil and ground water near chromated copper arsenate-treated utility poles. J Environ Qual 32:507-514.

*Zakharyan R, Wu Y, Bogdan GM, et al. 1995. Enzymatic methylation of arsenic compounds: Assay, partial purification, and properties of arsenite methyltransferase and monomethylarsonic acid methyltransferase of rabbit liver. Chem Res Toxicol 8(8):1029-1038.

Zakharyan RA, Healy SM, Chaga G, et al. 1998. Purification and properties of the arsenite methylating isoenzymes of rabbit liver. Toxicologist 42(1-S):324.

*Zakharyan RA, Wildfang E, Aposhian HV. 1996. Enzymatic methylation of arsenic compounds. III. The marmoset and tamarin, but not the Rhesus, monkeys are deficient in methyltransferases that methylate inorganic arsenic. Toxicol Appl Pharmacol 140(1):77-84.

*Zaldívar R. 1974. Arsenic contamination of drinking water and foodstuffs causing endemic chronic poisoning. Beitr Pathol 151:384-400.

*Zaldívar R. 1977. Ecological investigations on arsenic dietary intake and endemic chronic poisoning in man: Dose-response curve. Zentralbl Bakteriol Hyg 164:481-484.

*Zaldívar R, Guillier A. 1977. Environmental and clinical investigations on endemic chronic arsenic poisoning in infants and children. Zentralbl Bakteriol Hyg 165:226-234.

*Zaldívar R, Prunés L, Ghai G. 1981. Arsenic dose in patients with cutaneous carcinomata and hepatic haemangio-endothelioma after environmental and occupational exposure. Arch Toxicol 47:145-154.

Zaloga GP, Deal J, Spurling T, et al. 1985. Unusual manifestations of arsenic intoxication. Am J Med Sci 289:210-214.

9REFERENCES

*Zanzoni F, Jung EG. 1980. Arsenic elevates the sister chromatid exchange (SCE) rate in human lymphocytes in vitro. Arch Dermatol Res 267:91-95.

Zeng H, Uthus EO, Combs GF. 2005. Mechanistic aspects of the interactions between selenium and arsenic. [Accepted for publication by J Inorg Biochem.]

Zhang X, Cornelis R, De Kimpe J, et al. 1996. Accumulation of arsenic species in serum of patients with chronic renal disease. Clin Chem 42(8 Pt 1):1231-1237.

Zhang X, Cornelis R, De Kimpe J, et al. 1997. Speciation of arsenic in serum, urine, and dialysate of patients on continuous ambulatory peritoneal dialysis. Clin Chem 43(2):406-408.

Zhao CO, Del Razo LM, Young M, et al. 1998. Role of c-myc overexpression in arsenic-induced malignant transformation. Toxicologist 42(1-S):322-323.

*Zhao CQ, Young MR, Diwan BA, et al. 1997. Association of arsenic-induced malignant transformation with DNA hypomethylation and aberrant gene expression. Proc Natl Acad Sci USA 94 (20):10907-10912.

Zheng X-H, Younis H, Turney KD, et al. 1998. Molecular alterations in renal cortical slices following exposure to sub-toxic levels of arsenite. Toxicologist 42(1-S):323.

Zheng Y, Wu J, Ng JC, et al. 2002. The absorption and excretion of fluoride and arsenic in humans. Toxicol Lett 133(1):77-82.

*Zhu J, Koken MHM, Quignon F, et al. 1997. Arsenic-induced PML targeting into nuclear bodies: Implications for the treatment of acute promyelocytic leukemia. Proc Matl Acad Sci 94:3978-3983.

*Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12:29-34.

*Zierler S, Theodore M, Cohen A, et al. 1988. Chemical quality of maternal drinking water and congenital heart disease. Int J Epidemiol 17(3):589-594.

*Zierold KM, Knobeloch L, Anderson H. 2004. Prevalence of chronic diseases in adults exposed to arsenic-contaminated drinking water. Am J Public Health 94(11):1936-1937.

Zumei F, Tian D, Xia Y, et al. 2000. Detection of DNA fragmentation in buccal cells from individuals chronically exposed to arsenic via drinking water. Proc Am Assoc Cancer Res 41:506.

10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo—Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ 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 mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD_{50})—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Inorganic Arsenic
CAS Numbers: 7440-38-2
Date: July 2005
Profile Status: Pre-Public Comment, Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 29
Species: Human

Minimal Risk Level (provisional): 0.005 [X] mg/kg/day [ ] ppm

Reference: Mizuta N, Mizuta M, Ito F, et al. 1956. An outbreak of acute arsenic poisoning caused by arsenic-contaminated soy-sauce (shōyu): A clinical report of 220 cases. Bull Yamaguchi Med Sch 4(2-3):131-149.

Experimental design: Mizuta et al. (1956) summarized findings from 220 poisoning cases associated with an episode of arsenic contamination of soy sauce in Japan. The soy sauce was contaminated with approximately 0.1 mg As/mL, probably as calcium arsenate. Arsenic intake in the cases was estimated by the researchers to be 3 mg/day (0.05 mg/kg/day, assuming 55 kg average body weight for this Asian population). Duration of exposure was 2–3 weeks in most cases. Clinical symptoms were recorded. Seventy patients were examined opthalmologically. Laboratory tests were performed on some patients and included hematology, urinalysis, fecal exam, occult blood in gastric and duodenal juice, biochemical examination of blood, liver function tests, electrocardiograph, and liver biopsy.

Effects noted in study and corresponding doses: The primary symptoms were edema of the face, and gastrointestinal and upper respiratory symptoms initially, followed in some patients by skin lesions and neuropathy. Other effects included mild anemia and leukopenia, mild degenerative liver lesions and hepatic dysfunction, abnormal electrocardiogram, and ocular lesions. For derivation of the acute oral MRL, facial edema and gastrointestinal symptoms (nausea, vomiting, diarrhea), which were characteristic of the initial poisoning and then subsided, were considered to be the critical effects.

Dose and end point used for MRL derivation: 0.05 mg As/kg/day

[ ] NOAEL [X] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [X] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[X] 1 [ ] 3 [ ] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: N/A

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: N/A

Was a conversion used from intermittent to continuous exposure?
If so, explain: N/A

Other additional studies or pertinent information that lend support to this MRL: The MRL is supported by the case of a man and wife in upstate New York who experienced gastrointestinal symptoms (nausea, diarrhea, abdominal cramps) starting almost immediately after beginning intermittent consumption of arsenic-tainted drinking water at an estimated dose of 0.05 mg As/kg/day (Franzblau and Lilis 1989). Gastrointestinal symptoms have been widely reported in other acute arsenic poisoning reports as well, although in some cases, the doses were higher and effects were severe, and in other cases, dose information was not available. The UF of 1 for intrahuman variability reflects the fact that the database includes persons of various ethnicities and age groups, including infants. The MRL is considered provisional because the gastrointestinal effects (nausea, vomiting, diarrhea, and occult blood in feces and gastric and duodenal juice) are serious and because serious neurological (hypesthesia in legs, abnormal patellar reflex) and cardiovascular (abnormal electrocardiogram) effects also occurred at the same dose. Although it is not customary to base an MRL on a serious LOAEL, public health concerns regarding arsenic suggested that a provisional value derived from these data would be useful for the general public.

Agency Contact (Chemical Manager): Selene Chou, Ph.D and Carolyn Harper, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Inorganic Arsenic
CAS Numbers: 7440-38-2
Date: July 2005
Profile Status: Pre-Public Comment, Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 130
Species: Human

Minimal Risk Level: 0.0003 [X] mg/kg/day [ ] ppm

References: Tseng, WP, Chu HM, How SW, et al. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J Natl Cancer Inst 40:453-463.

Tseng, WP. 1977. Effects and dose-response relationships of cancer and Blackfoot disease with arsenic. Environ Health Perspect 19:109-119.

Experimental design: Tseng et al. (1968) and Tseng (1977) investigated the incidence of Blackfoot disease and dermal lesions (hyperkeratosis and hyperpigmentation) in a large number of poor farmers (both male and female) exposed to high levels of arsenic in well water in Taiwan. A control group consisting of 17,000 people was identified. The authors stated that the incidence of dermal lesions increased with dose, but individual doses were not provided. However, incidence data were provided based on stratification of the exposed population into low (<300 µg/L), medium (300–600 µg/L), or high (>600 µg/L) exposure levels. Doses were calculated from group mean arsenic concentrations in well water, assuming the intake parameters described by Abernathy et al. (1989). Accordingly, the control, low-, medium-, and high-exposure levels correspond to doses of 0.0008, 0.014, 0.038, and 0.065 mg As/kg/day, respectively. The NOAEL identified by Tseng (1977) (0.0008 mg As/kg/day) was limited by the fact that the majority of the population was less than 20 years of age and the incidence of skin lesions increased as a function of age, and because the estimates of water intake and dietary arsenic intake are highly uncertain. Schoof et al. (1998) estimated that dietary intakes of arsenic from rice and yams may have been 15–211 µg/day (mean 61 µg/day), based on arsenic analyses of foods collected in Taiwan in 1993–1995. Use of the 50 µg/day estimate would result in an approximate doubling of the NOAEL (0.0016 mg/kg/day).

Effects noted in study and corresponding doses: A clear dose-response relationship was observed for characteristic skin lesions:

0.0008 mg As/kg/day	= control group (NOAEL)
0.014 mg As/kg/day	= hyperpigmentation and keratosis of the skin (less serious LOAEL)
0.038–0.065 mg As/kg/day	= increased incidence of dermal lesions

Dose and end point used for MRL derivation: 0.0008 mg As/kg/day

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)

[ ] 1 [x] 3 [ ] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: The arithmetic mean concentration of arsenic in well water for the control group (0.009 mg/L) was converted to a NOAEL of 0.0008 mg As/kg/day as described below:

$$\left[\left(\frac{0.009mg}{L}\times\frac{4.5L}{day}\right)+\frac{0.002mg}{day}\right]\div 55kg = 0.0008mgAs/kg/day$$

This NOAEL conversion assumed a water intake of 4.5 L/day and a body weight of 55 kg, and includes an estimation of arsenic intake of 0.002 mg As/kg/day from food. These assumptions are detailed in Abernathy et al. (1989). This approach to deriving a chronic oral MRL is identical to EPA's approach to deriving a chronic oral RfD.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: N/A

Was a conversion used from intermittent to continuous exposure?
If so, explain: N/A

Other additional studies or pertinent information that lend support to this MRL: The MRL is supported by a number of well conducted epidemiological studies that identify reliable NOAELs and LOAELs for dermal effects. Southwick et al. (1981) identified a NOAEL of 0.006–0.007 mg As/kg/day for dermal lesions in several small populations in Utah. Harrington et al. (1978) identified a NOAEL of 0.003 mg As/kg/day for dermal effects in a small population in Alaska. Mazumder et al. (1988) identified a NOAEL of 0.009 mg As/kg/day and a LOAEL of 0.006 mg As/kg/day for pigmentation changes and hyperkeratosis in a small population in India. Haque et al. (2003) identified a LOAEL of 0.002 mg As/kg/day for hyperpigmentation and hyperkeratosis in a case-control study in India. Cebrian et al. (1983) identified a NOAEL of 0.0004 mg As/kg/day and a LOAEL of 0.022 mg As/kg/day in two regions in Mexico. Borgono and Greiber (1972) and Zaldivar (1974) identified a LOAEL of 0.02 mg As/kg/day for abnormal skin pigmentation in patients in Chile, and Borgono et al. (1980) identified a LOAEL of 0.01 mg As/kg/day for the same effect in school children in Chile. Valentine et al. (1985) reported a NOAEL of 0.02 mg As/kg/day for dermal effects in several small populations in California. Collectively, these studies indicate that the threshold dose for hyperpigmentation and hyperkeratosis is approximately 0.002 mg As/kg/day.

Agency Contacts (Chemical Managers): Selene Chou, Ph.D and Carolyn Harper, Ph.D.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to "Chemical x" via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system,

which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

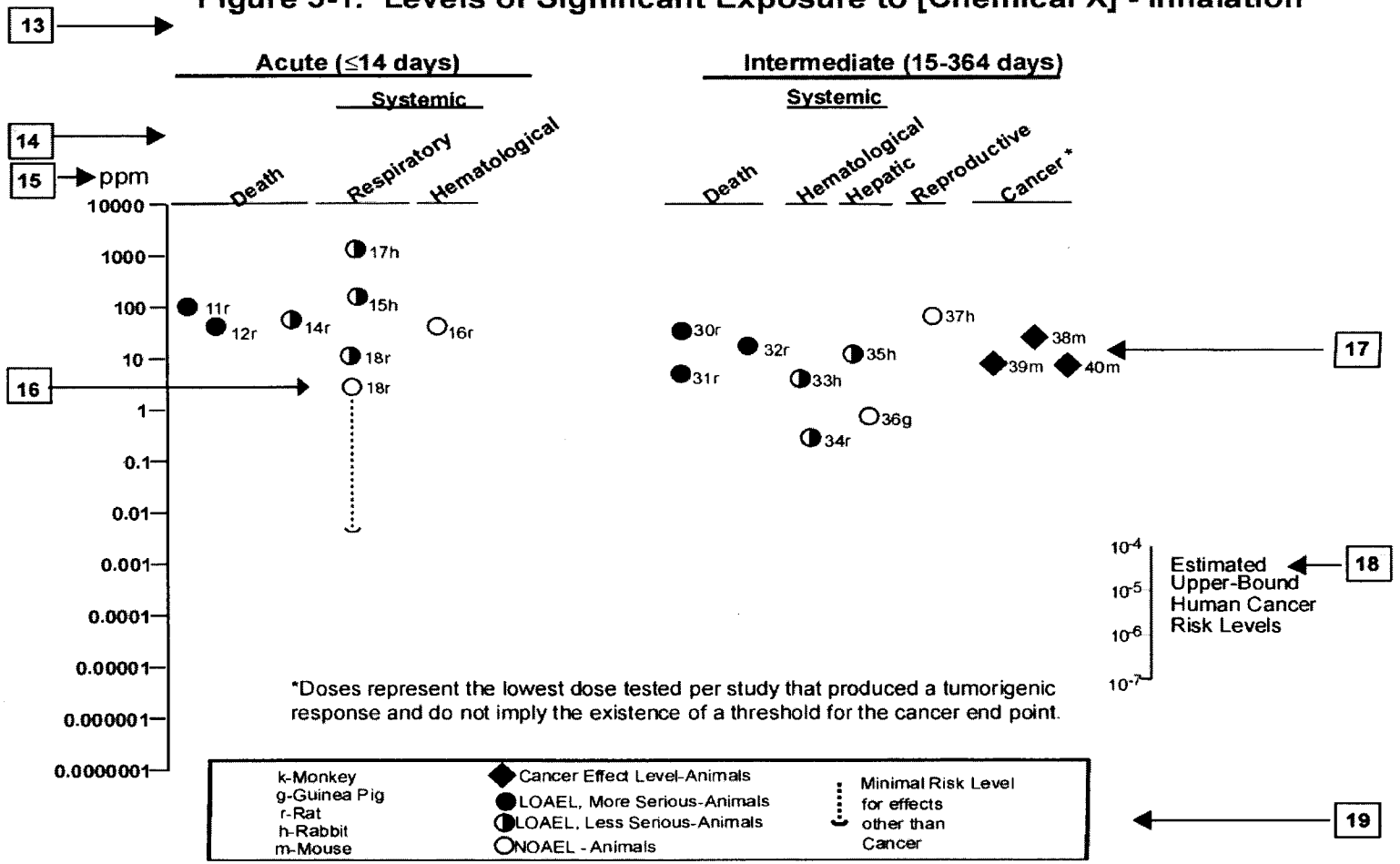
SAMPLE

Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

						LOAEL		

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



*** DRAFT FOR PUBLIC COMMENT***

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	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water

OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D. INDEX

absorbed dose....210
adenocarcinoma....58, 202, 215
adsorbed....213, 271, 272, 314, 316, 322
adsorption....271, 272, 310
aerobic....278
ambient air....56, 280, 301, 310
anaerobic....278
anemia....25, 47, 133, 230
aspartate aminotransferase (see AST)....135
AST (see aspartate aminotransferase)....135
bioaccumulation....275, 282, 285
bioavailability....171, 172, 173, 279, 309, 310, 311, 317, 319, 325
biomarker....209, 210, 212, 213, 214, 235, 329, 338
blood cell count....47
body weight effects....50, 140, 141, 155
breast milk....9, 174, 181, 208, 233, 302, 305, 314
cancer....6, 7, 16, 18, 22, 23, 30, 43, 55, 56, 57, 58, 59, 60, 127, 139, 147, 148, 149, 150, 151, 152, 153, 157, 170, 200, 201, 202, 206, 207, 214, 215, 216, 223, 226, 227, 229, 233, 234, 235, 236, 341, 345
carcinogen....7, 18, 23, 146, 151, 202, 341, 344, 345
carcinogenic....7, 23, 24, 29, 30, 32, 151, 153, 203, 226, 234, 341, 344
carcinogenicity....23, 32, 148, 151, 152, 153, 203, 226, 344
carcinoma....23, 58, 59, 147, 151, 153, 158, 162
cardiac arrhythmia....19, 129
cardiovascular....17, 18, 19, 20, 25, 26, 43, 45, 46, 127, 129, 131, 137, 155, 206, 230
cardiovascular effects....17, 19, 20, 45, 46, 128, 129, 131
chromosomal aberrations....157, 166, 202, 209
clearance....21, 170, 180, 181, 182
crustaceans....295
death....7, 9, 29, 43, 60, 127, 128, 145, 146, 150, 153, 155, 174, 200, 208
deoxyribonucleic acid (see DNA)....159, 165, 166, 168
dermal effects....17, 18, 19, 26, 49, 138, 139, 155, 224, 225, 341
DNA (see deoxyribonucleic acid)....158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 201, 202, 203, 210, 219, 220, 227, 232, 236
dopamine....143
endocrine....137, 138, 155, 204, 205
endocrine effects....137
erythema....19, 155
fetal tissue....9
fetus....147, 175, 205, 228, 318
gastrointestinal effects....21, 25, 46, 47, 60, 131, 132, 341
general population....15, 44, 130, 179, 209, 301, 310, 316, 319, 320, 321, 323
genotoxic....29, 157, 166
genotoxicity....157, 166, 202, 227
groundwater....4, 16, 259, 261, 262, 269, 272, 277, 282, 283, 286, 287, 288, 301, 316, 320, 325, 326
growth retardation....146
half-life....210, 277, 279, 320

hematological effects 47, 48, 133, 134
hepatic effects 48, 134, 135, 214
homeopathic 300
hydroxyl radical 201
immune system 51, 228, 229
immunological 24, 29, 51, 141, 156
immunological effects 24
K_{ow} 243, 244, 245, 246, 247, 321
LD_{50} 127
leukemia 15, 17, 19, 236, 257
leukopenia 25, 133
lymphoreticular 51, 141, 156
melanoma 149
milk 174, 208, 305, 307, 314
mucociliary 21, 47, 316
musculoskeletal effects 48, 134
neonatal 145, 208, 233
neoplastic 152
neurobehavioral 142, 146, 204, 207
norepinephrine 143
nuclear 202, 330
ocular effects 50, 140, 156
odds ratio 51, 150
oxidative phosphorylation 201
pancytopenia 224
partition coefficients 196
pharmacodynamic 182
pharmacokinetic 182, 183, 184, 188, 189, 190, 191, 193, 194, 205, 233, 236
placenta 9, 145, 174, 175, 208
placental barrier 175, 208
rate constant 186, 196, 199
renal effects 48, 49, 136, 137
retention 179, 215, 216, 254, 309
salivation 143
sarcoma 152
solubility 31, 172, 279, 310
spermatogonia 159, 166
thyroid 138, 153
toxicokinetic 29, 31, 58, 169, 178, 211, 215, 229, 231, 232, 233
tremors 52, 143
tumors 18, 23, 59, 147, 149, 150, 151, 152, 153, 157, 202, 203, 208, 214
volatilization 278

537

537