TOXICOLOGICAL PROFILE FOR ASBESTOS

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

September 2001

DISCLAIMER

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

UPDATE STATEMENT

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

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

FOREWORD

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

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

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

Each profile includes the following:

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

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

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

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

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

Jeffrey P. Koplan

Jeffrey P. Koplan, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

*Legislative Background

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 prepared 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 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); 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); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

The Toxicological Profile for asbestos reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on asbestos. Health care providers treating patients potentially exposed to asbestos 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 asbestos 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 this Toxicological Profile to address child health issues:

Section 1.6	**How Can Asbestos Affect Children?**
Section 1.7	**How Can Families Reduce the Risk of Exposure to Asbestos?**
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**
Appendix F	**Consultation on Tremolite and Other Related Asbestos**

Other information available at ATSDR Information Center

Phone: 1-888-42-ATSDR or 1-404-498-0110 ***Fax:*** 1-404-498-0057
E-mail: atsdric@cdc.gov ***Internet:*** http://www.atsdr.cdc.gov

National Public Health Activities regarding Tremolite Asbestos Exposure: Medical Testing, Libby, Montana, Summer 2000 - Over 6,000 Libby, Montana, residents screened for asbestos-related diseases associated with living or working near a vermiculite mine contaminated with a fibrous amphibole. *National Assessment of Vermiculite Sites, Mortality Review of Cancer and Noncancer Cases Associated with Asbestos Exposure, and other projects.*

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

US Environmental Protection Agency (USEPA) - *Asbestos Ombudsman Office*: 1-800-368-5888. Addresses regulations concerning asbestos in public schools and other facilities containing asbestos that are being renovated or demolished. *Washington Office*: 202-260-2090.

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

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

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

Referrals

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

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

CONTRIBUTORS

ASBESTOS WORK GROUP:

G. Douglas Hanley, M.D., R.S.
Susan Kess, M.D., M.P.H.
Yee-Wan Stevens, M.S.
Sharon Wilbur, M.A.
Malcolm Williams, D.V.M., Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

CONTRACT SUPPORT TEAM:

Peter R. McClure, Ph.D., D.A.B.T.
David W. Wohlers, Ph.D.
Gloria W. Sage, Ph.D.
Mark R. Osier, Ph.D.
A. Rosa McDonald, Ph.D.
Syracuse Research Corporation, North Syracuse, NY

REVIEW AND POLICY TEAM:

Sherlita Amler, M.D., M.S.
William Cibulas, Ph.D.
Rich Nickle, B.S.
Anne Olin, B.S.J.
Cassandra Smith, M.S.
Carolyn Tylenda, M.S., D.D.M., Ph.D.
John Wheeler, Ph.D., D.A.B.T.
ATSDR, Division of Toxicology, Atlanta, GA

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.

PEER REVIEW

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

1. Bruce Case, M.D., Associate Professor of Pathology, McGill University Faculty of Medicine, Montreal, Canada;

2. Philip Landrigan, M.D., Ethel H. Wise Professor of Community and Preventive Medicine, Mount Sinai School of Medicine, Mamaroneck, NY;

3. Morton Lippman, Ph.D., Director, Human Exposure and Health Effects Program, Nelson Institute of Environmental Medicine, New York University Medical Center, Tuxedo, NY;

4. William Nicholson, Ph.D., Professor Emeritus, Mount Sinai School of Medicine, Fair Lawn, NJ.

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

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

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

CONTENTS

FOREWORD v

QUICK REFERENCE FOR HEALTH CARE PROVIDERS vii

CONTRIBUTORS ix

PEER REVIEW xi

LIST OF FIGURES xvii

LIST OF TABLES xix

1. PUBLIC HEALTH STATEMENT 1
   1.1 WHAT IS ASBESTOS? 1
   1.2 WHAT HAPPENS TO ASBESTOS WHEN IT ENTERS THE ENVIRONMENT? 2
   1.3 HOW MIGHT I BE EXPOSED TO ASBESTOS? 3
   1.4 HOW CAN ASBESTOS ENTER AND LEAVE MY BODY? 4
   1.5 HOW CAN ASBESTOS AFFECT MY HEALTH? 5
   1.6 HOW CAN ASBESTOS AFFECT CHILDREN? 7
   1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO ASBESTOS? 8
   1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ASBESTOS? 10
   1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH? 11
   1.10 WHERE CAN I GET MORE INFORMATION? 12

2. RELEVANCE TO PUBLIC HEALTH 15
   2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ASBESTOS IN THE UNITED STATES 15
   2.2 SUMMARY OF HEALTH EFFECTS 17
   2.3 MINIMAL RISK LEVELS 22

3. HEALTH EFFECTS 23
   3.1 INTRODUCTION 23
   3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE 23
      3.2.1 Inhalation Exposure 24
         3.2.1.1 Death 39
         3.2.1.2 Systemic Effects 39
         3.2.1.3 Immunological and Lymphoreticular Effects 47
         3.2.1.4 Neurological Effects 48
         3.2.1.5 Reproductive Effects 48
         3.2.1.6 Developmental Effects 48
         3.2.1.7 Cancer 48
      3.2.2 Oral Exposure 57
         3.2.2.1 Death 57
         3.2.2.2 Systemic Effects 63
         3.2.2.3 Immunological and Lymphoreticular Effects 64
         3.2.2.4 Neurological Effects 64
         3.2.2.5 Reproductive Effects 64

3.2.2.6 Developmental Effects . . . 65
3.2.2.7 Cancer . . . 65
3.2.3 Dermal Exposure . . . 71
3.2.3.1 Death . . . 71
3.2.3.2 Systemic Effects . . . 71
3.2.3.3 Immunological and Lymphoreticular Effects . . . 71
3.2.3.4 Neurological Effects . . . 71
3.2.3.5 Reproductive Effects . . . 71
3.2.3.6 Developmental Effects . . . 71
3.2.3.7 Cancer . . . 71
3.3 GENOTOXICITY . . . 71
3.4 TOXICOKINETICS . . . 79
3.4.1 Absorption . . . 80
3.4.1.1 Inhalation Exposure . . . 80
3.4.1.2 Oral Exposure . . . 81
3.4.1.3 Dermal Exposure . . . 81
3.4.2 Distribution . . . 81
3.4.2.1 Inhalation Exposure . . . 81
3.4.2.2 Oral Exposure . . . 83
3.4.2.3 Dermal Exposure . . . 83
3.4.2.4 Other Routes of Exposure . . . 83
3.4.3 Metabolism . . . 84
3.4.3.1 Inhalation Exposure . . . 84
3.4.3.2 Oral Exposure . . . 85
3.4.3.3 Dermal Exposure . . . 85
3.4.3.4 Other Routes of Exposure . . . 85
3.4.4 Elimination and Excretion . . . 86
3.4.4.1 Inhalation Exposure . . . 86
3.4.4.2 Oral Exposure . . . 87
3.4.4.3 Dermal Exposure . . . 87
3.4.4.4 Other Routes of Exposure . . . 87
3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models . . . 87
3.4.5.1 Summary of PBPK Models . . . 90
3.4.5.2 Asbestos PBPK Model Comparison . . . 90
3.4.5.3 Discussion of Model . . . 91
3.5 MECHANISMS OF ACTION . . . 92
3.5.1 Pharmacokinetic Mechanisms . . . 93
3.5.2 Mechanisms of Toxicity . . . 96
3.5.3 Animal-to-Human Extrapolations . . . 100
3.6 ENDOCRINE DISRUPTION . . . 101
3.7 CHILDREN'S SUSCEPTIBILITY . . . 101
3.8 BIOMARKERS OF EXPOSURE AND EFFECT . . . 105
3.8.1 Biomarkers Used to Identify or Quantify Exposure to Asbestos . . . 106
3.8.2 Biomarkers Used to Characterize Effects Caused by Asbestos . . . 110
3.9 INTERACTIONS WITH OTHER CHEMICALS . . . 111
3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE . . . 113
3.11 METHODS FOR REDUCING TOXIC EFFECTS . . . 115
3.11.1 Reducing Peak Absorption Following Exposure . . . 115
3.11.2 Reducing Body Burden . . . 115
3.11.3 Interfering with the Mechanism of Action for Toxic Effects . . . 116
3.12 ADEQUACY OF THE DATABASE . . . 119
3.12.1 Existing Information on Health Effects of Asbestos . . . 119

3.12.2 Identification of Data Needs 121
3.12.3 Ongoing Studies 131

4. CHEMICAL AND PHYSICAL INFORMATION 135
4.1 CHEMICAL IDENTITY 135
4.2 PHYSICAL AND CHEMICAL PROPERTIES 139

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL 143
5.1 PRODUCTION 143
5.2 IMPORT/EXPORT 144
5.3 USE 146
5.4 DISPOSAL 147

6. POTENTIAL FOR HUMAN EXPOSURE 149
6.1 OVERVIEW 149
6.2 RELEASES TO THE ENVIRONMENT 154
6.2.1 Air 154
6.2.2 Water 155
6.2.3 Soil 155
6.3 ENVIRONMENTAL FATE 156
6.3.1 Transport and Partitioning 156
6.3.2 Transformation and Degradation 156
6.3.2.1 Air 156
6.3.2.2 Water 157
6.3.2.3 Sediment and Soil 157
6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT 157
6.4.1 Air 158
6.4.2 Water 164
6.4.3 Sediment and Soil 165
6.4.4 Other Environmental Media 165
6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE 168
6.6 EXPOSURES OF CHILDREN 175
6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES 180
6.8 ADEQUACY OF THE DATABASE 181
6.8.1 Identification of Data Needs 181
6.8.2 Ongoing Studies 185

7. ANALYTICAL METHODS 187
7.1 BIOLOGICAL SAMPLES 189
7.2 ENVIRONMENTAL SAMPLES 192
7.3 ADEQUACY OF THE DATABASE 192
7.3.1 Identification of Data Needs 195
7.3.2 Ongoing Studies 196

8. REGULATIONS AND ADVISORIES 197

9. REFERENCES 205

10. GLOSSARY 319

APPENDICES

A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS A-1

B. USER'S GUIDE B-1

C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS C-1

D. RISK ASSESSMENT SUMMARY D-1

E. INDEX E-1

F. CHEMICAL-SPECIFIC HEALTH CONSULTATION: TREMOLITE-RELATED ASBESTOS F-1

LIST OF FIGURES

3-1 Levels of Significant Exposure to Asbestos—Inhalation (Human Studies) 33

3-2 Levels of Significant Exposure to Asbestos—Inhalation (Animal Studies) 38

3-3 Levels of Significant Exposure to Asbestos—Oral 62

3-4 Summary of Calculated Gastrointestinal Cancer Risks from Ingestion of Asbestos 70

3-5 Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance 89

3-6 Existing Information on Health Effects of Asbestos 120

4-1 Basic Polysilicate Structures of Asbestos 137

6-1 Frequency of NPL Sites with Asbestos Contamination 150

LIST OF TABLES

3-1 Levels of Significant Exposure to Asbestos—Inhalation (Human Studies) 26

3-2 Levels of Significant Exposure to Asbestos—Inhalation (Animal Studies) 35

3-3 Levels of Significant Exposure to Asbestos—Oral 58

3-4 Summary of NTP Lifetime Asbestos Feeding Studies 67

3-5 Genotoxicity of Asbestos *In Vivo* 72

3-6 Genotoxicity of Asbestos *In Vitro* 74

3-7 Ongoing Studies on the Health Effects of Asbestos 132

4-1 Chemical Identity of Asbestos 136

4-2 Physical and Chemical Properties of Asbestos 140

5-1 Facilities that Produce, Process, or Use Asbestos 145

6-1 Releases to the Environment from Facilities that Produce, Process, or Use Asbestos 152

6-2 Asbestos Levels in Ambient Air Around Taiwanese Factories 160

6-3 Exposure to Airborne Asbestos in U.S. Buildings 162

6-4 Summary of Typical General Population and Occupational Exposures 169

6-5 Exposure to Airborne Asbestos in Nonproduction Departments of the Pulp and Paper Industry 172

6-6 Exposure to Airborne Asbestos During Asbestos Abatement 173

6-7 Exposure to Airborne Asbestos During Building Maintenance or Repair 176

7-1 Analytical Methods for Determining Asbestos in Biological Samples 191

7-2 Analytical Methods for Determining Asbestos in Environmental Samples 193

8-1 Regulations and Guidelines Applicable to Asbestos 198

1. PUBLIC HEALTH STATEMENT

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

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Asbestos has been found in at least 83 of the 1,585 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which asbestos is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

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

If you are exposed to asbestos, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), the fiber type (mineral form and size distribution), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle (including whether you smoke tobacco), and state of health.

1.1 WHAT IS ASBESTOS?

Asbestos is the name given to a group of six different fibrous minerals (amosite, chrysotile, crocidolite, and the fibrous varieties of tremolite, actinolite, and anthophyllite) that occur naturally in the environment. One of these, namely chrysotile, belongs to the serpentine family of minerals, while all of the others belong to the amphibole family. All forms of asbestos are hazardous, and all can cause cancer, but amphibole forms of asbestos are considered to be somewhat more hazardous to health than chrysotile. Asbestos minerals consist of thin, separable

fibers that have a parallel arrangement. Nonfibrous forms of tremolite, actinolite, and anthophyllite also are found naturally. However, because they are not fibrous, they are not classified as asbestos minerals. Amphibole asbestos fibers are generally brittle and often have a rod- or needle-like shape, whereas chrysotile asbestos fibers are flexible and curved. Chrysotile, also known as white asbestos, is the predominant commercial form of asbestos; amphiboles are of minor commercial importance. Asbestos fibers do not have any detectable odor or taste. They do not dissolve in water or evaporate and are resistant to heat, fire, chemical and biological degradation. Because of these properties, asbestos has been mined for use in a wide range of manufactured products, mostly in building materials, friction products, and heat-resistant fabrics. Since asbestos fibers may cause harmful health effects in people who are exposed, all new uses of asbestos have been banned in the United States by the EPA.

See Chapters 4 and 5 for more information on the properties and uses of asbestos.

1.2 WHAT HAPPENS TO ASBESTOS WHEN IT ENTERS THE ENVIRONMENT?

Asbestos fibers do not evaporate into air or dissolve in water. However, pieces of fibers can enter the air and water from the weathering of natural deposits and the wearing down of manufactured asbestos products. Small diameter fibers and fiber-containing particles may remain suspended in the air for a long time and be carried long distances by wind or water currents before settling. Larger diameter fibers and particles tend to settle more quickly. Asbestos fibers are not able to move through soil. They are generally not broken down to other compounds in the environment and will remain virtually unchanged over long periods. However, the most common form of asbestos, chrysotile, may have some minor mineral loss in acidic environments. Asbestos fibers may break into shorter pieces or separate into a larger number of individual fibers as a result of physical processes. When asbestos fibers are breathed in, they may get trapped in the lungs. Levels of fibers in lung tissue build up over time, but some fibers, particularly chrysotile fibers, can be removed from or degraded in the lung with time.

See Chapters 5 and 6 for more information on the behavior of asbestos in the environment.

1.3 HOW MIGHT I BE EXPOSED TO ASBESTOS?

Asbestos minerals are widespread in the environment. They may occur in large natural deposits, or as contaminants in other minerals. For example, tremolite asbestos may occur in deposits of chrysotile, vermiculite, and talc. Asbestos may be found in soil that is formed from the erosion of asbestos-bearing rock. You are most likely to be exposed to asbestos by breathing in asbestos fibers that are suspended in air. These fibers can come from naturally occurring sources of asbestos or from the wearing down or disturbance of manufactured products including insulation, automotive brakes and clutches, ceiling and floor tiles, dry wall, roof shingles, and cement. However, these products do not always contain asbestos. Low levels of asbestos that present little, if any, risk to your health can be detected in almost any air sample. For example, 10 fibers are typically present in a cubic meter (fibers/m^3) of outdoor air in rural areas. (A cubic meter is about the amount of air that you breathe in 1 hour.) Health professionals often report the number of fibers in a milliliter (mL) (equivalent to a cubic centimeter [cm^3]) of air rather than in a cubic meter of air. Since there are one million cm^3 (or one million mL) in a cubic meter, there typically would be 0.00001 fibers/mL of asbestos in air in rural areas. Typical levels found in cities are about 10-fold higher.

Close to an asbestos mine or factory, levels may reach 10,000 fibers/m^3 (0.01 fibers/mL) or higher. Levels could also be above average near a building that contains asbestos products and that is being torn down or renovated or near a waste site where asbestos is not properly covered up or stored to protect it from wind erosion.

In indoor air, the concentration of asbestos depends on whether asbestos was used for insulation, ceiling or floor tiles, or other purposes, and whether these asbestos-containing materials are in good condition or are deteriorated and easily crumbled. Concentrations measured in homes, schools, and other buildings that contain asbestos range from about 30 to 6,000 fibers/m^3 (0.00003–0.006 fibers/mL). People who work with asbestos or asbestos-containing products (for example, miners, insulation workers, asbestos abatement workers, and automobile brake mechanics) without proper protection are likely to be exposed to much higher levels of asbestos fibers in air. In addition, custodial and maintenance workers who are making repairs or

installations in buildings with asbestos-containing materials may be exposed to higher levels of asbestos. Since vermiculite and talc may contain asbestos, occupational workers and the general population may be exposed to asbestos when using these products.

You can also be exposed to asbestos by drinking asbestos fibers that are present in water. Even though asbestos does not dissolve in water, fibers can enter water by being eroded from natural deposits or piles of waste asbestos, from asbestos-containing cement pipes used to carry drinking water, or from filtering through asbestos-containing filters. Most drinking water supplies in the United States have concentrations of less than 1 million fibers per liter (MFL), even in areas with asbestos deposits or with asbestos-cement water supply pipes. However, in some locations, water samples may contain 10–300 million fibers per liter or even higher. The average person drinks about 2 liters of water per day.

See Chapters 3 and 6 for more information on how you could be exposed to asbestos.

1.4 HOW CAN ASBESTOS ENTER AND LEAVE MY BODY?

If you breathe asbestos fibers into your lungs, some of the fibers will be deposited in the air passages and on the cells that make up your lungs. Most fibers are removed from your lungs by being carried away or coughed up in a layer of mucus to the throat, where they are swallowed into the stomach. This usually takes place within a few hours. Fibers that are deposited in the deepest parts of the lung are removed more slowly. In fact, some fibers may move through your lungs and can remain in place for many years and may never be removed from your body. Amphibole asbestos fibers are retained in the lung longer than chrysotile asbestos fibers.

If you swallow asbestos fibers (either those present in water or those that are moved to your throat from your lungs), nearly all of the fibers pass along your intestines within a few days and are excreted in the feces. A small number of fibers may penetrate into cells that line your stomach or intestines, and a few penetrate all the way through and get into your blood. Some of these become trapped in other tissues, and some are removed in your urine.

If you get asbestos fibers on your skin, very few of these fibers, if any, pass through the skin into your body.

See Chapter 3 for more information on how asbestos enters and leaves your body.

1.5 HOW CAN ASBESTOS AFFECT MY HEALTH?

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

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

Information on the health effects of asbestos in people comes mostly from studies of people who were exposed in the past to levels of asbestos fibers (greater than or equal to 5 μm in length) in workplace air that were as high as 5 million fibers/m^3 (5 fibers/mL). Workers who repeatedly breathe in asbestos fibers with lengths greater than or equal to 5 μm may develop a slow buildup of scar-like tissue in the lungs and in the membrane that surrounds the lungs. This scar-like tissue does not expand and contract like normal lung tissue and so breathing becomes difficult. Blood flow to the lung may also be decreased, and this causes the heart to enlarge. This disease is called asbestosis. People with asbestosis have shortness of breath, often accompanied by a cough. This is a serious disease and can eventually lead to disability or death in people exposed to high amounts of asbestos over a long period. However, asbestosis is not usually of concern to people exposed to low levels of asbestos. Changes in the membrane surrounding the lung, called pleural plaques, are quite common in people occupationally exposed to asbestos and are sometimes found in people living in areas with high environmental levels of asbestos.

Effects on breathing from pleural plaques alone are usually not serious. There is conflicting evidence as to whether their presence in a person accurately predicts more serious disease development in the future.

Asbestos workers have increased chances of getting two principal types of cancer: cancer of the lung tissue itself and mesothelioma, a cancer of the thin membrane that surrounds the lung and other internal organs. These diseases do not develop immediately following exposure to asbestos, but appear only after a number of years. There is also some evidence from studies of workers that breathing asbestos can increase the chances of getting cancer in other locations (for example, the stomach, intestines, esophagus, pancreas, and kidneys), but this is less certain. Members of the public who are exposed to lower levels of asbestos may also have increased chances of getting cancer, but the risks are usually small and are difficult to measure directly. Lung cancer is usually fatal, while mesothelioma is almost always fatal, often within a few months of diagnosis. Some scientists believe that early identification and intervention of mesothelioma may increase survival.

The levels of asbestos in air that lead to lung disease depend on several factors. The most important of these are (1) how long you were exposed, (2) how long it has been since your exposure started, and (3) whether you smoked cigarettes. Cigarette smoking and asbestos exposure increase your chances of getting lung cancer. Also, there is a scientific debate concerning the differences in the extent of disease caused by different fiber types and sizes. Some of these differences may be due to the physical and chemical properties of the different fiber types. For example, several studies suggest that amphibole asbestos types (tremolite, amosite, and especially crocidolite) may be more harmful than chrysotile, particularly for mesothelioma. Other data indicate that fiber size dimensions (length and diameter) are important factors for cancer-causing potential. Some data indicate that fibers with lengths greater than 5.0 μm are more likely to cause injury than fibers with lengths less than 2.5 μm. (1 μm is about 1/25,000 of an inch.) Additional data indicate that short fibers can contribute to injury. This appears to be true for mesothelioma, lung cancer, and asbestosis. However, fibers thicker than 3.0 μm are of lesser concern, because they have little chance of penetrating to the lower regions of the lung.

The health effects from swallowing asbestos are unclear. Some groups of people who have been exposed to asbestos fibers in their drinking water have higher-than-average death rates from cancer of the esophagus, stomach, and intestines. However, it is very difficult to tell whether this is caused by asbestos or by something else. Animals that were given very high doses of asbestos in food did not get more fatal cancers than usual, although some extra nonfatal tumors did occur in the intestines of rats in one study.

Several government offices and regulatory agencies have considered all of the evidence regarding the carcinogenicity of asbestos. The Department of Health and Human Services (DHHS) has determined that asbestos is known to be a human carcinogen. The EPA has determined that asbestos is a human carcinogen. The International Agency for Research on Cancer (IARC) has determined that asbestos is carcinogenic to humans.

See Chapters 2 and 3 for more information on how asbestos can affect your health.

1.6 HOW CAN ASBESTOS AFFECT CHILDREN?

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

Asbestos exposure in both children and adults may occur while breathing air in or near buildings (public or private) containing asbestos building materials or near asbestos-related industrial operations. Children breathe differently and have different lung structures than adults. It is not known if these differences may cause a greater amount of asbestos fibers to stay in the lungs of a child when they are breathed in than in the lungs of an adult. Children drink more fluids per kilogram of body weight than adults and can also be exposed through asbestos-contaminated drinking water. Eating asbestos-contaminated soil and dust is another source of exposure for children. Certain children intentionally eat soil, and all young children eat more soil than adults through hand-to-mouth activities. Historically, family members have also been exposed to asbestos that was carried home on the clothing of other family members who worked in asbestos mines or mills. Breathing of asbestos fibers may result in difficulty in breathing, lung cancer, or

mesothelioma (another form of cancer associated with asbestos exposure). These diseases usually appear many years following the first exposure to asbestos and are therefore not likely to be seen in children. But since it may take up to 40 or more years for the effects of exposure to be seen, people who have been exposed to asbestos at a young age may be more likely to contract these diseases than those who are first exposed later in life. In the small number of studies that have specifically looked at asbestos exposure in children, there is no indication that younger people might develop asbestos-related diseases more quickly than older people. Developing fetuses and infants are not likely to be exposed to asbestos through the placenta or breast milk of the mother. Results of animal studies do not indicate that exposure to asbestos is likely to result in birth defects.

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

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

The most important way that families can lower their exposures to asbestos is to be aware of the sources of asbestos in their homes and avoid exposure to these sources. The most important source of asbestos in a home is from damaged or deteriorating asbestos-containing insulation, ceiling, or floor tiles. Should you suspect that your house may contain asbestos, contact your state or local health department or the regional offices of EPA to find out how to test your home for asbestos and how to locate a company that is trained to remove or contain the fibers. Federal law requires schools to identify asbestos-containing material in school buildings and take appropriate action to control release of asbestos fibers.

If you live close to where asbestos and certain other ores are mined or processed, where a building that contains asbestos products is being torn down or renovated, or a waste site where asbestos is not properly covered, then the levels of asbestos in dust and wind-blown soil may be higher. Pets can also bring asbestos into the home by carrying dust or dirt on their fur or feet if they spend time in places that have high levels of asbestos in the soil. Swallowing of asbestos in

house dust or soil is a potential exposure pathway for children. This problem can be reduced in many ways. Regular hand and face washing to remove asbestos-containing dusts and soil, especially before meals, can lower the possibility of asbestos fibers on the skin being accidentally swallowed while eating. Families can lower exposures to asbestos by regularly cleaning the home of dust and tracked in soil. Door mats can help lower the amount of soil that is tracked into the home; removing your shoes before entering will also help. Planting grass and shrubs over bare soil areas in the yard can lower the contact that children and pets may have with soil and reduce the tracking of soil into the home.

You can bring asbestos home in the dust on your hands or clothes if you work in the mining or processing of minerals that contain asbestos, in asbestos removal, or in buildings with damaged or deteriorating asbestos. Federal law regulates work practices to limit the possibility of asbestos being brought home in this way. 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. Your employer should have Material Safety Data Sheets (MSDSs) for many of the chemicals used at your place of work, as required by the Occupational Safety and Health Administration (OSHA). Information on these sheets should include chemical names and hazardous ingredients, important properties (such as fire and explosion data), potential health effects, how you get the chemical(s) in your body, how to handle the materials properly, and what to do in an emergency. Your employer is legally responsible for providing a safe workplace and should freely answer your questions about hazardous chemicals. Either OSHA or your OSHA-approved state occupational safety and health program can answer any further questions and help your employer identify and correct problems with hazardous substances. OSHA and/or your OSHA-approved state occupational safety and health program 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.

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

The most common test used to determine if you have received sustained exposure to asbestos is a chest x-ray. A chest x-ray is recommended for detecting exposure to asbestos only in persons who have sustained relatively heavy exposure. A chest x-ray is of no value for detecting evidence of asbestos exposure in a person whose exposure to asbestos has been only brief or transient. The x-ray cannot detect the asbestos fibers themselves, but it can detect early signs of lung disease caused by asbestos. While other substances besides asbestos can sometimes produce similar changes in the lungs, this test is usually reliable for detecting asbestos-related effects produced by long-term exposures at relatively high concentrations of asbestos fibers. Other tests, such as gallium-67 lung scanning and high-resolution computed tomography, are also useful in detecting changes in the lungs. However, there are currently no means of detecting exposure-related effects from commonly encountered environmental exposures.

The most reliable test to determine if you have been exposed to asbestos is the detection of microscopic asbestos fibers in pieces of lung tissue removed by surgery, but this is a very invasive test. A test can also be run to determine the presence of asbestos fibers in material rinsed out of the lung. However, this test can cause some discomfort. Asbestos fibers can also be detected in mucus (sputum), urine, or feces, but these tests are not reliable for determining how much asbestos may be in your lungs. Low levels of asbestos fibers are found in these materials for nearly all people. Higher-than-average levels can show that you have been exposed to asbestos, but it is not yet possible to use the results of this test to estimate how much asbestos you have been exposed to, or to predict whether you are likely to suffer any health effects.

See Chapters 3 and 7 for more information about how asbestos can be measured in people and in the environment.

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

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

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

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

The federal government has taken a number of steps to protect citizens from exposure to asbestos. First, on July 12, 1989, EPA established a ban on new uses of asbestos. Uses established before this date are still allowable. Second, EPA has established regulations that require school systems to inspect for asbestos and, if damaged asbestos is found, to eliminate or reduce the exposure, either by removing the asbestos or by covering it up so it cannot get into the air. In addition, EPA provides guidance and support for reducing asbestos exposure in other public buildings. Third, EPA regulates the release of asbestos from factories and during building demolition or renovation to prevent asbestos from getting into the environment. EPA also regulates the disposal of waste asbestos materials or products, requiring these to be placed only

in approved locations. Fourth, EPA has proposed a limit of 7 million fibers per liter on the concentration of long fibers (length greater than or equal to 5 μm) that may be present in drinking water. Fifth, FDA regulates the use of asbestos in the preparation of drugs and restricts the use of asbestos in food-packaging materials. NIOSH has recommended that inhalation exposures not exceed 100,000 fibers with lengths greater than or equal to 5 μm per m^3 of air (0.1 fibers/mL). OSHA has established an enforceable limit on the average 8-hour daily concentration of asbestos allowed in air in the workplace to be 100,000 fibers with lengths greater than or equal to 5 μm per m^3 of air (0.1 fibers/mL). Additional sources of information about asbestos are the 10 regional offices of the EPA. Most EPA regional offices have an asbestos coordinator.

See Chapter 8 for more information about regulations and guidelines to protect people from exposure to asbestos.

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

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

* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)
Fax: 1-404-498-0057

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

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ASBESTOS IN THE UNITED STATES

Asbestos is a generic term for a group of six naturally-occurring, fibrous silicate minerals that have been widely used in commercial products. These minerals are more commonly found in nonfibrous forms that are not asbestos. Asbestos minerals fall into two groups or classes, serpentine asbestos and amphibole asbestos. Chrysotile, a serpentine asbestos, possesses relatively long and flexible crystalline fibers that are capable of being woven. Amphibole asbestos has crystalline fibers that are substantially more brittle than serpentine asbestos. Amphibole asbestos includes amosite, crocidolite, and fibrous forms of tremolite, anthophyllite, and actinolite (see Chapter 4 and Appendix F for more information on chemical and physical properties of asbestos). Over 99% of asbestos used in the United States is chrysotile. As a result of its low cost and desirable properties such as heat and fire resistance, wear and friction characteristics, tensile strength, heat, electrical and sound insulation, adsorption capacity, and resistance to chemical and biological attack, asbestos has been used in a very large number of applications and types of products. In most of its applications, asbestos is bonded with other materials such as Portland cement, plastics, and resins. In other applications, asbestos is used as a loose fibrous mixture or woven as a textile. Use of asbestos in the United States has been declining for 2 decades largely due to health concerns. In 1997, asbestos consumption was 6% of what it was in 1980. The 1997 domestic consumption pattern was 48% for roofing products, 29% for friction products (automobile clutch, brake, and transmission components), and 17% for packing and gaskets (see Chapter 5 for more information on production, import, use, and disposal of asbestos).

Asbestos fibers are chemically inert—they do not evaporate, dissolve, burn, or undergo significant reactions with most chemicals. They do not undergo significant degradation in the environment. Although asbestos is not volatile, small fibers and clumps of fibers may be released to air as dust. Asbestos occurring in natural mineral deposits may be released to the atmosphere when these deposits are disturbed—as in mining operations or during building and construction (see Appendix F for information on occurrence of asbestos in other mineral deposits). Asbestos fibers may also be released during the processing of asbestos minerals and the manufacture, application, use, demolition, and disposal of asbestos-containing products. Asbestos released into the atmosphere will be transported by wind and settle on the ground. Small fibers may remain suspended for long periods of time and be transported long

distances. Asbestos may be released into surface water by erosion and runoff, transported in water, and deposited in the sediment.

Numerous measurements have been performed to determine the concentration of asbestos fibers in environmental media, primarily air. These studies have reported results in a variety of units, including PCM f/mL (fibers per mL air=fibers per cm^3, measured by phase contrast microscopy) and TEM f/mL (fibers measured by transmission electron microscopy) (see Section 3.2.1 and Chapter 6 for additional information regarding exposure and exposure units). Definition of a fiber is critical in these methods. The most widely used definition of a fiber among health professionals is a particle that has a length 5 μm and a length/width ratio of 3:1. Although numerous exposure and health effects studies have employed the PCM method for analysis of airborne asbestos concentrations, the method is not capable of detecting fibers smaller in diameter than approximately 0.2–0.3 μm and these thinner fibers may pose a significant health threat (see Chapter 3 for additional information on the relationships between fiber size and health risk). The PCM method is also incapable of distinguishing between asbestos fiber types or between asbestos and nonasbestos fibers. TEM can be used to detect fibers with diameters as small as 0.01 μm and distinguish between asbestos and nonasbestos fibers, as well as fiber types. Although TEM is the preferred method for measuring air concentrations of asbestos, epidemiological studies of occupational exposure to relatively high levels of asbestos, such as those experienced prior to the institution of recent occupational exposure limits (currently 0.1 f/mL), employed PCM or midget impinger particle counting. Particle counting yielded measurements of mass of particles per volume of air. Reported health effects have predominantly been expressed in terms of PCM concentrations (see Section 3.2.1 for a discussion of the uncertainties in converting from midget impinger particle mass per volume to PCM f/mL). Therefore, comparisons between environmental exposure data and occupational exposures associated with adverse health effects can be most readily made using measurements expressed in terms of PCM.

Inhalation is the primary route by which the general population might be exposed to asbestos. Small quantities of asbestos fibers are ubiquitous in air, arising from natural sources (weathering of asbestos-containing minerals), from windblown soil from hazardous waste sites, deterioration of automobile clutches and brakes, or breakdown of asbestos-containing materials such as insulation (mainly chrysotile). The results of numerous measurements indicate that average concentrations of asbestos in ambient outdoor air are within the range of 10^{-8}– 10^{-4} PCM f/mL; levels in urban areas may be an order of magnitude higher than those in rural areas. Even higher concentrations (up to 0.4 f/mL) have been measured in ambient air surrounding Taiwanese factories that manufacture asbestos-containing products.

Indoor air concentrations of asbestos ranged from approximately 10^{-5} to 10^{-4} f/mL in a study of air concentrations measured in a total of 315 U.S. public and commercial facilities. See Chapter 6 and Appendix F for more detailed information regarding concentrations of asbestos in environmental media.

2.2 SUMMARY OF HEALTH EFFECTS

Epidemiological studies of asbestos-exposed workers and supporting animal studies indicate that inhalation of asbestos is the principal route of exposure of public health concern. Some epidemiological studies have also indicated that oral exposure may be linked to the development of gastrointestinal cancer. Depending largely on size and shape, deposition of inhaled asbestos fibers may occur in lung tissue. Some fibers may be removed by mucociliary clearance or macrophages while others may be retained in the lungs for extended periods. Inhalation exposure is, therefore, generally regarded as cumulative, and exposures have been expressed in terms of concentration of fibers over time or PCM fiber-years/mL (f-yr/mL). Studies in humans and animals indicate that inhalation exposure to asbestos fibers may lead to the development of pulmonary disease including asbestosis and/or lung cancer and mesothelioma of the pleura or peritoneum (see Chapter 2 and Appendix F for more detailed information on evidence for these health effects). In general, noncancer effects in other tissues have not been detected; however, the development of cancer in other tissues (e.g., gastrointestinal tissues) in some worker populations may be related to asbestos exposure. Asbestos-related lung diseases (malignant and nonmalignant) or signs of these diseases have been reported in groups of occupationally exposed humans with cumulative exposures ranging from about 5 to 1,200 f-yr/mL. Such cumulative exposures would result from 40 years of occupational exposure to concentrations ranging from 0.125 to 30 f/mL. Currently, U.S. OSHA regulations require that workplace air concentrations of asbestos not exceed 0.1 f/mL. Although asbestos-related effects have been primarily reported after chronic exposures to asbestos in an occupational setting, these effects have also been described following relatively brief occupational exposures. Exposures of this magnitude are usually not encountered by the general public.

Cancer. There is no doubt that inhalation of asbestos can lead to increased risk of lung cancer and mesothelioma. This has been conclusively demonstrated in numerous studies of occupationally exposed workers, and has been confirmed in a number of animal experiments. For lung cancer, the magnitude of the risk appears to be a complex function of a number of parameters, the most important of which are: (1) the level and the duration of exposure; (2) the time since exposure occurred; (3) the age at which exposure occurred; (4) the tobacco-smoking history of the exposed person; and (5) the type and size distribution of the asbestos fibers.

The last parameter is of special practical importance, since the variability in potency among fibers means that cancer risk from asbestos exposure may vary widely from location to location. Some of this variation may be attributable to differences between the mineral types, but fiber size (length and thickness) appear to be of prime importance. There is strong evidence from animal inhalation studies, intrathoracic and intraperitoneal dosing studies, and *in vitro* studies that long fibers are more carcinogenic than short fibers. However, this should not be construed to mean that shorter fibers are totally without carcinogenic potency. The relation between fiber size and carcinogenicity may vary between lung cancer and mesothelioma, but this is not yet clear.

There is some evidence from animal studies that asbestos-induced lung cancer stems from regions in the lung with advanced fibrosis (asbestosis); however, lung cancer with chrysotile was also produced at fiber concentrations that did not lead to detectable fibrosis.

Because of the large number of variables, it is difficult to make reliable predictions of the magnitude of the cancer risk that may result from exposures of the general population to asbestos levels that are likely to be encountered outside the workplace. Although there is considerable uncertainty in the estimates, EPA calculated, using a linear, no-threshold model, that lifetime exposure to asbestos dust containing 0.0001 fibers >5 μm in length per mL of air could result in about 2–4 excess cancer deaths (lung cancer plus mesothelioma) per 100,000 people. In 2001, EPA has been in the process of reviewing its cancer risk estimates for asbestos.

While lung cancer and mesothelioma are generally associated with chronic exposure to asbestos, there are several studies that indicate that short-term exposures are also of concern. For example, it has been noted that workers exposed to asbestos for only 1–12 months had an increased risk of developing lung cancer a number of years later. In animals, mesotheliomas developed in two rats exposed to high concentrations of amosite or crocidolite for only 1 day. These data are not extensive enough to define the dose- or time-dependency of health risks from short-term exposure to asbestos, but the data do indicate that short-term exposures should not be disregarded.

Asbestos exposure is also suspected of increasing the risk of cancer in the gastrointestinal tract, although the evidence is less consistent than for lung cancer or mesothelioma. Data supporting this view have been derived mainly from three types of studies. First, some studies of workers exposed to asbestos by inhalation have noted small excesses in death rates from gastrointestinal cancer. This is presumed to be due to the transfer of inhaled fibers from the lung to the gastrointestinal tract. Second, some studies

suggest that populations with high levels of asbestos fibers in drinking water may have increased risk of gastrointestinal cancers. Third, one lifetime feeding study in rats indicated that intermediate-length chrysotile can increase the frequency of benign intestinal tumors in male rats. There are several findings, however, that do not support the association. The excess gastrointestinal mortalities noted in workers and in populations exposed through drinking water were usually quite small (from an epidemiological point of view), the follow-up period was of insufficient duration, and consistent results were not found across studies. Also, it is very difficult to determine whether the excesses are due to asbestos or to other factors (exposure to other chemicals, misdiagnosis, dietary factors, alcohol intake, etc.). With regard to the one positive tumorigenicity finding in animals, this must be balanced against the fact that the tumors were both infrequent and benign, and that no significant excess of gastrointestinal tumors was noted in a number of other adequate animal cancer bioassays.

There is some indication that asbestos exposure may have increased the risk of laryngeal cancer in some groups of asbestos workers, but the evidence is not as strong as that for lung cancer and mesothelioma. There is little evidence for the carcinogenicity of asbestos at other sites, although several cases of malignant mesothelioma of the tunica vaginalis testis have been reported in patients with histories of occupational exposure to asbestos.

Several government office and regulatory agencies have considered the evidence regarding the overall carcinogenicity of asbestos. The Department of Health and Human Services (DHHS) has determined that asbestos is known to be a human carcinogen. The EPA has determined that asbestos is a human carcinogen (Group A). In addition, the International Agency for Research on Cancer (IARC) has determined that asbestos is carcinogenic to humans (Group 1). These conclusions are based primarily on the evidence that asbestos causes lung cancer and mesothelioma. A number of researchers and regulatory groups have reviewed the weight-of-evidence on the issue of cancer at other sites after inhalation exposure to asbestos in the workplace, and have reached differing conclusions. For example, some believe that the data constitute substantial evidence that inhalation of asbestos in the workplace does increase risk of cancer at other sites. In contrast, others feel that the evidence is not adequate to reach a firm conclusion, and some believe that the apparent increases in gastrointestinal cancer are probably due to other factors (misdiagnosis, diet, alcohol, disease history, etc.) and cannot be attributed to asbestos. As these conflicting analyses illustrate, when epidemiological studies provide limited evidence for a small increase in cancer risk at a site, it is difficult to distinguish between two alternative interpretations: (1) the risk is real, and inconsistencies in the data are due to limitations in the sensitivity and accuracy of epidemiological studies; or (2) the risk is not real, and the apparent effects are attributable to other causes

or reasons. In view of the limitations and uncertainties in the data available, it does not appear that a definitive distinction can currently be drawn between these alternatives. However, it seems only prudent to consider increased risk of gastrointestinal cancer an effect of concern. This conclusion is similar to that reached by a working group for the U.S. DHHS.

Respiratory Effects. Deposition of asbestos fibers in the lung can lead to substantial nonneoplastic fibrotic injury and may even cause death. This disease, termed asbestosis, results from a prolonged inflammatory response stimulated by the presence of the fibers in the lung. Alveolar macrophages, which normally phagocytize foreign bodies deposited in the lungs, seek to engulf the asbestos fibers and remove them. While short fibers may be cleared in this way, long fibers cannot be removed, and this results in an ongoing focal inflammatory response. With time, some fibers move from the lung to the interstitium where additional inflammatory events take place leading to the development of interstitial pulmonary fibrosis and a progressive loss of lung compliance and respiratory function.

Signs of lung fibrosis and increased mortality associated with asbestosis or nonmalignant respiratory disease have been observed in groups of workers with chronic cumulative exposures as low as 15–70 f-yr/mL for signs of lung fibrosis and 32–1,271 f-yr/mL for asbestosis-associated mortality. The mortality experience associated with asbestosis or nonmalignant respiratory disease in cohorts of exposed workers appears to provide the best available source for describing exposure-response relationships for the development of asbestos-related lung fibrosis. However, a major limitation with the resultant descriptions is that there is very limited information for responses at low levels of exposure experienced by modern workers in regulated nations (<0.1–0.2 f/mL) or at levels experienced in many nonoccupational exposure scenarios ($3x10^{-6}$–$6x10^{-3}$ f/mL). Uncertainty associated with this lack of information may be decreased with results from prospective cohort mortality studies of workers involved in asbestos-related occupations under currently regulated conditions or retrospective studies of workers who entered asbestos-related occupations after 1970 or 1980 when respective occupational limits of 5 and 2 f/mL were recommended in the United States.

Studies of two cohorts of workers exposed to chrysotile asbestos, one from a Carolina textile plant, and the other from Quebec mines and mills, appear to have received the most recent attention by the research and regulatory community because they represent quality studies that provide widely varying estimates of risk for the development of nonmalignant or malignant lung disease associated with the most common type of asbestos. The available data indicate that, at equivalent exposure levels, the risk is greater for textile workers than for miners or millers; these data have been used to develop statistical models that estimate low, but not negligible, risk (2/1,000) for asbestosis-related mortality with chronic exposure to

current occupational exposure limits of 0.1 f/mL. Several authors consider the mortality experience of the Carolina textile cohort to be atypical relative to other asbestos-exposed cohorts and, in the absence of a reliable explanation of this uniqueness, have cautioned against its use in quantitative health assessments for other exposure scenarios to asbestos fibers (see Section 3.2.1.2 for further discussion). Further extrapolation to lower levels of asbestos typically found in ambient air or in the indoor air of homes or public buildings suggests that asbestosis may not be of concern for most people in the general population without occupational exposure to asbestos.

Another tissue that may be affected in humans exposed to asbestos in air is the pleura. The most common effect is the formation of thickened fibrous areas called plaques, but diffuse thickening and fibrosis may also occur, as may areas of pleural effusions. An increased incidence of pleural plaques has been noted at relatively low cumulative exposures (approximately 0.12 f-yr/mL). Localized pleural plaques are not thought to be of significant health concern, although diffuse pleural thickening and circumscribed pleural plaques are associated with impairment of respiratory function. This may also be due to subclinical alveolitis or interstitial fibrosis not detected by routine chest radiograms. These plaques are normally very mild, but may be severe in a few cases probably associated with high exposures.

A few studies have also reported an increased incidence of laryngitis in workers exposed to asbestos. These data suggest that the upper airways may also be affected by asbestos exposure.

Immunological and Lymphoreticular Effects. Studies of workers suffering from asbestos-related diseases such as asbestosis or mesothelioma indicate that the cellular immune system in such patients can be depressed. This is an effect of particular interest and concern since impaired immune surveillance may contribute to the increased incidence of cancer in asbestos-exposed people. Moreover, variation in immune system functional capability might be an important determinant of why some people develop cancer or asbestosis while others, with approximately equal exposures, do not. However, it is very difficult to distinguish whether the alterations in immune function noted in such studies are the cause or the result of asbestos-induced disease. The frequency of impaired cellular immunity in exposed workers without clinically-apparent disease is generally low, although some studies have noted alterations in lymphocyte distribution and impairment of natural killer (NK) cells. This could mean that the immunological changes do not occur until the disease develops (i.e., the changes are the result of the disease). Alternatively, it could mean that workers with immune systems that are not impaired by asbestos do not get serious disease, while workers whose immune systems are injured by asbestos do tend to develop disease (i.e., effects on the immune system are the cause of the disease). Available data do not

allow a firm distinction between these alternatives at present, but the possible immunotoxic effects of asbestos are of clear concern. Results from animal studies provide supporting evidence of direct and indirect effects of asbestos on the immune system, although the specific roles of these effects in the etiology of asbestos-induced pulmonary diseases are not well understood and are under current investigation. For example, experiments with mice indicate that asbestos exposure decreases the number and cytotoxic activity of interstitial pulmonary NK cells and that genetically impaired cell-mediated immunity may be a predisposing factor in asbestos fibrosis.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

No MRLs were derived for inhalation exposure to asbestos for any duration. Results from epidemiological studies of cohorts of workers chronically exposed to airborne asbestos fiber concentrations ranging from about 5 to 20 f/mL provide convincing evidence of the development of asbestos-induced lung fibrosis, but a chronic MRL was not derived due to the large degree of uncertainty in extrapolating from the available data to levels of exposure that may be several orders of magnitude lower than current U.S. occupational exposure limits (0.1 f/mL). Data regarding the adverse health effects associated with acute- or intermediate-duration exposure to asbestos are lacking or are too limited to support the derivation of an MRL.

Oral MRLs

No MRLs were derived for oral exposure to asbestos for any duration. No studies were located regarding noncancer health effects in humans orally exposed to asbestos fibers, although asbestos cement pipes have been used in some community water systems for many years. Because ingested asbestos fibers are poorly absorbed, the tissue most highly exposed to ingested asbestos is the gastrointestinal tract epithelium. A few studies reported some histological or biochemical changes in gastrointestinal tract cells of rats chronically exposed to oral doses of asbestos, but, in an extensive series of lifetime dietary exposure studies in rats and Syrian hamsters, comprehensive microscopic evaluation of tissues and organs found no excess nonneoplastic lesions in the gastrointestinal epithelium or in other tissues or organs in animals exposed to daily doses as high as 500–830 mg/kg/day. The weight of evidence indicates that asbestos ingestion does not cause any significant noncarcinogenic effects in the gastrointestinal tract or other tissues, and supports the generally held perception that oral exposure to asbestos does not present a high priority public health concern for noncancer effects.

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 asbestos. 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 in Chapter 10 and Appendix C.

The profile also contains a health consultation on tremolite asbestos, a name that has been used in the popular press to refer to fibrous amphibole that occurs in vermiculite ore from Libby Montana (Appendix F).

It is important to recognize that asbestos is not a single substance, but is the generic name for a family of six related polysilicate fibrous minerals of which one (chrysotile) belongs to the serpentine family and five (actinolite, amosite, anthophyllite, crocidolite, and tremolite) belong to the amphibole family. These minerals differ from each other in physical and chemical properties, and each mineral can exist in a wide range of fiber sizes. These differences between fiber type and, more importantly, fiber size (length and diameter) are believed to be important determinants of the health risks posed by asbestos.

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 asbestos are indicated in Tables 3-1, 3-2, and 3-3 and Figures 3-1, 3-2 and 3-3. Because cancer effects could occur at lower exposure levels, Figures 3-1 and 3-4 show 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.

3.2.1 Inhalation Exposure

Units of Exposure. Consideration and comparison of quantitative data on asbestos inhalation studies are complicated by the fact that a number of different methods have been used to measure asbestos levels in air. Currently, the standard method for measuring asbestos concentrations in workplace air employs

phase contrast microscopy (PCM). A particle visible under PCM is counted as a fiber if it is 5 micrometers (μm) long and has a length/thickness ratio of 3:1. However, the method cannot detect fibers thinner than about 0.3 μm and cannot distinguish between asbestos fibers and other fibers (NIOSH 1987). Nevertheless, because currently available risk factors for asbestos are expressed in terms of PCM fibers, all air concentration data in this section are expressed in terms of PCM fibers/milliliter (f/mL) unless otherwise noted. It should be noted, however, that PCM analytical methods have improved substantially since early asbestos studies were performed, with an increase in numbers of fibers detected (Rickards 1994).

When data on airborne levels are available only in terms of mass/volume (e.g., mg/m^3), it is not possible to accurately convert these to units of PCM fibers/mL, because the ratio between mass and fiber number depends on fiber type and size distribution and because of the measuring technique employed. For the purposes of making rough calculations when a more accurate conversion factor is not available, it has been assumed that a concentration of 1 mg/m^3 in air is equal to 33 PCM f/mL (EPA 1986a).

Older occupational studies measured dust exposure in units of million particles per cubic foot (mppcf). This method did not distinguish fibrous from nonfibrous particles and used relatively low magnification, so only the largest particles and fibers were detectable. When a more accurate value is not available, it has been assumed that a concentration of 1 mppcf is equal to 3 PCM f/mL (BOHS 1968).

Overview of Health Effects. Studies in humans and animals indicate that inhalation of asbestos fibers may lead to fibrotic lung disease (asbestosis), pleural plaques and thickening, and cancer of the lung, the pleura, and the peritoneum. It may also increase the risk of cancer at other sites, but the evidence is not strong. Significant effects on other tissues have not been detected. A number of researchers have found that the occurrence of asbestosis and lung cancer correlates with cumulative exposure (that is, the product of concentration [PCM fibers/mL] multiplied by years of exposure). Therefore, human exposures are expressed below as PCM f-yr/mL. Animal data are provided in terms of exposure level (PCM f/mL) and duration, and the cumulative exposure can be found simply by calculating the product. However, due to differences in clearance rates and lifespan as well as other differences, cumulative doses in animals are not expected to be directly comparable to cumulative doses in humans. Studies that provide reliable dose-response information on the inhalation effects of asbestos in humans are summarized in Table 3-1 and Figure 3-1, and data in animals are summarized in Table 3-2 and Figure 3-2. The findings are discussed below.

TABLE 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form[b]
INTERMEDIATE EXPOSURE							
Systemic							
1	Human	6 mo aver. (occup)	Resp		25.1 M (increased incidence of parenchymal & pleural radiographic abnormalities, > 20 yr after first exposure)		Ehrlich et al. 1992 AM
2	Human	12.7 mo, mean (1 d to 17.3 yr, range) (occup)	Resp			54 M (increased risk for fatal nonmalignant respiratory disease)	Levin et al. 1998 AM
3	Human	8 mo (SD= 14.9) (occup)	Resp		53.2 M (minor parenchymal & pleural radiographic changes in about 10% & 30% of subjects, 20 years after exposure)		Shepherd et al. 1997 AM
Cancer							
4	Human	12.7 mo, mean (1 d to 17.3 yr, range) (occup)				54 M (CEL: increased SMRs for lung cancer & pleural mesothelioma)	Levin et al. 1998 AM

TABLE 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form[b]
CHRONIC EXPOSURE							
Systemic							
5	Human	7.9 yrs, median (occup)	Resp			32 M (slightly increased incidence of fatal nonmalignant or malignant respiratory disease with 20-40 year latency)	Albin et al. 1996 CH AM CR
6	Human	10+ yr (occup)	Resp	25 M	38 M (increased percentage (7%) of workers with early signs of respiratory impairment)		BOHS 1983 CH
7	Human	>20 yr, most cases	Resp			1271 M (autopsied cases of asbestosis with median lung fiber concentration, 41 f/ug tissue)	Case and Dufresne 1997 CH
8	Human	<10, 11-20, >20 yr (occup)	Resp	20 M	62 M (increased incidence of subjects with parenchymal & pleural abnormalities in chest x-ray)		Dave et al. 1997 NS
9	Human	1.1-2.7 yr (occup)	Resp	23 M		71 M (increased risk for fatal asbestosis)	de Klerk et al. 1991 CR
10	Human	10-30 yr (occup)	Resp	17		68 (increased SMRs for fatal pneumoconiosis)	Dement et al. 1994; Brown et al. 1994 CH
11	Human	>15 yr (occup)	Resp	2.6 M			Demers et al. 1998 NS

TABLE 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form[b]
12	Human	6-14 yr (occup)	Resp		30 M (increased prevalence of breathlessness)	616 M (increased prevalence of breathlessness and low FVC)	Enarson et al. 1988 CH
13	Human	>9 yr (occup)	Resp			100 M (increased prevalence of fatal asbestosis & non-malignant respiratory disease)	Finkelstein 1983 CH CR
14	Human	9.9 & 7.5 yr, M&F (occup)	Resp	4	22 M (increased score for pulmonary fibrosis in autopsy cases; 3.3 on a scale of 12)	73 M (increased score for pulmonary fibrosis autopsy cases; 7.9 on a scale of 12)	Green et al. 1997 CH
15	Human	3-51 yr (occup)	Resp			300 M (increased prevalence of fatal asbestosis)	Henderson and Enterline 1979 CH CR AM
16	Human	3.8 yr aver. (occup)	Resp			99 M (fatal asbestosis with latency of +20 yr)	Hughes et al. 1987 CH CR AM
17	Human	1->20yr (occup)	Resp		70 M (5% excess of subjects with lung parenchymal abnormalities)		Irwig et al. 1979 CR AM
18	Human	19.7-21.1 yr (2.3-51 yr)	Resp	5 M	20 M (increased risk for profusion of opacities & wall thickening in chest x-rays)		Jakobsson et al. 1995b CH CR AM
19	Human	5-31 yr (occup)	Resp	18	207 (significantly increased incidence of chronic laryngitis)		Kambic et al. 1989 AM CH CR
20	Human	(occup)	Resp	45		195 M (increased rate of fatal pneumoconiosis)	Liddell et al. 1997 CH

TABLE 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form[b]
21	Human	1-20 yr (occup)	Resp	15 M		45 M (increased rate of fatal nonmalignant respiratory disease)	McDonald et al. 1982 CH AM CR
22	Human	1-20 yr (occup)	Resp	90 M		180 M (increased rate of fatal nonmalignant respiratory disease)	McDonald et al. 1983 CH
23	Human	20+ yr (occup)	Resp			450 M (increased rate of fatal asbestosis)	Nicholson et al. 1979 CH
24	Human	>5 yr (occup)	Resp			170 M (increased rate of fatal nonmalignant respiratory disease)	Peto et al. 1985 CH CR
25	Human	NS (occup)	Resp	3.5		15 M (increased incidence of autopsy cases with slight to severe asbestosis, 16-30 yr after first exposure)	Sluis-Cremer 1991 CR AM
26	Human	15 yr aver. (occup)	Resp			20 M (cases of pulmonary fibrosis with functional impairment)	Wollmer et al. 1987 CH
	Cancer						
27	Human	> 3 mo (occup; full range not reported				26 M (CEL: mesothelioma)	Albin et al. 1990a CH CR AM
28	Human	7.9 yrs, median (occup)				32 M (CEL: mesothelioma)	Albin et al. 1996 CH AM CR

TABLE 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form[b]
29	Human	1-20 yr (occup)				400 M (CEL: lung cancer, mesothelioma)	Amandus and Wheeler 1987 TR AC
30	Human	40 yr residential (20-70 yr, range)				27 M (CEL: 4 M & 2F cases of mesothelioma in a 10-yr period among <200 villagers)	Coplu et al. 1996 TR
31	Human	1.0, 1.6 yr (occup)				55 M (CEL: lung cancer)	de Klerk et al. 1991; 1996 CR
32	Human	10-30 yr				5 M (CEL: increased SMRs for lung cancer)	Dement et al. 1994; Dement and Brown 1994; Brown et al. 1994 CH
33	Human	(occup)				180 M (CEL: lung cancer, gastrointestinal cancer, mesothelioma)	Enterline et al. 1987 CH CR AM
34	Human	>9 yr (occup)				44 M (CEL: lung cancer, mesothelioma)	Finkelstein 1983 CH CR
35	Human	1- >60 mo				14 M (CEL: mesothelioma)	Hansen et al. 1998 CR
36	Human	3-51 yr (occup)				180 M (CEL: lung cancer, mesothelioma)	Henderson and Enterline 1979 CH CR AM
37	Human	3.8 yr aver. (occup)				50 M (CEL: lung cancer, mesothelioma)	Hughes et al. 1987 CH CR AM

TABLE 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form[b]
38	Human	NS (occup)				0.7 B (CEL: significant association between pleural malignant mesothelioma & asbestos occupational exposure; case/control study)	Iwatsubo et al. 1998 NS
39	Human	1->20 yr (occup)				1050 M (CEL: lung cancer)	Liddell et al. 1997 CH
40	Human	1-20 yr (occup)				90 M (CEL: lung cancer)	McDonald et al. 1982 CH AM CR
41	Human	1-20 yr (occup)				90 M (CEL: lung cancer)	McDonald et al. 1983 CH
42	Human	>2 yr (occup)				10 (CEL: lung cancer, gastrointestinal cancer and mesothelioma)	Newhouse and Berry 1979 CR CH AM
43	Human	20+ yr (occup)				450 M (CEL: lung cancer, mesothelioma)	Nicholson et al. 1979 CH
44	Human	>5 yr (occup)				72 M (CEL: lung cancer, mesothelioma)	Peto et al. 1985 CH CR

TABLE 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies (continued)

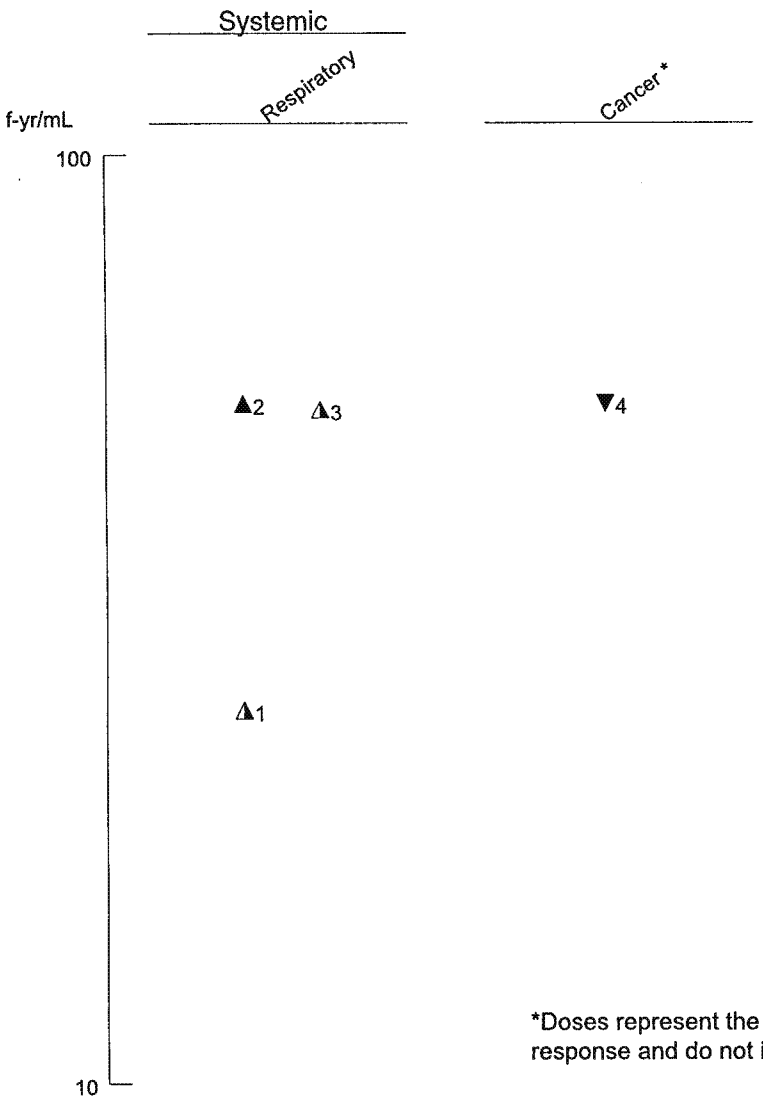
Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form[b]
45	Human	<2 - >10 yr (occup)				450 M (CEL: lung cancer, mesothelioma)	Weill et al. 1979 CH CR AM

[a]The number corresponds to entries in Figure 3-1.
[b]The first type of asbestos listed below represents that which predominated in the workplace air; other secondary types that may have been present follow.

AC = actinolite; AM = amosite; aver. = average; B = both (male/female); CEL = cancer effect level; CH = chrysotile; CR = crocidolite; d = day(s); F = female; f/ug = fibers per microgram; FVC = forced vital capacity; f-yr/mL = fiber-years per milliliter; LOAEL = lowest-observed-adverse-effect-level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect-level; NS = not specified; (occup) = occupational; Resp = respiratory; SD = standard deviation; SMR = standard mortality ratio; TR = tremolite; yr = year(s)

Figure 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human studies

Intermediate (15-364 days)

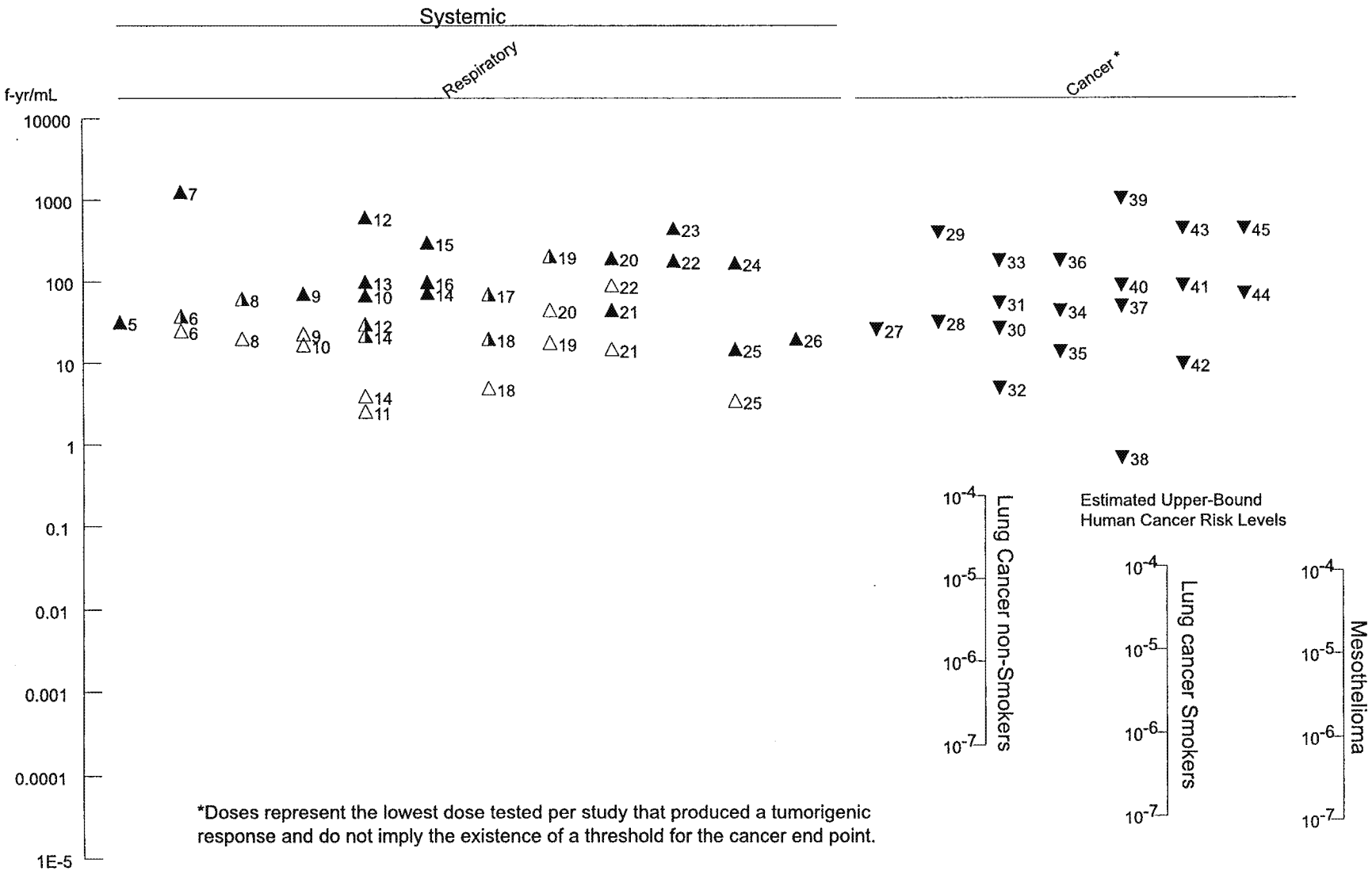


*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

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				

Figure 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human studies (*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 end point.

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				

TABLE 3-2. Levels of Significant Exposure to Asbestos - Inhalation - Animal Studies

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (PCM f/mL)	LOAEL Less serious (PCM f/mL)	LOAEL Serious (PCM f/mL)	Reference/ chemical form
ACUTE EXPOSURE							
Systemic							
1	Mouse B10.D2/nSn	5 hr	Resp			132 M (fibrosis)	McGavran et al. 1989 CH
INTERMEDIATE EXPOSURE							
Systemic							
2	Rat PVG	15 wk 5 d/wk 7 hr/d	Resp			330 M (diffuse fibrosis)	Donaldson et al. 1988a CH
CHRONIC EXPOSURE							
Systemic							
3	Rat Wistar	1 yr 1-5 d/wk 7 hr/d	Resp			70 M (fibrosis)	Davis et al. 1980a CH
4	Rat Wistar	1 yr 1-5 d/wk 7 hr/d	Resp			330 M (fibrosis)	Davis et al. 1980a AM
5	Rat NS	12 mo	Resp			330 (fibrosis)	Davis et al. 1980b AM CH
6	Rat Wistar	12 mo 5 d/wk 7 hr/d	Resp			1600 M (fibrosis)	Davis et al. 1985 TR
7	Rat Wistar	12 mo 5 d/wk 7 hr/d	Resp			2060 M (fibrosis)	Davis et al. 1986a AM-L

TABLE 3-2. Levels of Significant Exposure to Asbestos - Inhalation - Animal Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (PCM f/mL)	LOAEL Less serious (PCM f/mL)	LOAEL Serious (PCM f/mL)	Reference/ chemical form
8	Rat CD	2 yr 4 d/wk 4 hr/d	Resp			54 (fibrosis)	Reeves et al. 1974 CH
9	Rat CD	2 yr 4 d/wk 4 hr/d	Resp			1105 (fibrosis)	Reeves et al. 1974 CR
10	Rat NS	2 yr 4 d/wk 4 hr/d	Resp			860 (fibrosis)	Reeves et al. 1974 AM
11	Rat Wistar	24 mo 5 d/wk 7 hr/d	Resp			350 (fibrosis)	Wagner et al. 1974 AM AN CR CH
12	Rat Wistar	12 mo 5 d/wk 7.5 hr/d	Resp			430 (fibrosis)	Wagner et al. 1980a CH
	Cancer						
13	Monkey Baboon	4 yr 5 d/wk 6 hr/d				1110 M (CEL: mesothelioma)	Goldstein and Coetzee 1990 AM
14	Monkey Baboon	4 yr 5 d/wk 6 hr/d				1130 (CEL: mesothelioma)	Goldstein and Coetzee 1990 CH CR
15	Monkey Baboon	6 hr/d 5 d/wk up to 898 d				1100 M (CEL: pleural and peritoneal mesothelioma)	Webster et al. 1993 AM
16	Rat Wistar	1 yr 5 d/wk 7 hr/d				1170 (CEL: lung adenoma, adenocarcinoma, and mesothelioma)	Davis and Jones 1988 CH-S

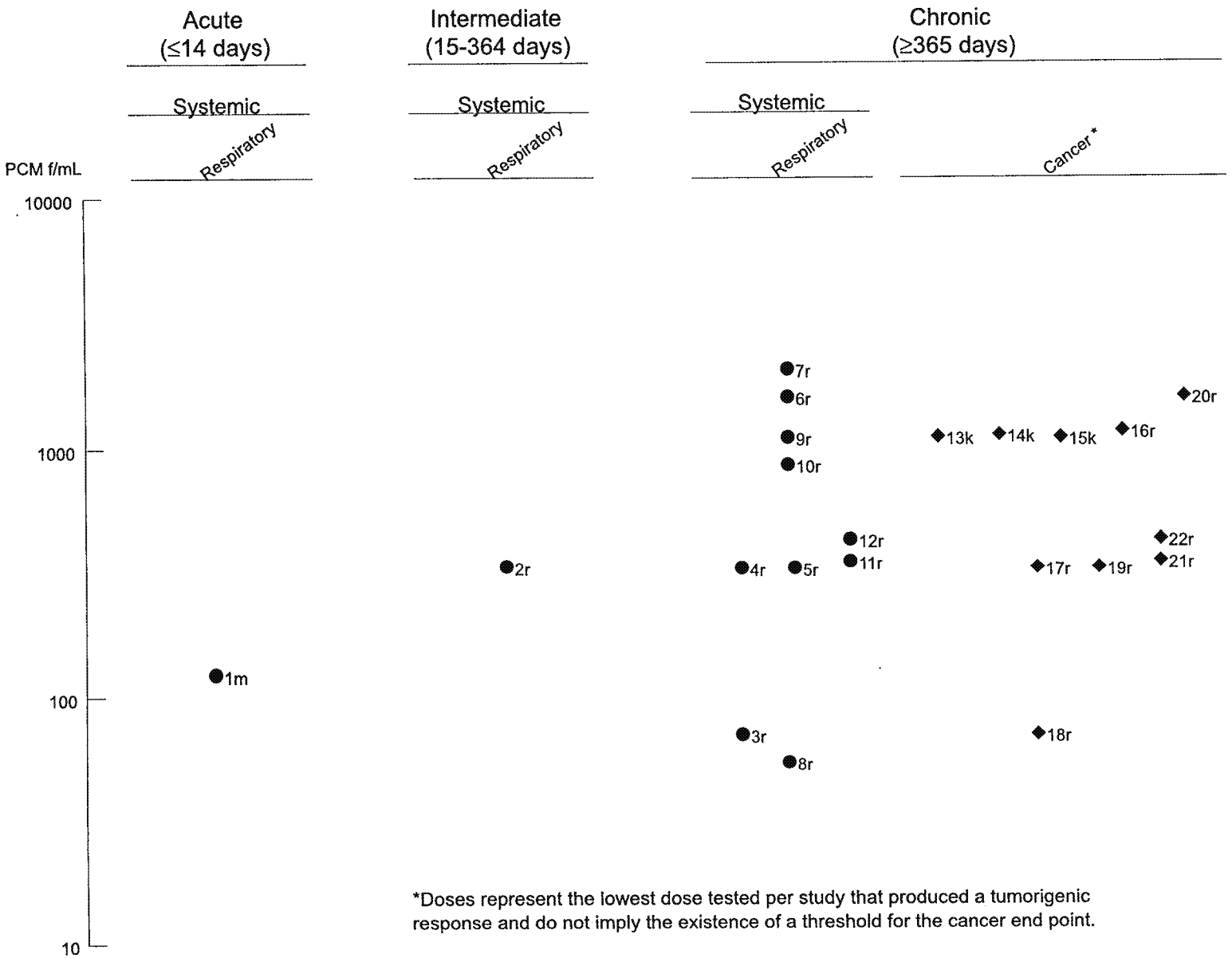
TABLE 3-2. Levels of Significant Exposure to Asbestos - Inhalation - Animal Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (PCM f/mL)	LOAEL Less serious (PCM f/mL)	LOAEL Serious (PCM f/mL)	Reference/ chemical form
17	Rat Wistar	1 yr 1-5 d/wk 7 hr/d				330 M (CEL: lung carcinomas, adenocarcinomas)	Davis et al. 1980a AM
18	Rat Wistar	1 yr 1-5 d/wk 7 hr/d				70 M (CEL: lung adenomas, adenocarcinomas, and squamous carcinomas)	Davis et al. 1980a CH
19	Rat NS	12 mo				330 (CEL: lung adenomas and carcinomas)	Davis et al. 1980b AM CH
20	Rat Wistar	12 mo 5 d/wk 7 hr/d				1600 M (CEL: lung adenoma, adenocarcinoma, squamous carcinoma, and mesothelioma)	Davis et al. 1985 TR
21	Rat Wistar	24 mo 5 d/wk 7 hr/d				350 (CEL: lung adenoma, adenocarcinoma, squamous carcinoma, and mesothelioma)	Wagner et al. 1974 AM AN CR CH
22	Rat Wistar	12 mo 5 d/wk 7.5 hr/d				430 (CEL: lung adenoma, adenocarcinoma, squamous carcinoma, and mesothelioma)	Wagner et al. 1980a CH

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

AM = amosite; AN = anthophyllite; CEL = cancer effect level; CH = chrysotile; CR = crocidolite; d = day(s); PCM f/mL = phase contrast microscopy fibers per milliliter; hr = hour(s); L = long; LOAEL = lowest-observed-adverse-effect-level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect-level; Resp = respiratory; S = short; TR = tremolite; wk = weeks(s); yr = year(s)

Figure 3-2. Levels of Significant Exposure to Asbestos - Inhalation - Animal studies



*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 end point.

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				

3.2.1.1 Death

No studies were located in which acute- or intermediate-duration inhalation exposure to asbestos led to lethality in humans or animals. Inhalation exposure to asbestos can lead to death or a shortened lifespan from asbestosis or cancer, as discussed in Sections 3.2.1.2 and 3.2.1.8, respectively.

3.2.1.2 Systemic Effects

No studies were located regarding significant hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, or metabolic effects in humans or animals after inhalation exposure to asbestos. Systemic effects observed after inhalation exposure and discussed below include respiratory, cardiovascular, and gastrointestinal effects. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects are summarized in Tables 3-1 and 3-2, and plotted in Figures 3-1 and 3-2.

Respiratory Effects. Numerous studies in humans have established that inhalation exposure to asbestos fibers can lead to a characteristic pneumoconiosis termed asbestosis. Published definitions of asbestosis generally concur that it is a diffuse interstitial fibrosis of the lungs caused by the inhalation of asbestos fibers (American Thoracic Society 1986; International Expert Meeting on Asbestos 1997; Mossman and Churg 1998). Persons with fully developed asbestosis have shortness of breath (dyspnea), often accompanied by rales or cough (Churg 1986a; Enarson et al. 1988; Finkelstein 1986), and display deficits in pulmonary function variables such as forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) (Glencross et al. 1997; Kilburn and Warshaw 1994; Miller et al. 1994; Rom 1992; Schwartz et al. 1994; Shepherd et al. 1997). In severe cases, impairment of respiratory function may ultimately result in death, and asbestosis has been associated with excess mortality in a number of groups of asbestos workers (Armstrong et al. 1988; de Klerk et al. 1991; McDonald et al. 1983; Peto et al. 1985; Selikoff et al. 1979).

Available evidence indicates that all asbestos fiber types are fibrogenic, although there may be some differences in potency among fiber types (Bignon and Jaurand 1983; Churg 1993; Davis 1972; EPA 1986a; Kamp and Weitzman 1997; McDonald et al. 1999). Most studies in humans have involved exposure to predominantly chrysotile, the most widely used type of asbestos (Albin et al. 1996; Berry et al. 1979; BOHS 1983; Case and Dufresne 1997; Cullen and Baloyi 1991; Dement et al. 1983; McDonald et al. 1983, 1984, 1999; Nicholson et al. 1979), but asbestosis has also been noted in populations exposed

mainly to amosite (Seidman et al. 1979), crocidolite (Armstrong et al. 1988; de Klerk et al. 1991, 1996; Luo et al. 1992; Sluis-Cremer 1991; Wignall and Fox 1982), tremolite (McDonald et al. 1986a), and anthophyllite (Meurman et al. 1974; Sluis-Cremer 1991). A number of animal studies have indicated that long fibers (e.g., 5 μm or more) have a higher fibrogenic activity, while short fibers have a lower fibrogenic activity (Adamson and Bowden 1987a, 1987b; Davis and Jones 1988; Davis et al. 1986a; Platek et al. 1985). This relationship may be associated with the inability of macrophages to engulf and remove fibers that are significantly larger than themselves (Bignon and Jaurand 1983).

Results from human studies, however, suggest that short asbestos fibers may also play a role in pulmonary fibrosis. In autopsy studies of groups of chrysotile miners and millers (Churg et al. 1989a) and amosite-exposed shipyard and insulation workers (Churg et al. 1990) with asbestosis, histologically-graded fibrosis was positively correlated with mean amphibole fiber concentration in lung tissue, but was negatively correlated with mean amphibole fiber length. Churg et al. (1989a, 1990) noted that the inverse relationship between degree of fibrosis and amphibole fiber length was suggestive that short fibers may be more important in the genesis of pulmonary fibrosis than was commonly believed based on the findings from animal studies showing a positive relationship between fiber length and fibrogenic activity. Case (1994) noted, however, that men with asbestosis in the group of autopsied chrysotile miners and millers showed lung concentrations of tremolite fibers longer than 8 μm that were higher than concentrations in men without asbestosis, and that six of seven miners/millers having any chrysotile or tremolite fibers longer than 20 μm had asbestosis. The latter observations suggest the importance of longer fibers. Case (1994) hypothesized that the greater concentrations of long tremolite fibers in these cases of asbestosis might also produce increased levels of shorter fibres (at autopsy) due to fiber breakage with time of retention in the lung. Case (1994) suggested that the counting method employed by Churg et al. (1989a, 1990) (that included short fibers down to the limits of detection) may more accurately quantify short fiber fragments, and that the fiber size class that is most responsible for fibrosis is unclear. Case (1994) further hypothesized that long fibers may initiate events, and that shorter fiber fragments, once they are present, may have increased effects on macrophage activity and subsequent fibrosis. Surface area has been proposed to play a role in amphibole fiber toxicity (Lippmann 1988), and, since shorter, thinner fibers have proportionally greater surface areas than longer, thicker fibers, may be involved in the inverse relationship observed by Churg et al. (1989a, 1990).

As shown in Table 3-1 and Figure 3-1, cumulative exposure levels that have been associated with radiographic, histologic, spirometric, or clinical signs of lung fibrosis in groups of chronically exposed workers include 38 f-yr/mL in British asbestos textile factory workers (BOHS 1983), 62 f-yr/mL in

Indian asbestos cement workers (Dave et al. 1997), 30 f-yr/mL in British Columbian chrysotile miners and millers (Enarson et al. 1988), 22 f-yr/mL in autopsied cases of deceased South Carolina chrysotile textile factory workers (Green et al. 1997), 10–30 f-yr/mL (midpoint=20 f-yr/mL) in Swedish asbestos cement workers (Jakobsson et al. 1995b; Wollmer et al. 1987), 70 f-yr/mL in South African crocidolite and amosite miners (Irwig et al. 1979), and 15 f-yr/mL in autopsied cases of deceased crocidolite and amosite miners and millers (Sluis-Cremer 1991).

Table 3-1 and Figure 3-1 also show that significantly increased mortality rates associated with asbestosis or other nonmalignant respiratory disease have been reported in groups of exposed workers with cumulative exposure estimates ranging from 32 to 1,271 f-yr/mL (Albin et al. 1996; Brown et al. 1994; Case and Dufresne 1997; de Klerk et al. 1991; Dement et al. 1994; Finkelstein 1983; Henderson and Enterline 1979; Hughes et al. 1987; Liddell et al. 1997; Nicholson et al. 1979; Peto et al. 1985; Sluis-Cremer 1991).

Whereas these studies involved chronic exposure to asbestos, increased incidences of radiographic abnormalities indicative of pulmonary fibrosis have been found in studies of New Jersey and Texas workers involved in the manufacture of amosite-insulated materials who were predominantly exposed for intermediate durations (medians of 6–12 months) at fiber concentrations that were as high as 5–100 f/mL, many fold higher than the current U.S. permissible exposure limit for workplace air, 0.1 f/mL (Ehrlich et al. 1992; Levin et al. 1998; Shepherd et al. 1997). These studies add to the evidence that asbestos-induced respiratory disease can take a long time (10–20 years) to develop and, in some individuals, continues to progress long after exposure has ceased (Finkelstein 1986; Mossman and Churg 1998; Wagner et al. 1974). Churg (1993) noted that early cases of asbestosis, when workplace air fiber concentrations were very high, had shorter latent development periods (5–6 years), compared with estimates of 10–20 years latency from studies of workers more recently exposed to lower fiber concentrations. This comparison suggests that there is an inverse relationship between intensity of exposure and time of disease development.

Several of the studies of occupationally exposed workers in Table 3-1 and Figure 3-1 provide general descriptions of exposure-response relationships for asbestos-induced nonmalignant respiratory effects, showing increasing severity or incidence of disease with increasing cumulative exposure and providing some indications of no-effect levels ranging from 2.6 to 90 f-yr/mL for signs of asbestosis or increased mortality associated with asbestosis (BOHS 1983; Dave et al. 1997; de Klerk et al. 1991; Dement et al. 1994; Demers et al. 1998; Green et al. 1997; Jakobsson et al. 1995b; Liddell et al. 1997; McDonald et al.

1983; Sluis-Cremer 1991; Wollmer et al. 1987). There are several complexities, however, in defining exposure-response relationships for asbestos-induced pulmonary fibrosis that make it difficult to derive reliable risk estimates for low-level exposure from the available studies. The complexities include uncertainties in exposure assessments for the studied workers, the variability among estimates of risk from various studies, inconsistent adjustment across studies for the possible confounding effect of tobacco smoking on development of pulmonary fibrosis, the possibility of differences in potency among different types of asbestos, the possibility of differential misdiagnosis and/or different end points in different studies, the likelihood of disease progression after exposure ceases, and the likelihood that mortality studies underestimate occurrence of asbestosis since asbestosis does not always cause death.

Another difficulty arises from the use of cumulative exposure (the product of exposure duration x intensity) as a surrogate exposure metric in the available studies. Finkelstein (1995) noted that the use of cumulative exposure requires the assumption that duration and intensity are equally important in determining the effective dose. Finkelstein further noted that if exposure estimates are inaccurate or inconsistently measured (which can be the case for many retrospective epidemiology studies), a finding of a statistically significant association between cumulative exposure and a health outcome can mislead one in having confidence in an apparent exposure-response relationship that is principally influenced by duration of exposure and not by exposure intensity.

In a recent review of the epidemiological evidence for asbestosis exposure-response relationships, the World Health Organization Task Group on Environmental Health Criteria for Chrysotile Asbestos (WHO 1998) concluded that "asbestotic changes are common following prolonged exposures of 5 to 20 f/mL" (these correspond to cumulative exposures of 50–200 f-yr/mL for a 10-year exposure) and that "the risk at lower exposure levels is not known." This group further concluded that although there may be subclinical respiratory changes induced by chrysotile at current levels of occupational exposure, "they are unlikely to progress to the point of clinical manifestation."

Presenting an alternative viewpoint, Stayner et al. (1997) statistically analyzed updated asbestosis-related mortality data for a cohort of South Carolina asbestos textile workers (the same data reported by Brown et al. 1994 and Dement et al. 1994) and predicted, by extrapolation, an excess lifetime risk of 2/1,000 for asbestosis mortality in white men exposed for 45 years at the Occupational Safety and Health Administration (OSHA) permissible exposure level for all forms of asbestos of 0.1 f/mL (4.5 f-yr/mL). Stayner et al. (1997) noted five major areas of uncertainty associated with this estimate including the extrapolation from relatively high exposure intensity to low intensity (average for the cohort was about

6 f/mL), the questionable accuracy of the exposure estimates for the cohort members, the absence of information on individual smoking habits in this cohort, the likelihood of disease misclassification, and the selection of an appropriate statistical model.

Several authors consider the mortality experience of the Carolina textile cohort to be atypical relative to other asbestos-exposed cohorts and, in the absence of a reliable explanation of this uniqueness, have cautioned against its use in quantitative health assessments for other exposure scenarios to asbestos fibers (Case et al. 2000; Hodgson and Darnton 2000). Estimates of lung cancer risk based on the South Carolina cohort are notably higher than estimates derived from other occupational cohorts exposed to predominately chrysotile asbestos (e.g., the Quebec chrysotile miner and miller cohort) or to mixed types of asbestos in other textile operations (Dement et al. 1994; Hodgson and Darnton 2000; Liddell et al. 1997, 1998; McDonald 1998b; Stayner et al. 1997). Stayner et al. (1997) acknowledged this difference, but concluded that "it would be prudent" to use estimates of risk from both cohorts to predict a range of potential risks for current occupational scenarios. The reasons for the difference are unknown, but may apply to both asbestosis and lung cancer. Proposed explanations include the possibility of uniform underestimation of exposure in the Carolina cohort, the possibility of exposure to longer and thinner fibers in the Carolina textile mill, and the possibility that mineral oil that was used to spray the raw fiber in Carolina (as a dust suppression measure) may have contributed to the increased incidence of lung cancer, but evidence for or against any of these possibilities is not strong (Case et al. 2000; Dement et al. 1994; McDonald 1998b; Stayner et al. 1997). For example, comparison of lung fiber concentrations in autopsied individuals from the Carolina and Quebec cohorts provide confirmatory information that the Quebec cohort was likely exposed to higher air concentrations of asbestos fibers of all length categories (including those >18 μm in length) than the Carolina cohort, although when all fibers were considered together, the mean fiber length of detected fibers in the Carolina group was greater than that of the Quebec cohort (Case et al. 2000; Sebastien et al. 1989). In an internal case-control analysis of the Carolina textile mortality experience, odds ratios for lung cancer were not significantly different among groups of subjects with different probable levels of oil exposure (Dement et al. 1994), but others have questioned the ability to correctly assign subjects in the cohort to oil exposure categories (Hodgson and Darnton 2000; McDonald 1998b).

A chronic inhalation MRL for asbestos-induced nonmalignant respiratory disease has not been derived (as reflected by a lack of MRL designation in Table 3-1 and Figure 3-1), because of the large degree of uncertainty in extrapolating to low levels of exposure from the available epidemiological data for workers with high levels of exposure (see also Chapter 2). The use of the data for the South Carolina textile

workers, the Quebec chrysotile miners and millers, or other occupational cohorts to estimate risk for development of fatal asbestosis with chronic exposure to asbestos at fiber concentration ranges likely to be encountered in ambient, nonoccupational outdoor or indoor air (about $3x10^{-6}$ to $6x10^{-3}$ PCM f/mL, see Chapter 6 for more information) would require additional extrapolation, and be even more uncertain, than the risk estimate for exposure to 0.1 f/mL from the Stayner et al. (1997) analysis.

Inhalation of asbestos fibers can lead not only to injury to the lung parenchyma, but also to a number of changes in the pleura (Boutin et al. 1989; Churg 1986a; Ehrlich et al. 1992; Jones et al. 1988b). The most common lesions are pleural plaques. These are generally oval areas of acellular collagen deposits, usually located on the inferior and posterior surfaces of the pleura. Diffuse thickening and fibrosis of the pleura may also occur, as may pleural effusions. The incidence of pleural abnormalities (usually detected by x-ray examination) is often quite high (10–60%) in people employed in asbestos-related occupations for subchronic (Ehrlich et al. 1992) and chronic durations (Amandus et al. 1987; Anton-Culver et al. 1989; Baker et al. 1985; Bresnitz et al. 1993; Gibbs 1979; Hsiao et al. 1993; Jarvholm et al. 1986; McDonald et al. 1986b; Ohlson et al. 1985; Ren et al. 1991; Viallat and Boutin 1980). Pleural abnormalities are also common in household contacts and family members of asbestos workers (where exposure is presumably due to asbestos carried home on the work clothes) (Anderson et al. 1976, 1979), in people living in areas where tremolite asbestos-containing whitewash materials have been used (Baris et al. 1988b; Constantopoulos et al. 1985, 1987b; Çöplü et al. 1996; Dumortier et al. 1998; Metintas et al. 1999; Sakellariou et al. 1996; Yazicioglu et al. 1980), and in people who live in regions with high asbestos levels in the soil (Boutin et al. 1989; Churg and DePaoli 1988; Jarvholm et al. 1986; Luo et al. 1992; Rey et al. 1993). An elevated incidence of pleural abnormalities (3.7%) was noted in long-time (70-year) residents of an area with elevated levels of asbestos in soil (Boutin et al. 1989). Cumulative exposure to asbestos in these residents was estimated to be 0.12 f-yr/mL. The incidence of pleural abnormalities (specifically, pleural thickening) in members of the general population of the United States was found to be 2.3% in males and 0.2% in females, most of which is probably due to occupational exposure to asbestos (Rogan et al. 1987). The health significance of asbestos-induced pleural abnormalities is not precisely defined; some researchers consider pleural plaques to be essentially benign (Jones et al. 1988b; Ohlson et al. 1984, 1985), whereas others have noted isolated pleural plaques to be associated with decreased ventilatory capacity (Bourbeau et al. 1990). In addition, some investigators (Edelman 1988c; Hillerdal 1994; Hillerdal and Henderson 1997; Nurminen and Tossavainen 1994) have suggested that pleural plaques are predictors of increased risk for lung cancer, whereas another analysis (Weiss 1993) have suggested that they are not. Diffuse pleural thickening can lead to decreased ventilatory capacity, probably because of the restrictive effect of pleural fibrosis (Baker et al. 1985; Britton 1982; Churg

1986a; Jarvholm and Larsson 1988; Jones et al. 1988b; McGavin and Sheers 1984; Miller et al. 1992; Rom and Travis 1992; Schwartz et al. 1990). In some cases, pulmonary impairment from pleural thickening can be very severe, even causing death (Miller et al. 1983).

Asbestos exposure may also produce adverse effects in the upper airways. A statistically significant higher incidence of laryngitis was noted in workers with chronic cumulative exposures >27 f-yr/mL compared with controls and exposed workers with cumulative exposures <18 f-yr/mL (Kambic et al. 1989; Parnes 1990). Although this effect has not been reported in a large number of studies, it is consistent with the idea of asbestos acting as an irritant on the laryngeal mucosa.

Fibrosis has been produced in animals by inhalation or by intratracheal exposure to chrysotile (Chang et al. 1988; Davis et al. 1980a, 1980b; Donaldson et al. 1988a; Green et al. 1986; Hesterberg et al. 1995, 1996, 1997; Mast et al. 1994, 1995; McGavran et al. 1989; Wagner et al. 1980a), amosite (Davis et al. 1986a; Reeves et al. 1971, 1974; Webster et al. 1993), anthophyllite (Wagner et al. 1974), crocidolite (Reeves et al. 1971, 1974; Wagner et al. 1974), and tremolite (Davis et al. 1985; Green et al. 1986; Sahu et al. 1975). There are some data from animal studies to suggest that crocidolite causes more severe inflammatory disease than chrysotile and is retained longer within the lungs (Berube et al. 1996; McConnell et al. 1994). As shown in Table 3-2 and Figure 3-2, fibrosis has been noted in rodents after exposure to 132 f/mL for 5 hours (McGavran et al. 1989), exposure to 330 f/mL for 7 hours/day, 5 days/week for 15 weeks (Donaldson et al. 1988a), and chronic exposure to 54–2,060 f/mL (Davis et al. 1980a, 1980b, 1985, 1986a; Reeves et al. 1974; Wagner et al. 1974, 1980a). In animals, histological signs of tissue injury can be detected at the site of deposited fibers within a few days, although in humans, measurable abnormalities of lung function do not usually appear for a number of years (Dement et al. 1983; Hughes et al. 1987; Kagan 1988; Schwartz et al. 1993).

Studies in animals indicate that asbestosis stems from the inflammatory response triggered in the lung by the deposition of asbestos fibers (Davis 1970; Quinlan et al. 1995), and that the inflammatory response to asbestos is enhanced by multiple exposures to asbestos fibers (Coin et al. 1996). Fibers deposited in the ciliated portion of the airway are removed by mucociliary transport (see Section 3.4.4) and do not appear to injure the lung. However, fibers deposited in the terminal bronchioles and alveoli are not cleared as rapidly, and these can stimulate an influx of macrophages (Chang et al. 1988), which then release a variety of inflammatory mediators (chemoattractants, lysosomal enzymes, activated oxygen species, growth factors, etc.) (Davis 1972; Hansen and Mossman 1987; Kagan 1988; Miller et al. 1978; Schwartz et al. 1993). This is thought to be responsible for the gradual loss of some epithelial cells and the

deposition of collagen by fibroblasts (Davis and Jones 1988; Davis et al. 1986c). With continued duration of exposure to asbestos fibers, increasing amounts of fibers are found in the lung interstitium and are associated with progressive interstitial fibrotic reactions (Pinkerton et al. 1984).

One of the many growth factors found in fibrotic lungs is tumor necrosis factor α (TNF-α). TNF-α is a powerful inducer of epithelial and mesenchymal cell proliferation which has been suggested as a central mediator of fibrotic lung disease. A recent study has demonstrated that genetically-altered mice without TNF-α receptor fail to develop fibro-proliferative lesions in response to asbestos exposure (Liu et al. 1998).

Cardiovascular Effects. No studies were located regarding a direct effect upon the cardiovascular system in humans after inhalation exposure to asbestos. However, increased ($p<0.01$) mortality from cardiovascular disease in workers exposed to asbestos has been reported (Doll 1955). Fibrosis of the lung can lead to increased resistance to blood flow through the pulmonary capillary bed, leading in turn to pulmonary hypertension and compensatory hypertrophy of the right heart (Selikoff and Lee 1978). This condition is known as cor pulmonale. Cor pulmonale may be detected by standard clinical and radiological tests of cardiac function and by changes in the electrocardiogram (Kokkola and Huuskonen 1979), although this is not a very sensitive test (Selikoff and Lee 1978). Cor pulmonale is usually associated with severe cases of asbestosis (Lemen et al. 1980), although pulmonary hypertension has been reported in some cases prior to measurable decreases in respiratory function (Tomasini and Chiappino 1981). Limited data from case reports suggest that constrictive pericarditis due to fibrous thickening may result from asbestos exposure (Davies et al. 1991).

No studies were located regarding cardiovascular effects in animals after inhalation exposure to asbestos.

Gastrointestinal Effects. The majority of asbestos fibers that are deposited in the respiratory tract during inhalation exposure are transported by mucociliary action to the pharynx, where they are swallowed (see Section 3.4). Consequently, the gastrointestinal epithelium is also directly exposed to fibers. While there is some evidence that inhalation exposure to asbestos may increase the risk of gastrointestinal cancer in humans (see Section 3.2.1.8), no information was located to indicate that any nonneoplastic effects occur in the gastrointestinal system after inhalation exposure.

No studies were located regarding gastrointestinal effects in animals after inhalation exposure to asbestos.

3.2.1.3 Immunological and Lymphoreticular Effects

A number of studies have investigated the status of the immune system in humans who have been exposed to asbestos. Although there is some variability, most studies indicate that cell-mediated immunity (measured by tests of dermal sensitization *in vivo* and lymphocyte responsiveness and function *in vitro*) is depressed in workers who have radiological evidence of asbestosis (deShazo et al. 1988; Gaumer et al. 1981; Kagan et al. 1977; Lange et al. 1986). For example, natural killer (NK) cells (unique lymphocytes thought to be a first line of defense against cancer cells) isolated from peripheral blood of patients with asbestosis had impaired cytotoxic potency (Kubota et al. 1985; Tsang et al. 1988). Additionally, decreased NK cell activity and increased NK cell number were noted in the peripheral blood of retired asbestos cement workers (Froom et al. 2000). Alterations in lymphocyte (Sprince et al. 1991, 1992) and leukocyte (Hurbankova and Kaiglova 1993) distribution have been noted in asbestos-exposed workers. Increased numbers of lymphocytes and $CD4^+$ cells were reported in men with occupational exposure to asbestos (Rom and Travis 1992), although numbers of total circulating lymphocytes were similar in asbestos workers compared to controls in another study (Al Jarad et al. 1992). Mediastinal lymph node enlargement has been reported in asbestosis patients (Sampson and Hansell 1992). Increased levels of IgA and IgG have been reported in asbestos-exposed individuals (Hurbankova and Kaiglova 1993; Nigam et al. 1993), and concentrations of autoantibodies (rheumatoid factor, antinuclear antibodies) tend to be abnormally high in asbestos-exposed workers (Anton-Culver et al. 1988; Pernis et al. 1965; Warwick et al. 1973; Zerva et al. 1989). In some cases, increased autoantibodies can lead to rheumatoid arthritis (Caplan's Syndrome), although this is more common in coal miners and workers with other pneumoconioses than in workers with asbestosis (Constantinidis 1977; Greaves 1979). Immunological abnormalities are usually mild or absent in asbestos-exposed workers who have not developed clinical signs of asbestosis (deShazo et al. 1988; Kagan 1988; Selikoff and Lee 1978; Warwick et al. 1973). Although the biological significance of these immunological changes is difficult to judge, they are of special concern because depressed immune function might be a factor in the etiology of asbestos-induced cancer (Lew et al. 1986). Exposures to asbestos associated with immunological effects generally have not been quantified.

Results from animal studies provide supporting evidence of direct and indirect effects of asbestos on the immune system, although the specific roles of these effects in the etiology of asbestos-induced pulmonary diseases are not well understood and are under current investigation. In support of observations of suppressed activity of peripheral natural killer cells in patients with asbestosis, the number and cytotoxic activity of interstitial pulmonary natural killer cells were found to be decreased in mice exposed to

inhaled chrysotile fibers (13.3 mg/m^3) 3 hours/day for 3 days compared with nonexposed controls (Rosenthal et al. 1998). In support of asbestos-induced hyperactivity of humoral immunity, humans occupationally exposed to crystalline asbestos display elevated serum γ-globulins (Lange et al. 1974). Results from experiments with genetically immunodeficient mice support the hypotheses that T lymphocytes may play a protective role against asbestos-induced lung inflammation and subsequent fibrotic responses, and that impaired cell-mediated immunity may be a predisposing factor in asbestos fibrosis. In these experiments, immunodeficient mice showed a larger increase in cell numbers in pulmonary lavage fluid (predominantly due to increase in neutrophils) and increased severity of pulmonary lesions in response to inhaled asbestos compared with immunologically normal mice of the same background or immunologically deficient mice that were "reconstituted" with lymphocytes (Corsini et al. 1994).

No studies were located regarding the following effects in humans or animals after inhalation exposure to asbestos:

3.2.1.4 Neurological Effects

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

A voluminous body of evidence establishes that inhalation exposure to asbestos increases the risk of lung cancer and mesothelioma in humans and animals. Some evidence suggests that inhalation exposure to asbestos increases the risk of cancer at other sites as well (especially the gastrointestinal tract). Each of these carcinogenic effects are discussed separately below.

Lung Cancer. Evidence for the role of asbestos in human lung cancer is derived primarily from studies of the cause of death of occupationally-exposed workers. For example, the causes of death in a very large cohort of insulation workers (17,800 men) in the United States and Canada have been studied (Selikoff et al. 1979). Between 1967 and 1976, there were 2,271 deaths in this group, of which 486 were attributable to lung cancer. This is 4.6 times the number of lung cancer deaths that would have been expected in this group based on the lung cancer rates in the average male population of the United States. Similar findings have been reported in a very large number of analogous studies under a wide variety of occupational circumstances. In a review, a statistically significant ($p<0.05$) increase in lung cancer death rates had been reported in 32 of 41 recent studies (EPA 1986a). In a recent meta-analysis of 69 asbestos-

exposed occupational cohorts reporting on cancer morbidity and mortality, Goodman et al. (1999) calculated a lung cancer meta-standard mortality ratio (SMR) of 1.63 (95% confidence interval [CI]=1.58–1.69); the highest meta-SMR (1.92, CI=95%=1.76–2.09) was among asbestos products manufacturing workers. Lung cancer has also been reported in household contacts and family members of asbestos workers, where exposure is presumably due to asbestos carried home on the work clothes (Magnani et al. 1993).

There is little doubt that all types of asbestos can cause lung cancer. For example, statistically significant increases in lung cancer mortality have been reported in workers exposed primarily to chrysotile (Case and Dufresne 1997; Dement et al. 1983, 1994; Huilan and Zhiming 1993; Liddell et al. 1997, 1998; McDonald et al. 1980, 1983, 1984, 1993, 1997; Nicholson et al. 1979), amosite (Seidman et al. 1979), crocidolite (Armstrong et al. 1988; de Klerk et al. 1989, 1991, 1996; Sluis-Cremer 1991; Wignall and Fox 1982), anthophyllite (Meurman et al. 1974, 1994), and tremolite (Amandus and Wheeler 1987; Kleinfeld et al. 1974; McDonald et al. 1986a), or to multiple fiber types (Albin et al. 1996; Enterline et al. 1987; Henderson and Enterline 1979; Hughes et al. 1987; Magnani and Leporati 1998; McDonald et al. 1982; Newhouse and Berry 1979; Peto et al. 1985; Weill et al. 1979).

As with most carcinogenic agents, there is a substantial latency period (10–40 years in humans) between the onset of exposure to asbestos and the occurrence of lung cancer (Dement et al. 1983; Huilan and Zhiming 1993; McDonald et al. 1983; Nicholson et al. 1979; Selikoff et al. 1979; Sluis-Cremer 1991). After sufficient time (e.g., 20 years), the risk of lung cancer in exposed workers is generally observed to increase in proportion to the cumulative exposure (f-yr/mL). Most researchers have found that the chances that asbestos exposure will lead to lung cancer depends not only on the cumulative dose of asbestos, but also on the underlying risk of lung cancer due to other factors (Enterline et al. 1987; EPA 1986a; McDonald et al. 1982, 1983; Peto et al. 1985). For example, asbestos exposure results in a greater increase in lung cancer risk in smokers than nonsmokers, possibly because smokers have a higher underlying risk of lung cancer than nonsmokers. Alternatively, the greater increase in lung cancer risk in smokers may be due to a synergism between tobacco smoke and asbestos fibers. (see Section 3.9 for additional discussion of the interaction between smoking and asbestos).

Using a predictive model based on an analysis of 11 sets of lung cancer mortality data for groups of textile production workers (Dement et al. 1983; McDonald et al. 1982, 1983; Peto 1980), friction products workers (Berry and Newhouse 1983; McDonald et al. 1984), insulation products workers (Seidman 1984; Selikoff et al. 1979), and cement products workers (Finkelstein 1983; Henderson and

Enterline 1979; Weill et al. 1979), EPA (1986a) estimated that continuous lifetime exposure to air containing 0.0001 f/mL of asbestos would result in about two cases of lung cancer per 100,000 smokers, a factor of 10 higher than that estimated for nonsmokers (0.2 per 100,000). EPA (1986a) excluded available data for asbestos miners and millers (McDonald et al. 1980; Nicholson et al. 1979; Rubino et al. 1979) from the analysis, based on the judgement that fiber characteristics of "preprocessed" asbestos in these environments would be different from those of "processed" asbestos fibers in the general environment. The corresponding cumulative lifetime exposures associated with excess risks of 10^{-7}–10^{-4} are shown in Figure 3-1. For smokers, cumulative exposures of 0.000035, 0.00035, 0.0035, and 0.035 f-yr/mL represent excess lung cancer risks of 10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4} respectively. For nonsmokers, cumulative exposures of 0.00035, 0.0035, 0.035, and 0.35 f-yr/mL represent excess lung cancer risks of , 10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4} respectively. Appendix D provides further details on the derivation of these risk estimates. While these values have been considered to be the best available for assessing risk from environmental exposures to airborne asbestos, the range of uncertainty is probably a factor of 2.5–10 (EPA 1986a). Currently (in 2001), EPA is in the process of reviewing their cancer risk estimates for asbestos fibers.

Several authors have suggested that the EPA model may overestimate the lung cancer risk from exposure to asbestos (Camus et al. 1998; Hughes 1994; Lash et al. 1997). An alternative statistical analysis of studies relating occupational cumulative exposure to asbestos and lung cancer mortality arrived at lung cancer potency estimates that were 4- to 24-fold lower than the EPA model potency estimate (Lash et al. 1997). Hughes (1994) noted that exclusion of the chrysotile asbestos miner and miller data in the EPA analysis led to a higher estimate of potency (i.e., slope of the exposure-response relationship) than would have been obtained if the data were included, and suggested that a lower potency estimate would be more appropriate for populations exposed to nontextile chrysotile such as that used in buildings. Camus et al. (1998) reported that the EPA model predicted a relative risk for death from lung cancer in a group of nonoccupationally exposed women who lived in two regions of Quebec with chrysotile mines that was at least 10-fold higher than the observed upper range for excess lung cancer deaths for this group. No statistically significant lung cancer excess was observed in this group of women. The SMR was 0.99 (95% CI 0.78–1.25), based on 71 observed lung cancer cases among 2,242 deaths from all causes (Camus et al. 1998). In defense of the EPA model predictions, Landrigan (1998) noted that "the strong possibility exists that the Camus calculations underestimate the risk of asbestos exposure", due to "1) the average fiber diameter in the Quebec mining townships is probably larger than average diameter encountered in industrial operations in the United States, because asbestos in the Quebec townships had not been subjected to the extensive machining that asbestos found in U.S. textile factories typically

undergoes; and 2) prevalence of cigarette smoking is much lower among women in rural Quebec than among blue-collar workers in the American south."

Although a number of studies seem to suggest that not all asbestos fibers types are equally likely to lead to lung cancer, the human evidence is disputed (see Hodgson and Darnton 2000, McDonald and McDonald 1997, and Stayner et al. 1996 for differing views on the evidence for differing lung cancer potency among asbestos fiber types). Some of this variation in potency between fibers may be due to differences between mineral types with respect to surface properties such as surface charge density (Bonneau et al. 1986; Davis et al. 1988), iron content (Lund and Aust 1992), and durability (Lippmann 1990), but the bulk of the available data indicate that fiber size (fiber thinness and length) may be the most important determinant of carcinogenic potential (see Section 3.5).

Some epidemiological studies have detected little or no increase in lung cancer risk until the cumulative dose of asbestos exceeds 25–100 f-yr/mL (Berry and Newhouse 1983; Hughes and Weill 1980; McDonald et al. 1980; Weill et al. 1979), and this has led to the proposal that there may be a dose threshold for asbestos-induced lung cancer (Browne 1986a, 1986b; Hodgson and Darnton 2000). However, a number of other studies indicate that lung cancer risk is linearly related to cumulative dose without any obvious threshold (Dement et al. 1983; Finkelstein 1983; Henderson and Enterline 1979; Hughes et al. 1987; McDonald et al. 1983; Seidman et al. 1979). In general, dose-response data from epidemiological studies lack the statistical power to detect small effects at low doses, so it is not possible to conclude from such data that a hazardous chemical does (or does not) have a threshold dose.

Studies in animals have reported increased incidence of lung cancer following chronic inhalation exposure to chrysotile (Davis and Jones 1988; Gross et al. 1967; Reeves et al. 1974; Wagner et al. 1974, 1980a), amosite (Davis et al. 1980a, 1980b, 1986a; Reeves et al. 1974), crocidolite (Reeves et al. 1971, 1974; Wagner et al. 1974), anthophyllite (Wagner et al. 1974), and tremolite (Davis et al. 1985). Exposure levels that have resulted in increased lung tumor frequency in animals range from 70 to 1,600 PCM f/mL. In general, tumors were characterized as adenomas, adenocarcinomas, and squamous cell carcinomas. There is some evidence from animal studies that mineral-fiber lung tumors arise from fibrotic areas of the lung (Davis and Cowie 1990).

Mesothelioma. Mesotheliomas are tumors arising from the thin membranes that line the chest (thoracic) and abdominal cavities and surround internal organs. Mesotheliomas are relatively rare in the general population, but are often observed in populations of asbestos workers. For example, in the mortality

study of insulation workers (in which 2,227 total deaths were analyzed), there were 175 deaths attributable to mesotheliomas, 63 arising from the pleural membrane, and 112 arising in the peritoneum (Selikoff et al. 1979). In contrast, published estimates of annual general population incidences of mesothelioma deaths include 2.8 and 0.7 per million for North American males and females, respectively, in 1972 (McDonald and McDonald 1980), an average of 1.75 per million in the U.S. for the period 1987–1996 (NIOSH 1999), and, for United States white males (the U.S. group with the highest mortality rate), 3.61 per million in 1987 and 2.87 per million in 1996 (NIOSH 1999). Mesotheliomas are often difficult to diagnose, so use of death certificate information may lead to an underestimate (Selikoff et al. 1979) or an overestimate (Bignon et al. 1979) of the true incidence of this disease.

Case-control studies have observed strong associations between the development of mesothelioma and occupational exposure to asbestos fibers (McDonald and McDonald 1980; McDonald et al. 1997; Spirtas et al. 1988, 1994; Teschke et al. 1997; Teta et al. 1983). For example, in a case-control study of 208 cases of malignant mesothelioma and 533 controls (who died of other noncancer causes) registered by the Los Angeles County Cancer Surveillance Program, the New York State Cancer Registry, and 39 large Veteran's Administration Hospitals, an elevated odds ratio of 9.8 (95% CI 4.7–21.1) was found for mesothelioma in men who reported ever having been occupationally exposed to asbestos (Spirtas et al. 1994). In a study of 344 North American malignant mesothelioma cases and 344 matched controls, employment for 10 or more years in the following trades was associated with increased relative risks of 46.0 (confidence intervals were not reported) for insulation work, 6.1 for asbestos production and manufacture, 4.4 for heating trades, 2.8 for shipyard work, and 2.6 for construction work (McDonald and McDonald 1980). In a study of 51 mesothelioma cases and 154 population-based controls from British Columbia, elevated odds ratios were found for several occupations likely to have involved asbestos exposure including sheet metal workers (OR=9.6, 95% CI 1.5–106), plumbers and pipe fitters (OR=8.3, 95% CI 1.5–86), and shipbuilding workers (OR=5.0, 95% CI 1.2–23) (Teschke et al. 1997).

Analyses of trends in mesothelioma mortality in Britain and Western Europe (Peto et al. 1995, 1999) indicate that the worst-affected birth cohort is men born around 1945–1950 (1/150 were projected to die of mesothelioma), whereas similar analyses of trends in the United States (Price 1997) indicate that the worst affected cohort is the 1925–1929 male birth cohort (with an estimated lifetime risk of 2/1,000). These trends mirror trends in raw asbestos consumption and a reduction in workplace airborne asbestos levels, with maximum exposure in the United States from the 1930s to the 1960s and in Britain and Western Europe in the 1970s (Peto et al. 1995, 1999; Price 1997). NIOSH (1999) has reported that age-

adjusted mortality rates for malignant neoplasm of the pleura in U.S. males showed a decline during the 1987–1996 period from 3.61 per million in 1987 to 2.87 per million in 1996.

Cases of mesothelioma have been reported in adults who had no occupational exposure to asbestos, but who lived with a parent, spouse, or sibling who was an asbestos worker and presumably carried asbestos home on the work clothes (Anderson et al. 1976; Inase et al. 1991; Magee et al. 1986; Magnani et al. 1993; McDonald and McDonald 1980; Voisin et al. 1994). As with other asbestos-related respiratory health effects, asbestos-induced mesothelioma appears to have a long latent period of development. For example, Anderson et al. (1976) described two cases of women who presumably experienced household contact with asbestos as children, when their fathers worked with asbestos, and developed clinically detected pleural mesothelioma more than 30 years later. In a review of 1,105 cases of malignant mesotheliomas associated with occupational exposure to asbestos, Lanphear and Buncher (1992) reported that 99% had a latent period >15 years, and calculated a median latent period of 32 years.

Cases of death from mesothelioma have been reported in studies of workers or in persons exposed environmentally to each of the main types of asbestos, including predominantly chrysotile (Albin et al. 1990a, 1990b; Berry 1997; McDonald et al. 1993; Selcuk et al. 1992; Tulchinsky et al. 1992), amosite (Levin et al. 1998; Seidman et al. 1979), crocidolite (Armstrong et al. 1988; de Klerk et al. 1989; Edward et al. 1996; Hansen et al. 1998; Jones et al. 1980a), tremolite (Amandus and Wheeler 1987; Baris et al. 1988a, 1988b; Constantopoulos et al. 1987a; Erzen et al. 1991; Kleinfeld et al. 1974; Langer et al. 1987; Luce et al. 2000; Magee et al. 1986; McConnochie et al. 1987; Metintas et al. 1999; Sahin et al. 1993; Sakellariou et al. 1996; Schneider et al. 1998; Selcuk et al. 1992; Yazicioglu et al. 1980), and a nonspecified asbestos type (Iwatsubo et al. 1998).

Although these findings suggest that all asbestos types can cause mesothelioma, there are several studies that suggest that amphibole asbestos (asbestiform tremolite, amosite, and crocidolite) may be more potent than chrysotile (Berry and Newhouse 1983; Churg 1986b; Churg and Wright 1989; Henderson and Enterline 1979; Hodgson and Darnton 2000; Hughes et al. 1987; Jones et al. 1980a; McDonald et al. 1989, 1997; Newhouse and Sullivan 1989; Rödelsperger et al. 1999; Rogers et al. 1991; Sluis-Cremer et al. 1992; Weill et al. 1979). For example, a group of workers in a friction materials plant that used mainly chrysotile, but also used crocidolite on two occasions, has been studied (Berry and Newhouse 1983). In a case-control analysis, it was found that the workers dying from mesothelioma (11 cases) were 8 times more likely to have been exposed to crocidolite than workers dying from other causes (Berry and Newhouse 1983). In case-control analyses of fiber concentrations in autopsied lungs of mesothelioma

subjects and subjects who died of other causes, relative risk for mesothelioma was significantly related to increasing concentrations of amphibole fibers longer than 5 μm (Rödelsperger et al. 1999), 8 μm (McDonald et al. 1989), or 10 μm (Rogers et al. 1991); significant relationships with increasing concentrations of chrysotile fibers were less apparent in these studies. In another approach, the chrysotile and amphibole content of lungs from persons dying from mesothelioma was examined, and it was found that mesotheliomas occurred in amphibole workers with much lower fiber burdens than those observed for chrysotile workers. The authors concluded that amphiboles were two orders of magnitude more potent for inducing mesothelioma than chrysotile (Churg and Wright 1989). This has led to the hypothesis that many cases of mesothelioma in chrysotile-exposed workers are actually due to the presence of amphibole contamination (Churg 1988; McDonald et al. 1989). However, it is difficult to draw strong inferences regarding the relative potency of different mineral types from lung burden data, because amphiboles are more stable in lung tissue than chrysotile (see Section 3.4.3.1). Based on an analysis of the ratio of excess deaths from mesothelioma to excess deaths from lung cancer in a number of studies, EPA concluded that crocidolite could be 2–4 times more potent for mesothelioma than chrysotile, but that this difference was generally overshadowed by differences in fiber size distribution and differences between cohorts (EPA 1986a). In a more recent analysis of exposure-response relationships for mesothelioma mortality in studies of 17 asbestos-exposed occupational cohorts, Hodgson and Darnton (2000) concluded that relative potencies ("exposure specific risk of mesothelioma") are in a ratio of 1:100:500 for chrysotile, amosite, and crocidolite, respectively.

Several studies (Newhouse and Berry 1976, 1979; Nicholson et al. 1982; Peto et al. 1982) have indicated that the risk of mesothelioma from a given level of exposure to asbestos depends primarily upon the time elapsed since exposure (latency), with risk increasing exponentially with time after a lag period of about 10 years. Whereas early studies indicated that diagnosis with mesothelioma was fatal within a short period of time, other studies indicate that survival time after diagnosis may be influenced by exposure intensity. In contrast to the situation for lung cancer, the effect of asbestos on mesothelioma risk does not appear to be increased by smoking (Berry et al. 1985; Hammond et al. 1979; Selikoff et al. 1980).

Using a predictive model developed from mesothelioma data from studies of asbestos insulation workers (Peto et al. 1982), asbestos textile workers (Peto 1980), amosite factory workers (Seidman 1984), and asbestos-cement workers (Finkelstein 1983), EPA (1986a) estimated that continuous lifetime exposure to air containing 0.0001 f/mL of asbestos would result in about 2–3 cases of mesothelioma per 100,000 persons. The corresponding cumulative lifetime exposures associated with excess risks of 10^{-4}–10^{-7} are shown in Figure 3-1. Cumulative exposure levels of 0.031, 0.0031, 0.00031, and

0.000031 f-yr/mL represent excess mesothelioma risks of 10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4}, respectively. Appendix D provides further details on the derivation of these risk estimates. Currently (in 2001), EPA is in the process of reviewing their cancer risk estimates for asbestos fibers.

In a recent analysis of the mesothelioma mortality data among 17 asbestos-exposed cohorts, Hodgson and Darnton (2000) estimated that cumulative exposures of 0.005, 0.01, or 0.1 f-yr/mL to crocidolite would produce about 10, 20, or 100 mesothelioma deaths per 100,000, respectively; for amosite, the respective mesothelioma risk estimates were 2, 3, or 15 deaths per 100,000. For chrysotile, Hodgson and Darnton (2000) concluded that mesothelioma risks were "probably insignificant", but noted that "highest arguable estimates" were insignificant, 1, and 4 deaths per 100,000 for cumulative exposure levels of 0.005, 0.01, and 0.1 f-yr/mL.

Animal studies also indicate that inhalation exposure to asbestos produces mesotheliomas. Mesotheliomas have been observed in rats exposed to chrysotile, amosite, anthophyllite, crocidolite, or tremolite at concentrations ranging from 350 to 1,600 f/mL for 1–2 years (Davis and Jones 1988; Davis et al. 1985; Wagner et al. 1974, 1980a) and in baboons exposed to either 1,110–1,220 f/mL for 4 years (Goldstein and Coetzee 1990) or 1,100–1,200 f/mL for up to 898 days (Webster et al. 1993). Incidences of mesothelioma ranged from 0.7 % to 42% in these studies.

Cancer at Other Sites. Mortality studies of asbestos workers have revealed small increases in the incidence of death from cancer at one or more sites other than the lung, the pleura, or the peritoneum, mostly in tissues of the gastrointestinal system. For example, a total of 99 deaths from cancers of the esophagus, stomach, colon, or rectum were observed in a cohort of 17,800 insulation workers, while only 59.4 deaths of this sort were expected (Selikoff et al. 1979). Similarly, 26 deaths from gastrointestinal cancer were observed in a group of 2,500 asbestos textile workers, where only 17.1 were expected (McDonald et al. 1983). In this study, there was an approximately linear increase in gastrointestinal cancer death rate with cumulative exposure to asbestos. Similar increases in gastrointestinal cancer rates in asbestos workers have been reported in other studies (Armstrong et al. 1988; Enterline et al. 1987; Gerhardsson de Verdier et al. 1992; Jakobsson et al. 1994; Kang et al. 1997; Neugut et al. 1991; Newhouse and Berry 1979; Pang et al. 1997; Raffn et al. 1989, 1996b; Seidman et al. 1979, 1986). Other mortality studies (e.g., Albin et al. 1990a; Hughes et al. 1987; McDonald et al. 1993; Peto et al. 1985) of asbestos workers, however, found no significantly increased risk for gastrointestinal or colorectal cancer. In a meta-analysis of available cohort studies, Frumkin and Berlin (1988) calculated, for cohorts having latent periods of 10–20 years and displaying SMRs for lung cancer greater than 2, pooled SMRs of

1.46 (95% CI, 1.00–2.13) for gastric cancer, 1.68 (1.34–2.09) for colorectal cancer, and 1.66 (1.32–2.08) for all gastrointestinal cancers. Homa et al. (1994) found similar results in another meta-analysis of the data. Homa et al. (1994) concluded that the results "suggested that exposure to amphibole asbestos maybe associated with colorectal cancer, but these findings may reflect an artifact of uncertification of cause of death". Homa et al. (1994) also concluded that "the results also suggest that serpentine asbestos is not associated with colorectal cancer." Other reviewers have concluded that the available data do not establish a causal relationship between occupational exposure to asbestos and the development of gastrointestinal cancers (Doll and Peto 1985, 1987; Edelman 1988a, 1989; Goodman et al. 1999; Weiss 1995).

Some studies have also noted excess deaths from, or reported cases of, cancers at other sites, such as the kidney (Enterline et al. 1987; Selikoff et al. 1979), brain (Kishimoto et al. 1992), and bladder (Bravo et al. 1988). Several cases of malignant mesothelioma of the tunica vaginalis testis have been reported in patients with histories of occupational exposure to asbestos (Fligiel and Kaneko 1976; Huncharek et al. 1995; Serio et al. 1992). Several epidemiological studies have also reported an increased risk of laryngeal cancer in workers exposed to asbestos (Muscat and Wynder 1991; Parnes 1990; Raffn et al. 1989; Smith et al. 1990). In contrast, a number of other epidemiological studies have not detected statistically significant associations between increased risk of cancers at sites other than the lung, pleura, or peritoneum and asbestos exposure (Acheson et al. 1982; de Klerk et al. 1989; Hughes et al. 1987; McDonald et al. 1984; Meurman et al. 1974; Molinini et al. 1992; Nicholson et al. 1979; Wignall and Fox 1982; Wortley et al. 1992).

Reviewers of the available evidence for asbestos-related cancer at sites other than the lung, pleura, and peritoneum appear to concur that the evidence is not strong. For example, Doll and Peto (1985, 1987) concluded from their review of the available epidemiological data and biological evidence that misdiagnosis or chance may be the simplest and most plausible explanation of asbestos-related cancer at any other site than the lung, pleura, or peritoneum. Kraus et al. (1995) concluded from a meta-analysis of 31 cohort studies and 24 case-control studies that most studies did not find a statistically significant association between occupational exposure to asbestos and laryngeal cancer and that the evidence of a causal relationship was weak. A separate meta-analysis (Goodman et al. 1999) of asbestos-exposed occupational cohorts resulted in a meta-SMR for laryngeal cancer of 1.57 (95% CI 0.95–2.45), suggestive of a possible association between asbestos and laryngeal carcinoma. In this meta-analysis, there was no clear association with urinary, reproductive, lymphatic, or hematopoietic cancers. Browne and Gee (2000) reviewed all identified studies of asbestos workers providing data on laryngeal disease and

concluded that the evidence did not indicate a positive association between asbestos exposure and laryngeal cancer.

All Cancer Effect Level (CEL) values from each reliable study for cancer are summarized in Tables 3-1 and 3-2, and plotted in Figures 3-1 and 3-2.

3.2.2 Oral Exposure

Units of Exposure. The principal way that humans are exposed to asbestos by the oral route is through ingestion of asbestos-contaminated drinking water (see Chapter 6). As discussed in Section 6.4.2, most asbestos fibers in water are chrysotile and are <5 μm in length. The concentration of asbestos in water is generally determined by transmission electron microscopy (TEM), and the results are expressed as millions of TEM fibers per liter (MFL). Although most laboratories currently count fibers as those particles with lengths >5 μm and aspect ratios >3:1 (in concordance with most regulatory definitions of an asbestos fiber), some studies have reported fiber concentrations using a lower length criterion. Since it is very difficult to convert from MFL to other units of dose, human exposure to asbestos via drinking water is reported below simply in terms of exposure level (MFL). In contrast, animal studies usually describe oral exposure in terms of mass (mg/day), and it is not often possible to accurately convert from this dose to units of exposure equivalent to those used for humans. Consequently, animal doses are reported below in units of mg/kg/day, and information on fiber dimensions is included when available.

Overview of Oral Health Effects. Studies in humans and animals indicate that ingestion of asbestos causes little or no risk of noncarcinogenic injury. However, there is some evidence that acute oral exposure may induce precursor lesions of colon cancer, and that chronic oral exposure may lead to an increased incidence risk of gastrointestinal tumors. Studies that provide quantitative data on the effects of ingested asbestos are summarized in Table 3-3 and Figure 3-3, and the data are discussed below.

3.2.2.1 Death

No studies were located regarding death in humans or animals after acute or intermediate oral exposure to asbestos. Feeding studies in rats and hamsters indicate that ingestion of high amounts (1% in the diet, equivalent to doses of 500–800 mg/kg/day) of chrysotile, amosite, crocidolite, or tremolite does not cause premature lethality, even when exposure occurs for a lifetime (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c).

TABLE 3-3. Levels of Significant Exposure to Asbestos - Oral

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ chemical form[b]
INTERMEDIATE EXPOSURE							
Reproductive							
1	Rat F344/N	2-12 wk		500			NTP 1985, 1988, 1990b, 1990c CH CR TR AM
2	Hamster Syrian	3-6 wk		830			NTP 1983, 1990a CH AM
Developmental							
3	Rat F344/N	2-12 wk		500			NTP 1985, 1988, 1990b, 1990c CH CR TR AM
4	Mouse CD-1	15 d Gd1-15		33 F			Schneider and Maurer 1977 CH
5	Hamster Syrian	3-6 wk		830			NTP 1983, 1990a CH AM
CHRONIC EXPOSURE							
Systemic							
6	Rat Wistar	25 mo	Gastro	100 M			Bolton et al. 1982a AM CR CH
7	Rat Sprague-Dawley	1.5 yr	Gastro			20 M (altered permeability of the intestines)	Delahunty and Hollander 1987 CH

TABLE 3-3. Levels of Significant Exposure to Asbestos - Oral (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ chemical form[b]
8	Rat NS	21 mo	Resp	2500 M			Gross et al. 1974 CH
			Cardio	2500 M			
			Gastro	2500 M			
			Hemato	2500 M			
			Musc/skel	2500 M			
			Hepatic	2500 M			
			Renal	2500 M			
			Dermal	2500 M			
9	Rat MRC Hooded	15 mo	Gastro		140 M (increased DNA synthesis)		Jacobs et al. 1978b CH
10	Rat F344/N	lifetime	Resp	500			NTP 1985, 1988, 1990c CH CR TR
			Cardio	500			
			Gastro	500			
			Hemato	500			
			Musc/skel	500			
			Hepatic	500			
			Renal	500			
			Endocr	500			
			Dermal	500			
			Bd Wt	500			

TABLE 3-3. Levels of Significant Exposure to Asbestos - Oral (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ chemical form[b]
11	Rat F344/N	lifetime	Resp	500			NTP 1990b AM
			Gastro	500			
			Hepatic	500			
			Renal	500			
			Bd Wt		500 M (15 (at weaning) to 37% (at 8 weeks) decreased mean body weight gain)		
			Bd Wt		500 F (15 (at weaning) to 25% (at 8 weeks) decreased mean body weight gain)		
12	Hamster Syrian	lifetime	Resp	830			NTP 1983, 1990a CH AM
			Cardio	830			
			Gastro	830			
			Hemato	830			
			Musc/skel	830			
			Hepatic	830			
			Renal	830			
			Endocr	830			
			Dermal	830			
			Bd Wt	830			
	Neurological						
13	Rat F344/N	lifetime		500			NTP 1985, 1988, 1990b, 1990c CH CR TR AM
14	Hamster Syrian	lifetime		830			NTP 1983, 1990a CH AM

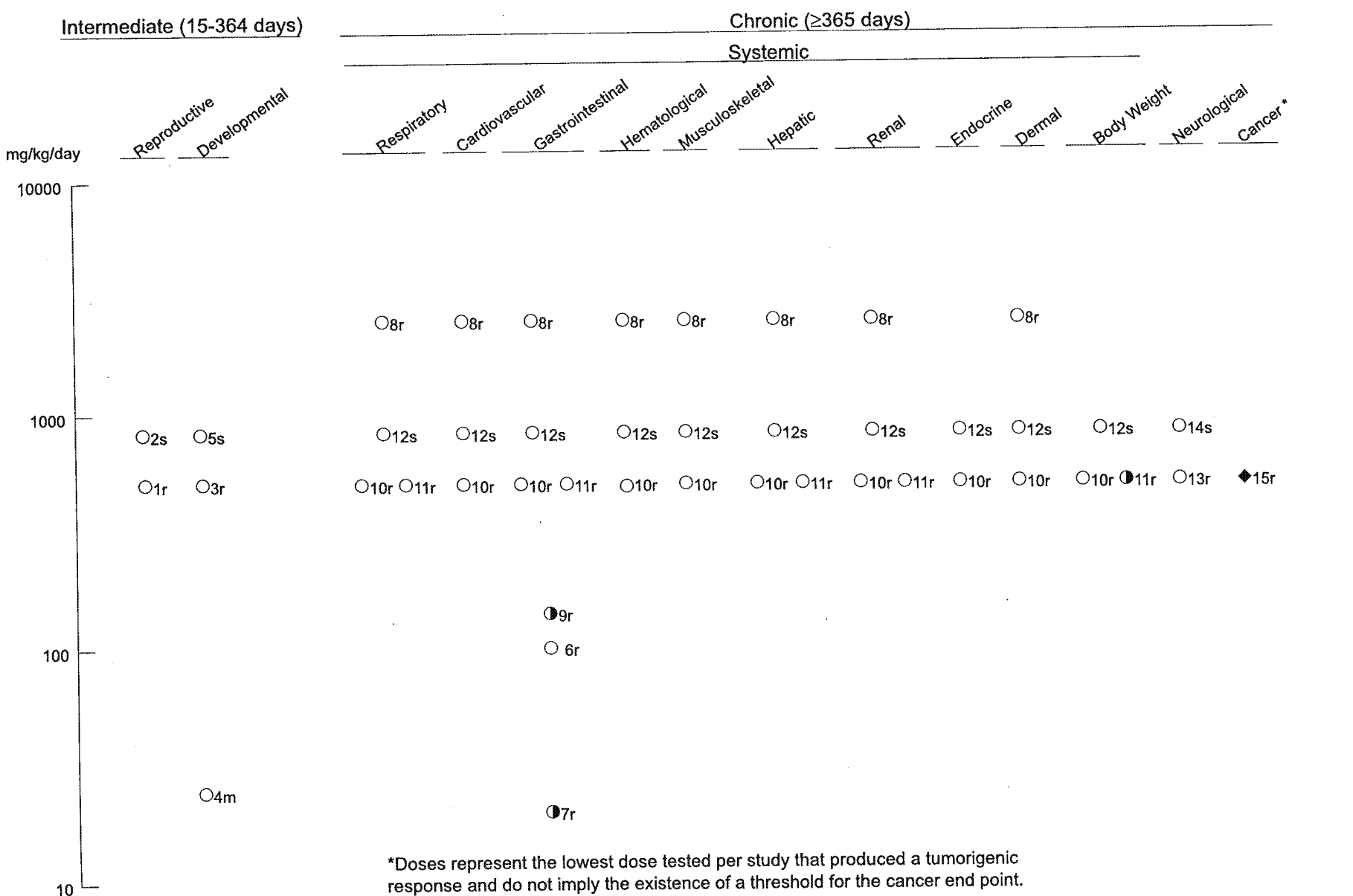
TABLE 3-3. Levels of Significant Exposure to Asbestos - Oral (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ chemical form[b]
	Cancer						
15	Rat F344/N	lifetime				500 M (CEL: intestinal polyps)	NTP 1985 CH-I

[a]The number corresponds to entries in Figure 3-3.

AM = amosite; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; CH = chrysotile; CR = crocidolite; d = day(s); DNA = deoxyribonecleic acid; Endocr = endocrine; (F) = feed; F = female; Gastro = gastrointestinal; Gd = gestation day; Hemato = hematological; I = intermediate; LOAEL = lowest-observed-adverse-effect-level; M = male; mg/kg/day = milligrams per kilogram per day; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect-level; NS = not specified; Resp = respiratory; TR = tremolite; (W) = water; wk = week(s); yr = year(s)

Figure 3-3. Levels of Significant Exposure to Asbestos - Oral



3.2.2.2 Systemic Effects

No studies were located regarding the respiratory, cardiovascular, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, or metabolic effects in humans after oral exposure to asbestos. Studies in rats and hamsters exposed to high doses (1% in the diet) of chrysotile, amosite, crocidolite, or tremolite have not detected histological or clinical evidence of injury to any systemic tissues (Gross et al. 1974; NTP 1983, 1985, 1988, 1990a, 1990b, 1990c), with the possible exception of mild effects on the gastrointestinal tract (see below). These findings are consistent with the concept that very few asbestos fibers cross from the gastrointestinal lumen into the blood (see Section 3.4.1), and that the risk of noncarcinogenic injury to tissues such as lung, heart, muscle, liver, kidney, skin, or eyes is negligible. The highest NOAEL values and all LOAEL values from reliable studies for systemic effects are summarized in Table 3-3 and plotted in Figure 3-3.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to asbestos. Because most ingested asbestos fibers are not absorbed into the body following oral exposure (see Section 3.4.1), the tissue most directly exposed to ingested asbestos is the gastrointestinal epithelium. A few studies in rats have described some histological or biochemical alterations in cells of the gastrointestinal tract after chronic exposure to oral doses of 20–140 mg/kg/day of chrysotile (Delahunty and Hollander 1987; Jacobs et al. 1978a, 1978b). Increased numbers of aberrant crypt foci, putative precursors of colon cancer, were induced in rats that were administered by gavage either a single dose (70 mg/kg/day) of chrysotile, a single dose (40 mg/kg/day) of crocidolite, or 3 doses (33 mg/kg/day) of crocidolite, although no dose-response was noted in the single dose of crocidolite regimen (Corpet et al. 1993). Mice that were administered either a single dose (100 mg/kg) of chrysotile or three doses (50 mg/kg/day) of crocidolite did not show increases in aberrant crypt foci (Corpet et al. 1993). However, no excess nonneoplastic lesions of the gastrointestinal epithelium have been detected in a number of other animal feeding studies (Bolton et al. 1982a; Donham et al. 1980; Gross et al. 1974), including an extensive series of lifetime studies in rats and Syrian hamsters in which such effects were carefully investigated (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c). Thus, the weight of evidence indicates that asbestos ingestion does not cause any significant noncarcinogenic effects in the gastrointestinal system.

Body Weight Effects. A single study reported a 15–37% decrease in body weight gain in rats exposed to 500 mg/kg/day amosite (NTP 1990b). Changes in food consumption do not explain the decreased body weight gain since treated rats had slightly higher food intakes than controls. Effects on body weight gain have generally not been observed in other studies (Gross et al. 1974; NTP 1983, 1985, 1988, 1990a, 1990c). The significance of this finding, therefore, is uncertain.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans or animals after oral exposure to asbestos.

3.2.2.4 Neurological Effects

No studies were located to indicate that ingestion of asbestos leads to neurological effects in humans. No histological or clinical evidence of neurological injury was detected in rats or hamsters chronically exposed to high doses (500 and 830 mg/kg/day, respectively) of chrysotile, amosite, crocidolite, or tremolite in the diet (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c). No clinical signs of neurological damage were noted after acute exposure of rats and mice to crocidolite (160 and 50 mg/kg/day, respectively) or to chrysotile (70 and 100 mg/kg/day, respectively) (Corpet et al. 1993).

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to asbestos. In animals, no histopathological changes in reproductive organs or effects on fertility were observed in rats or Syrian hamsters exposed to chrysotile, amosite, crocidolite, or tremolite (500 and 830 mg/kg/day, respectively) in the diet during gestation and lactation (through parental exposure) and throughout life until spontaneous death (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c). The highest NOAEL values from reliable studies for reproductive effects are summarized in Table 3-3 and plotted in Figure 3-3.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to asbestos. No teratogenic effects were noted in rats or hamsters exposed to chrysotile, amosite, crocidolite, or tremolite (500 and 830 mg/kg/day, respectively) during gestation, lactation (though parental exposure), and throughout their lives until spontaneous death (NTP 1983, 1985, 1988, 1990b, 1990c), although standard developmental toxicity examinations of intrauterine contents at the end of gestation were not conducted in these bioassays. A slight reduction in pup birth weight was noted in some cases (NTP 1985, 1990a), but it seems unlikely that this was the result of any direct effect on the fetus. In the only available standard developmental toxicity study, no exposure-related effects on pregnancy outcome, percentages of resorptions, fetal weight, or number of malformed fetuses were found in mice exposed from gestation days 1 through 15 to drinking water containing 0, 1.43, 14.3, or 143 μg chrysotile asbestos/mL in drinking water (approximate doses of 0, 0.3, 3.3, and 33 mg/kg/day, respectively) (Schneider and Maurer 1977). The highest NOAEL values from reliable studies for developmental effects are summarized in Table 3-3 and plotted in Figure 3-3.

3.2.2.7 Cancer

As discussed in Section 3.2.1.8, a number of epidemiological studies of workers exposed to asbestos fibers in workplace air suggest that workers may have an increased risk of gastrointestinal cancers. It is usually assumed that any effect of asbestos on the gastrointestinal tract after inhalation exposure is most likely the result of mucociliary transport of fibers from the respiratory tract to the gastrointestinal tract (see Section 3.4.4). Because of these findings, a number of researchers have investigated the carcinogenic risk (especially the risk of gastrointestinal cancer) in humans and animals when exposure to asbestos occurs by the oral route.

Human Studies. A number of epidemiological studies have been conducted to determine if human cancer incidence is higher than expected in geographical areas where asbestos levels in drinking water are elevated (usually in the range of 1–300 MFL) (Andersen et al. 1993; Conforti et al. 1981; Howe et al. 1989; Kanarek et al. 1980; Levy et al. 1976; Polissar et al. 1982, 1984; Sadler et al. 1984; Sigurdson et al. 1981; Toft et al. 1981; Wigle 1977). Most of these studies have detected increases, some of which were statistically significant, in cancer death or incidence rates at one or more tissue sites (mostly gastrointestinal) in populations exposed to elevated levels of asbestos in their drinking water. However, the magnitudes of the increases in cancer incidence are usually rather small, may be related to other risk

factors such as smoking, and there is relatively little consistency in the observed increases, either within studies (i.e., between sexes) or between studies.

The basis of these inconsistent findings is not certain. On one hand, it seems likely that at least some of the apparent associations are random or are due to occupational exposures (Polissar et al. 1982, 1984; Toft et al. 1981; Wigle 1977). On the other hand, failure of some studies to detect effects may be due to lack of statistical power, stemming from limitations regarding study design, exposure level and duration, latency since exposure, population size and mobility, population density, exposure to other risk factors, differences in sensitivity between sexes and groups, differences in asbestos fiber types and size, and numerous other possible confounding factors. In a review of data from eight independent epidemiological studies, it was concluded that the number of positive findings for neoplasms of the esophagus, stomach, pancreas, and prostate were unlikely to have been caused by chance alone (Marsh 1983). In another review, Kanarek (1989) noted that there were relatively consistent findings for increased stomach and pancreatic cancer among the studies. However, none of the studies provided a basis for identification of an oral exposure level that may be definitely stated as having caused increased death from cancer. Part of the uncertainty may be attributable to differences in analytical methods used in the different studies to measure fiber concentrations in drinking water (e.g., differences in selection of dimensional criteria for definition of a fiber, in sampling techniques, and in processing techniques). In a more recent review, Cantor (1997) concluded that results from epidemiologic studies of populations exposed to high concentrations of asbestos in drinking water are inconsistent and are not adequate to evaluate cancer risk from asbestos in drinking water, but noted that some of the results are suggestive of elevated risks for gastric, kidney, and pancreatic cancer. Cantor (1997) further noted that the issue of asbestos in drinking water causing these types of cancer warrants further investigation.

Animal Data. Early animal studies on gastrointestinal cancer from ingested asbestos were mostly negative (Cunningham et al. 1977; Gross et al. 1974), although some studies yielded increases in tumor frequency that were not statistically significant (Bolton et al. 1982a; Donham et al. 1980; Ward et al. 1980). More recently, a series of large scale, lifetime feeding studies have been performed by the National Toxicology Program (NTP). In this series of studies, animals were exposed during gestation and lactation (through parental diets) and throughout their lives until spontaneous death occurred. These studies have also yielded mostly negative results, although some suggestive increases in tumor frequencies did occur (see Table 3-4). An increased incidence of benign adenomatous polyps of the large intestine was observed in male rats exposed to 500 mg/kg/day intermediate range chrysotile (65% of all fibers over 10 μm) in the diet (NTP 1985). These tumors were not observed either in female rats or in

Table 3-4. Summary of NTP Lifetime Asbestos Feeding Studies

Asbestos type	Species	Median length (μm)	Size distribution	Carcinogenic effects	Comments	Conclusion	Reference
Amosite	Rat	4.37	74% >6 μm	Increased C-cell carcinoma (males)	Not considered treatment related	Not carcinogenic	NTP 1990b
				Increased leukemia (males)	Questionable biological and statistical significance		
	Syrian hamster	4.37	74% >6 μm	None		Did not cause a carcinogenic response	NTP 1983
Crocidolite	Rat	10	73% >8 μm	None		Did not cause a carcinogenic response	NTP 1988
Tremolite	Rat	No data	22% >5 μm	None		Did not cause a carcinogenic response	NTP 1990c
Chrysotile (short range)	Rat	0.66	30% >4.5 μm	None		No evidence of carcinogenicity	NTP 1985
Chrysotile (intermediate range)	Rat	0.82	60% >5.4 μm	Benign intestinal polyps (males)	Not significant based on concurrent controls; highly significant based on historical controls	Some evidence of carcinogenicity	NTP 1985
				Clitoral gland neoplasm (females)	Not significant compared to historical controls	No evidence of carcinogenicity	

Table 3-4. Summary of NTP Lifetime Asbestos Feeding Studies *(continued)*

Asbestos type	Species	Median length (μm)	Size distribution	Carcinogenic effects	Comments	Conclusion	Reference
Chrysotile (short range)	Syrian hamster	0.66	30% >4.5 μm	Adrenal cortical adenomas (males)	Not significant compared to historical controls	Not carcinogenic	NTP 1990a
Chrysotile (intermediate range)	Syrian hamster	0.82	60% >5.4 μm	Adrenal cortical adenomas (males and females)		Not carcinogenic	NTP 1990a

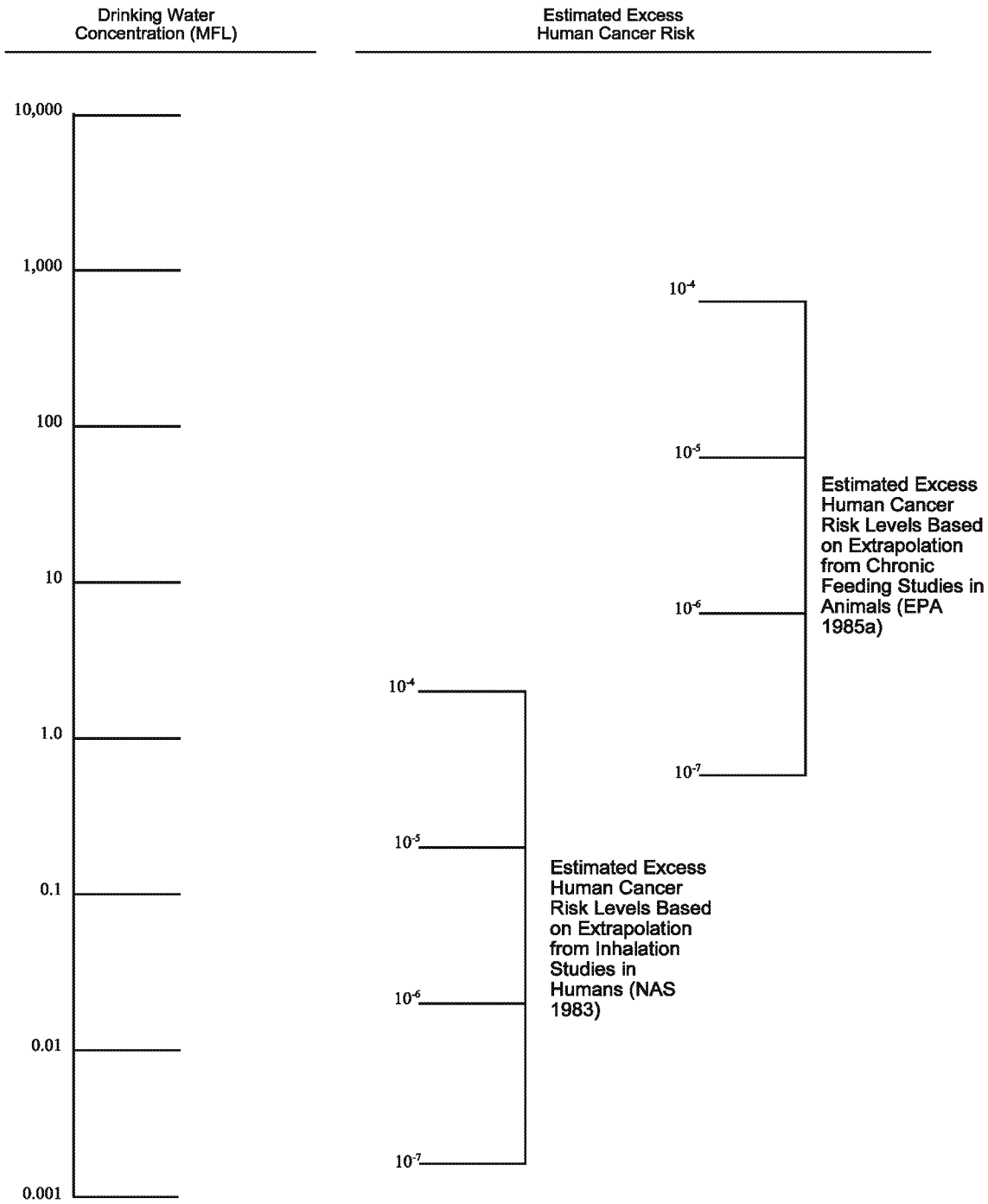
Syrian hamsters exposed to the same diet. Aberrant crypt foci, putative precursors of colon cancer, were induced in rats given acute doses of chrysotile (70 mg/kg/day) or crocidolite (33 mg/kg/day) by gavage (Corpet et al. 1993). Overall, however, the data were interpreted as providing "some evidence" of carcinogenicity for intermediate range chrysotile fibers. No tumorigenicity was noted for short-range chrysotile (NTP 1985).

Quantitative Risk Estimate. None of the available epidemiological studies of cancer risk in humans exposed to asbestos in drinking water are suitable for estimating quantitative dose-response relationships. However, both EPA and the National Academy of Sciences (NAS) have sought to estimate the risk of gastrointestinal cancer after oral exposure by extrapolating dose-response data from occupational studies (EPA 1980a; NAS 1983). As noted before, this approach rests on the assumption that the observed excess gastrointestinal cancer risk in the occupational studies is due to the swallowing of fibers that have been deposited in the respiratory tract. These calculations indicate that lifetime ingestion of water containing 1.0 MFL would produce an excess gastrointestinal cancer risk of about $3x10^{-5}$–$1x10^{-4}$ (EPA 1980a; NAS 1983). It should be noted that this approach requires a number of assumptions, and that the risk estimates should be considered to be only approximate. It is also important to note that if these risk estimates are correct, then the expected relative risk of gastrointestinal cancer in populations consuming drinking water at concentrations of 1–200 MFL would be quite low, and would likely not be consistently detectable in epidemiological studies (NAS 1983).

Another quantitative estimate of gastrointestinal cancer risk has been calculated based on the incidence of benign intestinal polyps in male rats exposed to 500 mg/kg/day of chrysotile (65% >10 μm long) in the diet (EPA 1985a). This calculation indicates that the lifetime excess risk from ingesting water containing 1.0 MFL would be about $1.4x10^{-7}$.

Figure 3-4 summarizes the risk estimates of NAS (1983) and EPA (1985a). It should be noted that these estimates differ by several orders of magnitude. Based on extrapolation from human inhalation studies, exposure levels of 0.0011, 0.011, 0.11, and 1.1 MFL in drinking water represent excess gastrointestinal cancer risks of 10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4}, respectively. Based on animal data, exposure levels of 0.71, 7.1, 71, and 710 MFL in drinking water represent excess gastrointestinal cancer risks of 10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4}, respectively. There are many possible reasons for this substantial difference, including uncertainty in each model's assumptions or conversion factors, differences in fiber potency (due to differences in type and/or length), and inherent differences between humans and rats. Appendix D provides further details

Figure 3-4. Summary of Calculated Gastrointestinal Cancer Risks from Ingestion of Asbestos



on the derivation of these risk estimates. Currently (2001), EPA is in the process of reviewing their cancer risk estimates for exposure to asbestos fibers.

3.2.3 Dermal Exposure

The only adverse health effect that has been reported after dermal contact with asbestos is the formation of small "warts" or corns. No quantitative dose-response data are available, but in a group of workers installing amosite insulation in ships, nearly 60% of the people had one or more of these lesions, mostly on the hands (Alden and Howell 1944). All of the workers with lesions reported an original pricking sensation and the feeling of a small splinter-like foreign body. This strongly indicates that the lesions are associated with penetration of the skin by a macroscopic spicule, although histological examination of the corns did not reveal the presence of a fiber. The corns develop within about 10 days and are painful at first. They later become highly cornified and do not appear to be of pathological concern (Alden and Howell 1944; Dupre et al. 1984; Selikoff and Lee 1978).

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

3.2.3.1 Death
3.2.3.2 Systemic Effects
3.2.3.3 Immunological and Lymphoreticular Effects
3.2.3.4 Neurological Effects
3.2.3.5 Reproductive Effects
3.2.3.6 Developmental Effects
3.2.3.7 Cancer

3.3 GENOTOXICITY

The genotoxicity of asbestos has been investigated *in vivo*, as summarized in Table 3-5, and *in vitro*, as summarized in Table 3-6.

Studies of exposed asbestos workers, residentially exposed Turkish villagers, mesothelioma patients, and lung cancer patients suggest that asbestos is genotoxic. The number of chromosomal aberrations and the rate of sister chromatid exchange were significantly elevated in the peripheral blood lymphocytes of

Table 3-5. Genotoxicity of Asbestos *In Vivo*

Species (test system)	End point	Results	Reference	Form
Mammalian cells:				
Human blood leukocytes	DNA strand breakage	+	Marczynski et al. 1994a	NS
Human blood leukocytes	DNA damage	+	Marczynski et al. 2000a	NS
Human blood leukocytes	DNA damage	+	Marczynski et al. 2000b	NS
Human blood lymphocytes	Chromosomal aberration	+	Fatma et al. 1991	NS
Human blood lymphocytes	Sister chromatid exchange	+	Donmez et al. 1996	AC
Human blood lymphocytes	Sister chromatid exchange	(+)	Rom et al. 1983	NS
Human blood lymphocytes	Sister chromatid exchange	(+)	Lee et al. 1999	CH
Human mesothelioma cells	Chromosomal aberration	+	Hansteen et al. 1993	CR, AM, AN
Human mesothelioma cells	Chromosomal aberration	+	Tiainen et al. 1989	CR, AM, AN
Human mesothelioma cells	Chromosomal aberration	+	Tammilehto et al. 1992	NS
Human mesothelioma cells	Chromosomal aberration	+	Pelin-Enlund et al. 1990	NS
Human mesothelioma cells	Chromosomal aberration	–	Segers et al. 1995	CR, CH
Human mesothelioma cells	Gene mutation (p53)	–	Kitamura et al. 1998	NS
Human mesothelioma cells	Gene mutation (p53)	–	Ni et al. 2000	NS
Human lung carcinoma cells	Gene mutation (FHIT)	+	Nelson et al. 1998	NS
Human lung carcinoma cells	Gene mutation (p53)	+	Guinee et al. 1995	NS
Human lung carcinoma cells	Gene mutation (p53)	+	Nuorva et al. 1994	NS
Human lung carcinoma cells	Gene mutation (p53)	+	Wang et al. 1995b	NS
Rat leukocytes	DNA strand breakage	–	Marczynski et al. 1994b	CR
Rat lung and liver cells	DNA strand breakage	+	Marczynski et al. 1994b	CR
Rat lung and liver cells	DNA strand breakage	+	Marczynski et al. 1994c	CR
Rat bone marrow cells	Chromosomal aberration	+	Fatma et al. 1992	CH
Rat mesothelioma cells	Chromosomal aberration	+	EPA 1988j	CH
Rat mesothelioma cells	Gene mutation (p53)	–	Ni et al. 2000	CR
Rat bone marrow cells	Sister chromatid exchange	–	Varga et al. 1996a	AN
Rat bone marrow cells	Sister chromatid exchange	–	Varga et al. 1996b	CR
Mouse lung cells	Gene mutation (*lacI*)	(+)	Rihn et al. 2000	CR

Table 3-5. Genotoxicity of Asbestos *In Vivo* (continued)

Species (test system)	End point	Results	Reference	Form
Nonmammalian cells:				
Drosophila	Chromosomal aberration	+	Osgood and Sterling 1991	AM, CH
Drosophila	Chromosomal aberration	–	Osgood and Sterling 1991	CR, TR

– = negative result; + = positive result; (+) = weakly positive; AC = actinolite; AM = amosite; AN = anthophyllite; CH = chrysotile; CR = crocidolite; FHIT = a tumor suppressor gene; NS = not specified; p53 = a tumor suppressor gene; TR = tremolite

Table 3-6. Genotoxicity of Asbestos *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Prokaryotic organisms:					
Salmonella typhimurium	Gene mutation	No data	–	Chamberlain and Tarmy 1977	CR, CH, AM,
S. typhimurium TA102	Gene mutation	No data	+	Faux et al. 1994	AN
Escherichia coli CP2	Gene mutation	No data	–	Chamberlain and Tarmy 1977	CR, AN
Mammalian cells:					
Human mesothelial cells	Chromosomal aberrations	No data	+	Olofsson and Mark 1989	CR, CH, AM
Human mesothelial cells	Chromosomal aberrations	No data	+	Dopp et al. 1997	AM, CR, CH
Human mesothelial cells	Chromosomal aberrations	No data	(+)	Pelin et al. 1995a	AM
Human mesothelial cells	Chromosomal aberrations	No data	+	Takeuchi et al. 1999	CR
Human lymphocytes	Chromosomal aberrations	No data	+	Valerio et al. 1980	CH
Human fibroblasts	Chromosomal aberrations	No data	–	Sincock et al. 1982	CH
Human lymphoblastoid cells	Chromosomal aberrations	No data	+	Sincock et al. 1982	CH
Human blood lymphocytes	Chromosomal aberrations	No data	+	Korkina et al. 1992	CH
Human lymphocytes	Chromosomal aberrations	No data	+	Emerit et al. 1991	CH
Human amniotic fluid cells	Chromosomal aberrations	No data	+	Dopp and Schiffman 1998	AM, CR, CH
Human promyelotic leukemia cells	Chromosomal aberrations	No data	–	Takeuchi et al. 1999	CR
Human fibroblasts	Sister chromatid exchange	No data	–	Casey 1983	NS
Human lymphoblastoid cells	Sister chromatid exchange	No data	–	Casey 1983	NS
Human peripheral lymphocyte	Gene mutation (HLA-A)		–	Both et al. 1994	CH
Human peripheral lymphocyte	Gene mutation (HLA-A)	No data	+	Both et al. 1994	CR
Human TK6 cells	Gene mutation (HGPRT; T)	No data	–	Kelsey et al. 1986	CR

Table 3-6. Genotoxicity of Asbestos *In Vitro (continued)*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Human-hamster hybrid cells	Gene mutation (HGPRT)	No data	+	Hei et al. 1992	CH
Human mesothelioma cells	Gene mutation (HLA-A)	No data	+	Both et al. 1995	CR
Human bronchial cells	DNA strand breakage	No data	–	Lechner et al. 1983	CR, CH, AM
Human mesothelial cells	DNA strand breakage	No data	+	Ollikainen et al. 1999	CR
Rat pleural mesothelial cells	Chromosomal aberrations	No data	+	Kravchenko et al. 1998	CH
Rat pleural mesothelial cells	Chromosomal aberrations	No data	+	Yegles et al. 1995	CH, CR, AM
Rat liver epithelial cells	Gene mutation (HGPRT)	No data	–	Reiss et al. 1982	CR, CH, AM
Rat fibroblast cells	Gene mutation (*lacI*)	No data	+	Lezon-Geyda et al. 1996	CH
Rat mesothelial cells	Sister chromatid exchange	No data	–	Kaplan et al. 1980	NS
Rat embryo cells	DNA strand breakage	No data	+	Libbus et al. 1989	CR
Rat mesothelial cells	Unscheduled DNA synthesis	No data	+	Dong et al. 1994	CH,CR
Rat mesothelial cells	Aneuploidy	No data		Yegles et al. 1993	CR
Mouse fibroblasts	Cell transformation	No data	–	Brown et al. 1983	CR,AM
Hamster tracheal epithelial	DNA strand breakage	No data	–	Mossman et al. 1983a	CR, CH
Chinese hamster CHO xrs-5	DNA strand breakage	No data	+	Okayasu et al. 1999a	CH
Chinese hamster CHO–K1 cells	Chromosomal aberrations	No data	+	Sincock 1977	CR, CH,
Chinese hamster CHO–K1 cells	Chromosomal aberrations	No data	+	Sincock and Seabright 1975	AM, AN
Chinese hamster CHO cells	Chromosomal aberrations	No data	+	Kenne et al. 1986	CR
Chinese hamster CHO cells	Chromosomal aberrations	No data	+	Kelsey et al. 1986	CR
Chinese hamster CHO cells	Chromosomal aberrations	No data		Sincock et al. 1982	CH
Chinese hamster V79 cells	Chromosomal aberrations	No data	+	EPA 1988j; Palekar et al. 1987	CR, CH
Chinese hamster V79 cells	Chromosomal aberrations	No data	+	Trosic et al. 1997	CH

Table 3-6. Genotoxicity of Asbestos *In Vitro (continued)*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Chinese hamster CHO cells	Chromosomal aberrations	No data	+	Donaldson and Golyasnya 1995	AM
Chinese hamster CHO cells	Gene mutation (HGPRT)	No data	–	Kenne et al. 1986	CR, CH, AM
Chinese hamster CCL 39 cells	Gene mutation (HPRT)	No data	(+)	Huang 1979	CR, CH, AM
Chinese hamster CHO cells	Sister chromatid exchange	No data	–	Kelsey et al. 1986	CR
Chinese hamster CHO cells	Sister chromatid exchange	No data	–	Casey 1983	NS
Chinese hamster CHO cells	Sister chromatid exchange	No data	+	Livingston et al. 1980	CR, CH, AM
Chinese hamster CHO cells	Sister chromatid exchange	No data	+	Babu et al. 1980	CH
Chinese hamster V79–4 cells	Sister chromatid exchange	No data	+	Price-Jones et al. 1980	CR
Chinese hamster V79 cells	Sister chromatid exchange	No data	–	Lu et al. 1994a	CH
Chinese hamster V79 cells	Sister chromatid exchange	No data	+	Trosic et al. 1997	CH
Chinese hamster V79 cells	Micronucleus assay	No data	+	Lu et al. 1994a	CH
Chinese hamster V79 cells	Micronucleus assay	No data	+	Lu et al. 1994b	CH
Chinese hamster V79 cells	Micronucleus assay	No data	+	Keane et al. 1999	CH
Syrian hamster cells	Chromosomal aberrations	No data	+	Lavappa et al. 1975	CH
Syrian hamster cells	Chromosomal aberrations	No data	+	Oshimura et al. 1986	CH
Syrian hamster embryo cells	Chromosomal aberrations	No data	+	Dopp et al. 1995a, 1995b	AM, CR, CH
Syrian hamster embryo cells	Chromosomal aberrations	No data	+	Dopp and Schiffman 1998	AM, CR, CH
Syrian hamster embryo cells	Cell transformation	No data	+	Hesterberg and Barrett 1984	CH, CR
Syrian hamster embryo cells	Cell transformation	No data	–	DiPaolo et al. 1983	AM, AN, CH, CR
Calf thymus DNA	DNA damage	No data	+	Adachi et al. 1992a	CR, CH, AM

– = negative result; + = positive result; (+) = weakly positive result; AM = amosite; AN = anthophyllite; CH = chrysotile; CHO = Chinese hamster ovary; CR = crocidolite; DNA = deoxyribonucleic acid; HGPRT and HPRT = hypoxanthine-guanine phosphribosyl transferase genetic locus; HLA-A = human lymphocyte antigen A genetic locus; NS = not specified; T = thymidine kinase genetic locus

asbestos workers compared to a control population (Fatma et al. 1991). The mean sister chromatid exchange rate was significantly increased (p=0.002) in nonsmoking asbestos insulators compared to a control population (Rom et al. 1983). The increase in sister chromatid exchange rate was not statistically significant in smoking asbestos insulators, and for the whole group (smokers and nonsmokers), the increase approached statistical significance (p=0.056). A marginally significant difference (p=0.069) in mean sister chromatid exchange rate between chrysotile-exposed workers and controls became significant (p=0.0473) after controlling for the effects of age and smoking (Lee et al. 1999). A group of residents from a Turkish village in which actinolite asbestos was used to paint walls and floors of homes had an elevated mean sister chromatid exchange rate in lymphocyte cells compared with a nonexposed control population (Donmez et al. 1996). An increased incidence of DNA double-strand breaks was noted in the leukocytes of asbestos workers compared to controls (Marczynski et al. 1994a). Increased incidences of DNA double strand breaks in lung and liver tissue (Marczynski et al. 1994b, 1994c) and chromosomal gaps and breaks in bone marrow cells (Fatma et al. 1992) were observed in rats exposed via intratracheal instillation of crocidolite instilled intratracheally with suspensions of crocidolite and chrysotile asbestos, respectively. In other studies, no increased frequency of sister chromatid exchange was found in bone marrow cells from rats orally exposed to anthophyllite or crocidolite (Varga et al. 1996a, 1996b). Asbestos induced aneuploidy in *Drosophila* (Osgood and Sterling 1991). In this assay system, chrysotile was more effective than amosite, whereas crocidolite and tremolite were relatively ineffective. Several studies have reported either chromosomal aberrations in the pleural effusion of mesothelioma patients (Hansteen et al. 1993) or significant correlations between specific chromosomal abnormalities and lung burden of asbestos in mesothelioma patients (Pelin-Enlund et al. 1990; Tammilehto et al. 1992; Tiainen et al. 1989). However, it is uncertain as to whether these chromosomal abnormalities were responsible for the development of mesothelioma, or whether the abnormalities were a result of the disease. Chromosomal aberrations in mesothelioma cells were not found in one study of human patients (Segers et al. 1995). Significant increases in the excretion of the DNA adduct 8-hydroxydeoxyguanosine, a marker of DNA damage, have been observed in the white blood cells and urine of asbestos workers (Marczynski et al. 2000a, 2000b; Tagesson et al. 1993). Abnormal p53 protein accumulation (suggestive of mutation in the p53 tumor suppressor gene) was detected significantly more often (p=0.027) in primary tumor tissue from lung cancer patients exposed to asbestos than in lung cancer patients without exposure (Nuorva et al. 1994). Mutations in the p53 gene occurred more frequently in two studies of primary tumor tissue from lung cancer patients with asbestos exposure compared with lung cancer patients without asbestos exposure (Guinee et al. 1995; Wang et al. 1995b). In another study of tumor tissue from lung cancer patients, asbestos exposure and smoking duration were each significantly associated (p<0.01) with deletions in the protein coding regions of another candidate tumor suppressor gene, FHIT (Nelson et

al. 1998). In contrast, mutations in the p53 gene were not found in tumor tissue samples from small numbers of mesothelioma patients (Kitamura et al. 1998; Ni et al. 2000) with definite histories of asbestos exposure or in rats with crocidolite-induced mesotheliomas (Ni et al. 2000).

Tests for gene mutations have been mixed, both *in vivo* and *in vitro*. Asbestos fibers were not mutagenic in initial tests of standard strains of *Salmonella typhimurium* and *Escherichia coli* (Chamberlin and Tarmy 1977), but mutagenic responses were found in a *S. typhimurium* strain, TA102, that is especially sensitive to oxidative mutagens (Faux et al. 1994).

In vitro tests on human peripheral lymphocytes and mesothelioma cells have been mixed with both positive and negative results for tests with crocidolite and chrysotile (Both et al. 1994, 1995; Hei et al. 1992; Kelsey et al. 1986). Studies by Both and coworkers (Both et al. 1994, 1995) suggest that crocidolite is a more potent mutagen than chrysotile, and that asbestos susceptibility is cell line specific. Cell line specificity may be due to differential phagocytic activity, with those cells exhibiting high levels of phagocytosis (e.g., mesothelioma cells) being more susceptible to asbestos (Takeuchi et al. 1999) than cells without such activity (e.g., lymphocytes). Studies in animal systems present a similar picture. Hei and coworkers reported an increased frequency of mutations in human-hamster hybrid cells exposed to chrysotile (Hei et al. 1992). These mutations consisted primarily of large deletions, which may not be detected as easily in other assay systems. Marginal evidence for weak mutagenicity of chrysotile, crocidolite, and amosite in Chinese hamster ovary (CHO) cells was reported by Huang (1979).

A large number of studies indicate that asbestos fibers can cause chromosomal aberrations in Chinese hamster ovary (CHO) and Syrian hamster embryo (SHE) cells. The aberrations include aneuploidy (usually polyploidy), fragmentation, breaks, rearrangements, gaps, dicentrics, inversions, and rings (Donaldson and Golyasnya 1995; Kelsey et al. 1986; Kenne et al. 1986; Lavappa et al. 1975; Oshimura et al. 1986; Palekar et al. 1987, 1988; Sincock 1977; Sincock and Seabright 1975; Sincock et al. 1982; Trosic et al. 1997). Aneuploidy was also induced in rat mesothelial cells *in vitro* using crocidolite (Yegles et al. 1993). Chromosomal aberrations have been produced by chrysotile in eight studies using human mesothelial, lymphocyte, and amniotic fluid cells (Dopp and Schiffmann 1998; Dopp et al. 1997; Emerit et al. 1991; Korkina et al. 1992; Olofsson and Mark 1989; Pelin et al. 1995b; Takeuchi et al. 1999; Valerio et al. 1980), but not in two others that used fibroblast and promyelocytic leukemia cells (Sincock et al. 1982; Takeuchi et al. 1999). The mechanism by which these clastogenic effects occur may be related to physical interference with chromosome segregation by the asbestos fiber during the mitotic process (Barrett et al. 1989; Malorni et al. 1990; Palekar et al. 1987).

Results of tests for other genotoxic effects (increased sister chromatid exchange, DNA strand breaks, DNA hydrolysis, cell transformations) have been mixed, with both negative (Brown et al. 1983; Casey 1983; DiPaolo et al. 1983; Kaplan et al. 1980; Kelsey et al. 1986; Lechner et al. 1983; Lu et al. 1994a; Mossman et al. 1983a; Price-Jones et al. 1980) and positive (Adachi et al. 1992a; Babu et al. 1980; Dong et al. 1994; Hesterberg and Barrett 1984; Libbus et al. 1989; Livingston et al. 1980; Okayasu et al. 1999a; Ollikainen et al. 1999; Trosic et al. 1997) results being noted. Adachi et al. (1992a) reported DNA damage as indicated by the formation of 8-hydroxy-2'-deoxyguanosine when fibers were incubated with calf thymus DNA and hydrogen peroxide. DNA strand breaks were noted in rat embryo cells exposed to crocidolite and CHO exposed to chrysotile (Okayasu et al. 1999a; Osgood and Sterling 1991). Emerit et al. (1991) reported that chrysotile induces the formation of a clastogenic factor when cultured rat pleural mesothelioma cells are exposed to the fibers *in vitro*, as ultrafiltrates of culture media from these cells induced chromosome damage in cultures of human lymphocytes used as a test system. These effects are equivocal, however, as there was no dose-response. Chrysotile induced increased numbers of cells with micronuclei (Keane et al. 1999; Lu et al. 1994b) and with two or more nuclei (Lu et al. 1994a) in Chinese hamster lung (V79) cells. Increases in unscheduled DNA synthesis have been reported using rat pleural mesothelial cells after exposure to crocidolite and chrysotile (Dong et al. 1994). Of special interest, the cell transformation reported by Hesterberg and Barrett (1984) was abolished when the fibers were milled to a short length.

These observations, especially the findings of cytogenotoxicity, are consistent with the greater observed carcinogenic potential of long asbestos fibers, and support possible mechanisms by which asbestos might be acting.

3.4 TOXICOKINETICS

Asbestos fibers may enter the body after inhalation or oral exposures. It is unlikely that any appreciable uptake of asbestos will occur after dermal exposure. The deposition and fate of the fiber in the lungs is largely dependent on its size and shape. Fibers that are deposited in the respiratory tract may be removed by mucociliary clearance or by macrophages, or they may be retained in the lung. Very few of the long fibers are likely to move through the lungs and be distributed to tissues other than the mesothelium. Longer fibers that are retained in the lung may undergo a number of processes including translocation, dissolution, fragmentation, splitting, or protein encapsulation. Long fibers that reside in the lung can become encapsulated in protein, forming what is often referred to as an "asbestos body" (the term "ferruginous body" is used when the nature of the core fiber is not known). These bodies are golden

brown in appearance, owing to the presence of iron. The protein coat is rich in ferritin (an iron storage protein) possibly arising from macrophages and giant cells. The formation of asbestos bodies may represent an attempt of macrophages to digest long fibers extracellularly (Koerten et al. 1990a, 1990b). Fibers that are retained in the lung or mesothelium for long periods of time are capable of producing chronic inflammation and fibrotic and tumorigenic effects. These effects may be mediated by direct interactions between the fiber and key cellular macromolecules, or they may be mediated by the production of reactive oxygen species and other cellular factors originating from alveolar macrophages. Fibers that enter the gastrointestinal tract, either by ingestion or mucociliary transport from the lungs, are mostly excreted in the feces, although a small fraction of the fibers may become lodged in cells or penetrate the gastrointestinal lining and enter other tissues.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

When asbestos fibers are inhaled, many are deposited on the epithelial surface of the respiratory tree. The number of fibers that are deposited, and the location within the airway where deposition occurs, is a function of the aerodynamic properties of the fibers. In humans, the fibers depositing in the upper airway consist mainly of relatively thick fibers (greater than about 3 μm), with thinner fibers being carried deeper into the distal airways and alveolar regions (Timbrell 1982). In rats, about 30–40% of typical fibers of chrysotile, amosite, and crocidolite, are retained, with most of these (about 60%) being deposited in the upper airways (nose, throat, and trachea) (Evans et al. 1973; Morgan et al. 1975). The median length for these fibers was 1–2 μm, while the median diameter was 0.2–0.4 μm. After intratracheal administration of chrysotile and amosite asbestos fibers in hamsters, chrysotile fibers were found to be primarily located near air duct bifurcations, while amosite fibers tended to be more distributed over the bronchial surface (Kimizuka et al. 1992). Many of these smaller fibers deposit preferentially at bifurcations in the terminal bronchioles and alveolar ducts (Brody 1986; Evans et al. 1973), with the number of fibers deposited at each location decreasing in proportion to the preceding airway path length and the number of preceding branch points (Pinkerton et al. 1986).

3.4.1.2 Oral Exposure

Animal studies indicate that most asbestos fibers that are ingested are not absorbed across the walls of the gastrointestinal tract (Gross et al. 1974). However, electron micrographic studies indicate that some fibers penetrate into the gastrointestinal epithelium (Storeygard and Brown 1977; Westlake et al. 1965). In addition, some fibers pass through the gastrointestinal wall and reach blood, lymph, urine, and other tissues (Carter and Taylor 1980; Cunningham and Pontefract 1973; Cunningham et al. 1977; Hallenbeck and Patel-Mandlik 1979; Patel-Mandlik and Millette 1983; Sebastien et al. 1980b; Weinzweig and Richards 1983). The mechanism by which asbestos fibers pass through the gastrointestinal wall is not known with certainty, but it has been noted that a wide variety of very small particles (i.e., 1 μm or less; e.g., starch granules, cellulose particles, pollen) can cross the gut by passing between (not through) the cells of the epithelial layer in a process termed persorption, and it seems likely that this may account for uptake of asbestos fibers as well (Volkheimer 1974). Available data are not sufficient to make a precise estimate of the fraction of ingested fibers that pass through the gastrointestinal wall, but there is agreement that it is a very small amount (Sebastien et al. 1980b; Weinzweig and Richards 1983). Several researchers have found that the average length of fibers in extra-gastrointestinal tissues or fluids is shorter than the average length of the fibers ingested (Cunningham et al. 1977; Patel-Mandlik and Millette 1983; Weinzweig and Richards 1983), suggesting that short fibers pass through the gastrointestinal epithelium more easily than long fibers.

3.4.1.3 Dermal Exposure

As discussed above (see Section 3.2.3), asbestos fibers can penetrate into the skin, producing asbestos warts. No studies were located that indicate that asbestos fibers can pass through the skin into the blood.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

As noted above, only a tiny fraction of inhaled fibers penetrate through the epithelial layer of the lungs. No quantitative studies were located regarding the distribution of these fibers in the rest of the body after inhalation exposure, but some appear to be retained in the pleura, with others passing into the lymphatics (Brody 1993; Hillerdal 1980; Holt 1983; Rudd 1989). Those fibers that enter the lymphatics are presumably able to reach other tissues of the body. Dogs exposed by nose-only inhalation to neutron-

activated crocidolite were found to have small amounts of radioactivity in the blood, liver, head, and gastrointestinal tract (Griffis et al. 1983). However, it is also possible that some small proportion of fibers originally deposited in the respiratory tract may reach other tissues following mucociliary transport of fibers to the gastrointestinal tract and uptake from that tissue (see Section 3.4.1.2).

Distribution of asbestos fibers within the lung has been investigated in a number of studies. Most fibers deposited in the airways are removed from the lung by mucociliary transport or by macrophages (see Section 3.4.4), but a small fraction remain in the lung for long periods (Jones et al. 1988a). In addition, some fibers appear to pass from the lung to the pleura (Boutin et al. 1996; Hillerdal 1980; Rudd 1989; Viallat et al. 1986). In humans, the presence of asbestos fibers in the pleura after inhalation exposure has been demonstrated by a number of researchers (Boutin et al. 1996; Jones et al. 1980b; Roggli and Longo 1991; Sebastien et al. 1980a; Stephens et al. 1987), but some concerns have been discussed of the possibility of contamination of tissues during pathological processing and fiber analysis (Case 1994). Available data are not sufficient to estimate the fraction of deposited asbestos fibers that penetrate the lung in this way, but it is probably quite small.

Intracellularly, asbestos fibers tend to be located near the nucleus. *In vitro* studies have indicated that during endocytosis, asbestos fibers were observed to be transported along the microtubule network to the perinuclear region (Cole et al. 1991; Malorni et al. 1990). The proximity of asbestos fibers to the nucleus may be an important factor regarding their genotoxicity and carcinogenicity.

Providing limited evidence that some transplacental transfer of asbestos fibers may occur, one group of investigators has reported that asbestos fibers were detected more frequently and at higher mean concentrations in human fetal and placental tissues associated with stillborn infants compared with placental tissue associated with liveborn infants from the same hospital (Haque et al. 1991, 1992, 1996, 1998). In the latest study from this group, asbestos fibers were found in 50% of fetal digests and 23% of placental digests from stillborn infants compared with 15% of liveborn placentas. Mean fiber concentrations in stillborn tissues and placenta tissues were comparable to one another (30,000–60,000 f/g), but were much greater than mean fiber concentration in liveborn placentas (19 f/g) (Haque et al. 1998). The source of maternal exposure in these studies was unknown, but was presumed by Haque et al. (1998) to be a mix of oral and inhalation environmental (not occupational) exposure. It is unknown if the increased number of fibers in the stillborn fetuses is attributable to increased maternal exposure to asbestos or to changes in fetal or placental factors, unrelated to asbestos exposure, influencing fiber tissue accumulation.

3.4.2.2 Oral Exposure

Asbestos fibers have been detected in blood (Weinzweig and Richards 1983) and lymph (Sebastien et al. 1980b) of rats exposed to oral doses of asbestos, suggesting that fibers penetrating the gut might be carried to tissues throughout the body. In support of this, asbestos fibers have been detected in the lung, kidney, liver, brain, heart, and spleen of rats that had been exposed to asbestos in the diet (Cunningham et al. 1977; Pontefract and Cunningham 1973). Highest levels of fibers were found in the omentum (a fold of the peritoneum connecting abdominal viscera to the stomach), supporting the idea that the fibers were emanating from the gastrointestinal tract. Although the diet fed to the animals was prepared using corn oil to minimize asbestos fiber inhalation, the possibility that some fiber inhalation took place cannot be eliminated (Cunningham et al. 1977).

3.4.2.3 Dermal Exposure

No studies were located regarding distribution of asbestos fibers after dermal exposure. It is generally considered that dermal uptake of asbestos is not significant.

3.4.2.4 Other Routes of Exposure

The distribution of asbestos fibers has been investigated in a number of studies after exposure via intratracheal or intravenous injection. The translocation of chrysotile fibers from the lung to the pleura and mesothelium has been observed in rats exposed by intratracheal injection (Fasske 1988; Viallat et al. 1986). Following intravenous injection of chrysotile fibers into pregnant rats, fibers were detected by electron microscopy at higher levels in liver and lung tissue in fetuses of exposed dams compared with levels in fetuses from nonexposed dams (Cunningham and Pontefract 1974). Asbestos fibers also were detected in digests of fetal and placental tissue following intravenous injection of pregnant mice with single doses of crocidolite suspensions (Haque and Vrazel 1998). These findings support those of Haque et al. (1991, 1992, 1996, 1998), suggesting that some transplacental transfer of asbestos fibers may occur.

3.4.3 Metabolism

3.4.3.1 Inhalation Exposure

Asbestos fibers are not metabolized in the normal sense of the word, and amphibole fibers that are retained in the lung do not appear to undergo any major changes (Bellmann et al. 1987; Carter and Taylor 1980; Roggli et al. 1987a). However, chrysotile fibers appear to undergo some type of breakdown or alteration in the lung. This conclusion is based primarily on measurements of asbestos levels in the lung as a function of exposure duration. With continuing exposure of animals, amphibole levels tend to rise linearly, whereas chrysotile levels reach a steady-state concentration within several months (Wagner et al. 1974) (see also Section 3.5.1). These data from animal studies are supported by a number of human studies in which the ratio of amphibole to chrysotile concentration in lung tissue was much higher than expected based on the composition of the inhaled fibers (Jones et al. 1980a, 1980b; Pooley 1976; Stephens et al. 1987; Wagner et al. 1982a, 1982b, 1986). Long chrysotile fibers (>10 or 18 μm) are expected to accumulate in humans with continued exposure, based on observations of an association between duration of exposure of chrysotile miners and millers and lung chrysotile fiber concentrations >18 μm in length (Case et al. 2000) and estimations of long clearance half times (>8 years) for lung-sequestered fibers in chrystotile miners and millers (Finkelstein and Dufresne 1999). Finkelstein and Dufresne (1999) discerned patterns in their data suggestive that lung concentrations of chrysotile fibers would reach plateaus in humans after decades of exposure under occupational conditions.

The basis of this apparent loss of chrysotile fibers is not clear, but it may be related to a slow dissolution of the fibers in tissue fluids or in macrophages (Fasske 1988; Jaurand et al. 1984), or to a separation of the fibers into much finer component fibrils (Bellmann et al. 1987; Coin et al. 1992, 1994; Cook et al. 1982; Roggli et al. 1987a). In the latter case, the apparent loss of fibers could be an artifact due to the inability of normal methods for fiber isolation and quantification in tissues to detect very fine fibrils. Loss of chrysotile has been reported to be related to the fragmentation of long fibers, resulting in the formation of smaller fibers (Churg et al. 1989a, 1989b). There appears to be preferential clearance of short asbestos fibers compared to long ones (Coin et al. 1992; Finkelstein and Dufresne 1999). For example, based on an analysis of lung fiber concentrations in 72 chrysotile miners and millers, years of exposure, and time since last exposure, long-term clearance half-times were estimated to be about 4 and 8 years for chrysotile fibers <5 μm and >10 μm in length, respectively (Finkelstein and Dufresne 1999). In contrast, clearance half-times were about 8 and 16 years for tremolite fibers <5 μm and >10 μm in length, respectively. (Short-term clearance times could not be measured in this analysis of lung fiber concentrations in

chronically exposed miners and millers.) Long fibers that reside in the lung can form asbestos bodies. The formation of asbestos bodies might represent an attempt by macrophages to digest these fibers extracellularly (Koerten et al. 1990a, 1990b).

3.4.3.2 Oral Exposure

No studies were located regarding any changes in asbestos fibers in the gastrointestinal tract *per se*. However, chrysotile fibers incubated in simulated gastric juice underwent leaching of magnesium ion from the silica framework, with a resultant change in net fiber charge from positive to negative (Seshan 1983), and chrysotile fibers with altered appearance and x-ray diffraction patterns were detected in the urine of animals (Hallenbeck and Patel-Mandlik 1979; Patel-Mandlik and Millette 1983). These observations, although limited, suggest that chrysotile fibers undergo some metal ion exchange and alterations in gross structure in biological fluids after oral exposure. Asbestos bodies have been detected is tissues such as the colon (Ehrlich et al. 1992), suggesting that this process may occur in extrapulmonary tissues as well.

3.4.3.3 Dermal Exposure

No studies were located regarding any changes in asbestos fiber composition or structure after dermal exposure.

3.4.3.4 Other Routes of Exposure

As stated above, asbestos fibers are not metabolized in the true sense of the word; however, a number of animal studies indicate that chrysotile fibers are physically altered in the lung after intratracheal injection. Following phagocytosis, chrysotile fibers were observed to decrease in size, become transparent, and, in some cases, break into fragments (Fasske 1988). Longitudinal splitting, resulting in a greater number of thinner fibers was noted for actinolite and amosite (Cook et al. 1982), and fragmentation, resulting in shorter fibers, was observed for chrysotile (Churg et al. 1989a, 1989b). These changes in fiber shape and size may directly impact fiber clearance and toxicity in the lung.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

The principal pathway by which fibers are removed from the respiratory tract is mucociliary transport. This is mediated by ciliated epithelial cells that produce and move the layer of mucus coating the epithelial tissue upwards toward the throat, where it is swallowed. Fibers deposited in this mucus layer are swallowed into the alimentary canal and most are ultimately excreted in the feces (Cunningham et al. 1976; Evans et al. 1973; Griffis et al. 1983; Morgan et al. 1978). However, a small number of fibers may penetrate through the epithelial layers of the lung and/or the gastrointestinal tract and are transferred to the blood and eventually to the kidney, where some of them may be excreted in the urine (Finn and Hallenbeck 1984). In addition, some fibers are not cleared from the lung, leading to a gradual accumulation with time (Case et al. 2000; Finkelstein and Dufresne 1999; Jones et al. 1988a; Wagner et al. 1974).

Animal studies indicate that clearance of fibers from the upper airways generally occurs within a few hours (Bolton et al. 1983; Evans et al. 1973). However, clearance from the lower airways is slower, with half-times ranging up to 160 days (Bellmann et al. 1987; Coin et al. 1992; Evans et al. 1973; Morgan et al. 1978). This slow clearance is mediated largely by macrophages, which engulf fibers in the bronchioles and alveoli (which are not ciliated), and carry them to the ciliated portion of the airway for transport upward (Holt 1974). Macrophages may also translocate some fibers from the lung to the pleura (Holt 1983). The clearance of chrysotile fibers from the lungs is dependent on fiber length. Animal and human data indicate that long fibers (in excess of 5 or 10 μm) are cleared from the lower airways more slowly than short fibers (Bellmann et al. 1987, 1994; Davis et al. 1986a, 1988; Finkelstein and Dufresne 1999; Morgan et al. 1978; Roggli et al. 1987a; Searl 1997; Warheit et al. 1997), probably because long fibers cannot be easily engulfed and moved by a single macrophage (Morgan et al. 1978). Fibers less than 1 μm in length were cleared from the rat lung with a half-life of less than 10 days, whereas fibers longer than 16 μm were cleared with a half-life of greater than 100 days (Coin et al. 1992; Searl 1997). Pulmonary clearance half-times for asbestos fibers must be viewed with caution, however, as a first-order kinetic model is generally not an adequate fit for the data (Hesterberg et al. 1996; Searl 1997). The preferential clearance of chrysotile over amphiboles (Finkelstein and Dufresne 1999; Jones et al. 1994) may be attributed to fragmentation of long fibers, resulting in the formation of shorter fibers which are more readily engulfed and moved by a single macrophage (Jones et al. 1994).

3.4.4.2 Oral Exposure

Nearly all asbestos fibers that are ingested are excreted in the feces. This is essentially complete within 48 hours following a single oral dose (Gross et al. 1974). Small numbers of fibers may also be excreted in the urine (Boatman et al. 1983; Hallenbeck and Patel-Mandlik 1979), but this accounts for only a very small fraction of the ingested dose (Cook and Olson 1979).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion of asbestos fibers after dermal exposure. It is generally considered that dermal exposure does not result in uptake of asbestos.

3.4.4.4 Other Routes of Exposure

Similar to observations made in inhalation studies, studies in which animals were exposed by intratracheal injection indicate that chrysotile fibers are preferentially cleared from the lung over amphiboles (Churg et al. 1989a, 1989b; Sebastien et al. 1990). The enhanced clearance was generally attributed to fragmentation of fibers, rather than dissolution. The resulting fibers are shorter and more readily engulfed and moved by alveolar macrophages.

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

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

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al.

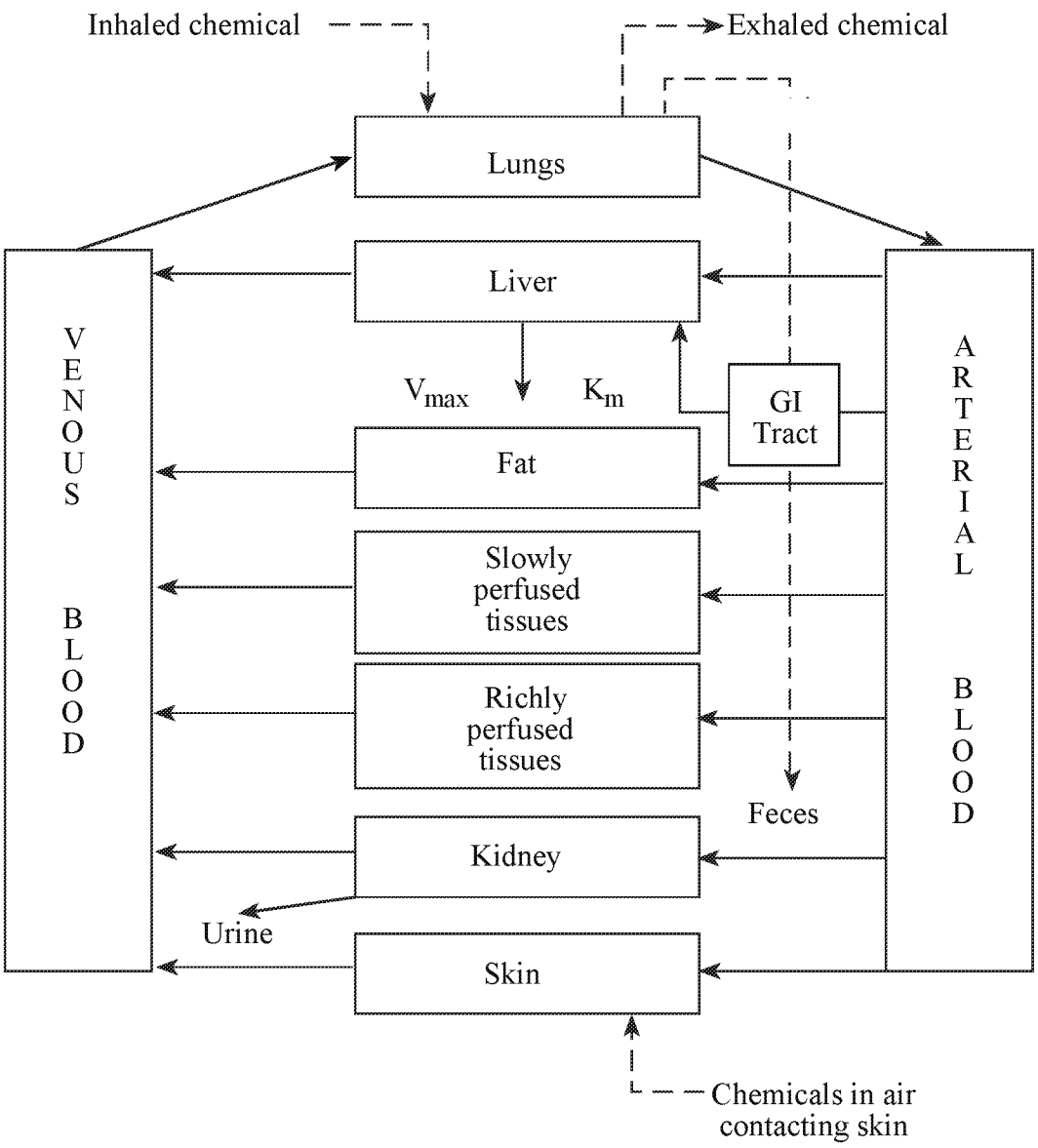
1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model.

Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

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

3.4.5.1 Summary of PBPK Models

No PBPK models specific for asbestos were located. While a number of physiologically-based models for deposition and clearance of inhaled insoluble material have been developed (ICRP 1994; Phalen et al. 1991; Stober and McClellan 1997; Stober et al. 1994), a direct application of these models to the kinetics of asbestos fibers in humans has not been reported.

3.4.5.2 Asbestos PBPK Model Comparison

The available models for evaluating the dispositional kinetics of insoluble materials vary considerably in their level of complexity, but they are predominantly based on similar basic concepts (for recent review, see Stober and McClellan 1997). Recent models for fiber deposition in rats (Asgharian and Anjilvel 1998) have been reported, as have several models for clearance (for recent review, see Stober and McClellan 1997). Many models focus on either deposition or clearance processes, rather than combining the two, although recent efforts have developed lung retention models for fibers in humans and rats that include deposition and clearance processes (Yu et al. 1996, 1997).

The most successful models divide the respiratory system into a number of compartments, with each compartment having a distinct set of deposition or clearance parameters. Deposition models generally divide based on the bronchiolar branch pattern, whereas clearance models tend to divide based on anatomical clearance pathways. For example, material deposited in the tracheobronchial region clears predominantly through the larynx and eventually to the gastrointestinal tract, doing so at a faster overall rate than clearance from the pulmonary region. As additional knowledge of the physiology of the various compartments is discovered, subcompartments are added, each with an additional set of parameters. By combining the parameters from the various subcompartments and estimating the overall contribution of that subcompartment to the total, an estimation of the overall kinetics of exposure can be achieved. The most recent example of this approach is the POCK (physiology-oriented compartmental kinetics) model (Stober et al. 1994), which has a large number of subcompartmental parameters, each with equations to model particle clearance. This would allow for the modeling of disease states wherein specific aspects of deposition and/or clearance are altered without significantly affecting the others (i.e., particle overload of alveolar macrophages). However, to date, the majority of models have focused primarily on particles rather than fibers (see Section 3.4.5.3 for further explanation).

3.4.5.3 Discussion of Model

Because the biopersistence of fibers, including asbestos, is a key determinant of their toxicity, the most appropriate models for the estimation of toxic responses are likely to be those that model the deposition and clearance of the inhaled fibers. Existing models lack a number of features that have prevented them from being adequately utilized to model the kinetics of asbestos exposures in humans. Perhaps the greatest hindrance to the development of PBPK models for asbestos (i.e., their parameterization, simulation, and validation) has been the lack of accurate exposure data to link with lung fiber burden data in humans. Exposure assessments in human studies have been primarily based on estimates made from descriptions of environmental conditions in the workplace, rather than direct measurements of airborne asbestos concentration. Additionally, measurements of pulmonary fiber content in humans are generally performed after the subject has died, often a number of years following the cessation of exposure. These two factors combine to make accurate modeling of asbestos deposition and clearance from the existing human data more difficult.

The majority of the existing kinetic models for describing the fate of fibers and particles within the respiratory system were developed based on inhalation studies in rats. While this has undoubtedly led to more accurate modeling, as the rat database is considerably more extensive than the human one, several aspects of rodent anatomy and physiology differ significantly from the corresponding human system. In particular, the respiratory system in rats is structured differently than humans. The rat lung possesses a different branching pattern, which is likely to affect the deposition of the asbestos fibers. The bronchial tree of the rat is also physically smaller than that of man. When combined with the fact that rats are obligate nose-breathers, which is not the case for humans, this results in fibers that are respirable by humans being not respirable by most rodents (Hofmann et al. 1989). These factors decrease the utility of the rodent models in predicting human disposition under similar exposure conditions.

An additional difficulty with many models lies in the fact that they were developed for modeling particles, not fibers. Differences in physical properties in these insoluble materials can influence deposition and clearance processes in the respiratory tract. For example, particles that are too large to be phagocytized by alveolar macrophages generally do not reach the deep lung, but instead deposit by impaction in the nasal passages or airways. In contrast, long, thin fibers (>15 μm in length, but <3 μm in diameter) are respirable and can reach the deep lung where they are unable to be phagocytized by macrophages, and thus, are unable to be effectively cleared. The decreased clearance rate of fibers with increasing fiber length is also not considered in the majority of the particle-based clearance models. Fiber

breakdown, lengthwise or transverse, is also not factored into particle-based models. These deficiencies make utilization of particle-based models of deposition and clearance for the prediction of the behavior of fibers, including asbestos, problematic.

Recently, mathematical models have been developed for the deposition and retention of refractory ceramic fibers in the alveolar region of lungs of rats (Yu et al. 1994, 1995, 1996) and humans (Yu et al. 1994, 1995, 1997). The development of the rat model was based on exposure and lung burden data (including information on distribution of fiber sizes) from studies of rats exposed chronically to airborne refractory ceramic fibers. The models include descriptions of deposition rates with tidal volume, breathing frequency, air concentration of fibers of specific diameters and lengths, and alveolar deposition fraction (a function of airway structure, lung morphometry, and ventilation parameters for fibers of specific diameters and lengths) as explanatory variables and description of rates of three simultaneous clearance processes (alveolar macrophage-mediated clearance, dissolution of fibers in the lung fluid, and breakage of long fibers into shorter fibers). Rates for the removal processes in humans were extrapolated from the rat data. The developed human model predicted lung burdens that were in general agreement with lung fiber counts for three workers exposed to refractory ceramic fibers (Yu et al. 1997). The development of similar rat and human models for asbestos fiber lung deposition and clearance may be useful to more accurately predict human health risks from available data from rat inhalation bioassays. The most useful models for deposition and clearance of asbestos fibers are likely to be complex and should account for differences associated with different types of asbestos fibers and different size distributions of fibers.

3.5 MECHANISMS OF ACTION

Fibers that persist within the lung or the mesothelium are capable of producing fibrogenic and tumorigenic effects in these tissues. Although the precise mechanisms by which asbestos fibers cause toxic injury have not been determined, data are available that indicate that both direct interaction between fibers and cellular components and cell-mediated pathways may be involved. In addition, the physical-chemical nature of the fiber appears to be an important determinant of toxicity. Though the various mechanisms are likely to interact extensively, they will be discussed individually below.

3.5.1 Pharmacokinetic Mechanisms

A number of physical and chemical properties such as fiber size, durability, and iron content are important determinants of asbestos toxicity. The dependence of toxicity on these fiber properties is discussed below.

Fiber Size. The size (length and diameter) of an asbestos fiber appears to be one of the most important determinants of its toxicity. Fiber size dictates respirability, deposition, and clearance from the lung. In general, only fibers <3 μm thick are capable of reaching lower airways (Timbrell 1982). Fibers longer than approximately 5–10 μm are generally cleared more slowly than fibers shorter than 5 μm (Bellmann et al. 1987; Finkelstein and Dufresne 1999; Hesterberg et al. 1996; Morgan et al. 1978; Roggli et al. 1987a; Searl 1997; Warheit et al. 1997). The maximum fiber length that can be engulfed by a single macrophage is approximately 16–17 μm (Coin et al. 1992; Lippmann 1990). Asbestos-associated diseases are attributable to fibers of different sizes. The strongest evidence for this conclusion comes from studies in animals, where chronic inhalation exposure to dust clouds rich in long fibers (those in excess of 5 μm) produces higher incidence of lung cancer than exposure to dust clouds rich in short fibers (mostly <5 μm) (Davis and Jones 1988; Davis et al. 1986a). Asbestosis has been associated with fibers longer than 2 μm, mesothelioma with fibers longer than 5 μm, and lung cancer with fibers longer than 10 μm (Lippmann 1988, 1990). The dose-response relationships for the production of mesothelioma in rats intraperitoneally injected with amosite, chrysotile, and crocidolite were similar when doses were expressed in terms of the number of long (>4–8 μm), thin (<0.25 μm) fibers (Davis et al. 1991a; Stanton et al. 1981). Lippman (1988, 1990) noted that, in general, fiber widths <0.1 μm have been associated with mesothelioma, but can be larger for asbestosis and lung cancer. It should be noted, however, that rats exposed to populations of relatively shorter and broader tremolite fibers (lengths greater than 4 μm and width up to 1.5 μm) showed a high incidence of mesothelioma (American Thoracic Society 1990; Stanton et al. 1981). Ultimately, the size of the fiber determines its residence time in the lung. Longer fibers remain in the lung or mesothelium, whereas shorter fibers are cleared (Coin et al. 1992; Searl 1997). Fibers with lengths >15–20 μm are incompletely ingested and dissolved by pulmonary macrophages, which is thought to lead to chronic and persistent inflammation and tissue damage (Coin et al. 1992; Davis 1989; Davis et al. 1986a; Eastes and Hadley 1996; Lippmann 1994).

Interestingly, Churg et al. (1989a, 1990) reported that the severity of fibrosis in asbestos workers exposed primarily to tremolite and chrysotile, or amosite was positively correlated with lung fiber concentrations, but was negatively correlated with fiber length. The negative correlation (while not establishing

causation between short fibers or fiber fragments and fibrosis) suggests that short fibers may be more important to some aspects of asbestos-mediated toxicity than previously thought. As discussed by Case (1994) (see also Section 3.2.1.2), observation of the negative correlation of fibrosis score with fiber length may be dependent on the selection of fiber length counting criterion. Case (1994) has hypothesized that long fibers may initiate events and shorter fiber fragments, once formed in the lung, may increase effects on macrophage activity and subsequent fibrosis. Another possible explanation for this observation is that fiber size is also related to fiber surface area (Lippman 1988, 1990). As mentioned above, fiber surface properties are important to toxicity. Smaller thinner fibers have a greater surface area per unit mass than larger thicker fibers, thereby allowing for greater interaction with cell macromolecules. In addition, increased surface area may be important to providing more catalytically active iron sites (see below) for hydroxyl radical formation from reactive oxygen species.

Fiber Durability. Fiber biopersistance is believed to be a major mechanism of fiber-induced pathogenicity (Hesterberg et al. 1998a, 1998b). Numerous studies have indicated that some asbestos fibers, particularly chrysotile fibers, undergo fragmentation (latitudinal breakage) and/or splitting (longitudinal breakage) (Bellmann et al. 1987; Churg et al. 1989a, 1989b; Coin et al. 1992; Cook et al. 1982; Fasske 1988; Roggli et al. 1987a). The importance of fiber size and surface area with respect to toxicity is discussed above. Both fragmentation and splitting serve to increase the number of fibers and fiber surface area; therefore, toxicity of the resulting fibers is likely to increase as well. However, fiber fragmentation results in shorter fibers which are more readily cleared from the lungs by alveolar macrophages, whereas fiber splitting is likely to result in no change in fiber clearance. Differences in fiber durability may account for the differences observed in fiber potency between chrysotile and amphiboles.

Fiber Type. A diversity of opinion exists regarding relative potencies of various asbestos fiber types with respect to fibrogenicity and carcinogenicity. Some investigators have proposed that amphibole fibers, such as tremolite, are more potent than chrysotile fibers in inducing fibrotic lung disease and lung cancer (Hodgson and Darnton 2000; McDonald 1998a; McDonald and McDonald 1997; McDonald et al. 1999; Mossman et al. 1990a). Others have suggested that the differences in the potency of chrysotile and amphibole fibers in inducing lung cancer cannot be reliably discerned from available data (Stayner et al. 1996). It is generally agreed that exposure to amphibole fibers can produce mesothelioma, and that the potency of amphibole fibers to produce mesothelioma is greater than that of chrysotile. Some investigators have indicated that mesotheliomas among chrysotile-exposed workers are largely caused by small amounts of tremolite fibers found in mined and processed chrysotile (Churg 1988; Churg et al.

1993; Lippmann 1994; McDonald 1998a; McDonald et al. 1997). Others indicate that chrysotile fibers may also induce mesothelioma (Frank et al. 1998; Langer and Nolan 1998; Smith and Wright 1996). In a statistical analysis of mesothelioma and lung tumor data from a series of studies in which rats were exposed to airborne asbestos fibers of different types (chrysotile, amosite, crocidolite, and tremolite), Berman et al. (1995) concluded that amphibole fibers were more potent than chrysotile in inducing mesotheliomas, but no difference could be discerned in potencies of these fiber types to induce lung tumors. Apparent differences in potency among fiber types may be related to differences in lung retention. Amphibole fibers appear to be retained in the lung for longer periods than chrysotile fibers (Albin et al. 1994; Churg 1994; Churg et al. 1993; Davis 1989; Wagner et al. 1974). It has been suggested that such differences in retention may serve as a partial explanation of why amphibole fibers appear to be more potent in producing mesotheliomas than chrysotile fibers (Mossman et al. 1990a; American Thoracic Society 1990) (see also Section 3.4.3.1).

Iron Content. Iron is a redox-active metal and can catalyze the formation of hydroxyl radicals from superoxide and hydrogen peroxide via the Haber-Weiss reaction (the potential role of oxidant species in asbestos toxicity is discussed in Section 3.5.2). Evidence supporting the importance of iron in asbestos-induced toxicity include the success of iron chelators (desferrioxamine) in inhibiting the production of reactive oxygen species and subsequent toxicity (Goodglick et al. 1989; Kamp et al. 1992; Lund and Aust 1991b; Mahmood et al. 1993; Simeonova and Luster 1995). Desferrioxamine has also been shown to decrease the ability of asbestos fibers to induce DNA single-strand lesions (Chao and Aust 1994; Kienast et al. 2000). Silicate fibers capable of producing pneumoconiotic changes were also able to serve as Haber-Weiss catalysts, whereas silicate fibers that were nonpneumoconiotic lacked this activity (Kennedy et al. 1989).

There are several possible sources of iron in the lung that may contribute to asbestos toxicity. One source of iron is the fiber itself. Crocidolite and amosite asbestos may contain levels of 26–36% iron by weight (Lund and Aust 1991a). A second source of iron is as a contaminant of asbestos. Iron-containing minerals such as pyrite, magnetite, nemalite, and iron ore often occur as contaminants of asbestos and can be deposited in the lung along with asbestos fibers (Fontecave et al. 1990). A third possible source of iron is from within the exposed animal. Ferritin (an iron-containing protein) is present in macrophages and giant cells. Iron metabolism was found to be altered in these cells by the presence of poorly digestible fibers (Koerten et al. 1990a). Iron is also a component of the protein-coat covering asbestos bodies (Ghio et al. 1997; Koerten et al. 1990a, 1990b). The extent to which each of these sources of iron

contribute to the catalysis of hydroxyl radical formation *in vivo* is uncertain and warrants further investigation.

3.5.2 Mechanisms of Toxicity

This section provides an overview of several potential mechanisms involved in the development of asbestos-induced health effects (direct interaction with macromolecules, active oxygen mechanisms, and other cell-mediated mechanisms). An expert panel convened by IARC concluded in 1996, "Overall, the available evidence in favor or against any of these mechanisms leading to the development of lung cancer and mesothelioma in either animals or humans is evaluated as weak" (IARC Expert Panel 1996). Pulmonary inflammatory factors (a subset of other cell-mediated mechanisms) were considered by the IARC panel as having the most support among the potential mechanisms involved. For additional information on the molecular mechanisms of asbestos-induced pulmonary disease discussed below, including potential interactions between a number of the mechanisms, see recent reviews (Kamp and Weitzman 1999; Kinnula 1999; Lee and Testa 1999; Murthy and Testa 1999; Robledo and Mossman 1999).

Direct Interaction. Asbestos fibers can adsorb to a variety of cellular macromolecules (e.g., proteins, membrane lipids, RNA, DNA). In rat lung microsomes, chrysotile fibers were found to bind to cytochrome P-450, thereby decreasing mono-oxygenase activity (Khan et al. 1992; Rahman et al. 1990). Chrysotile and crocidolite fibers were found to bind to artificial lipid membranes *in vitro*, thereby increasing membrane rigidity (Gendek and Brody 1990). This effect was also noted in erythrocytes, and may be responsible in part for the *in vitro* hemolytic activity of asbestos fibers. The interaction between asbestos fibers and cell membranes was mediated in part by surface charge (positively charged chrysotile fibers can become associated with negatively charged membrane constituents), and also fiber binding to fibronectin, a glycoprotein found in abundance in the alveolar lining fluid (Brown et al. 1991). Dielectric changes in membrane properties and cell interiors have been observed in cultured human mesothelial cells exposed to crocidolite fibers (Dopp et al. 2000). Peterson et al. (1993) noted that the integrity of cultured human lung epithelial cells was compromised by chrysotile, resulting in increases in epithelial permeability that occurred in the absence of cell death and inflammatory cells. The coulombic forces between the asbestos fiber and macromolecules (DNA, RNA, and protein) may induce conformational changes (Brown et al. 1998; Chang et al. 1990), and these changes could affect protein function and chromosomal fidelity. Surface charge density may also be an important factor in fiber potency (Bonneau et al. 1986; Davis et al. 1988). In some studies, asbestos fibers were observed to interfere with

cytokinesis (Jensen and Watson 1999). Fibers found to be translocated near the nucleus can interact with the cytoskeleton and interfere with chromosome segregation (Ault et al. 1995; Malorni et al. 1990) or with micronucleus formation (Lu et al. 1994a). Deletions of chromosome segments (particularly the short arm of chromosome 3 and portions of chromosomes 1, 6, 9, 15, and 22) have been noted in human mesothelioma cells or cell lines (Balsara et al. 1999; Barrett et al. 1989; Bell et al. 1997; Cheng et al. 1993, 1994; Flejter et al. 1989; Lee et al. 1996; Lu et al. 1994b; Taguchi et al. 1993), and interference with chromosome segregation may at least partially account for this (Barrett et al. 1989). Recent work by J.R. Testa and coworkers (see Murthy and Testa 1999) indicates that certain tumor suppressor genes are frequently altered in the regions of asbestos-induced deletions, although underlying mechanisms have not been clearly elucidated.

Additional evidence supporting the importance of fiber surfaces comes from studies in which the fiber surfaces have been altered. Modification of asbestos fiber surfaces with certain dyes, alkyl groups, or phosphate was found to decrease their *in vitro* hemolytic and cytotoxic activity (Awadalla et al. 1990; Brown et al. 1990, 1991; Habashi et al. 1991). However, relative to untreated chrysotile fibers, alteration of the fiber surface chemistry (via HCl treatment) did not significantly alter the results of a genotoxicity test that assessed the induction of micronuclei in Chinese hamster lung fibroblasts treated *in vitro* (Keane et al. 1999). Cyclical stretching of cultured human alveolar cells during exposure to asbestos fibers (as might occur during normal breathing) resulted in increased production of the proinflammatory cytokine interleukin-8, presumably in response to a direct mechanical interaction between asbestos fibers and the alveolar cells. This response was enhanced when the fibers were coated with fibronectin (Tsuda et al. 1999). In general, these data suggest that direct interactions between asbestos fibers and key cellular molecules may be responsible, at least in part, for asbestos-related health effects.

Active Oxygen Mechanism. In response to asbestos fibers, alveolar macrophages produce reactive oxygen species in an attempt to digest the fiber. The reactive oxygen species include hydrogen peroxide and superoxide radical anion (O_2^-) (Cantin et al. 1988; Case et al. 1986; Hansen and Mossman 1987; Nyberg and Klockars 1991; Roney and Holian 1989). These reactive oxygen species are relatively mild oxidants. However, they can spontaneously react with each other, producing hydroxyl radicals that are much more potent oxidants. This reaction is often referred to as the Haber-Weiss or Fenton reaction (Garcia et al. 1988; Weitzman and Graceffa 1984; West 1985). The Haber-Weiss reaction is greatly enhanced in the presence of redox-active metals such as iron. Numerous *in vitro* studies have linked the production of reactive oxygen species to asbestos-induced lipid peroxidation (Fontecave et al. 1990; Goodglick et al. 1989; Yano 1988), cytotoxicity (Garcia et al. 1988; Goodglick and Kane 1990; Iguchi

and Kojo 1989; Kennedy et al. 1989; Shatos et al. 1987), cell proliferation (Marsh and Mossman 1991), genotoxicity (Chao et al. 1996; Fung et al. 1997a; Kienast et al. 2000; Korkina et al. 1992; Lund and Aust 1991a, 1992; Xu et al. 1999), and apoptosis (Broaddus et al. 1996, 1997). *In vitro* studies have also shown that the effects of asbestos are diminished by the addition of catalase and superoxide dismutase (enzymes that catalyze the decomposition of reactive oxygen species), free radical scavengers (ascorbic acid, bemitil, mannitol, salicylate, 5,5'-dimethyl-1-pyroline N-oxide, rutin, vitamin E) (Brown et al. 1998; Faux and Howden 1997; Garcia et al. 1988; Goodglick and Kane 1990; Goodglick et al. 1989; Iguchi and Kojo 1989; Kienast et al. 2000; Korkina et al. 1992; Lund and Aust 1992; Yano 1988), or calcium channel inhibitors (Ishizaki et al. 1997; Lim et al. 1997). Cell membrane lipids have been shown to undergo peroxidation, resulting in increased membrane permeability in rat lung fibroblasts cultured with asbestos (Iguchi et al. 1993). Additional evidence supporting the involvement of reactive oxygen species in asbestos toxicity comes from *in vivo* studies. Intratracheal instillation of chrysotile asbestos in rats has been shown to lead to hydroxyl radical formation (Schapira et al. 1994). Activities of superoxide dismutase, glutathione peroxidase, and catalase were significantly elevated in rats exposed to crocidolite by inhalation (Janssen et al. 1992). Decreases in a number of antioxidants known to protect against oxidative stress were observed in alveolar macrophages or the bronchoalveolar lavage of rats exposed to asbestos fibers via intratracheal instillation (Abidi et al. 1999; Kaiglová et al. 1999). Levels of superoxide dismutase and plasma malondialdehyde (an indicator of lipid peroxidation) were significantly elevated in asbestos workers compared to controls (Kamal et al. 1989, 1992). Lipid peroxidation was noted in cells and fluid from bronchoalveolar lavage of rats after exposure to crocidolite (Ghio et al. 1998; Petruska et al. 1991); endogenous peroxidase activity was noted in macrophages from pleural lavage of mice after intraperitoneal injection of crocidolite (Branchaud et al. 1993). Cytotoxic and oxidative responses indicative of oxidative stress were observed in alveolar macrophages and peripheral red blood cells (RBCs) of rats exposed to crocidolite or chrysotile fibers via intratracheal instillation (Afaq et al. 1998). Interestingly, uptake of asbestos fibers into epithelial cells is increased by reactive oxygen species (Hobson et al. 1990; Peterson and Kirschbaum 1998). Overall, the data collectively indicate that the production of reactive oxygen species is likely to be an important component of the mechanism of asbestos-induced toxicity.

Other Cell-Mediated Mechanisms. In addition to the release of active oxygen species, alveolar macrophages and other cells, including pleural mesothelial and lung cells, release a number of cellular factors in response to asbestos exposure. These factors are mediators of a number of cellular reactions including inflammation, macrophage recruitment and cell proliferation (for reviews, see Driscoll et al. 1997; Xing et al. 1999). Chronic stimulation of these pathways can result in a gradual loss of some

epithelial cells, proliferation and deposition of collagen by fibroblasts, or alterations of cellular phenotype (Davis and Jones 1988; Davis et al. 1986c; Holian et al. 1997; Lasky et al. 1996). These data suggest that the effects of asbestos exposure may be mediated by stimulation of the autocrine (same cell) and paracrine (different cell) systems.

Recent work has suggested potentially important mechanistic roles for a number of nuclear regulatory proteins, oncogenes, proto-oncogenes, and second messenger proteins. Among these are nuclear factor-κβ (NF-κβ) (Barchowsky et al. 1998; Cheng et al. 1999b; Driscoll et al. 1998; Faux and Howden 1997; Luster and Simeonova 1998; Mossman et al. 1997; Oettinger et al. 1999; Simeonova and Luster 1996), activator protein-1 (AP-1), including its subunits of c-fos, c-jun, and fra-1 (Faux and Howden 1997; Fung et al. 1997b; Heintz et al. 1993; Janssen et al. 1995; Mossman et al. 1997; Sandhu et al. 2000; Zanella et al. 1999), p53 (Hayashi et al. 1996; Johnson and Jaramillo 1997), *ras* (Hayashi et al. 1996; Nelson et al. 1999), tyrosine kinases (Peterson and Kirschbaum 1998), and protein kinase c (PKC) (Fung et al. 1997b; Lim et al. 1997; Simeonova and Luster 1996). Interestingly, a number of these factors have been shown to influence the production of other cellular factors (Barnes 1997; Blackwell and Christman 1997; Cheng et al. 1999b). Additionally, cellular oxidant status has been shown to influence the behavior of AP-1 and NF-κβ (Janssen and Sen 1999; Janssen et al. 1995; Simeonova et al. 1997). The latter two observations have served to further the view that NF-κβ and AP-1 play roles in asbestos-induced lung injury, as they would allow for the integration of several of the mechanisms proposed above (i.e., asbestos-associated iron could generate oxygen radicals, leading to the increased activity of nuclear factors, which induce cytokine genes, leading to cell infiltration and proliferation).

A number of the factors mentioned above also participate in the pathways regulating pulmonary inflammation. Although poorly understood, the inflammatory response is thought to play an important role in the development of asbestos-induced pulmonary disease and is the one mode of toxic action for which there are supporting human data from *in vitro* and *in vivo* studies (IARC Expert Panel 1996). Asbestos exposure has been shown to elicit a complement-dependant increase in the number of alveolar macrophages at sites of asbestos deposition (Warheit et al. 1984, 1985, 1986, 1988). Other chemotactic factors include leukotrienes (Dubois et al. 1989; Garcia et al. 1989; Hayes et al. 1990), prostaglandins (Bissonnette et al. 1989, 1990; Garcia et al. 1988), and interleukins (Boylan et al. 1992; Griffith et al. 1994; Luster and Simeonova 1998; Perkins et al. 1993). One factor that has been particularly well-studied with regards to its role in the asbestos-induced inflammatory response is TNF-α. A number of studies have demonstrated a role of TNF-α in the inflammatory response following asbestos exposure in animals (Dubois et al. 1989; Liu et al. 1998; Simeonova and Luster 1995) and humans (Zhang et al.

1993). Asbestos-associated TNF-α has been shown both to induce and to be induced by oxidant species (Pietarinen-Runtti et al. 1996; Simeonova and Luster 1995). Reduction of TNF-α *in vivo* results in a protection from asbestos-induced fibrotic changes (Brass et al. 1999; Liu et al. 1998). Some of the asbestos-induced inflammatory reactions may be related to fiber type. For example, crocidolite, but not chrysotile, induced increased production of TNF-α and interleukin 1β in cultured rat alveolar macrophages exposed for up to 14 days, whereas chrysotile, but not crocidolite, increased production of superoxide anion and nitric oxide radicals (Mongan et al. 2000).

3.5.3 Animal-to-Human Extrapolations

The vast majority of experimental studies of asbestos have been performed in rodent model systems. Results from inhalation studies indicate that rats are suitable qualitative models for asbestos-induced pulmonary diseases, demonstrating chronic inflammation, pulmonary fibrosis (see Section 3.2.1.2), lung cancer (see Section 3.2.1.8), and mesothelioma (see Section 3.2.1.8) following chronic asbestos exposure. Hamsters seem to be more sensitive than rats to mesothelioma development, but less sensitive to the development of pulmonary tumors (Warheit and Hartsky 1994).

Some investigators have suggested that rats may be less sensitive to the development of asbestos-related mesotheliomas than humans. Rödelsperger and Woitowitz (1995) reported, based on the studies of McDonald et al. (1989, 1993) and Doll and Peto (1985), an increased risk in humans for mesothelioma at pulmonary fiber burdens as low as 0.2 f/μg dry weight, whereas a 44-week rodent exposure yielded a 6,000-fold higher lung fiber burden (1,250 f/μg), but less than a 1% incidence of mesothelioma. One possible explanation for this putative difference in sensitivity is that the shorter lifespan of rodents compared to humans, combined with the long latency period for asbestos-related diseases (generally 10 years), does not allow for late-developing respiratory effects to develop in rodents. Alternately, it may relate to differences in deposition and clearance patterns between rats and humans (Asgharian et al. 1995; Hofmann et al. 1989). However, this alternative explanation is difficult to verify because the deposition and clearance patterns for asbestos in humans are poorly described. Additional research on deposition and clearance of asbestos fibers in humans may help to properly address this issue.

3.6 ENDOCRINE DISRUPTION

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, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. Some scientists believe that chemicals with the ability to disrupt the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. Others believe that endocrine disrupting chemicals do not pose a significant health risk, particularly in light 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 compounds are derived from plants and are similar in structure and action as endogenous estrogen. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (EPA 1997). As a result, endocrine disruptors may play a role in the disruption of sexual function, immune suppression, and neurobehavioral function. Endocrine disruption is also thought to be involved in the induction of breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans or animals after exposure to asbestos. No *in vitro* studies were located regarding endocrine disruption by asbestos.

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).

As discussed in Section 3.2 and Chapter 2, numerous studies of occupationally-exposed adult workers identify respiratory effects including interstitial fibrosis, lung cancer, and pleural and/or peritoneal mesotheliomas, as critical health effects, of concern from exposure to airborne asbestos. Typically, these health effects follow chronic exposures and exhibit latencies of 10–40 years, although some cases of asbestosis and pleural plaques have been reported following subchronic exposure.

Some investigators have associated childhood exposures (e.g., from asbestos-laden clothing of occupationally-exposed family members or close childhood proximity to asbestos mining operations) with development of asbestos-related respiratory diseases in adulthood (Anderson et al. 1976; Inase et al. 1991; Magee et al. 1986; McDonald and McDonald 1980; Voisin et al. 1994; Wagner et al. 1960). Malignant mesothelioma is a rare childhood neoplasm that does not appear to be associated with asbestos exposure, in contrast to mesothelioma in adults. Only 80 suspected cases were identified in the literature as of 1988 (Fraire et al. 1988); of these, only 2 girls (3 and 17 years of age) had a history of possible exposure to asbestos. In a more recent published case report, mesothelioma was diagnosed in a 17-year-old boy who lived in a rural setting, had no familial relations with an asbestos worker, and had been exposed daily to asbestos fibers in a cosmetic talc from about 9–12 years of age (Andrion et al. 1994). There was no information regarding the asbestos level in the talc, but the boy exhibited a lung tissue asbestos concentration of 0.51×10^6 f/g dry tissue (62% chrysotile and 38% tremolite). It is not recommended that this value be compared to the mean lung asbestos fiber concentration of 0.11×10^6 f/g , reported by Case et al. (1994) for 60 U.S. children, because there are appreciable variations in lung burden methods and results between laboratories. Andrion et al. (1994) noted, however, that based on lung fiber concentrations determined by their referring laboratory for 85 general autopsy cases of adult subjects living in a polluted urban setting, the boy's asbestos fiber burden was unusually high for a rural dweller and was within the range for the highest 16th percentile of this sample of urban dwellers (range from 0.2 to 3.0×10^6 f/g). The estimated latency period of 8 years is short relative to a latency period of greater than 15 years in 99% of 1,105 adult cases of asbestos-induced mesotheliomas in occupationally-exposed workers reviewed by Lanphear and Buncher (1992). It is uncertain if the relatively short latency period in this case was related to an increased age-related susceptibility, a relatively high exposure level, or an individual susceptibility unrelated to age.

A cohort of 4,659 former residents of Wittenoom, Western Australia, who had lived there between 1943 and 1993 for at least 1 month, and were environmentally, but not occupationally, exposed to asbestos (crocidolite), was studied by Hansen et al. (1998). The rate of mesothelioma in the cohort increased significantly with time from first environmental exposure, duration of exposure, and cumulative exposure.

However, incidence of mesothelioma was not significantly related to age of first exposure (treated as a continuous variable and adjusting for all other variables). Those first exposed as children under 10 years of age exhibited a lower incidence of mesothelioma than those first exposed at an older age.

The lack of reports of asbestos-related respiratory diseases in children suggest that children may not develop respiratory diseases during childhood in response to environmental or "paraoccupational" exposure to asbestos. The long-term retention of asbestos fibers in the lung and the long latency period for onset of asbestos-related respiratory diseases suggest that individuals exposed earlier in life may be at greater risk to the eventual development of respiratory problems than those exposed later in life, but direct evidence for this hypothesis is not available. In contrast, incidence of mesothelioma was not significantly related to age of first exposure in the study by Hansen et al. (1998).

Studies examining age-related susceptibility to airborne asbestos in animals were not located. There was no indication from the available literature that specialized respiratory defense mechanisms might be less active or underdeveloped in children relative to adults. An association has been noted between the slow N-acetyltransferase 2 (NAT2) genotype and the increased risk for developing mesothelioma or nonmalignant respiratory disease in adults exposed to high levels of asbestos (Hirvonen et al. 1995, 1996; see Section 3.10 for more details). To date, it is uncertain if that reported early developmental differences in the expression of NAT2 (Leeder and Kearns 1997) may lead to developmental differences in susceptibility to asbestos toxicity.

No information was located specifically concerning health effects in children exposed to asbestos by the oral or dermal routes. Childhood exposures are likely to result in responses similar to those reported in adults (see Sections 3.2.2 and 3.2.3).

No human studies were located regarding asbestos-related developmental toxicity by any exposure route, but one group of investigators has reported that asbestos fibers were detected more frequently and at higher mean concentrations in tissues from stillborn infants than in placental tissues from live births (Haque et al. 1991, 1992, 1996, 1998). It is unclear if the differences in asbestos tissue counts between these stillborn and liveborn groups are related to either differences in maternal environmental exposure leading to transplacental transfer of fibers, nonexposure-related differences in fetal or placental factors leading to a breach of the normal fetal/placental barrier and an accumulation of fibers in fetal and placental tissue, or sample contamination. Transplacental transfer of asbestos fibers has been demonstrated in pregnant rats and mice given single bolus intravenous injections of asbestos suspensions

(Cunningham and Pontefract 1974; Haque and Vrazel 1998), but the tissue counts in both of these experiments were highly variable. For example, the range of concentrations in 36 digests of fetal tissues sacrificed 1 hour after injection in the mouse experiment ranged from 116 to 30,342 f/g (Haque and Vrazel 1998). This variability may due to an inconsistent mass breakthrough of fibers associated with the bolus intravenous administration (Cunningham and Pontefract 1974). It is expected that the extent of transplacental transfer of fibers would be much less with inhalation, oral, or dermal exposures.

No animal developmental toxicity studies were located for inhalation or dermal routes of exposure. Results from chronic oral studies in rats and hamsters provided no indication of potential for developmental toxicity (exposure was through gestation, weaning, and adulthood), except for some slight reductions in pup birth weight (which might possibly be secondary to asbestos exposure) (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c). Likewise, no exposure-related developmentally toxic effects were found in pregnant mice exposed during gestation to asbestos in drinking water at concentrations as high as 143 μg/mL (Schneider and Maurer 1977).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

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

substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to asbestos 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 asbestos 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 Asbestos

Principal biomarkers of exposure to asbestos fibers include the detection and counting of fibers or asbestos bodies in bronchoalveolar lavage fluid samples (De Vuyst et al. 1982, 1988, 1997; Dumortier et al. 1990, 1998; Roggli et al. 1994a; Sebastien et al. 1988a; Teschler et al. 1994; Tuomi et al. 1991b), sputum samples (McDonald et al. 1988, 1992; Sebastien et al. 1988b), or in autopsied or surgically resected lung tissue samples (Case 1994; Churg 1982; Churg and Warnock 1981; Churg and Wright 1994; Churg et al. 1993; de Klerk et al. 1996; Dodson et al. 1999; Dufresne et al. 1995, 1996a, 1996b; Sebastien et al. 1989). Asbestos bodies are collections of fibers (usually of length >8 μm) with a protein-iron coating (also known as ferruginous bodies) that, when observed in lung tissue sections in conjunction with fibrosis, have been proposed to be used in the diagnosis of asbestosis (Churg 1989; Craighead et al. 1982). Whereas light microscopy can be used to detect and count asbestos bodies, most uncoated fibers in tissue or fluid samples are too small to be visible (Dodson et al. 1999). Transmission or scanning electron microscopy is used to detect and count uncoated asbestos fibers in lung tissue or fluid samples, and electron diffraction or energy-dispersive x-ray analysis is used to determine asbestos type (e.g.,

chrysotile, anthophyllite, tremolite) (NIOSH 1994b). These biomarkers provide indicators of retained internal dose, the cumulative net result of deposition and clearance of inhaled asbestos fibers.

Analyses of bronchoalveolar lavage fluid samples or sputum samples can directly reflect alveolar concentrations of retained fibers and, although they do not reflect the proportion of deposited fibers that may move to the interstitium (Case 1994; Pinkerton et al. 1984), can provide information regarding past exposure to asbestos, especially to amphibole fibers. Obtaining sputum samples is much less invasive than obtaining bronchoalveolar lavage samples. In Libby, Montana vermiculite miners and millers exposed to fibrous tremolite, counts of asbestos bodies in sputum samples closely reflected intensity and duration of past exposure (Sebastien et al. 1988b), but asbestos body counts in sputum samples from volunteers from other cohorts of workers exposed to asbestos (predominately chrysotile or lower levels of amphibole fibers than in Libby) did not reliably reflect past levels of exposure (McDonald et al. 1988, 1992). Concentrations of asbestos bodies in bronchoalveolar lavage fluid samples have been reported to reflect past exposure to asbestos fibers in a number of studies (De Vuyst et al. 1988, 1997; Dumortier et al. 1990, 1998; Roggli et al. 1994a; Teschler et al. 1994; Tuomi et al. 1991b) and to correlate with lung tissue concentrations of asbestos bodies (De Vuyst et al. 1988; Sebastien et al. 1988a; Teschler et al. 1994), but exposure to amphibole fibers may be better reflected than exposure to chrysotile fibers. For example, Sebastien et al. (1988a) reported a statistically significant correlation ($r=0.74$, $p<0.0001$) between concentrations of asbestos bodies in bronchoalveolar fluid samples (which ranged from 0.05 to 10^4 asbestos bodies/mL) and concentrations in lung parenchyma tissue samples (which ranged from 40 to 8.9×10^6 asbestos bodies/g dried lung parenchyma) in 69 patients who had either an open lung biopsy or an autopsy. Sebastien et al. (1988a) concluded that bronchoalveolar concentrations exceeding 1 asbestos body /mL predict that the parenchymal concentration will be in excess of 1,000 asbestos bodies/g dry tissue and that the patient will have experienced "a nontrivial asbestos exposure." Dumortier et al. (1990) reported that, in brake lining and asbestos cement workers, the core fiber of the asbestos bodies was usually amphibole fibers, but chrysotile cores were found in most recently exposed brake lining workers examined. A statistically significant correlation between asbestos body concentrations in bronchoalveolar fluid samples and lung parenchyma samples was also found in 20 patients with histories of occupational exposure to mixed (chrysotile and amphibole) asbestos fibers (Teschler et al. 1994). Concentrations of uncoated amphibole fibers (fibers were counted as particles with nearly parallel long edges, lengths >1 μm, and aspect ratios >3:1) in bronchoalveolar fluid samples were correlated with concentrations of uncoated amphibole fibers in lung parenchyma, but concentrations of uncoated chrysotile fibers in fluid samples were not correlated with concentrations in lung parenchyma samples (Teschler et al. 1994). Teschler et al. (1994) concluded that concentrations of asbestos bodies and amphibole fibers in

bronchoalveolar fluid samples reliably predict lung concentrations of retained amphibole fibers, but not retained chrysotile fibers, and that negative findings for asbestos bodies in bronchoalveolar fluid samples do not necessarily rule out significant exposure to asbestos fibers.

Analysis of concentrations of asbestos bodies (by light microscopy) or asbestos fibers (by electron microscopy) in lung tissue samples may represent more accurate reflections of past asbestos exposure than analysis of bronchoalveolar fluid or sputum samples, but these approaches are not without difficulties, especially for assaying exposure to chrysotile fibers, which are more rapidly cleared than amphibole fibers (Case 1994; Churg and Wright 1994). Although asbestos bodies can form on lung retained chrysotile, amphibole cores appear to be more prevalent in general populations and asbestos-exposed occupational groups, even though exposure may have primarily involved chrysotile (Case 1994; Dumortier et al. 1990). Correlations between lung concentrations of asbestos bodies and concentrations of retained uncoated asbestos fibers in numerous studies have been observed most consistently for amphibole fibers and generally not for chrysotile fibers (Albin et al. 1990b; Case et al. 1994; Karjalainen et al. 1996a, 1996b).

Comparison of lung fiber concentrations across studies and laboratories and establishment of benchmark lung fiber concentrations to indicate occupational exposure are difficult due to differences in preparative and sampling methods, types of electron microscope and magnification, and criteria for defining and counting fibers (Gylseth et al. 1985). In addition, numerous studies of measured indices of occupational asbestos exposure, such as years of exposure or cumulative exposure, and lung retained fiber concentrations generally have shown significant correlations between exposure and concentrations of retained amphibole fibers, but do not generally show a correlation between exposure and retained chrysotile fiber concentrations (see Churg and Wright 1994 for review of many of these studies). These findings are generally taken to reflect much faster clearance of the major proportion of deposited chrysotile fibers compared with amphibole fibers. However, studies (Case 1991; Case and Sebastien 1987, 1989) conducted by a single laboratory of Quebec chrysotile miners and millers, their families, residents without familial connections to the mines and mills, and referent residents who did not live close to the mines found that lung concentrations of chrysotile fibers, tremolite fibers, and asbestos bodies were related to increasing proximity of residence to the mines and increasing degree of domestic or occupational exposure. From the results of these studies, Case (1994) concluded that asbestos body concentrations over 250 asbestos bodies/g dry lung and chrysotile or tremolite fiber concentrations greater than $1x10^5$ fibers/g dry lung were "robust indicators of mining area residence".

For the attribution of asbestos exposure in individual cases, recommendations have been made to combine all available exposure data, including work history, radiological and histological findings, and lung concentrations of asbestos bodies and fibers when appropriate (Case 1994; Karajalainen et al. 1996a, 1996b). Benchmark concentrations of $0.1–1x10^6$ fibers/g dry lung have sometimes been used as indicators of occupational asbestos exposure (Case 1994; International Expert Meeting on Asbestos 1997). Their application to ascertain or validate occupational exposure in individual cases, however, especially those involving chrysotile exposure, is expected to result in both false positives and false negatives, because of the variability in the association between exposure measures and retained fiber concentrations (Becklake and Case 1994; Case 1994; Karajalainen et al. 1994a; Takahashi et al. 1994; Williams et al. 1995). Some of this variability is likely attributable to analytical variability due to contamination or loss in processing, variability in retention of fibers in different regions of the lung and variability in sampling of different lung regions, variability in exposure parameters including fiber type, length, and width, and variability in individuals' physiological parameters influencing retention.

Concentrations of retained fibers in autopsied or resected lung tissue samples also have been used as exposure variables in several case-control studies designed to characterize potential dose-response relationships for asbestos-induced mesothelioma and attribute risk to specific fiber types and size classes (McDonald et al. 1989; Rödelsperger et al. 1999; Rogers et al. 1991). Results from these studies indicated that relative risk for mesothelioma was significantly related to increasing concentrations of amphibole fibers longer than 5 μm (Rödelsperger et al. 1999), 8 μm (McDonald et al. 1989), or 10 μm (Rogers et al. 1991). Significant relationships with increasing concentrations of retained chrysotile fibers were less apparent in these studies. Rödelsperger et al. (1999) and McDonald et al. (1989) did not find statistically significant trends for increasing relative risks (odds ratios) with increasing retained chrysotile fiber concentrations. Rogers et al. (1991) found a statistically significant trend for increasing relative risks with increasing chrysotile fiber concentration (all lengths included), but this was only found in a subgroup of cases and controls with only chrysotile fibers detected in their lungs.

Asbestos fibers have also been measured in urine (see Section 7.1), and limited data indicate that above average exposures in the workplace (Finn and Hallenbeck 1984) and through drinking water (Cook and Olson 1979) can be detected by this means. However, only a tiny fraction of inhaled or ingested fibers is excreted in the urine, and the quantitative relationship between exposure and urinary fiber concentration appears quite variable. Moreover, urinary levels presumably are mainly a reflection only of recent exposures. Thus, urinary analysis for fibers has not been established or validated as a reliable means of biomonitoring for chronic asbestos exposure.

3.8.2 Biomarkers Used to Characterize Effects Caused by Asbestos

The most common means of characterizing the effects of inhalation exposure to asbestos in living persons is the chest x-ray (e.g., Amandus et al. 1987; Anton-Culver et al. 1989; Jones et al. 1988b; McDonald et al. 1986b). The International Labour Office (ILO) established a classification system for profusion of opacities in chest radiographs that includes four categories of increasing severity, each with three subcategories: 0 (0/-, 0/0, 0/1); 1 (1/0, 1/1, 1/2); 2 (2/1, 2/2, 2/3), and 3 (3/2, 3/3, 3/4) (ILO 1989). Chest radiographs are capable of detecting both pleural and parenchymal abnormalities, but sensitivity and specificity are limited (Gefter and Conant 1988). In particular, x-ray changes are rarely detectable until after some degree of physiological impairment has occurred (Aberle et al. 1988a). A more sensitive method is gallium-67 lung scanning, which often can detect asbestos-induced inflammation and other lung abnormalities prior to their detection by x-ray (Bisson et al. 1987; Hayes et al. 1989; Klaas 1993). Computerized tomography (CT) and high-resolution computed tomography (HRCT) may also be superior to conventional radiological examination in some cases (Aberle et al. 1988a, 1988b; Akira et al. 1991; Al Jarad et al. 1993; Friedman et al. 1988; Gamsu et al. 1989; Klaas 1993; Murray et al. 1995; Neri et al. 1994, 1996; Oksa et al. 1994; Sluis-Cremer et al. 1984). Magnetic resonance imaging may also be used to identify asbestos-induced lung abnormalities (Bianchi et al. 1997; Boraschi et al. 1999).

Quantitative analysis of lung function is also used for evaluating the effects of asbestos inhalation (e.g., Ernst et al. 1989; Finkelstein 1986; Kilburn et al. 1995). The specific end points of greatest value are FEV_1 and FVC, since these are most affected by fibrotic changes in the lung. Changes in biphasic lung carbon monoxide diffusing capacity may be better suited for detecting early decreases in lung function due to asbestos exposure (Dujic et al. 1992; Wang et al. 1998). Most studies find that respiratory changes parallel radiological changes (e.g., Britton 1982; Cordier et al. 1987; Di Lorenzo et al. 1996; Dujic et al. 1992; Markowitz et al. 1997; Miller et al. 1996), although several studies report measurable respiratory decrements in the absence of radiological changes (Ohlson et al. 1984; Wang et al. 1997; Weill et al. 1975).

The American Thoracic Society (1986) adopted a set of criteria for the diagnosis of asbestosis that includes a reliable history of asbestos exposure, an appropriate time interval between exposure and detection, and the following clinical criteria: (a) chest radiographic evidence of small irregular opacifications of a profusion of 1/1 or greater using the ILO classification; (b) a restrictive pattern of lung impairment with a forced vital capacity below the lower limit of normal; (c) a diffusing capacity below the lower limit of normal; and (d) bilateral late or pan inspiratory crackles at the posterior lung bases not

cleared by cough. The International Expert Meeting on Asbestos (1997) similarly specified that the confident diagnosis of interstitial fibrosis of the lung as a consequence of exposure to asbestos dust (i.e., asbestosis) requires, in addition to clinical features and architectural tissue abnormalities typical of interstitial fibrosis, a history of significant exposure to asbestos dust, or the detection of asbestos fibers or bodies in lung tissue greatly in excess of that seen in the general population. This group further specified that a histological diagnosis of asbestosis requires identification of diffuse interstitial fibrosis in lung tissue remote from tumors, in addition to the presence of 2 or more asbestos bodies in 1-cm^2 areas of sectioned lung tissue or uncoated lung-retained fiber counts outside of the range for general-population counts from the same laboratory.

Examination of cells and cellular factors present in lung lavage fluid and blood serum may be used to indicate early changes associated with asbestos-induced fibrosis. A number of human studies have shown that the differential cell count (Hayes et al. 1989; Rom 1991) and levels of fibronectin (Begin et al. 1986; Rom 1991), procollagen III (Begin et al. 1986), and hyaluronic acid (Cantin et al. 1992) are elevated in the lung lavage fluid of asbestos workers as compared to nonexposed controls. A significant elevation of the amino-terminal peptide of procollagen III (PIIINP) was found in the serum of asbestos workers when compared to controls (Cavalleri et al. 1991). Also, excretion of the oxidative DNA adduct, 8-hydroxy-deoxyguanosine, has been shown to be increased in the urine of asbestos workers and therefore, might be used to indicate DNA damage (Tagesson et al. 1993).

It is important to stress that radiological, lung lavage, and respiratory tests must be evaluated in conjunction with thorough occupational and environmental history and physical examination. Other causes of lung injury (e.g., smoking, occupational exposures to other chemicals, lung infections) also must be considered when evaluating exposure to asbestos.

3.9 INTERACTIONS WITH OTHER CHEMICALS

In epidemiological studies, an interaction between two risk factors is generally defined as a departure from an additive or multiplicative model of relative risks when both risk factors are present (Steenland and Thun 1986). With respect to lung cancer, some studies indicate that the interaction between asbestos and smoking is greater than additive (DHHS 1985; Selikoff et al. 1968). The most dramatic data include an age-standardized mortality ratio of 5.17 for nonsmoking asbestos workers, 10.85 for smokers not exposed to asbestos, and 53.20 for asbestos-exposed smokers (Hammond et al. 1979). The risk from combined exposure clearly exceeds the predicted risk based on additivity (15.0), and the data suggest a

multiplicative interaction. Other studies have found that smoking increases the risk of lung cancer from asbestos exposure more than predicted by additivity, but often less than predicted by a multiplicative model (Liddell et al. 1997, 1998; McDonald et al. 1980; Saracci 1987; Selikoff et al. 1980; Thomas and Whittemore 1988).

The mechanism by which smoking and asbestos interact to increase risk of lung cancer is not known, but several hypotheses (which are not mutually exclusive) have been suggested. One possible mechanism is a smoking-induced decrease in clearance of fibers from the lung, perhaps by interference with ciliary action or macrophage activity (Plowman 1982), leading in turn to increased penetration of the respiratory epithelium by fibers (Hobson et al. 1988; McFadden et al. 1986). For example, significantly higher concentrations of chrysotile and amosite fibers were found in airway mucosa of lungs from smokers, compared with nonsmokers, who had heavy occupational exposure to asbestos (Churg and Stevens 1995). In guinea pigs, clearance of short chrysotile fibers was decreased by 30% after 1 month in those coexposed to cigarette smoke compared to animals exposed to chrysotile alone (Churg et al. 1992). Exposure of explanted rat tracheobronchial epithelial cells to ozone or cigarette smoke resulted in increased retention of asbestos fibers, suggesting that a direct enhancement of fiber uptake may also be involved (Churg et al. 1996, 1998). Increased asbestos fiber retention was also noted in rats exposed to ozone *in vivo* (Pinkerton et al. 1989). Another proposal is that asbestos fibers (either in air or in the lung) may adsorb carcinogenic substances present in smoke, thereby increasing levels of these substances in the lung (Menard et al. 1986; Mossman et al. 1983b). Asbestos fibers may also catalyze the transformation of other compounds to reactive intermediates (Graceffa and Weitzman 1987). Kamp et al. (1998) speculated that iron-induced reactive oxygen species, produced following exposure to both cigarette smoke and asbestos fibers, might cause damage to DNA in pulmonary epithelium. Finally, on the assumption that cancer is a multistep process, asbestos and smoking could interact by affecting different steps in the process. An interaction of this sort between dimethylbenzanthracene and asbestos has been demonstrated in a two-stage carcinogenicity assay *in vitro* (Topping and Nettesheim 1980), with asbestos displaying effects characteristic of a promoter. Asbestos and chemical carcinogens may act synergistically to cause cell proliferation (Mossman et al. 1984; Sekhon et al. 1995) and metaplasia in cells of the lung, events proposed to be involved in tumor development (Mossman et al. 1984).

There is also good evidence that smoking increases the risk of asbestosis. For example, the death rate from asbestosis was found to be 2.8 times higher in asbestos-exposed smokers than in asbestos-exposed nonsmokers (Hammond et al. 1979; Selikoff et al. 1980). Evidence of increased frequency of clinical signs of asbestosis (rales, dyspnea, crepitations) in smoking versus nonsmoking workers has been

observed (Berry et al. 1979; Lerman et al. 1986), as has a synergistic effect of smoking on the occurrence of parenchymal opacities in the lungs of asbestos workers (Blanc et al. 1988). On the other hand, several researchers have reported that the effects of asbestos and smoking on these signs are additive rather than synergistic (Begin et al. 1987a; Hnizdo and Sluis-Cremer 1988; Weiss 1984).

In contrast to the interactive effect of smoking on lung cancer and fibrosis, smoking does not appear to increase the risk of mesothelioma (Berry et al. 1985; Hammond et al. 1979; Selikoff et al. 1980).

Data are not available on interactive effects between asbestos and other substances after oral exposure of humans. In animals, chronic oral exposure to asbestos caused no convincing increase in tumors in animals that had been treated with a known intestinal carcinogen (dimethylhydrazine) compared to the incidence in animals treated with dimethylhydrazine alone (NTP 1983, 1985, 1990b). However, these studies were judged to be inconclusive, since the doses of dimethylhydrazine employed gave either too few or too many gastrointestinal tumors to allow easy detection of an effect by asbestos (NTP 1983, 1990b). Gamma radiation, in combination with asbestos fibers, has been shown to synergistically enhance the oncogenic transformation of mouse embryo fibroblasts (Hei et al. 1984).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to asbestos than will most persons exposed to the same level of asbestos 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 asbestos, or compromised function of organs affected by asbestos. Populations who are at greater risk due to their unusually high exposure to asbestos are discussed in Section 6.7, Populations With Potentially High Exposures.

Studies of workers who are exposed to asbestos in workplace air indicate that not all people who are exposed to equal doses of asbestos are equally affected. As discussed in Section 3.9, it is likely that one main source of this variability in susceptibility between people is smoking history or the degree of exposure to other risk factors with which asbestos interacts. As discussed in Section 3.7, another potential factor may be age at first exposure. The long-term retention of asbestos fibers in the lung and the long latency period for the onset of asbestos-related respiratory diseases suggest that individuals exposed earlier in life may be at greater risk to the eventual development of respiratory problems than those exposed later in life. A recent study of nonoccupationally exposed residents of an Australian

asbestos-mining region, however, found no significant association between age of first exposure and incidence of mesothelioma (Hansen et al. 1998).

Variability in susceptibility to asbestos-induced respiratory tissue damage may be related to individual genetic differences in ability to detoxify reactive electrophilic molecules (e.g., reactive oxygen radicals and nitrogen oxide) produced during pulmonary disposition of fibers. Glutathione S-transferases have been proposed to be important Phase II enzymes that protect against electrophile-induced tissue damage by catalyzing conjugation with reduced glutathione. One class of glutathione S-transferases, GSTμ, has been hypothesized to be particularly important, as deletion of the GSTM1 gene that encodes this enzyme has been associated with increased risk for mesothelioma (Hirvonen et al. 1995), other cancers (Hirvonen 1997), and nonmalignant pulmonary disorders (Hirvonen et al. 1996; Kelsey et al. 1997) in case-control studies of asbestos-exposed people. In contrast, no significant association has been found for deficiency of the θ class of glutathione S-transferases (encoded by the GSTT1 gene) and increased risk for asbestos-related nonmalignant lung disorders (Hirvonen et al. 1996; Jakobsson et al. 1995a; Kelsey et al. 1997). The null GSTM1 and GSTT1 genotypes occur in about 50 and 15–25% of Caucasians, respectively (Hirvonen 1997).

NAT2 is another Phase II enzyme that displays genetic polymorphisms (one associated with slow acetylation and another with fast acetylation) that also may be associated with susceptibility to asbestos toxicity. Among a group of subjects exposed to high levels of asbestos, individuals who lacked the GSTM1 gene and had the slow NAT2 genotype showed a 4-fold increased risk for developing nonmalignant respiratory disorders and an 8-fold increased risk for developing mesothelioma compared with individuals with the GSTM1 gene and the fast NAT2 genotype (Hirvonen et al. 1996). In another study, no significant association was found between the NAT2 and GSTM1 genotypes and lung cancer; however, subjects in this study were exposed to relatively low levels of asbestos (Saarikoski et al. 2000). Although the mechanism of how slow acetylation may increase susceptibility to asbestos is uncertain, Hirvonen et al. (1995, 1996) have hypothesized that, compared with fast acetylators, slow NAT2 acetylators may accumulate greater amounts of polyamines (which stimulate cell proliferation) due to a slower acetylation rate in their catabolism. Related to this hypothesis is the observation that asbestos fibers induce ornithine decarboxylase in hamster cells, resulting in stimulation of polyamine synthesis and resultant cell proliferation (Marsh and Mossman 1991). Other less specific lines of evidence provide support for the hypothesis that genotype may be important in determining susceptibility to asbestos-related disease. For example, Huncharek et al. (1996) found increased incidence of cancer among parents of mesothelioma cases compared with parents of controls without mesothelioma.

As discussed in Section 3.2.1.3, results from experiments showing a larger increase in cell numbers in pulmonary lavage fluid and increased severity of pulmonary lesions in response to inhaled asbestos in immunologically deficient mice compared with immunologically normal mice of the same genetic background (Corsini et al. 1994) suggest that genetic differences in cell-mediated immunological capabilities may be another predisposing factor in the etiology of asbestos-induced lung diseases.

Recent studies have shown that a high percentage of human mesotheliomas also test positive for the presence of Simian Virus 40 (SV40). Based on this finding, it has been suggested that SV40-infected individuals who are exposed to asbestos might be at increased risk for developing mesothelioma (see summaries of Carbone 1999 and Carbone et al. 2000).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to asbestos. 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 asbestos. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Standard texts of medical toxicology (e.g., Ellenhorn et al. 1997; Goldfrank et al. 1998) do not provide specific information about treatment immediately following exposure to asbestos since the major health hazards of asbestos are associated with chronic rather than acute exposure.

3.11.1 Reducing Peak Absorption Following Exposure

The most important route of asbestos exposure is inhalation, but acute effects are not of primary concern as the major health hazards that are associated with chronic exposure, and can have latencies of more than 30 years. Public health initiatives have therefore focused on reducing initial exposure rather than reducing postexposure absorption.

3.11.2 Reducing Body Burden

As discussed in Section 3.4.4 inhaled asbestos fibers that are deposited in the lung are principally removed by mucociliary transport into the alimentary canal and eventually are excreted in the feces.

Chrysotile fibers appear to be cleared more readily than amphibole fibers, and long fibers are cleared more slowly than short fibers (Coin et al. 1992; Morgan 1991).

One study suggests that subjects who stop smoking after already having been exposed to asbestos see some improvement in lung health (Waage et al. 1996), but long term data for the efficacy of cessation of smoking in large cohorts of individuals previously exposed to asbestos are not available.

To date, there is no method to remove asbestos from lungs. As discussed in Section 3.9, smoking and exposure to asbestos appear to interact synergistically to produce pulmonary fibrosis and lung cancer. This interaction may be explained, at least in part, by demonstrations that smoking impairs the ability of the lungs to remove inhaled fibers (Churg and Stevens 1995; Churg et al. 1992). These findings suggest that cessation of smoking may lead to enhanced fiber clearance in asbestos-exposed workers who are also smokers. Workers likely to be exposed to asbestos through maintenance work in buildings (e.g., carpenters, plumbers, electricians, and custodial workers) should receive education about this possible synergism and be encouraged not to smoke.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanisms by which asbestos causes toxic effects have not yet been clearly determined, and there are no proven methods of interfering with them. Methods of interference can be suggested based on the current understanding of the mechanisms of action derived from animal and human studies, but these methods will require additional research before they can be put to use.

Current research on the toxic effects of asbestos suggests that both direct binding and cell-mediated pathways may be involved (see Section 3.5). Asbestos fibers can bind to various cell macromolecules (proteins, membranes, DNA, and RNA) leading to a variety of direct cellular effects such as increases in cell permeability, conformational changes affecting protein function, and physical interference with chromosome segregation leading to chromosome deletion (Barrett et al. 1989; Chang et al. 1990; Malorni et al. 1990). Modification of the surface of asbestos fibers can decrease their *in vitro* toxic effects (Awadalla et al. 1990; Brown et al. 1990, 1991; Habashi et al. 1991), and these data suggest that direct interactions between asbestos fibers and cell molecules are partly responsible for asbestos-related toxicity.

A second proposed mechanism in asbestos toxicity involves active oxygen species. When exposed to asbestos, alveolar macrophages attempt to phagocytize the fiber and then digest it by producing reactive

oxygen species. These include hydrogen peroxide and superoxide radical anion (O_2^-), which are relatively mild oxidants (Cantin et al. 1988; Case et al. 1986; Hansen and Mossman 1987). However, hydrogen peroxide and superoxide can spontaneously react with one another to produce hydroxyl radicals, which are much more potent oxidants. This reaction is enhanced by the presence of iron which can come from the fiber itself, as a contaminant associated with the asbestos, or from the exposed animal's tissues (Fontecave et al. 1990; Koerten et al. 1990a; Lund and Aust 1991a).

Both *in vivo* and *in vitro* studies have linked production of reactive oxygen species to asbestos-induced cellular effects including lipid peroxidation, cytotoxicity, cell proliferation, genotoxicity, and apoptosis (see Section 3.5). The uptake of asbestos fibers into epithelial cells is also increased by reactive oxygen species (Hobson et al. 1990; Peterson and Kirschbaum 1998).

Free radical scavengers may prove to be successful in interfering with the mechanism of action for asbestos. *In vitro* studies have shown that the effects of asbestos can be diminished by compounds that reduce the levels of reactive oxygen species, such as free radical scavengers (ascorbic acid, bemitil, mannitol, salicylate, 5,5'-dimetyl-l-proline N-oxide, rutin, vitamin E, vitamin A) and enzymes that catalyze the decomposition of reactive oxygen species (catalase, superoxide dismutase). An *in vitro* study assessing the antioxidant efficiency of the flavonoids, quercitin and rutin, and their ability to protect against asbestos-induced cell injury found that both compounds reduced both the production of oxygen radicals and the cell injury resulting from asbestos exposure (Kostyuk et al. 1996). One *in vivo* study reported a dose-dependent inhibition of lung injury, inflammation, and asbestosis in rats treated with polyethylene glycol-conjugated catalase (Mossman et al. 1990b).

Vitamin A has been widely studied in the field of cancer prevention, and studies have shown that smokers who consume more dietary vitamin A from foods have a lower risk for lung cancer (Mayne et al. 1998). Vitamin A is generally given as a dietary supplement in one of two forms, either as retinol (vitamin A) or as β-carotene, a precursor which is converted by the body to vitamin A. An investigation focusing on dietary intake of vitamin A in asbestos workers (40 subjects) reported that subjects who had developed bronchial metaplasia reported a lower intake of dietary vitamin A than those without the condition (Mayne et al. 1998).

Supplementing the diet with vitamin A (retinol or β-carotene) has been shown to increase ventilatory function (Chuwers et al. 1997). However, intervention trials with supplements of vitamin A have shown an increased risk of lung cancer, with the carotene and retinol efficiency trial, CARET, being terminated

early because interim results showed that the intervention group (treated simultaneously with both retinol and β-carotene) was developing more cancer than the controls (Omenn et al. 1996a, 1996b). A study carried out on a large cohort (1,024 individuals) of occupationally exposed asbestos workers in Australia (de Klerk et al. 1998) studied the relative efficacy of the two most common forms of vitamin A, β-carotene and retinol. The authors concluded that there was no benefit from the administration of β-carotene, but that there were significantly lower rates of mesothelioma among the subjects taking retinol. Another study by the same authors (Musk et al. 1998) found that subjects (1,203 exposed asbestos workers) supplied with vitamin A (retinol) had lower rates of malignant mesothelioma and lung cancer than subjects who chose not to participate. However, the reduction was not statistically significant, although it did increase with time and may therefore reflect a long-term protective effect. In general, results from the various clinical trials of vitamin A carried out to date do not look very promising. Supplements of β-carotene had detrimental effects, while the results with retinol are borderline.

Another possible method of reducing the production of hydroxy radicals is by the chelation of iron. Iron chelators such as deferoxamine have been successful at inhibiting the *in vitro* production of hydroxyl radicals (Goodglick et al. 1989; Lund and Aust 1991b; Weitzman and Graceffa 1984). By binding to asbestos fibers, deferoxamine blocks their ability to participate in redox reactions that produce hydroxyl radicals. A study in mice demonstrated the binding of desferroxamine to crocidolite fibers *in vivo* (Weitzman et al. 1988). It should be noted that other iron chelators such as citrate, EDTA, or nitriloacetate actually lead to an increased production of hydroxyl radicals (Lund and Aust 1991b, 1992). Although these chelators are successful in binding iron, they do not prevent iron from participating in the Fenton reaction, and it is possible that by mobilizing iron from the fiber, these chelators may actually make the iron more redox-active.

Adenosine 3',5'-cyclic monophosphate (cAMP) has been shown to reduce pulmonary edema and lung toxicity caused by factors other than asbestos. An *in vitro* study by Vatche and coworkers (Israbian et al. 1994) found that cAMP diminished asbestos-induced cytotoxicity by maintaining intracellular ATP levels and inhibiting cellular replication rather than by affecting asbestos-induced oxygen radical production. This may represent another alternative strategy to free-oxygen radical scavengers for limiting asbestos-induced lung damage.

In addition to the effects described above, cells exposed to asbestos respond by the production of a large number of different factors including, leukotrines, interleukins, growth factors, chemoattractants, and

nitric oxide (see Section 3.5). These factors mediate a wide range of cell responses including inflammation, macrophage recruitment, and cell proliferation. Recent research has also suggested that nuclear regulatory proteins, oncogenes, proto-oncogenes and secondary messenger proteins may play an important mechanistic role. Additional research to better understand the interaction of these responses may provide clues for the development of new therapeutic approaches.

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 asbestos 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 asbestos.

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 Asbestos

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to asbestos are summarized in Figure 3-6. The purpose of this figure is to illustrate the existing information concerning the health effects of asbestos. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 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.

Figure 3-6. Existing Information on Health Effects of Asbestos

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

Human

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

Animal

● Existing Studies

There have been a very large number of studies, both in humans and animals, focusing on the major health effects associated with inhalation (asbestosis, lung cancer, and mesothelioma) and oral exposure (gastrointestinal cancer). There have also been a number of studies on immune system changes in humans exposed by inhalation, but this has not been investigated in people exposed orally. There are few formal studies focusing on other possible effects of asbestos. However, because so few fibers are able to penetrate from the lungs or the gastrointestinal tract into the body, there is little reason to believe that other effects are of major concern.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Only a few inhalation or oral studies have sought to determine the effects of short-term exposures to asbestos. There are no human data on noncancer effects after acute exposures, and no acute-duration MRLs have been derived. However, there is one study in animals in which a single exposure produced fibrosis of the lung (McGavran et al. 1989), and one study that suggests that a single high inhalation exposure might cause cancer (Wagner et al. 1974). This is a potentially important point, since some people might have one or two significant exposures to asbestos during their life. With current regulations and state of knowledge regarding asbestos toxicity; however, the likelihood of acute high-level exposures for most people is small and studies of health effects in humans with such exposures are unlikely to be established. Additional studies on the long-term effects of acute inhalation exposure in animals may be useful to determine if this is of concern, and if it is, to define the dose-response relationship for cancer, fibrosis, and other biologic outcomes. Although oral exposure to high levels of asbestos is unlikely, acute oral exposure to asbestos in rats and mice have been shown to cause aberrant crypt foci, putative precursor lesions of colon cancer (Corpet et al. 1993). Further studies to investigate the development of these lesions, especially after the ingestion of asbestos in drinking water, may be useful.

Dermal exposure to amosite asbestos in shipbuilding workers resulted in the development of warts or corns, predominately on the hands (Alden and Howell 1944). The corns usually developed within 10 days of an original pricking sensation and the feeling of a small splinter-like foreign body. Histological examination of such corns did reveal the presence of asbestos fibers, and the corns were generally taken to be of no pathological concern (Alden and Howell 1944; Dupre et al. 1984; Selikoff and Lee 1978). There are no indications in available data that dermal absorption of asbestos fibers may occur to any significant extent.

Intermediate-Duration Exposure. Several studies (Ehrlich et al. 1992; Jones et al. 1980a; Seidman et al. 1979, 1986; Shepherd et al. 1997) in humans suggest that workers exposed to asbestos for periods of 1–12 months may subsequently develop asbestos-associated pleural changes or lung disease. However, these studies do not provide sufficient dose-response data to derive a reliable intermediate-duration inhalation MRL. A single study in animals reported fibrosis after intermediate exposure to asbestos (Donaldson et al. 1988a). Further inhalation studies in rats to investigate the fibrogenic and carcinogenic risks from intermediate-duration exposures may be helpful in assessing the risks in humans who may only be exposed for a limited period. It should be noted, however, that the parallel development of asbestos fiber lung retention models for rats and humans will likely increase the usefulness of the rat toxicity data. Such models may increase the accuracy of extrapolating from the rat data to predict human health risks (see Sections 3.4.5 and 3.5.3. for discussion of difficulties in developing these models). Several intermediate-duration oral studies in animals have been performed, and these have not revealed any evidence of noncancer effects (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c; Schneider and Maurer 1977). In the absence of data to suggest that a significant noncancer risk exists after oral exposure, it does not seem that additional studies of this sort are critical.

Chronic-Duration Exposure and Cancer. Epidemiological studies provide descriptions of exposure-response relationships for signs of lung fibrosis and for increased rates of mortality associated with nonmalignant respiratory disease in workers with estimated chronic cumulative exposures as low as about 15–70 and 30–1,200 f-yr/mL, respectively (see Section 3.2.1.2 for references). The studies, however, do not provide information for responses at lower cumulative exposure levels, at air levels experienced by more modern workers in regulated nations (from <0.1–0.2 to 2–5 f/mL), or at air levels that may be experienced by people in relatively polluted nonoccupational exposure scenarios (up to about 0.01 f/mL). No chronic inhalation MRL was derived due to the large degree of uncertainty in extrapolating from data for high-level exposures to low levels that might be experienced by populations surrounding hazardous waste sites with asbestos. Epidemiological research approaches that may decrease this uncertainty are described below in Section 3.12.2 Epidemiological and Human Dosimetry Studies.

Studies in animals provide supporting evidence for the fibrogenicity of airborne asbestos (see Section 3.2.1.2. for references). However, the extrapolation of exposure-response relationships for asbestos-induced lung fibrosis in laboratory animals to humans is not recommended due to the long persistence of fibers in humans, the relatively short life-span of laboratory animals, and the anatomical and physiological differences between laboratory animals and humans that influence rates of lung deposition and clearance of asbestos fibers. The development of physiologically-based mathematical

lung retention models for asbestos fibers in rats and humans and the application of the models to extrapolate from available rat chronic toxicity data may decrease uncertainty in predicting risks for pulmonary fibrosis (and respiratory tract cancers) in humans exposed to low levels of asbestos. This research approach is discussed further below in Section 3.12.2. More discussion of the difficulties in developing such models and extrapolating from animals to humans are discussed in Sections 3.4.5 and 3.5.3.

The carcinogenic effects of chronic inhalation exposure to asbestos (i.e., lung cancer and pleural mesothelioma) have been amply demonstrated, both in humans and animals (see Section 3.2.1.2 for references). However, a number of important issues remain to be resolved. In particular, it would be useful to know whether there are maximum and/or minimum lengths and diameters beyond which fibers lack carcinogenic effects, or whether there are continuous gradients of carcinogenicity as a function of fiber type, length, and diameter. In this regard, additional research on the mechanism of carcinogenicity may be more useful than additional epidemiological or chronic exposure animal studies. This would include studies on the molecular and cellular mechanisms by which asbestos fibers cause lung cancer and mesothelioma (and pulmonary fibrosis).

Along these same lines, further work would be helpful in defining other fiber characteristics that are important determinants of carcinogenicity. It is suspected, for example, that amphiboles, such as crocidolite and tremolite asbestos, are more likely to cause mesothelioma than chrysotile, but it is not certain if this is attributable to differences in fiber length alone or to differences in chemical properties (e.g., fiber morphometry, iron content, durability in biological fluids and tissues). Consequently, additional animal studies of the relative carcinogenic potency of airborne asbestos fibers of different types (e.g., chrysotile versus amphibole asbestos), carefully matched with regard to fiber size distribution, may be valuable.

Another area where further research may be useful is the synergistic interaction between asbestos and other risk factors for lung cancer, especially smoking. Particularly helpful may be further studies on the mechanism of such interactions, since this could help improve current means of predicting the consequences of exposures to substances such as cigarette smoke.

In view of the uncertainty regarding the risk of gastrointestinal cancer following direct or indirect ingestion of asbestos, further research in this area may be useful. Although an extensive series of lifetime feeding studies have already been performed by NTP, only two of these studies (NTP 1983, 1985)

focused on the issue of fiber length in oral carcinogenicity. Further studies to investigate the role of fiber length in gastrointestinal cancer may be useful, with special emphasis on whether there is a minimum length below which carcinogenic risk is minimal. This would have considerable practical consequence in evaluating the potential risk to human health associated with ingestion of asbestos in drinking water. Additional epidemiological studies that include exposure both after occupational inhalation and community drinking water ingestion could also be helpful, especially if they were carefully designed to address the uncertainties and limitations in the evidence currently available.

Genotoxicity. The genotoxic effects of asbestos have been studied *in vivo* to a limited extent in humans (Donmez et al. 1996; Fatma et al. 1991; Hansteen et al. 1993; Lee et al. 1999; Marczynski et al. 1994a, 2000a, 2000b; Pelin-Enlund et al. 1990; Rom et al. 1983; Tammilehto et al. 1992; Tiainen et al. 1989) and animals (EPA 1988j; Fatma et al. 1992; Marczynski et al. 1994b, 1994c). These studies generally reported chromosomal aberrations with asbestos exposure. Most *in vitro* studies in eukaryotic cells indicate that asbestos is clastogenic, causing a variety of chromosomal aberrations; some studies also suggest that asbestos may be mutagenic, although the results for tests of gene mutagenesis have been mixed, both *in vitro* and *in vivo* (see Section 3.3). Further studies to determine the mechanism of clastogenicity, the dependency of clastogenicity on fiber size and type, and the relative genotoxic sensitivity of different respiratory and gastrointestinal epithelial cells may lead to the identification of cellular, biochemical, or genetic responses to asbestos that may be amenable to therapeutic intervention.

Reproductive Toxicity. There are no studies in humans on the potential reproductive effects of asbestos exposure. There is limited evidence from studies in animals that chronic ingestion of asbestos does not injure reproductive tissues, and that exposure during gestation does not reduce fertility (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c). This indicates that reproductive effects are probably not of concern, and indeed, there is little mechanistic basis for thinking that this could occur. For these reasons, further studies on this end point do not appear critical, but it should be noted that standard two-generation reproductive toxicity studies in animals exposed to ingested, inhaled, or dermally applied asbestos are not available.

Developmental Toxicity. Studies on potential developmental effects in humans exposed to asbestos are restricted to reports from one group of investigators reporting that asbestos fibers were detected in fetal and placental tissues from stillborn infants more frequently and at higher concentrations than in placental tissue from liveborn infants (Haque et al. 1991, 1992, 1996, 1998). Understanding of the toxicological significance of these observations awaits confirmation and explanation from further

research in other laboratories. It is presently unclear if the noted differences in fiber concentrations between stillborn and liveborn tissue are due to differences in maternal exposures, differences in fetal or placental factors unrelated to asbestos exposure, or specimen contamination.

Studies in animals have not detected any evidence of teratogenic effects in rats and hamsters exposed for life (including during gestation and lactation) to different types of asbestos by the oral route (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c). However, decreased body weights at birth and later in life were noted in some cases (NTP 1985, 1990c). It seems likely that these effects either were random or were secondary to reduced food intake by the dams. No developmentally toxic effects were found following exposure of pregnant mice to asbestos in drinking water at concentrations as high as 143 μg/mL (Schneider and Maurer 1977). Asbestos fibers have been reported to cross the placenta following bolus intravenous injections of asbestos suspensions into rats and mice (Cunningham and Pontefract 1974; Haque and Vrazel 1998). These data were quite variable, and thus could be due, at least in part, to a mass breakthrough of fibers that might be associated with the bolus intravenous exposure protocol. It is expected that transplacental transfer of fibers following environmental exposures (inhalation, oral, or dermal) to asbestos may be of a much smaller magnitude.

The available data suggest that developmental toxic effects are not a critical public health concern from asbestos exposure. Additional animal studies on fetal and postnatal development as affected by inhalation exposure may be helpful to confirm or discard this suggestion.

Immunotoxicity. There are numerous studies of the immune system in workers (active or retired) exposed to asbestos in workplace air (deShazo et al. 1988; Froom et al. 2000; Kagan et al. 1977; Pernis et al. 1965; Sprince et al. 1991, 1992; Warwick et al. 1973). These studies indicate that the immune system may be depressed in individuals who have developed clinical signs of injury, such as asbestosis or cancer. However, the cause-effect relationship between the immunological changes and the asbestos-related diseases is not certain. Also, it is not known if similar effects occur after oral exposure, or if the effects are inhalation specific. Prospective studies on this subject may be useful, both in discerning the importance of immune system injury in the etiology of asbestos-induced disease, and determining whether impaired immune function can be used as a possible early test of individual sensitivity to asbestos.

Neurotoxicity. There are no reliable indications in studies of humans or animals that exposure to asbestos leads to neurotoxicity. Even though tests have not been performed to search for possible subtle effects, there is little reason to suspect that this is an effect of concern, and detailed studies on this effect do not appear to be essential.

Epidemiological and Human Dosimetry Studies. There have been a very large number of epidemiological studies performed on workers exposed in the past to relatively high concentrations of asbestos in air. Further epidemiological studies on populations with lower exposure levels may be useful to decrease the uncertainty that asbestos-induced respiratory diseases may develop with chronic exposure to current levels of asbestos inside buildings, in the ambient environment, and/or near waste sites. Prospective cohort mortality studies of workers involved in asbestos-related occupations under currently regulated conditions or retrospective studies of workers who entered asbestos-related occupations after 1970 or 1980 when respective occupational limits of 5 and 2 f/mL were recommended in the United States (ACGIH 1998) may be particularly useful. Other groups of people that may warrant study include family members of asbestos workers, maintenance workers (such as plumbers, electricians, carpenters, and custodial workers) in buildings with asbestos-containing materials, sailors exposed aboard ships, or nonoccupationally exposed residents of communities with current or past mining or manufacturing operations involving asbestos (e.g., Libby, Montana). End points of concern would include not only cancers, but also pulmonary fibrosis, pleural changes, and respiratory and immune function.

Of special value in any ongoing or future epidemiological study, either of health effects associated with the workplace or the ambient environment, are good exposure data, including quantitative data on the intensity and duration of exposure for each member of the study group, and the type and dimensions of the fibers involved. Accurate exposure data linked to lung fiber concentration data from resected or autopsied lung tissue (that describe distributions of fiber dimensions and mineralogical types) would be useful for the development of human lung retention models, similar to those being developed for refractory ceramic fibers (Yu et al. 1997) that incorporate current understanding of factors influencing the rates of deposition and clearance of asbestos fibers (e.g., breathing patterns, airway morphometry, fiber dimensions, and fiber mineralogy). Such models may decrease uncertainty in extrapolating from data for humans exposed to high exposure levels to predict risks for malignant or nonmalignant respiratory disease in humans exposed to low levels of asbestos. If rat lung retention models are also developed, then human lung retention models may be useful in extrapolating from available rat inhalation toxicity data to provide alternative estimates of human health risks associated with low-level exposure to asbestos.

Biomarkers of Exposure and Effect.

Exposure. The most relevant parameter for quantifying exposure to asbestos is the body burden of retained fibers (Case 1994; Churg 1982; Churg and Warnock 1981; Churg and Wright 1994; Dodson et al. 1999; Dufresne et al. 1995, 1996a, 1996b; Gylseth et al. 1985; Sebastien et al. 1989; Wagner et al. 1986). However, there are no methods currently available for measuring tissue levels of fibers in living persons other than by biopsy (see Section 3.8.1 for discussion of strengths and weaknesses of using retained fiber concentrations in lung tissue as indicators of past exposure). Uses of concentrations of asbestos bodies and uncoated fibers in bronchoalveolar lavage and sputum samples as biomarkers of exposure also have been examined in several studies, but these approaches have not been fully developed as quantitative indicators of exposure (see Section 3.8.1). Fibers can also be detected in urine and feces (Cook and Olson 1979; Finn and Hallenback 1984), but these methods would likely reflect only recent exposures (within the last several days) and not the cumulative tissue burden. Efforts to develop a noninvasive method for measuring fiber levels in tissues (especially in the lung) would be particularly valuable in assessing human exposures to asbestos.

Effect. No specific and sensitive biomarkers of asbestos-induced disease are known. Chest x-rays can detect both the noncarcinogenic and carcinogenic lesions produced by asbestos in the lung and pleura, but usually not until after significant injury or change has occurred (Anton-Culver et al. 1989; Jones et al. 1988b). Similarly, spirometric tests of lung function can detect early stages of asbestos-induced disease, but only after functional decrements (Ernst et al. 1989; Finkelstein 1986). Further studies would be valuable to determine if changes such as depressed immune system function or altered levels of other biochemical parameters can be used as an indicator of risk of asbestos-induced cancer or fibrosis. Also, further efforts would be valuable to improve diagnostic methods for detecting early asbestos-related effects, such as high-resolution computed tomography to detect pleural thickening or pleural plaques (Aberle et al. 1988a, 1988b) and lung carbon monoxide diffusing tests to detect early decreases in lung function (Dujic et al. 1992; Wang et al. 1998). In general, there is a need for the development of more noninvasive asbestos-specific biomarkers of effect. Additional research on potential associations between particular genetic polymorphisms and susceptibility to asbestos-induced lung disease may lead to new biomarkers of susceptibility.

Absorption, Distribution, Metabolism, and Excretion. Because asbestos consists of insoluble fibers, it does not undergo absorption, distribution, metabolism, or excretion in a fashion similar to most other chemicals. With respect to inhalation exposure, the toxicokinetic parameters of greatest relevance are the extent and location of fiber deposition in the respiratory tract, the rate of fiber removal by mucociliary transport, and translocation of fibers within and across the lung. A number of studies are available on lung deposition and clearance of asbestos fibers in animals (e.g., Bolton et al. 1983; Coin et al. 1992; Evans et al. 1973; Morgan et al. 1975; Timbrell 1982). Use of these data to develop predictive lung retention models for animals, parallel to the development of human lung retention models, may decrease the uncertainty in estimating human health risks associated with low-level exposure to asbestos fibers. In contrast to data for laboratory animals, human data poorly describe relationships between exposure levels and lung retention of asbestos fibers. Additional research linking accurate exposure data with lung fiber burden data in humans is likely to result in the development of human lung retention models and aid both in the description of patterns of deposition and clearance of asbestos fibers in humans. Additional studies on the dissolution and breakage of asbestos fibers of various dimensions and types in human and animal respiratory tract fluids and cells may also aid in the development of these models. Additional research clarifying the biological and mineralogical parameters that influence asbestos fiber migration and penetration through the lungs into the peripheral lung and pleural membrane, possibly determinants of mesothelioma risk, is also warranted.

Available data are not sufficient to make a precise estimate of the fraction of ingested fibers that pass through the gastrointentinal wall, but there is agreement that it is a very small amount and not of significant toxicological concern (Sebestien et al. 1980b; Weinzweig and Richards 1983).

Comparative Toxicokinetics. Available data from chronic rat inhalation bioassays show similar asbestos-induced respiratory effects to those in humans associated with occupational exposure to asbestos (pulmonary fibrosis, lung cancer, and pleural mesothelioma), but the use of the rat data to predict human health risks from exposure to airborne asbestos has a number of areas of uncertainty, including those associated with interspecies differences in lifespan, airway morphometry, and breathing patterns. The development of rat and human lung retention models that incorporate species differences in anatomical and physiological parameters influencing deposition and clearance of asbestos fibers may decrease the uncertainty in making human health risk predictions from the rat data and to allow comparisons with low-level risk estimates derived from the available epidemiological data. The previous section outlined several areas of comparative toxicokinetics research that are likely to aid in the development of these models.

Methods for Reducing Toxic Effects. The most important route of exposure to asbestos is by inhalation of asbestos fibers that are deposited in the lung. The acute effects of exposure have not been much studied, as the major health hazards are believed to be associated with chronic exposure. The mechanisms by which asbestos causes toxic effects have not yet been clearly determined (IARC Expert Panel 1996), and there are no proven methods of interfering with them, nor is it currently possible to reduce toxicity by reducing body burden after exposure. Further information as to the mechanisms of asbestos toxicity is a primary data need that may eventually lead to therapeutic approaches for reducing toxic effects from asbestos.

There is some evidence that smoking and asbestos inhalation interact synergistically to produce pulmonary fibrosis and lung cancer (see Section 3.9). One study suggests that subjects who stop smoking after having already been exposed to asbestos see some improvement in lung health (Waage et al. 1996), but long term data for the efficacy of cessation of smoking in large cohorts of asbestos-exposed individuals may help to confirm or reject this suggestion.

Current research on the mechanism of asbestos toxicity suggests that a combination of direct binding and cell mediated pathways are involved (see Section 3.5). *In vitro* studies indicate that involvement of iron-catalyzed production of reactive oxygen species in the mechanism of action for asbestos (Fontecave et al. 1990; Garcia et al. 1988; Korkina et al. 1992; Shatos et al. 1987; Weitzman and Graceffa 1984), and a large number of *in vitro* studies (see Sections 3.5 and 3.11) have shown that compounds that reduce the levels of reactive oxygen species, either by scavenging them, or by catalyzing their decomposition, can reduce the cell injury resulting from asbestos exposure. Inhibition of lung injury, inflammation, and asbestosis has been reported *in vivo* in an animal inhalation model of disease using polyethylene glycol-conjugated catalase (Mossman et al. 1990b).

A number of iron chelators have also been successful *in vitro* at limiting the production of hydroxyl radicals (Goodlick et al. 1989; Lund and Aust 1991b; Weitzman and Graceffa 1984). Some iron chelators, however, actually lead to increased production of hydroxyl radicals (Lund and Aust 1991b, 1992) and, although they chelate the iron, they do not prevent it taking part in the Fenton reaction. Their use as a treatment for asbestos exposure is therefore less likely than that of compounds that directly reduce the levels of reactive oxygen species. Additional *in vivo* studies that evaluate the efficacy of such compounds may lead to the development of a method for reducing the toxic effects of asbestos.

Adenosine 3',5'-cyclic monophosphate (cAMP) has been shown to reduce pulmonary edema and lung toxicity caused by factors other than asbestos. An *in vitro* study by Vatche and coworkers (Israbian et al. 1994) found that cAMP diminished asbestos-induced cytotoxicity by maintaining intracellular ATP levels and inhibiting cellular replication rather than by affecting asbestos-induced oxygen radical production. This may represent another worthwhile alternative strategy to free-oxygen radical scavengers for limiting asbestos-induced lung damage.

Children's Susceptibility. There is a lack of reports on asbestos-related respiratory diseases in children, but childhood exposure to asbestos has been associated with the development of respiratory diseases in adulthood (Anderson et al. 1976; Andrion et al. 1994; Fraire et al. 1988; Inase et al. 1991; Lanphear and Buncher 1992; Magee et al. 1986; Voison et al. 1994; Wagner et al. 1960). The long-term retention of asbestos fibers in the lung and the long latency period for the onset of asbestos-related respiratory diseases suggest that individuals exposed earlier in life may be at greater risk to the eventual development of respiratory problems than those exposed later in life. Direct evidence in support of this hypothesis, however, is not available. In contrast, no significant association was found between incidence of mesothelioma and age of first exposure in a study of residents of an Australian mining region who had no history of occupational exposure to asbestos (Hansen et al. 1998). To date, there is no persuasive evidence that children have a greater susceptibility to asbestos toxicity than adults.

If groups of children exposed to known levels of asbestos could be identified, the lifetime studies could be designed to assess long-term effects of childhood exposure to asbestos. Respiratory effect end points could be compared to those in occupationally-exposed adults in an effort to assess susceptibility in children relative to adults. However, due to changes in the use of asbestos during the past several decades, it may be difficult to identify such groups of children.

Animal experiments could be designed to determine whether there are age-related differences in pulmonary responses to inhaled asbestos fibers (e.g., fibrosis, cell proliferation, gene expression, macrophage production of reactive chemicals). For example, adult rats have been shown to display, within 20 days, a range of dose-related changes in pulmonary inflammation indices, increases in pulmonary cell proliferation, and increases in the severity of pulmonary fibrosis in response to short-term inhalation exposure to asbestos concentrations of approximately 60 and 2,800 f/mL (Quinlan et al. 1994, 1995). Comparing the results of these studies with results from replicate studies with juvenile rats may demonstrate age-related susceptibility to asbestos toxicity that is not directly related to latency of disease development in juveniles relative to adults. However, the relevance of such models for assessment of

age-related susceptibility of cancer effects in humans may be limited due to species differences in anatomy, physiology, and duration of lifetime.

Data needs related to developmental effects associated with prenatal and postnatal exposures to asbestos were discussed previously in Section 3.12.2.

Child health data needs relating to exposure are discussed in Section 5.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Ongoing studies pertaining to Asbestos have been identified and are shown in Table 3-7.

Table 3-7. Ongoing Studies on the Health Effects of Asbestos[a]

Investigator	Affiliation	Research description	Sponsor
Aust, A E	Utah State University, Logan, UT	Role of O_2 radicals and iron in asbestos-induced cancer	NIEHS
Barrett, JC	NIEHS, NIH	Role of mutagenesis in carcinogenesis	NIEHS
Broaddus, VC	University of California San Francisco, San Francisco, CA	Protective role of apoptosis in asbestos pleural injury	NIEHS
Brody, AR	Tulane University of Louisiana, New Orleans, LA	Epithelial growth factors in environmental lung disease	NHLBI
Brody, AR	Tulane University of Louisiana, New Orleans, LA	Growth factors in asbestos-induced pulmonary fibrosis	NIEHS
Dinse, G	NIEHS, NIH	Statistical analysis of human cancer data	NIEHS, NIH
Garshick, E	Department of Veterans Affairs, Medical Center Brockton, MA	Screening for occupational and respiratory disorders	VA
Gerwin, BI	Division of Basic Sciences - NCI	In vitro studies of human mesothelial cells	NCI, NIH
Goodman, GE	Fred Hutchinson Cancer Research Center, Seattle, WA	Caret–coordinating center	NCI
Guthrie, GD	Mineralogical Society of America	Mineralogical Society of America Workshop on the health effects of mineral dusts	USDOE Energy Research
Hei, TK	Columbia University Health Sciences, New York, NY	Mechanisms of fiber carcinogenesis	NIEHS
Hei, TK	Columbia University Health Sciences, New York, NY	Mutagenicity of mineral fibers	NIEHS
Heintz, NH	University of Vermont & St Agric College, Burlington, VT	Asbestos and NO_2 in environmental lung disease	NIEHS
Ho, Y	Wayne State University, Detroit, MI	The nature of lung antioxidant defense mechanisms	NHLBI

Table 3-7. Ongoing Studies on the Health Effects of Asbestos *(continued)*

Investigator	Affiliation	Research description	Sponsor
Holian, A	University of Texas Health Science Center Houston, Houston, TX	Analysis of human macrophage function in response to fibrogenic particulates	NCRR
Hoyle, GW	Tulane University of Louisiana, New Orleans, LA	Pulmonary fibrosis in PDGF transgenic mice	NHLBI
Hunninghake, GW	University of Iowa, Iowa City, IA	Mechanisms of cytokine production in asbestosis	NCRR
Hunninghake, GW	Department of Veterans Affairs, Medical Center, Iowa City, IA	Regulation of alveolar macrophage function	VA
Kadiiska, M	NIEHS, NIH	Transition metal mediated free radical formation *in vitro* and *in vivo*	NIEHS
Kamp, DW	Department of Veterans Affairs, Medical Center, Chicago, Il	Mechanisms of asbestos-induced alveolar epithelial cell injury	VA
Kane, AB	Brown University, Providence, RI	Pathogenesis of mesenchymal tumors induced by asbestos	NIEHS
Kelsey, KT	Harvard University, Boston, MA	LOH at 3P and P53 and K-RAS mutation in lung cancer beta-carotene/retinol	NIEHS
Kriebel, D	University of Massachusetts Lowell, Lowell, MA	Lung cancer and exposure to chrysotile and amphiboles	NCI
Libbus, B	Integrated Laboratory S, Durham, NC	Fiber-induced DNA damage and carcinogenicity	HHS
Morris, GF	Tulane University of Louisiana, New Orleans, LA	P53 in asbestos induced lung disease	NIEHS
Mossman, BT	University of Vermont, Soule Medical Bldg, Alumni Building, Burlington, VT	EGFR signaling pathways by particulates in lung disease	NIEHS
Mossman, BT	University of Vermont, Soule Medical Bldg, Alumni Building, Burlington, VT	Molecular signaling by oxidant stress in lung epithelium	NHLBI

Table 3-7. Ongoing Studies on the Health Effects of Asbestos *(continued)*

Investigator	Affiliation	Research description	Sponsor
Oakes, D	University of Rochester, Rochester, NY	Statistical analysis of multiple event time data	NCI
Palmer, CJ	University of Vermont, Burlington, VT	Asbestos-induced cell proliferation via an ERK5 pathway	NIEHS
Rose, C	University of Colorado Health Sciences Center, Denver, CO	Sputum cytology and urinary bombesinlike peptide levels	NCRR
Schapira, RM	Department of Veterans Affairs, Medical Center, Milwaukee, WI	Lung arginine uptake and metabolism after particulate matter exposure	VA
Schenker, MB	University of California Davis, Davis, CA	Environmental asbestos and mesothelioma in California	NCI
Stewart, PA	NCI, NIH	Studies of occupational cancer—occupational exposure assessment	Division of Cancer Etiology
Takaro, T	University of Washington, Seattle, WA	Combined effect of radiation and asbestos in producing pulmonary fibrosis	NIOSH
Testa, JR[b]	Fox Chase Cancer Center, Philadelphia, PA	Molecular genetic alterations in malignant mesothelioma	NCI
Thorne, PS	University of Iowa, Iowa City, IA	Core–inhalation toxicology	NIEHS
Tolbert, PE	Emory University, Atlanta, GA	Environmental risk factors for lymphomas and sarcomas	NCI

[a]Information from FEDRIP (2000) unless otherwise indicated.
[b]Testa (1999)

DNA = deoxyribonucleic acid; NCI = National Cancer Institute; NCRR = National Center for Research Resources; NHLBI = National Heart, Lung, and Blood Institute; NIEHS = National Institute of Environmental Health Sciences; NIH = National Institutes of Health; NIOSH = National Institute for Occupational Safety and Health; USDA = United States Department of Agriculture; USDOE = United States Department of Energy; VA = Veterans' Administration

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Asbestos is a generic term for a group of six naturally-occurring, fibrous silicate minerals that have been widely used in commercial products. Asbestos minerals fall into two groups or classes, serpentine asbestos and amphibole asbestos. It should be noted that serpentine and amphibole minerals also occur in nonfibrous or nonasbestiform forms. These nonfibrous minerals, which are *not* asbestos, are much more common and widespread than the asbestiform varieties. Serpentine asbestos, which includes the mineral chrysotile, a magnesium silicate mineral, possesses relatively long and flexible crystalline fibers that are capable of being woven. Amphibole asbestos, which includes the minerals amosite, crocidolite, tremolite, anthophyllite, and actinolite, form crystalline fibers that are substantially more brittle than serpentine asbestos and is more limited in being fabricated. This group can form a variety of polymeric structures through formation of Si-O-Si bonds. For the amphibole class of asbestos (amosite, crocidolite, tremolite, anthophyllite, and actinolite), the polymeric structure consists of a linear double chain, as shown in (see Figure 4-1 [top]). These chains crystallize into long, thin, straight fibers, which are the characteristic structure of this type of asbestos. For the serpentine class (chrysotile), the polymeric form is an extended sheet (see Figure 4-1, [bottom]). This extended sheet tends to wrap around itself forming a tubular fiber structure. These fibers are usually curved ("serpentine"), in contrast to the straight morphometry of the amphiboles. Some of the asbestos minerals are solid solution series, since they show a range of chemical formulas as a result of ion or ionic group substitutions. Tremolite and actinolite form such a series with iron replacing magnesium as one goes from tremolite to actinolite. The definition of how much iron must be present before tremolite becomes actinolite is not universally recognized and has changed over time (Wylie and Verkouteren 2000). Wylie and Verkouteren also cited the sodic-calcic amphiboles, winchite and richterite, which form a solid solution series and are not regulated under Federal Regulations (EPA 1987d; OSHA 1998a, 1998b). Asbestiform varieties of these amphiboles were found in vermiculite ore in Libby Montana (Wylie and Verkouteren 2000). Table 4-1 lists common synonyms and other pertinent identification information for asbestos (generic) and the six individual asbestos minerals.

The geological or commercial meaning of the word asbestos is broadly applied to fibrous forms of the silicaceous serpentine and amphibole minerals mentioned above. Asbestos minerals form under special physical conditions that promote the growth of fibers that are loosely bonded in a parallel array (fiber bundles) or matted masses. The individual fibrils, which are readily separated from the bundles of fibers, are finely acicular, rodlike crystals. Deposits of fibrous minerals are generally found in veins, in which

Table 4-1. Chemical Identity of Asbestos

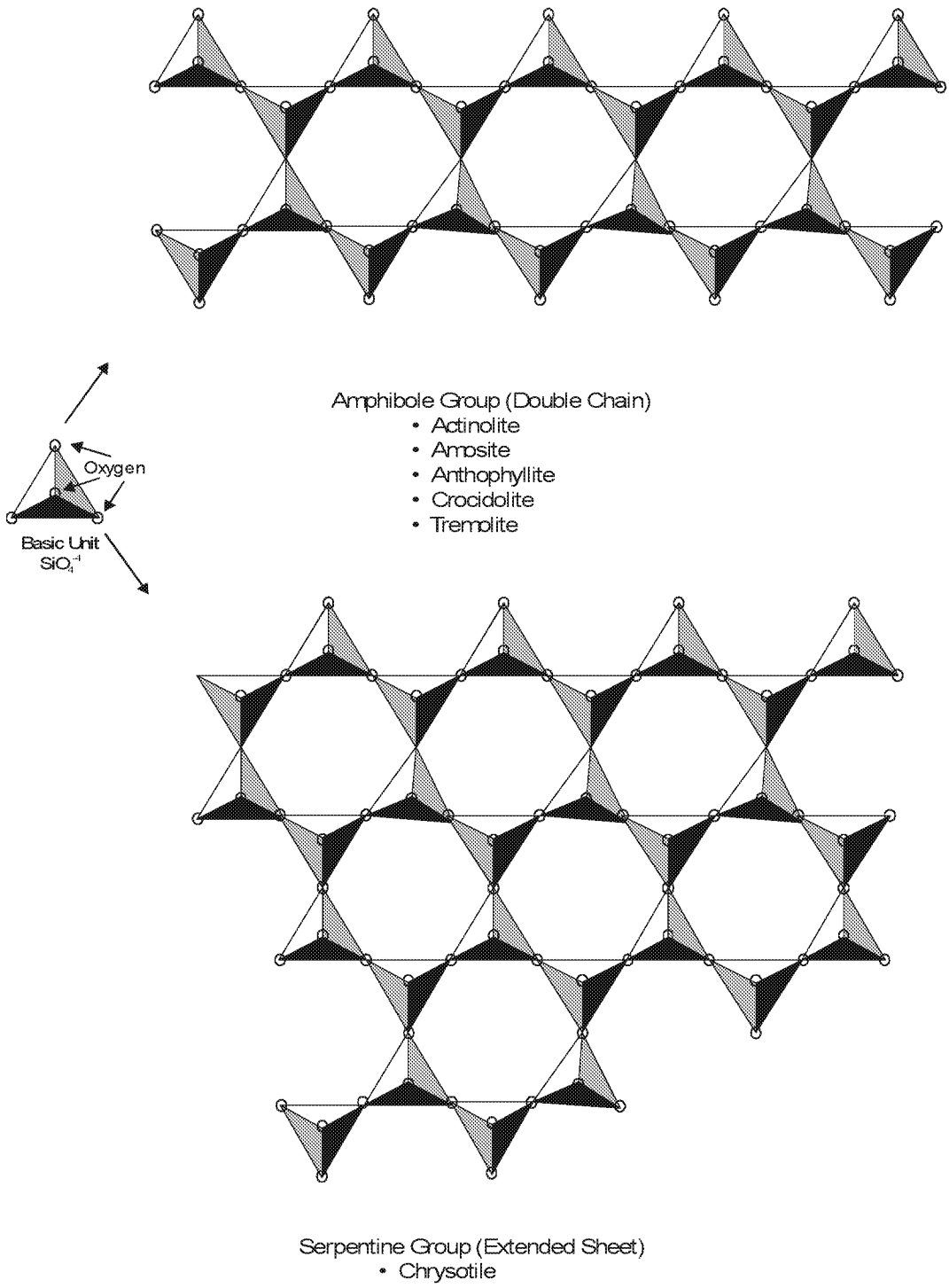
Characteristic	Asbestos	Amosite	Chrysotile	Tremolite[a]	Actinolite[a]	Anthophyllite	Crocidolite
Synonyms	No data	Mysorite, brown asbestos; fibrous cummingtonite/ grunerite	Serpentine asbestos; white asbestos	Silicic acid; calcium magnesium salt (8:4)	No data	Ferroantho-phyllite; azbolen asbestos	Blue asbestos
Trade name	No data	No data	Avibest; Cassiar AK; Calidria RG 144; Calidria RG 600	No data	No data	No data	No data
Chemical formula	No data	$[(Mg,Fe)_7Si_8O_{22}(OH)_2]_n$	$Mg_3Si_2O_5(OH)_4$	$[Ca_2Mg_5Si_8O_{22}(OH)_2]_n$	$[Ca_2(Mg,Fe)_5Si_8O_{22}(OH)_2]_n$	$[(Mg,Fe)_7Si_8O_{22}(OH)_2]_n$	$[NaFe_3^{2+}Fe_2^{3+}Si_8O_{22}(OH)_2]_n$
Chemical structure				See Figure 4-1			
Identification numbers:							
CAS registry	1332-21-4	12172-73-5	12001-29-5	14567-73-8	13768-00-8	17068-78-9	12001-28-4
NIOSH RTECS	CI6475000	BT6825000	GC2625000	XX2095000	AUO550000	CA8400000	GP8225000
EPA hazardous waste	No data	No data	No data	No data	No data	No data	No data
OHM/TADS	7217043	No data	No data	No data	No data	No data	No data
DOT/UN/NA/ IMCO shipping	IMCO 9.0 UN2212 UN2212	No data	IMCO 9.3 UN2590	No data	No data	No data	No data
HSDB	511	2957	2966	4212	No data	No data	No data
NCI	CO8991	No data	C61223A	CO8991	No data	No data	CO9007

[a]Tremolite and actinolite form a continuous mineral series in which Mg and Fe(II) can freely substitute with each other while retaining the same three-dimensional crystal structure. Tremolite has little or no iron while actinolite contains iron (Jolicoeur et al. 1992; Ross 1981; Skinner et al. 1988).

Sources: EPA 1985b; HSDB 2001a, 2001b, 2001c, 2001d; IARC 1977

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

Figure 4-1. Basic Polysilicate Structures of Asbestos*



* Adapted from Hurlbut and Klein 1977

the fibers are at right angles to the walls of the vein. In the general mineralogical definition, fiber size is not specified. Health regulatory agencies use a more limited definition of asbestos fibers, and therefore, only a subset of asbestos fibers are subject to regulations and used in reporting fiber concentrations. U.S. workplace air regulations apply to chrysotile, crocidolite, amosite, and the asbestiform varieties of anthophyllite, tremolite, and actinolite (OSHA 1992). Prior to 1992, these regulations referred to chrysotile, crocidolite, amosite, anthophyllite, tremolite, and actinolite. Since nonasbestiform and asbestiform varieties of the last three minerals have the same name, new legislation was needed to specifically exclude the nonasbestiform varieties of these minerals. The word asbestos is often added after the mineral (e.g., tremolite asbestos) to signify that the asbestiform variety of the mineral is being referred to. This is not necessary for chrysotile, crocidolite, or amosite because the nonasbestiform varieties have different names (i.e., serpentine, riebeckite, and cummintonite-grunerite). OSHA defended the change in definition by noting that there was a lack of substantial evidence that exposed employees would be at significant risk because the nonasbestiform tremolite, anthophyllite, and actinolite were not regulated in the asbestos standard. OSHA (1992) noted that nonasbestiform amphibole airborne particles are regulated by a separate standard for "not otherwise specified" particulate dusts to protect against "the significant risks of respiratory effects which all particulates create at higher levels of exposure." OSHA defines an asbestos fiber for counting purposes as a particle with a length >5 μm and a length:width ratio (aspect ratio) >3:1. It should be noted that other agencies use different definitions of asbestos fibers for counting purposes. For example, EPA defines a fiber as any particle with aspect ratio >5:1 when analyzing bulk samples for fiber content.

Most amphibole and serpentine minerals in the earth's crust are of nonfibrous forms and are therefore not asbestiform. Fibrous forms may occur together with nonfibrous forms in the same deposits. Nonasbestiform amphiboles may occur in many diverse forms, including flattened prismatic and elongated crystals and cleavage fragments. These crystals exhibit prismatic cleavage with an angle of about 55 between cleavage planes. When large pieces of nonfibrous amphibole minerals are crushed, as may occur in mining and milling of ores containing the minerals, microscopic fragments may be formed that have the appearance of fibers but are generally shorter and have smaller length:width ratios (i.e., particle length >5 μm and a length:width ratio >3:1) than particles traditionally defined as fibers by health regulatory agencies (American Thoracic Society 1990; Case 1991; Ross 1981; Skinner et al. 1988). However, some cleavage fragments may fall within the dimensional definition of a fiber and be counted as an asbestos fiber in air samples or biological samples, unless evidence is provided that the particles are nonasbestiform.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Asbestos fibers are basically chemically inert, or nearly so. They do not evaporate, dissolve, burn, or undergo significant reactions with most chemicals. In acid and neutral aqueous media, magnesium is lost from the outer brucite layer of chrysotile. Amphibole fibers are more resistant to acid attack and all varieties of asbestos are resistant to attack by alkalis (Chissick 1985; WHO 1998). Table 4-2 summarizes the physical and chemical properties of the six asbestos minerals.

Table 4-2. Physical and Chemical Properties of Asbestos

Property	Amosite	Chrysotile	Tremolite	Actinolite	Anthophyllite	Crocidolite
Molecular weight[a]	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Color	Brown, gray, greenish	White, gray, green, yellowish	White to pale green[b]	Green[b]	Gray, white, brown-gray, green	Lavender, blue, green
Physical state	Solid	Solid	Solid	Solid	Solid	Solid
Flexibility	Fair	Good	Brittle	Fair to brittle	Fair to brittle	Good
Melting point/ decomposition temperature	600–900 C	800–850 C	1,040 C	No data	950 C	800 C
Specific gravity	3.43	2.55	2.9–3.2	3.0–3.2	2.85–3.1	3.37
Solubility:						
Water	Insoluble	Insoluble	Insoluble	Insoluble	Insoluble	Insoluble
Organic solvents	Insoluble	Insoluble	Insoluble	Insoluble	Insoluble	Insoluble
Acids[c]	12.00	56.00	No data	No data	2.13	3.14
Bases[c]	6.82	1.03	No data	No data	1.77	1.20
Isoelectric point	5.2–6.0	11.8	No data	No data	No data	No data
Electrical charge at neutral pH	Negative	Positive	No data	No data	Negative	Negative
Length distribution in UICC reference samples						
% >1 μm	46	36–44	No data	No data	46	36
% >5 μm	6	3–6	No data	No data	5	3
% >10 μm	1	1–3	No data	No data	1	0.7

Table 4-2. Physical and Chemical Properties of Asbestos *(continued)*

Property	Amosite	Chrysotile	Tremolite	Actinolite	Anthophyllite	Crocidolite
Flammability limits	Nonflammable	Nonflammable	Nonflammable	Nonflammable	Nonflammable	Nonflammable
Conversion factors[d]						

Sources: Chissick 1985; EPA 1980a, 1985b; HSDB 2001a, 2001b, 2001c, 2001d; IARC 1977; Jolicoeur et al. 1992; Kayser et al. 1982; NAS 1977; Ross 1981; Skinner et al. 1988; SRI 1982.

[a]All forms of asbestos are indefinite polymers.
[b]Tremolite and actinolite form a continuous mineral series in which Mg and Fe(II) can freely substitute with each other. With increasing iron content, the color of tremolite, typically creamy white, takes on a greenish cast.
[c]Percent loss in weight due to loss of counter-ions; silicate structure remains intact.
[d]See text, Section 3.2

UICC = Union Internationale Centre le Cancer

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

5.1 PRODUCTION

The production volume of asbestos mines in the United States has decreased substantially from a peak of over 299 million pounds (136,000 metric tons) in the late 1960s and early 1970s (SRI 1982) to 112 million pounds (51,000 metric tons) in 1987, 37 million pounds (17,000 metric tons) in 1989, and 14,000 metric tons in 1993 (U.S. Bureau of Mines 1994; USGS 1998). Production dwindled to 15.4 million pounds (7,000 metric tons) in 1997, 13.2 million pounds (6,000 metric tons) in 1998, and was estimated to remain at 13.2 million pounds (6,000 metric tons) in 1999 (USGS 2000).

While the production and use of asbestos in the United States and Western Europe has declined in recent years as a result of health concerns and bans on many of its uses, there continues to be extensive sales and use of asbestos in South and Central America, Asia, and Africa. World production was estimated as 1.9 million metric tons in 1996. The leading producers in order of declining production volumes were Russia, Canada, China, Brazil, Zimbabwe, and Kazakhstan (Anonymous 2000; Karnak Corporation 1998; Nicholson and Landrigan 1996; USGS 1999b). Nearly all of the asbestos produced worldwide is chrysotile; over 99% of asbestos used in the U.S. has been chrysotile (USGS 2000).

In the past, asbestos was produced by companies in California, Arizona, North Carolina, and Vermont, but many of these companies suspended asbestos mining operations in the 1970s. In 1985, three U.S. companies produced asbestos fibers: Calaveras Asbestos, Ltd., Calaveras County, California; KCAC, Inc., San Benito County, California; and Vermont Asbestos Group, Orleans County, Vermont. By 1997, only one company was mining asbestos in the United States, KCAC Inc., San Benito County, California (USGS 1997, 1999b). The company mines a highly sheared serpentinite composed of matted short fiber chrysotile and unfractured serpentinite (also called a mass fiber deposit). The U.S. resources of serpentinite asbestos, while large, are mostly composed of short fibers. The chrysotile with the longest fibers comes from Zimbabwe.

In the United States, asbestos was mainly mined in open pits in which ore was blasted or drilled from the pit, crushed, dried, and stored until milling. The milling process removes asbestos fibers from the ore by a series of crushing, fiberizing, screening, aspirating, and grading operations. More recently, an alternative method of mining was developed in order to reduce fiber air emission. This method uses bulldozers and scrapers (rather than blasting) to remove the ore from the pit. The ore is watered down to

prevent air dispersion of the fibers, and is crushed, sized, and screened while wet. After being dewatered, the fibers are pelletized, dried, and prepared for shipment either as pellets or further processed to yield open fibers (EPA 1988i).

Table 5-1 lists the number of facilities in each state that reported producing, processing, or using asbestos (friable), the intended use, and the range of maximum quantity of asbestos that is stored on site. The data listed in Table 5-1 are derived from the Toxics Release Inventory (TRI99 2001). Only 'friable' asbestos is required to be reported. Starting in 1998, seven new industrial sectors were required to report their releases to the TRI. One of these new industrial sectors, Resource Conservation and Recovery Act (RCRA) hazardous waste treatment and disposal facilities, often has large amounts of asbestos on site. The TRI data should be used with caution since only certain types of facilities are required to report (EPA 1999b). Therefore, this is not an exhaustive list.

5.2 IMPORT/EXPORT

Most of the asbestos used in the United States is imported; domestic production is mostly exported. Imports from 1950 to 1974 varied from about 1,287 million pounds to 1,580 million pounds (585,000–718,000 metric tons) per year. During the late 1970s, imports began decreasing, with a sharp drop after 1980. By 1984, imports declined to 462 million pounds (210,000 metric tons) and in 1997 and 1998 they had dipped to 46.2 million pounds (21,000 metric tons) and 35.2 million pounds (16,000 metric tons), respectively. Imports for 1999 are estimated to be 33 million pounds (15,000 metric tons) (USGS 2000). Between 1995 and 1998, 99% of imports came from Canada. In 1999, Canada supplied 91% of imports (USGS 1999b). The United States also imported approximately 60,100 metric tons of asbestos- and cellulose-fiber cement products in 1999. These products were in the form of flat sheets and panels (93%), corrugated sheets (4%), and pipes (1%).

Exports of asbestos were low until the mid-1960s when a significant increase in exports occurred. In recent years, export volumes have generally decreased from 132 million pounds (60,000 metric tons) in 1987 to 48 million pounds (22,000 metric tons) in 1991and 39.6 million pounds (18,000 metric tons) in 1994. In 1999, exports of unmanufactured asbestos were approximately 47.7 million pounds (21,700 metric tons), of which approximately 15.4 million pounds (7,000 metric tons) were of domestic origin. These exports included asbestos crudes, fiber, stucco sand, and refuse. Re-exports of Canadian fiber probably accounted for the bulk of the remaining exports. Exports and re-exports of friction products—brake linings, disk pads, and mounted disk linings accounted for 81% of the values of all

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	1	100	999	13
AZ	1	100,000	999,999	2, 3, 8
CA	7	1,000	9,999,999	2, 3, 8, 13
FL	2	10,000	99,999	2, 3, 8, 9
IL	2	10,000	99,999	2, 3, 8, 13
IN	2	10,000	999,999	2, 3, 8
KS	1	10,000	99,999	2, 3, 12
KY	3	1,000	99,999	1, 5, 9, 13
LA	8	1,000	999,999	1, 2, 3, 5, 8, 9, 10, 11, 12, 13
MD	1	10,000	99,999	9
MI	1	1,000	9,999	13
NC	1	10,000	99,999	13
NJ	2	10,000	999,999	8, 9
NV	2	10,000	99,999	12, 13
NY	3	10,000	999,999	2, 3, 8, 9, 13
OH	3	1,000	999,999	1, 2, 3, 4, 5, 8
OK	1	1,000	9,999	13
OR	2	10,000	999,999	2, 3, 8, 13
PA	3	10,000	999,999	2, 3, 8, 13
SC	2	10,000	99,999	1, 2, 3, 5, 8
TN	2	10,000	999,999	8, 9
TX	7	100	999,999	1, 2, 3, 5, 8, 9, 12, 13
UT	3	1,000	9,999,999	1, 5, 13
VA	2	10,000	99,999	1, 2, 3, 5, 9
WA	1	10,000	99,999	12
WV	1	10,000	99,999	11
WY	1	10,000	99,999	1, 5, 10

Source: TRI99 2001

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

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

manufactured asbestos products. The quantity of these exports and whether they were produced in the United States was not reported (SRI 1982; U.S. Bureau of Mines 1992, 1994; USGS 1997, 1999a, 1999b).

5.3 USE

Asbestos has been used in a broad variety of industrial applications which draw upon its low cost and desirable properties such as heat and fire resistance, wear and friction characteristics, tensile strength, heat, electrical and sound insulation, adsorption capacity, and resistence to chemical and biological attack. At the peak of its demand, about 3,000 applications or types of products were listed for asbestos. In most of its applications, asbestos is bonded with other materials such as Portland cement, plastics, and resins. In other applications, asbestos is used as a loose fibrous mixture or woven as a textile.

Consumption of asbestos in the United States has been declining for two decades. Reported consumption of asbestos in the United States was 790 million pounds (359,000 metric tons) in 1980, 497 million pounds (226,000 metric tons) in 1984, 185 million pounds (84,000 metric tons) in 1987, 81 million pounds (35,000 metric tons) in 1991, 73 million pounds (33,000 metric tons) in 1994, and 46 million pounds (21,000 metric tons) in 1997. By 1998 and 1999, U.S. consumption of asbestos had declined to 34.8 million pounds (15,800 metric tons) per year. The 1999 domestic consumption pattern was 61% for roofing products, 19% for gaskets, and 13% for friction products (automobile clutch, brake, and transmission components). Roofing products, gaskets, and friction products will continue to be the only significant domestic markets for asbestos in the foreseeable future. Only chrysotile is presently used for manufacturing in the United States (USGS 1999b). Ninety-four percent of chrysotile consumed was grade 7, a short (3 μm) fiber. Only 0.4% of the asbestos used were long fibers (6–9.5 μm); these were mostly used in plastics (Chissick 1985; Jolicoeur et al. 1992; SRI 1982; USGS 1997, 1999b; U.S. Bureau of Mines 1992, 1994).

In 1973, EPA prohibited the spraying of asbestos-containing material on buildings and structures for fireproofing and insulation purposed. The ban on the use of spraying was later expanded to include applications for decorative purposes. The Consumer Product Safety Commission banned other uses including its inclusion in patching compounds and asbestos heat shields in hair dryers. In October 1991, a United States federal court overturned an EPA regulation (1989f) know as the 'Asbestos Ban and Phase Out Rule' that would have prohibited the manufacture, importation, processing, and distribution in commerce of asbestos and most asbestos-containing products by 1997 under the Toxic Substances

Control Act (TSCA) (U.S. Bureau of Mines 1992; Vu 1993). At present, only asbestos-containing products that were not being manufactured, imported, or processed on July 12, 1989 remain subject to the prohibition requirements of the EPA regulation (EPA 1992a). Specific products which remain subject to the rule will be documented by EPA.

Substitutes for asbestos are constantly being developed (EPA 1989f). Nonasbestos friction materials are currently being used in disc brake pads, and substitutes have been developed for drum brake linings. Substitutes include fibers made of carbon, steel, cellulose, ceramics, glass, and wollastonite and organic fibers made from aramid, polyethylene, polypropylene, and polytetrafluoroethylene (USGS 2000). No single substitute was as versatile and as cost effective as asbestos.

5.4 DISPOSAL

Currently, friable asbestos-containing wastes may only be deposited in landfills that are approved and regulated by the federal government. Regulations include wetting or using dust suppression agents, covering with at least 15 cm (6 inches) of nonasbestos-containing material, and deterring public access with a fence or natural barrier (EPA 1990a). These regulations are intended to ensure that asbestos at these sites is not dispersed into the environment. No data were located on amounts of friable asbestos in such sites. Nonfriable asbestos waste is considered to be a nonhazardous waste and can be disposed of in any landfill. There is no significant recycling of asbestos (USGS 2000). However, Cassiar Mines and Metals, Inc., a Canadian company that owns a mine in British Columbia, is currently producing chrysotile from its stockpiles and mine tailings (USGS 1999b). It is also developing a magnesium plant using stockpiled chrysotile and serpentinite as a source material.

According to the TRI, in 1996, an estimated 750 pounds of asbestos (friable) were released to publicly owned-treatment works (POTWs) by facilities producing, processing, or using asbestos, and an estimated 3.3 million pounds were transferred off-site (TRI96 1999). In 1999, 4.8 million pounds of friable asbestos was transferred off-site, presumably for disposal (TRI99 2001). Starting in 1998, seven new industrial sectors were required to report their releases to the TRI. Asbestos was transferred off-site from only one of these industrial sectors, RCRA hazardous waste treatment and disposal facilities; the amount transferred was 2.4 million pounds.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Asbestos has been identified in at least 83 of the 1,585 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2001). However, the number of sites evaluated for asbestos is not known. The frequency of these sites can be seen in Figure 6-1. All of these sites are located in the United States.

Although asbestos is neither volatile nor soluble, small fibers or clumps of fibers may occur in suspension in both air and water. These fibers are very stable and do not undergo significant degradation in the environment. Large fibers are removed from air and water by gravitational settling at a rate dependent upon their size, but small fibers may remain suspended for long periods of time.

The general population is exposed to low levels of asbestos primarily by inhalation. Small quantities of asbestos fibers are ubiquitous in air. They may arise from natural sources (e.g., weathering of asbestos-containing minerals), from windblown soil from hazardous waste sites where asbestos is not properly stored, and from deterioration of automobile clutches and brakes or breakdown of asbestos-containing (mainly chrysotile) materials, such as insulation. Tremolite asbestos is a contaminant in some vermiculite and talc. These sources would also contribute to asbestos levels in air. Higher levels of airborne asbestos occur near asbestos mines and may occur near industries that produced asbestos-containing products (Case 1991; Case and Sebastien 1987, 1989; WHO 1998). While the use of asbestos in most products has been phased out, higher asbestos levels may be present in soil near these industries. Higher exposure levels may result when asbestos is released from asbestos-containing building materials such as insulation, ceiling tiles, and floor tiles that are in poor condition or disturbed. In general, levels of asbestos in air inside and outside buildings with undisturbed asbestos-containing materials are low, but indoor levels may be somewhat higher than outside levels. In most cases, the exposure of the general population to asbestos has been found to be very low. The concentrations of asbestos fibers in outdoor air are highly variable, ranging from below 0.1 ng/m^3 (equivalent to $3x10^{-6}$ f/mL measured by phase contrast microscopy [PCM]) in rural areas to over 100 ng/m^3 ($3x10^{-3}$ PCM f/mL) near specific industrial sources such as asbestos mines. Typical concentrations are $1x10^{-5}$ PCM f/mL in rural areas and up to an order of magnitude higher in urban areas. In the vicinity of an asbestos mine or factory, levels may reach 0.01 f/mL or higher. The concentration of fibers in indoor air is also highly variable, depending on the amount and condition of asbestos-containing materials in the building. Typical concentrations range from

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

1 to 200 ng/m^3 (3x10^{-5} to 6x10^{-3} PCM f/mL) (Nicholson 1987). For a human exposed for a lifetime (70 years), this range of exposures corresponds to cumulative doses of approximately 0.002–0.4 PCM f-yr/mL. Children may be exposed to asbestos in the same ways that adults are exposed outside the workplace—from asbestos in air, especially near emission sources or in buildings with deteriorating asbestos-containing material. Since children are more apt to play in dirt, they may be exposed to higher levels of asbestos if the dirt they are playing in contains asbestos and they inhale the dust.

Fibers in water arise mainly by erosion of natural deposits of asbestos or by corrosion of fibers from pipes made with asbestos-containing cement. Asbestos concentrations in most water supplies are less than 1 million fibers per liter (MFL), but may exceed 100 MFL in some cases. For a human consuming 2 L/day, this would yield a dose of about 2–200 million fibers per day.

Occupational exposure occurs primarily through inhalation of asbestos-containing air in the workplace. Workers involved in the mining and processing of asbestos ores or in the production of asbestos-containing products may be exposed to asbestos fibers in air. The presence of asbestiform minerals has been detected in certain mining areas, and people employed in mining and processing of other ores may therefore be exposed to asbestos. In particular, tremolite asbestos can be found in certain sources of vermiculite or talc. It is also a contaminant in the chrysotile mined in Quebec, Canada (Case et al. 2000; Frank et al. 1998; Sebastien et al. 1989; Srebro and Roggli 1994). Asbestos-containing material had been commonly used in buildings in insulation, fireproofing, dry wall, ceiling and floor tile, and other materials, and disturbing this material might release asbestos fibers into the air. Therefore, workers involved in demolition work or asbestos abatement, as well as in building maintenance and repair, are potentially exposed to higher levels of asbestos.

According to the Toxics Release Inventory (TRI), in 1999, total releases of asbestos (friable) to the environment (including air, water, and soil) from 87 facilities that reported producing, processing, or using asbestos were 13.6 million pounds (TRI99 2001). Table 6-1 lists amounts released from these facilities grouped by state.

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

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
AL	3	0	No data	No data	49,048	49,048	No data	49,048
AR	1	23	No data	No data	No data	23	2	25
AZ	1	0	No data	No data	No data	0	336	336
CA	9	255	No data	No data	3,242,237	3,242,492	103,699	3,346,191
DE	1	No data	No data	No data	No data	No data	No data	No data
FL	3	103	No data	No data	No data	103	5,726	5,829
IL	4	250	No data	No data	No data	250	1,500	1,750
IN	2	0	No data	No data	No data	0	264	264
KS	1	19	No data	No data	No data	19	2,800	2,819
KY	3	250	No data	No data	59,160	59,410	880,084	939,494
LA	12	19	0	No data	636,000	636,019	268,890	904,909
MD	1	No data	No data	No data	No data	No data	22,908	22,908
MI	1	0	No data	No data	No data	0	No data	0
NC	2	No data	No data	No data	No data	No data	24,000	24,000
NJ	2	175	No data	No data	186	361	3,080	3,441
NV	2	1	No data	No data	76,000	76,001	No data	76,001
NY	5	17	0	No data	770,000	770,017	78,829	848,846
OH	3	1,371	0	No data	No data	1,371	178,000	179,371
OK	1	18	No data	No data	100,579	100,597	No data	100,597
OR	3	0	No data	No data	8,157,587	8,157,587	170	8,157,757

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

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
PA	4	252	0	No data	0	252	433,414	433,666
SC	2	2	No data	No data	No data	2	160	162
TN	2	107	No data	No data	No data	107	145,100	145,207
TX	10	253	0	No data	3,560	3,813	200,532	204,345
UT	3	20	No data	No data	450,426	450,446	42,003	492,449
VA	2	296	No data	No data	No data	296	2,451,886	2,452,182
WA	1	1	No data	No data	No data	1	No data	1
WV	1	No data	No data	No data	0	0	No data	0
WY	2	No data	No data	No data	29,000	29,000	No data	29,000
Total	87	3,432	0	No data	13,573,783	13,577,215	4,843,383	18,420,598

Source: TRI99 2001

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

6.2 RELEASES TO THE ENVIRONMENT

According to the TRI, in 1999, total releases of asbestos (friable) to the environment (including air, water, and soil) from 87 facilities that reported producing, processing, or using asbestos were 13.6 million pounds (TRI99 2001). Table 6-1 lists amounts released from these facilities grouped by state. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

6.2.1 Air

Although asbestos is not volatile, small fibers and clumps of fibers may be released to air as dust. Asbestos originating from the weathering of natural deposits of asbestos-bearing rocks is found in air and has been deposited in ice cores dating back to 1750. No estimates of the amounts of asbestos released to the air from natural sources is available. Asbestos is much more likely to be released to the atmosphere when asbestos deposits are disturbed—as in mining operations. In Canada, over 95% of asbestos is mined in open-mining operations that involve drilling and blasting, and this contributes more air emissions than underground mining operations (Sebastien et al. 1984). Other anthropogenic sources of asbestos emissions besides mining are the crushing, screening, and milling of the ore, the processing of asbestos into products, the use of asbestos-containing materials, and the transport and disposal of asbestos-containing wastes.

In 1992, the EPA estimated that emissions from asbestos processing, including milling, manufacturing, and fabrication were about 2,240 pounds per year (EPA 1992b). This estimate assumed full compliance with the current National Emission Standards for Hazardous Air Pollutants (NESHAP) (EPA 1990a) applicable to asbestos. Based on new data, EPA later determined that asbestos emissions from processing facilities were much lower than the original estimates used to list these facilities as source categories under the 1990 Clean Air Act Amendments of 1992 (OSHA 1994).

Another potential source of asbestos release to air is from clutches and brakes on cars and trucks; a wide range of air concentrations of asbestos fibers (0.004–16.0 f/mL) has been reported in numerous air sampling studies of workplaces during maintenance and replacement of vehicle brakes (WHO 1998). Release of asbestos from insulation or other building materials is discussed in Section 6.4.1, below. Estimated asbestos emissions from waste disposal from all sources were about 499,000 pounds

(22.7 metric tons) per year (EPA 1990a). If all sources were in full compliance with the NESHAP for asbestos, waste disposal emissions would be reduced to 1,320 pounds (600 kg) per year (EPA 1990a).

According to TRI, in 1999, the estimated release of asbestos (friable) was 3,432 pounds to the air from 87 facilities that reported producing, processing, or using asbestos. This accounted for about 0.02% of total environmental releases (TRI99 2001). Table 6-1 lists amounts of asbestos released from these facilities to air.

Asbestos has been identified in air at 17 of the 1,585 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2001).

6.2.2 Water

Asbestos is released to water from a number of sources, including erosion of natural deposits and waste piles, corrosion from asbestos-cement pipes, and disintegration of asbestos roofing materials with subsequent transport via rainwater into cisterns, sewers, etc. (Millette et al. 1980). Waste water from asbestos-related industries may also carry significant burdens of asbestos fibers (EPA 1976). The total amount of asbestos released to water has been estimated to be 110,000–220,000 pounds (50–100 metric tons) per year (NRC 1984).

According to TRI, in 1999, no asbestos (friable) was released to water from 87 facilities that reported producing, processing, or using asbestos (TRI99 2001). Table 6-1 lists the amount of asbestos released from these facilities.

Asbestos has been identified in groundwater and surface water samples respectively collected from 11 and 9 of the 1,585 current or former NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2001).

6.2.3 Soil

Soil may be contaminated with asbestos by the weathering of natural asbestos deposits, or by land-based disposal of waste asbestos materials. While disposal of waste asbestos to landfills was a common practice in the past, current regulations restrict this practice (see Chapters 5 and 8).

In 1999, the disposal of 13,573,783 pounds of asbestos (friable) on land was reported by 87 U.S. facilities that produced, processed, or used asbestos (TRI99 2001). An additional 4,843,383 pounds of asbestos were transferred to other locations, including publically owned treatment works (POTWs), in 1999, and it is likely that most of this was ultimately released on land. No asbestos was injected underground in 1999. Table 6-1 lists the amounts of asbestos released from these facilities by state.

Asbestos has been identified in soil and sediment samples respectively collected from 27 and 7 of the 1,585 current or former NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2001).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Asbestos fibers are nonvolatile and insoluble, so their natural tendency is to settle out of air and water, and deposit in soil or sediment (EPA 1977, 1979c). However, some fibers are sufficiently small that they can remain in suspension in both air and water and be transported long distances. For example, fibers with aerodynamic diameters of 0.1–1 μm can be carried thousands of kilometers in air (Jaenicke 1980), and transport of fibers over 75 miles has been reported in the water of Lake Superior (EPA 1979c). Adsorptive interactions between the fibers and natural organic contaminants may favor coagulation and precipitation of the fibers (EPA 1979c).

6.3.2 Transformation and Degradation

6.3.2.1 Air

Asbestos fibers in air are not known to undergo any significant transformation or degradation (EPA 1979c).

6.3.2.2 Water

Chrysotile asbestos may undergo some dissolution in the aquatic environment, especially at low pH. Magnesium hydroxide leaches from the outer brucite layer, but the basic silicate structure of the fiber remains intact. Amphibole asbestos is much more resistant to attack in acidic media (Chissick 1985; Choi and Smith 1972; Morgan and Holmes 1986; WHO 1998).

Asbestos degrades in the environment very slowly (NRC 1984). Although the estimated half-life of asbestos in aquatic systems is not known, it is expected to be quite long (NRC 1984), and asbestos may persist in the environment virtually unchanged for very long periods of time following its release (EPA 1989f).

6.3.2.3 Sediment and Soil

Asbestos fibers are not known to undergo significant transformation or degradation in soil.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Numerous measurements have been performed to determine the concentration of asbestos fibers in environmental media, primarily air. These studies have reported their results in a variety of units, including ng/m^3 (measured by midget impinger counting analysis), TEM f/mL (fibers measured by transmission electron microscopy), and PCM f/mL (fibers measured by phase contrast microscopy). The most accurate and sensitive method for measuring asbestos fiber content in air is electron microscopy, and preferably transmission electron microscopy (TEM) must be used. Phase contrast microscopy cannot distinguish between asbestos and nonasbestos fibers or between different types of asbestos. However, in certain occupational settings where the predominant fiber is asbestos, PCM should give an adequate measure of asbestos concentration. In nonoccupational environments where a large fraction of the fibers are not asbestos (e.g., wool, cotton, glass), PCM may greatly overestimate the asbestos levels in air. Regulations regarding asbestos determine what fibers are counted in the analysis. Established methods define fiber material having a length 5 μm and a length to diameter ratio of 3:1. In the same air sample, the fibers counted by TEM can be 50–70 times higher than those counted by PCM. This relates to the fact that PCM cannot detect fibers less than about 0.20–0.30 μm in diameter while TEM is capable of detecting fibers with diameters as small as 0.01 μm. Therefore, PCM may miss thin fibers as well as include nonasbestos fibrous material. The conversion factors between fibers counted by PCM and those

counted by TEM are highly variable, depending on the size and length distribution of the fibers. No single set of factors will be accurate for all samples, although a conversion factor can be established for specific fiber types and occupational settings. A comparison was made between fiber counts by PCM and TEM using samples from a chrysotile mine, crusher, mill and tailings site, a brake manufacturing industry, and a taping products industry (Verma and Clark 1995). It was anticipated that such a study would allow extrapolations to be made from occupational exposures to low-level nonoccupational exposures. Fibers from 65 filters were counted using PCM and TEM, and ratio of the fiber counts by the two methods determined for various operations and locations. In addition, the fiber determinations by TEM were made to include different groups of fibers. The fiber concentration ratios determined were TEM to PCM for all TEM fibers, for all TEM asbestos fibers, for TEM asbestos fibers with length >5 μm and diameter <3 μm, and for TEM asbestos fibers with length >5 μm and diameters >0.3 μm and <3 μm. The results for 'all TEM fibers' and 'all TEM asbestos fibers' showed that for the operations studied, the airborne fibers were 93–100% asbestos. The fiber concentration ratios of TEM to PCM for 'all asbestos fibers' were highly variable for the different samples, ranging between 19 and 76. The high of 76 was for milling where a predominance of small fibers resulted from more efficient dust collection. The fiber concentration ratios of TEM to PCM for 'TEM fibers of length >5 μm and diameter >0.3 μm and <3 μm' was fairly consistent, varying between 1.2 and 10.4 but mostly <4.4 or between 1.4 and 3.2 when data were grouped by operation rather than by individual occupations or locations. This indicates that this method of counting and sizing the fibers was consistent. The TEM fibers of length >5 μm and diameter >0.3 μm and <3 μm was 4–18% of the total TEM fibers. The proportion of long, thin fibers increased as the asbestos operation moved from the primary sector (mining) to end use (manufacturing).

In 1984, the NRC (1984) recommended that a conversion be used to measure asbestos fibers. It was suggested that crude approximations could be achieved by assuming that 1 PCM f/mL is equal to 60 TEM f/mL. Both 1 PCM f/mL and 60 TEM f/mL are approximately equal to a mass concentration of 30 $\mu g/m^3$. Since the health effects data regarding inhalation exposure to asbestos are usually expressed in terms of PCM f/mL, ambient air data reported in units of ng/m^3 or TEM f/mL are converted to units of PCM f/mL using the factors suggested by NRC (1984).

6.4.1 Air

Ambient outdoor air, remote from any special sources, is generally found to contain 0.001–0.1 ng/m^3 of asbestos ($3x10^{-8}$–$3x10^{-6}$ PCM f/mL) (NRC 1984). Another source reports the average concentration of asbestos fibers in rural outdoor air as $1x10^{-5}$ PCM f/mL (HEI 1991). In urban areas, most ambient air

concentrations range from 0.1 to 10 ng/m^3 (3x10^{-6}–3x10^{-4} PCM f/mL), but may range up to 100 ng/m^3 (3x10^{-3} PCM f/mL) as a result of local sources (Corn 1994; EPA 1991b; IARC 1977; Nicholson and Pundsack 1973; Selikoff et al. 1972). The median concentration in U.S. cities has been estimated to be 2.3 ng/m^3 (7x10^{-5} PCM f/mL) (NRC 1984). Two other investigations of asbestos in outdoor air in the United States reported levels of asbestos from not detected (ND) to 8x10^{-3} PCM f/mL, with a median of 3x10^{-4} PCM f/mL and a mean of 5x10^{-5} PCM f/mL (WHO 1998). These levels are sufficiently low that they are not likely to be of significant health concern to most people. Near industrial operations involving asbestos, levels may be as high as 50–5,000 ng/m^3 (10.0015–15 PCM f/mL) (IARC 1977). A recent analysis of monitoring data for asbestos in ambient air worldwide estimated rural and urban levels at about 1x10^{-5} TEM f/mL (2x10^{-7} PCM f/mL) and 1x10^{-4} TEM f/mL (2x10^{-6} PCM f/mL), respectively (HEI 1991). Higher levels were measured near source-dominated locations.

Average asbestos fiber concentrations (>5 m) in chrysotile mining towns in Quebec that had been 0.08 f/mL in 1973 and 1974 declined to 0.007 by 1982 and have remained below 0.01 f/mL between 1982 and 1994 (WHO 1998). A comprehensive study of asbestos air levels around various asbestos-related industries was conducted in Taiwan (Chang et al. 1999). Samples (n=246) were obtained as a function of distance around 41 factories producing cement, friction products, textiles, tile, insulation, and refractory materials. Samples around 14 of these plants, randomly chosen to include all types of plants, were analyzed by TEM; the remainder of the samples were analyzed by PCM. The results of this study appears in Table 6-2. In general, the asbestos concentrations around asbestos-related industries were low and inversely related to distance from the factory. The large geometric standard deviation reflects unevenly distributed levels for the same type of plant. Asbestos levels around refractory plants were low indicating a low release during the wet, clay-like material in the manufacturing process. In contrast, higher levels of asbestos fibers were found around textile plants where the manufacturing process is dry and open. Asbestos concentrations obtained by PCM were much higher than those obtained by TEM. This overestimation of fiber concentrations by PCM is much greater when the levels of nonasbestos fibers are high. For the same factory, levels of TEM asbestos substances were generally lower than nonasbestos substances and in some samples combined concentration of asbestos and nonasbestos substances were similar to results obtained by PCM.

McDonald et al. (1986b) reported that TEM and chemical analysis of samples of airborne fibers from various locations of the Libby, Montana, vermiculite mine and mill showed several morphologies (straight with uniform diameter, needle shape, and curved), chemical content compatible with the

Table 6-2. Asbestos Levels in Ambient Air Around Taiwanese Factories

Factory type	Number of factories	Method	GM (GSD) asbestos concentrations (f/mL)		
			Distance from factory		
			200 m	400 m	600 m
Cement	5	TEM	0.006 (1.230)	0.007 (1.487)	0.006 (1.301)
		PCM	0.01 (3.49)	0.01 (2.91)	<0.01
Friction	3	TEM	0.008 (2.441)	0.008 (1.978)	0.002 (2.221)
		PCM	0.01 (322)	0.02 (2.88)	<0.01
Textile	2	TEM	0.012 (2.221)	0.020 (1.432)	0.006 (1.765)
		PCM	0.02 (3.21)	0.02 (3.33)	<0.01
Ground tile	2	TEM	0.033 (1.412)	0.021 (1.421)	0.025 (2.321)
		PCM	0.4 (3.21)	<0.01	0.01 (2.21)
Insulation	1	TEM	0.012 (2.321)	0.020 (2.210)	0.006 (2.773)
		PCM	<0.01	<0.01	<0.01
Refractory	1	TEM	<0.0001	<0.0001	<0.0001
		PCM	<0.01	<0.01	<0.01
Overall	14	TEM	0.0015 (1.943)	0.0011 (2.022)	0.007 (2.221)
		PCM	0.06 (3.29)	0.01 (3.21)	0.01 (2.21)

Source: Chang et al. 1999

GM = geometric mean; GSD geometric standard deviation; PCM = phase contrast microscopy; TEM = transmission electron microscopy

tremolite-actinolite series with some evidence of sodium content; ranges for diameter, length, and length:width ratio of 0.1–2, 1–70, and 3–100 μm, respectively. Greater than 60% of fibers were reported to be longer than 5 μm (McDonald et al. 1986b). Tremolite asbestos is a contaminant in some vermiculite.

Asbestos fibers may be released to indoor air due to the possible disturbance of asbestos-containing building materials such as insulation, fireproofing material, dry wall, and ceiling and floor tile (EPA 1991b; HEI 1991; Spengler et al. 1989). Measured indoor air values range widely, depending on the amount, type, and condition (friability) of asbestos-containing materials used in the building. For example, asbestos in floor tile is less friable than that in insulation or sprayed coatings. The release of asbestos fibers from asbestos-containing materials (ACM) is sporadic and episodic. Human activity and traffic may facilitate release of asbestos fibers and stir up asbestos-containing dust. Therefore, monitoring performed at night or on weekends may underestimate human exposure to asbestos in buildings. In addition, asbestos levels are apt to be higher in some areas of a building (e.g., boiler room) than in others and these areas may not be accessible to most people using the building. In a review of indoor air monitoring data from a variety of locations, Nicholson (1987) reported that arithmetic mean concentrations ranged from 1 to 200 ng/m^3 ($3x10^{-5}$ to $6x10^{-3}$ PCM f/mL). In a survey performed by EPA (1988c), levels of asbestos in 94 public buildings that contained asbestos ranged from not detected (ND) to 0.2 TEM f/mL (ND–$3x10^{-3}$ PCM f/mL), with an arithmetic mean concentration of 0.006 TEM f/mL (10^{-4} PCM f/mL) (Spengler et al. 1989). Analysis of data based on air samples from 198 buildings with ACM indicated mean asbestos levels ranging from $4x10^{-5}$ to $2.43x10^{-3}$ TEM f/mL ($7x10^{-7}$–$4x10^{-5}$ PCM f/mL) (HEI 1991). Asbestos concentrations in 41 schools that contained asbestos ranged from ND to 0.1 TEM f/mL (ND–$2x10^{-3}$ PCM f/mL), with an arithmetic mean of 0.03 TEM f/mL ($5x10^{-4}$ PCM f/mL) (EPA 1988c; Spengler et al. 1989). Another study reported average concentrations of airborne asbestos fibers 5 μm in length of $8.0x10^{-5}$ and $2.2x10^{-5}$ TEM f/mL in 43 nonschool buildings and 73 school buildings, respectively (Chesson et al. 1990; HEI 1992; Spengler et al. 1989). The average outdoor level in these studies were comparable to those measured indoors (Spengler et al. 1989). Building survey and air sampling, both inside and outside the building was conducted on 315 buildings nationwide over a 5-year period. The study was undertaken by consultants for defendants for litigation from buildings in which asbestos removal was alleged to be necessary because of risk to occupants from exposure to asbestos-containing materials (Lee et al. 1992). In the study a total of 2,892 air samples were obtained and analyzed by TEM. Public, commercial, residential, school and university buildings were included in the study, all of which were occupied. The airborne asbestos concentrations from this study (see Table 6-3) include all chrysotile and amphibole particles having a length:width ratio 3, concentrations of fibers 5 μm long, and the

Table 6-3. Exposure to Airborne Asbestos in U.S. Buildings[a]

			Asbestos structure and fiber concentrations						
			Asbestos structures[b] (f/mL)			Fibers[c] (f/mL)		Optical equivalents (f/mL)[d]	
Building type	Number of buildings	Number of Samples	Mean	Median	90th percentile	Mean[e]	90th percentile	Mean[e]	90th percentile
School	177	921	0.04015	0.01017	0.08134	0.00018	0.00071	0.00011	0.00056
University	78	426	0.00865	0.00165	0.02543	0.00008	0.00000	0.00007	0.00000
Commercial	28	213	0.00162	0.00101	0.00476	0.00003	0.00000	0.00002	0.00000
Public	32	123	0.00538	0.00335	0.01551	0.00016	0.00054	0.00007	0.00015
Residential	1	10	0.00486			0.00000		0.00000	
Outdoor		759	0.00188	0.00000	0.00437	0.00005	0.00000	0.00002	0.00000
Personal		106	0.00866	0.00316	0.02368	0.00012	0.00000	0.00009	0.00000
Indoor[f]	315		0.02485			0.00013		0.00008	

Source: Lee et al. 1992

[a]All analyses performed by TEM.
[b]All asbestos particles having a length:width ratio 3.
[c]Asbestos fibers 5 μm long.
[d]Optically equivalent asbestos fibers (i.e., fibers 5 m long and 0.25 m in width).
[e]Median concentrations for all categories are 0.00000 f/mL.
[f]Indoor air samples include schools, universities, public, commercial, and residential buildings.

GM = geometric mean; GSD = geometric standard deviation; TEM = transmission electron microscopy

concentration of structures with lengths of 5 μm and widths of at least 0.25 μm. The latter category is referred to as "optically equivalent" structures and represent those structures that would have been identified by PCM. The average concentration of all asbestos structures was 0.025 f/mL. The average concentration of asbestos fibers 5 μm was 1.3×10^{-4} f/mL, while for those that could be detected by optical methods, it was 8.0×10^{-5} f/mL. In 48% of indoor samples and 75% of outdoor samples, no asbestos fibers 5 μm were found. There are significant differences in the concentration of total asbestos structures among building types, but not for fibers 5 μm. Additionally, there was no difference in the indoor and outdoor levels of asbestos fibers 5 μm for commercial, public, or university buildings, although a higher level indoors was found for school buildings. Outdoor levels were consistently lower than indoor levels when all asbestos structures were considered. Most of the chrysotile fibers were very thin (97% less than 0.2 μm in diameter [and would have been missed by PCM]) and short (85% less than 1 μm long). Only 2% of the fibers were amphiboles and these fibers were generally longer and thicker than the chrysotile fibers.

In studies from a Health Effects Institute-Asbestos Research Study, mean concentrations of fibers 5 μm ranged from 0 to 2.5×10^{-4} f/mL in public and commercial buildings and from 1.0×10^{-5} to 1.11×10^{-3} f/mL in schools and universities (Lee et al. 1992). Average concentrations in the United States are 10–100 times less than those found in Britain, Germany, and Canada. The structures found in buildings are much smaller and coarser than those found in occupational settings. Corn (1994) reported the mean, 90th percentile, and maximum asbestos levels in 231 buildings, including schools, universities, and public, commercial, and residential buildings as 1.0×10^{-4}, 5.1×10^{-4}, and 2.06×10^{-3} PCM f/mL, respectively; outdoor levels were 6.0×10^{-5} f/mL.

A study of 49 buildings in the United States reported mean asbestos fiber levels of 9.9×10^{-4} PCM f/mL in buildings with no ACM, 5.9×10^{-4} PCM f/mL in buildings with ACM in good condition, and 7.3×10^{-4} PCM f/mL in buildings with damaged ACM (WHO 1998). In general, direct comparison of levels inside and outside ACM buildings indicates that typical (nondisturbed) indoor levels are usually low, but may be higher than outside levels (Chesson et al. 1990). Buffing asbestos-containing floor tile in a commercial building led to a small increase in asbestos bodies <5 μm long, but no increase in those >5 μm in length (Demyanek et al. 1994).

Asbestos may also be released to indoor air from the use of asbestos-contaminated household water (Hardy et al. 1992; Webber et al. 1988). Limited studies indicate that both amphibole and chrysotile

fibers can be aerosolized by portable home humidifiers (Hardy et al. 1992). The airborne asbestos concentrations in the home were directly proportional to the asbestos concentrations in the water used in the humidifiers.

6.4.2 Water

The concentration of asbestos fibers in water (expressed as million TEM fibers per liter, MFL) varies widely. Concentrations in most areas are <1 MFL (EPA 1979b), but values of 1–100 MFL and occasionally higher have been detected in areas contaminated by erosion from natural asbestos deposits (EPA 1976; Kanarek et al. 1980) or from mining operations (Sigurdson et al. 1981).

Sources of asbestos in drinking water may be a result of natural deposits from releases due to the use of asbestos-cement pipes in water distribution systems. The amount of asbestos contributed from asbestos-cement pipe is negligible in some locations (Hallenbeck et al. 1978), but may result in concentrations of 1–300 MFL at other locations (Craun et al. 1977; Howe et al. 1989; Kanarek et al. 1981). In one reported incident, grossly deteriorated asbestos-cement pipe in the water distribution system resulted in water concentrations of asbestos up to 1,850 MFL (Webber et al. 1989). The variability in the amount of fibers coming from asbestos-cement pipe appears to depend on a number of parameters, but is mostly related to characteristics of the water such as low pH and low hardness, which influence the rate at which the water can corrode the pipe (NAS 1982). In a recent Austrian study, the asbestos content of drinking water that was contaminated by natural asbestos deposits or the use of asbestos cement pipe was compared with that in control areas (Neuberger et al. 1996). In 10 areas with asbestos deposits and 14 areas that had asbestos-cement pipes, the asbestos concentration in drinking water was low (median 32,000 total asbestos fibers per liter) and was not significantly different from 6 control areas. The highest concentration, 190,000 f/L, was found in an area with natural asbestos deposits at the source of the supply. In areas without natural deposits, the increased asbestos concentration was not significant and was unrelated to aggressiveness of the water supply or to age or length of the pipe. It should be noted that asbestos-cement pipes in areas with aggressive water are coated in Austria. Elevated asbestos concentrations of asbestos were found in water in an uncoated asbestos-cement cistern. In a similar study involving 59 aqueducts in Tuscany, Italy, 76% of the samples were below the detection limit of 0.002 MFL (Cherubini et al. 1998). Asbestos fibers in the other samples were present at concentrations lower than 0.04 MFL. Samples of aggressive water taken from asbestos-cement pipes were too few to determine whether a significant correlation existed between water quality and asbestos release from the

pipes. The majority of all fibers found in these studies was chrysotile, and most fibers were less than 5 μm in length (Hallenbeck et al. 1978; Millette et al. 1980; Neuberger et al. 1996; Pitt 1988).

6.4.3 Sediment and Soil

The serpentine and amphibole mineral groups occur over a wide a range of geological environments. The preponderance of these minerals are of a nonfibrous form. Fibrous forms of these mineral groups are minor constituents of many rocks and can be found in soils. For example, tremolite asbestos is found as an impurity in some commercially mined deposits of talc, vermiculite, and chrysotile (Amandus et al. 1987; Boutin et al. 1989; Case 1991; Davis et al. 1985; Lockey et al. 1984; McDonald et al. 1986a; Ross 1981; Skinner et al. 1988). Ross (1981) has reviewed the occurrence of different forms of asbestos minerals and the history of their exploitation. The occurrence of asbestiform minerals is a function of the chemical composition of the underlying rock and the temperatures and pressures that were instrumental in forming these rocks. Commercially exploitable deposits of asbestos minerals are associated with certain types of rocks and for some asbestos minerals, these deposits are rare.

No studies were located regarding the concentration of asbestos fibers that occur in soil. Asbestos was found in about 80% of a number of samples of street dirt at concentrations ranging from 100 million to 1 billion fibers per gram (f/g) (Pitt 1988). These were primarily chrysotile fibers, but most were <2 μm in length and therefore, were not comparable with fiber concentrations that are 5 μm. The concentration of fibers 5 μm in length was not reported. It is likely that the main source of this asbestos was release from automobile brakes.

6.4.4 Other Environmental Media

Tremolite-actinolite is present in or around some deposits of chrysotile asbestos. However, levels of amphibole asbestos in commercial chrysotile were not reported. Tremolite is a contaminant in talc from New York and California, but the extent and fibrosity of the tremolite is unclear (DOL 1980; Wagner et al. 1982c; American Thoracic Society 1990). The tremolite in some talc from California has been described as flake-like and that from New York as having fine fibers (Wagner et al. 1982a). Some tremolite in the chrysotile from Quebec has been described as having coarse fibers. A British survey of talc powders used for various purposes identified 3 out of 24 samples as containing tremolite. Ten of 20 samples of cosmetic talc purchased in New York City between 1971 and 1975 contained 1–14% (w/w) of fibrous tremolite and anthophyllite (Paoletti et al. 1984). Paoletti et al. (1984) conducted a survey of

asbestos fibers in talc powders from Italian and international markets using electron microscopy, electron diffraction, and x-ray microanalysis. The fiber criteria used was that accepted by the Council of European Communities (i.e., those having a length:width ratio 3 and a width <3 μm). Three of 14 samples of talc provided by European Pharmacopoeia from the international market contained tremolite asbestos; in 2 of the samples, the percent of asbestos fibers was about 20% by weight. In the 15 samples of Italian industrial, pharmaceutical, and cosmetic talc, 7 contained fibers of tremolite, ranging from 0.2 to 1.6% by weight. Interestingly, about three-quarters of the asbestos fibers observed in each sample had diameters less than about 0.4 μm and therefore, were probably below the resolving power of phase contrast microscopy.

Raw vermiculite (vermiculite concentrate) is a mica-like mineral that rapidly expands upon heating to produce a lightweight, bulky material, vermiculite, that is used in fireproofing, insulation, packaging, and in horticultural/agricultural products, as a soil conditioner, fertilizer carrier, etc. One of the largest vermiculite deposits in the United States is in Libby, Montana, where raw vermiculite was mined and milled from 1923 until 1990. Vermiculite from the mine was marketed under the trade name Zonolite. Atkinson et al. (1982) found fibrous tremolite-actinolite, nonfibrous tremolite-actinolite, and nonfibrous anthophyllite in raw ore and vermiculite concentrate samples from the vermiculite mine and mill in Libby, Montana: fibrous tremolite-actinolite accounted for ~21–26% of the weight of raw ore and 2–6% of the weight of vermiculite concentrate (as cited in Amandus et al. 1987). In a 1984 study of samples from Libby, Montana conducted by W.R. Grace, fiber percentage by weight varied from 3.5 to 6.4% in raw ore and from 0.4 to 1.0% in the concentrate (cited in Amandus et al. 1987). Amandus et al. (1987) noted that among 599 fibers counted in eight airborne membrane filter samples from Libby, 96 and 16% had length:width ratios >10 and >50, respectively. Percentages of fibers with lengths >10, >20, and >40 μm were 73, 36, and 10%, respectively. Moatamed et al. (1986) analyzed samples of vermiculite ores from Libby, Montana; Louisa County, Virginia; and South Africa for the presence of amphibole fiber (asbestos) contamination. Two samples of Montana unexpanded vermiculite ore were determined to have 0.08 and 2.0% amphibole content by weight; two samples of expanded Montana vermiculite both showed 0.6% amphibole content. The South African unexpanded and expanded samples showed 0.4 and 0.0% amphibole content, respectively. The unexpanded and expanded Virginia samples were both determined to be 1.3% amphibole by weight. The number of fibers detected by microscopy in the Virginia samples were reported to be "extremely low" in comparison to the Montana samples, and the South African vermiculite samples showed a "near absence of fibers" or "rare, short fibrous structures." Based on energy-dispersive x-ray analysis of random fibers in the samples, the fibers in the Montana and Virginia samples were classified predominantly as actinolite, whereas the fibers in the South African samples were

predominantly anthophyllite. The size of fibers in the Montana and South African samples indicate that these amphiboles were asbestiform, while the actinolite present in the Virginia samples may have been predominantly nonasbestiform cleavage fragments (Moatamed et al. 1986).

Recently, EPA conducted a survey of vermiculite products, primarily those used in gardening, to determine whether products currently on the market contain asbestos and if so, whether consumers are at risk from using these products (EPA 2000d). Five of the 16 products purchased in garden stores in the Seattle area contained asbestos, 3 of which contained enough asbestos to be quantified reliably. These samples contained between 0.1 and 2.8% tremolite-actinolite asbestos. Samples taken from the same bag of material were variable in fiber concentration with higher levels of fibers found in the fine particles taken from the bottom of a bag. The use of these products were then simulated to see whether the fibers became airborne. Fibers were detected in air samples at (0.16–0.95 f/mL) from the Zonolite Chemical Packaging. Asbestos was detected in 17 of an additional 38 vermiculite products purchased around the country, of which only 5 contained quantifiable levels. The study concluded that consumers face only minimal health risks by using vermiculite products and these can be minimized by keeping the product moist to avoid creating dust and using the product in well ventilated areas. Fibrous and nonfibrous tremolite has been detected in vermiculite from both Montana and South Carolina, but the levels in South Carolina vermiculite may be lower (American Thoracic Society 1990). Actinolite was found in Virginia samples, but at lower levels than in Montana vermiculite and mostly as cleavage fragments (Moatamed et al. 1986).

In the past, filters made from asbestos were employed in the preparation of wines, beers, and other items consumed by humans, and asbestos concentrations in these materials ranged from 1 to 10 MFL (Cunningham and Pontefract 1973). Analysis of 47 brands of sake purchased in Japan from 1983 to 1985 indicated that asbestos concentrations in sake ranged from less than the detection limit (7.8×10^{-3} MFL) to 196 MFL (Ogino et al. 1988).

The use of asbestos filters in food or pharmaceutical preparation has been discontinued in the United States, and intake of asbestos through foods or drugs is now unlikely.

Asbestos fibers may be incorporated in sewage sludge as a result of their presence in waste water. Asbestos has been reported in municipal sewage sludges and sewage sludge composts from large and small cities in the United States (Manos et al. 1991, 1993; Patel-Mandlik et al. 1988). Asbestos was detected in 34 of 51 sludge ash samples at levels ranging from 1 to 10% by volume (Manos et al. 1991).

In a 1993 study of the prevalence of asbestos in sludge from 16 sewage plants in large American cities, asbestos was detected in 13 of the sludges at up to 7% by volume (Patel-Mandlik et al. 1994). The sludge disposal methods of the participating treatment plants were land application, 44%; land filling, 37%; and incineration, 19%.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

As noted above, the concentrations of asbestos found in indoor air, outdoor air, and drinking water vary widely, and it is not possible to calculate human exposure levels accurately except on a site-by-site basis. With this limitation in mind, Table 6-4 presents some rough estimates of exposure levels for a general population living in an urban or suburban area and for asbestos workers. The exposure levels used for the general public are intended to represent the central portion of the typical range of exposures; thus, some persons could be exposed to higher levels, while others could be exposed to less. The workplace air concentration used to estimate worker exposure (0.1 f/mL) is the same as the current U.S. workplace exposure limit (OSHA 1998a, 1998b, 1998c). Actual workplace exposures could be higher or lower. It has been estimated that about 568,000 workers in production and services industries and 114,000 in construction industries may be exposed to asbestos in the workplace (OSHA 1990). Rough estimates of dose of fibers transferred to the gastrointestinal tract after inhalation exposure were calculated using the same assumptions (e.g., 30% of inhaled fibers are transferred to the gastrointestinal tract) as employed in similar calculations by NAS (1983).

The exposure of the general population (nonoccupational exposure) to asbestos in both indoor and outdoor air is extremely low. Older buildings may contain ACM, which had been used for insulation, surface treatment (e.g., fireproofing), floor and ceiling tiles, insulating boards, and spackling, patching, and plastering compounds and asbestos levels are generally higher in indoor air than outdoors (HEI 1991; Spengler et al. 1989). However, exposure appears to be low regardless of whether the buildings do not contain ACM, contain ACM in good condition, or contain damaged ACM (Spengler et al. 1989). As mentioned in Section 6.4.4, the release of asbestos fibers from ACM is sporadic and episodic, and human activity and traffic in occupied buildings would result in higher air concentration of asbestos fibers than in unoccupied buildings. Unfortunately, many investigators fail to report the time when monitoring was performed and whether the building was occupied at the time. One recent investigation found mean asbestos levels in indoor air of occupied buildings having ACM to be 8.0×10^{-5} f/mL, while outdoor air levels were 2.0×10^{-5} f/mL; in both cases, median levels were below detection limits (Lee et al. 1992). Exposure of custodial and maintenance personnel would be higher as they are more likely to be in areas

Table 6-4. Summary of Typical General Population and Occupational Exposures

Exposed population	Exposure medium	Typical concentration	Assumed exposure	Cumulative exposure level (f-yr/mL)	Estimated dose to gastrointestinal tract[a] (MF/day)
General population	Ambient (outdoor) air	$2x10^{-6}$ PCM f/mL	20 m^3/day, 70 years (10% of time outdoors)[e]	0.000014[b]	0.0000012[c]
	Indoor air[e]	$3x10^{-6}$ PCM f/mL	20 m^3/day, 70 years (90% of time indoors)[b]	0.00019[f]	0.000016[g]
	Drinking water	0.017 MFL[e]	2 L/day	–	0.034
Asbestos worker	Workplace air	0.1 PCM f/mL[h]	40 years, 8 m^3/day, 5 days/week, 49 weeks/year[i]	1.1[j]	0.16[k]

[a]Assumes 30% of inhaled fibers are transferred to stomach (NAS 1983)
[b]Approximate value based on EPA 1989e
[c]Cumulative exposure level (values in []): Typical concentration [$2x10^{-6}$ f/mL] x Life span [70 years] x Fraction of time outdoors [0.1]
[d]Dose to gastrointestinal tract:(values in []): Typical concentration [$2x10^{-6}$ f/mL] x Volume inhaled/day [20 m^3] x Fraction of time outdoors [0.1] x Fraction of inhaled fibers transferred to gastrointestinal tract [0.3] x 10^6 mL/m^3 x 10^{-6} MF/f
[e]Millette et al. 1980; concentration converted from TEM basis to PCM basis using 1 TEM f=1/60 PCM f (NRC 1984).
[f]Cumulative exposure level (values in []): Typical concentration [$3x10^{-6}$ f/mL] x Life span [70 years] x Fraction of time indoors [0.9]
[g]Dose to gastrointestinal tract:(values in []): Typical concentration [$3x10^{-6}$ f/mL] x Volume inhaled/day [20 m^3] x Fraction of time indoors [0.9] x Fraction of inhaled fibers transferred to gastrointestinal tract [0.3]x10^6 mL/m^3 x 10^{-6} MF/f
[h]Time-weighted average (TWA) Permissible Exposure Limit (PEL) (OSHA 1998c)
[i]NAS 1983
[j]Cumulative exposure level (values in []): Typical concentration [0.1 f/mL] x Working life span [40 years] x Fraction of air breathed in workplace [8 m^3/day/20 m^3/day x 5 days/7 days x 49 weeks/52 weeks]
[k]Dose to gastrointestinal tract:(values in []): Typical concentration [0.1 f/mL] x Volume inhaled/workday [8 m^3 x 5 days/7 days x 49 weeks/52 weeks] x Fraction of time outdoors [0.1] x Fraction of inhaled fibers transferred to gastrointestinal tract [0.3]x10^6 mL/m^3 x 10^{-6} MF/f

f/mL = fibers per milliliter; MF = million fibers; MFL = million fibers per liter; PCM = phase contrast microscopy; TEM = transmission electron microscopy

of a building that may contain asbestos (e.g., boiler room) and may come into contact or disturb ACM, thereby increasing air levels during the course of their activities.

People living in the vicinity of asbestos mines and asbestos-related industries may be exposed to higher levels of asbestos (Case 1991; Case and Sebastien 1987, 1989; Churg 1986b; Churg and DePaoli 1988). The magnitude of such exposures tend to be overestimated when researchers use PCM in situations where the concentrations of nonasbestos fibers are high (e.g., around textile and friction product factories) or if the actual concentration of asbestos is very low (e.g., around refractory plants). In their investigation of exposure levels around asbestos-related industries in Taiwan, Chang et al. (1999) found differences in asbestos fiber levels around different types of plants; those using dry and more mechanical operations (e.g., textiles) tended to have higher levels than other plants. Also, asbestos levels were inversely related to distance from the plant. In a study of the contribution of airborne asbestos fibers to the work environment from the operation of an overhead crane having asbestos brake pads, the 8-hour time-weighted-average (TWA) asbestos fiber concentration ranged from <0.005 to 0.011 f/mL (PCM) and from <0.0026 to 0.0094 f/mL (TEM) (Spencer et al. 1999). No asbestos fibers were detected by TEM during the operation of the cranes.

Workers involved in mining of asbestos or minerals contaminated with asbestos or manufacturing or using asbestos-containing products may be occupationally exposed to elevated levels of asbestos. Average asbestos fiber concentrations (>5 m) in the Quebec chrysotile mining industry declined markedly from 16 f/mL in 1973 to 2 f/mL in 1978 and has remained below 2 f/mL between 1978 and 1994 (WHO 1998). The highest asbestos concentration in 1973 was 52 f/mL.

A simulation of bandsawing sheet asbestos gasket material was performed in order to retrospectively evaluate worker exposure from this operation (Fowler 2000). The work was performed on 1/8-inch chrysotile asbestos (80%)/neoprene sheet (purchased in 1996) using a conventional 16-inch woodworking bandsaw. Personal samples and area samples at the breathing zone were assessed using PCM, TEM (total), and TEM (>5 μm). Personal air concentrations of fibers >5 μm during bandsawing were between 2.2 and 4.9 f/mL by PCM. The personal air concentrations by TEM were higher; 22.2–49.3 f/mL for all asbestos fibers and 8.2–17.6 f/mL for fibers >5 μm. Area results were somewhat lower with PCM results between 0.75 and 2.3 f/mL and TEM results in the ranges of 14.3–22.7 f/mL (total) and 5.7–7.6 f/mL (>5 μm). These results show that airborne fiber levels were well above the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs) of 0.1 and 1.0 f/mL for PEL (TWA) and PEL (ceiling), respectively.

A similar simulation was performed by Esmen and Corn (1998) to estimate the exposure of workers in the historically important process of splitting open bags of asbestos and transferring the contents to a container. In splitting open a bag of powdery material, there is generally an immediate but short duration release of material. Exposure depends on the number of bags opened and the air exchange rate. The 8-hour TWA exposure levels were determined for various scenarios and air exchange rates using PCM (fibers >3 μm). In the case where one 4.5 kg bag of chrysotile asbestos was opened and boxed every 15 minutes for 8 hours, air asbestos levels ranged from 21 f/mL at 0.5 air exchanges per hour (ACH) to 0.45 f/mL at 30 ACH. Peak exposure levels reached 80 f/mL.

In 1985, a comprehensive study of Japanese plants producing asbestos-containing products was conducted to assess exposure levels to asbestos fibers using phase-contrast microscopy. Personal exposures ranges were 0.07–0.66, 0.25–0.41, and 0.06–0.78 f/mL for disintegrating (feeding), mixing, and cutting/grinding/drilling processes, respectively (Higashi et al. 1994). Exposure levels were <0.3 f/mL in 70% of the workplaces in 1985 and 98% of workplaces in 1992. Concentrations in a new, well-controlled plant were <0.1 f/mL. Bulgarian workers engaged in the production of asbestos gaskets and filter materials at two plants were exposed to 0.04–0.38 and 0.04–0.43 f/mL of asbestos (Strokova et al. 1998).

As part of an international epidemiological study of cancer incidence and mortality among workers in the pulp and paper industry, the International Agency for Research on Cancer (IARC) coordinated a study involving researchers in 15 countries in gathering exposure measurements taken between 1956 and 1993 for nonproduction departments in the industry from previously unpublished studies (Teschke et al. 1999). The results are shown in Table 6-5. Exposure to asbestos was found in three areas: maintenance, construction, cleaning; storage, yard, loading, shipping; and steam and power generation with 16, 50, and 0% of exposures in these departments exceeding 0.2 f/mL.

Building materials used in older buildings such as insulation, dry wall, roofing, and flooring often contain asbestos. Occupational exposure to asbestos during asbestos abatement work is an area of concern. Lange and Thomulka (2000a, 2000b, 2000c) and Lange et al. (1996) collected both area and personal samples during various abatement projects and their results suggest that occupational levels were low with no value exceeding the OSHA PEL (see Table 6-6). In general, abatement of boiler and pipe insulation produced the highest airborne fiber levels and abatement of floor tile and mastic produced the lowest. Personal samples, which had higher concentration levels than area samples, are suggested to be

Table 6-5. Exposure to Airborne Asbestos in Nonproduction Departments of the Pulp and Paper Industry[a]

Department	Number of mills	Number of samples	Mean (f/cc)	Median (f/cc)	Maximum (f/cc)	Type	Percent less than LOD	LOD (f/cc)	Percent greater than TLV[a]
Maintenance, construction, cleaning	12	31	0.081	0.004	0.5	TWA	42	0.001	16
Storage, loading, shipping	4	26	7.2	0.18	28	TWA	19	0.010	50
Steam and power generation	6	16	0.013	0	0.1	TWA	56	0.005	0

Source: Teschke et al. 1999

[a]TLV (1995-6) = 0.2 f/cc

LOD = limit of detection; TLV = threshold limit value; TWA = time-weighted average

Table 6-6. Exposure to Airborne Asbestos During Asbestos Abatement[a]

Material abated	Number of samples	Concentration range (f/mL)	Arithmetic mean (SD) (f/mL)	Geometric mean (GSD) (f/mL)	Type[b]	Reference
Roofing material (wet method)	12[c]	0.0047–0.0752	0.015 (0.014)	0.011 (2.53)	Personal (non-TWA)	Lange and Thomulka 2000b
	17	<0.0006–0.0162	0.006 (0.006)	0.004 (2.82)	Area (non-TWA)	
Floor tile and mastic	10[c]	<0.008–0.094	0.022 (0.017)	0.015 (2.54)	Personal (non-TWA)	Lange and Thomulka 2000a
	13[c]	<0.002–0.067	0.010 (0.008)	0.006 (2.73)	Area (non-TWA)	
Dry wall[d]	25[c]	0.12–3.16	0.76 (0.57)	0.59.(1.94)	Personal (TWA)	Lange and Thomulka 2000c
Floor tile and mastic	23	0.01–0.08	0.04 (0.04)	0.03 (1.71)	Personal (TWA)	Lange and Thomulka 2000c
Pipe/boiler in a crawl space	102	0.005–1.542	0.202	0.149 (2.33)	Area	Lange et al. 1996
Pipe/boiler in a crawl space[e]	42	0.005–0.998	0.192	0.097 (3.17)	Area	
Pipe/boiler in a crawl space[e]	42	0.005–0.957	0.187	0.089 (2.75)	Personal	
Ceiling tile removal in mini-containment	11	0.005–0.331	0.043	0.019 (2.09)	Area	
Ceiling tile removal in mini-containment	9	0.005–0.154	0.022	0.007 (3.38)	Personal	
Transite removal	41	0.005–0.278	0.077	0.048 (3.50)	Personal	

Table 6-6. Exposure to Airborne Asbestos During Asbestos Abatement[a] *(continued)*

Material abated	Number of samples	Concentration range (f/mL)	Arithmetic mean (SD) (f/mL)	Geometric mean (GSD) (f/mL)	Type[b]	Reference
Floor tile and mastic (solvent method) removal	14	0.005–0.010	0.005	0.005	Area	
Mastic removal (blast method)	4	0.005–0.005	0.005	0.005	Area	

[a]Analysis by TEM.
[b]8-Hour TWA concentrations assume exposure only during sample periods. TWA levels refer to mean concentrations.
[c]One outlier excluded from calculation of means and standard deviations.
[d]Respirators are required for dry wall abatement.

GSD = geometric standard deviation; SD = standard deviation; TEM = transmission electron microscopy; TWA = time-weighted average

the best measure of occupational exposure. Higher exposure levels occur during dry wall abatement, but respirators are required for this type of abatement work.

Workers involved in custodial and maintenance and repair work in asbestos-containing buildings may be exposed to elevated asbestos levels in the workplace. The results of some recent studies in this area appear in Table 6-7. In all cases, the 8-hour TWA exposures for personal sampling were below the OSHA PEL of 0.1 f/mL for fibers above 5 μm. Mlynarek et al. (1996) found that the highest 8-hour TWA exposure occurred during ceiling tile replacement followed by high efficiency particulate air (HEPA) vacuuming or wet wiping of dust and debris. In their study of asbestos exposure of maintenance personnel in five buildings who worked above the ceiling in proximity to spray-applied fireproofing, Corn et al. (1994) found that less than a maximum of 5% of a worker's total working time was spent in such activity. Exposures were below the OSHA PEL with only simple protective measures employed such as HEPA vacuuming and wetting down of surfaces. Exposure would have been reduced substantially more by the use of respirators for the relatively short period of time maintenance personnel spent above the ceiling. Routine floor tile maintenance procedures such as spray-buffing, wet-stripping, and ultra high speed burnishing can result in elevated levels of airborne asbestos. TEM analysis showed that over 98% of the asbestos structures were below 5 μm in length and would not be detected or counted by PCM (Kominsky et al. 1998a, 1998b). Only in the case of ultra high speed burnishing was the OSHA PEL exceeded. However, this was due to the generation of nonasbestos particles during the burnishing process and therefore do not reflect actual asbestos exposure. This example underscores the limitations of PCM in interpreting workplace exposure.

The geometric mean asbestos body and crocidolite fiber content in 90 former workers in the Wittenoon crocodiolite industry in Western Australia were 17.5 asbestos bodies/g wet tissue and 183 TEM f/μg dry tissue, respectively (de Klerk et al. 1996). The geometric mean intensity of exposure, duration of exposure, and cumulative exposure were 20 f/mL, 395 days, and 20.9 f-yr/mL, respectively. The fiber concentration in the lung was correlated to the intensity and duration of exposure.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in 3.7 Children's Susceptibility.

Table 6-7. Exposure to Airborne Asbestos During Building Maintenance or Repair[a]

Material abated	Number of samples	Concentration range[b] (f/mL)	Arithmetic mean (SD) (f/mL)	TWA mean (Max) (f/mL)	Type[b]	Reference
Ceiling removal/installation	6	0.000–0.035	0.0149		Personal	Corn 1994; Corn et al. 1994
Ceiling removal/installation	18	0.001–0.044	0.0112		Area	
Electrical/plumbing	10	0.002–0.216	0.0619		Personal	
Electrical/plumbing	4	0.004–0.054	0.0308		Area	
HVAC work	8	0.000–0.077	0.0202		Personal	
HVAC work	23	0.001–0.024	0.0068		Area	
Miscellaneous work	4	0.000–0.031	0.0082		Personal	
Miscellaneous work	9	0.000–0.083	0.0108		Area	
Removal/encapsulation	4	0.015–0.115	0.0614		Personal	
Removal/encapsulation	10	0.003–0.019	0.0109		Area	
Run cable	33	0.001–0.228	0.0167		Personal	
Run cable	33	0.000–0.086	0.0080		Area	
ACM debris cleanup	9	0.012–0.36	0.074	0.0077 (0.028)	Personal	Mlynarek et al. 1996
Bulk sample collection	31	0.0030–0.17	0.034	0.0042 (0.024)	Personal	
Cable pull	37	0.011-0.20	0.048	0.013 (0.037)	Personal	
Ceiling tile replacement	67	0.030-3.5	0.35	0.030 (0.21)	Personal	
Ceiling tile replacement	18	0.0020–0.056	0.011	0.0027 (0.0088)	Area	

Table 6-7. Exposure to Airborne Asbestos During Building Maintenance or Repair[a] *(continued)*

Material abated	Number of samples	Concentration range[b] (f/mL)	Arithmetic mean (SD) (f/mL)	TWA mean (Max) (f/mL)	Type[b]	Reference
Electrical installation	14	0.010–0.11	0.037	0.011 (0.026)	Personal	
Electrical repair	24	0.003–0.052	0.020	0.0091 (0.027)	Personal	
Fluorescent lamp replacement	78	0.0054–0.065	0.025	0.0059 (0.018)	Personal	
Fluorescent lamp replacement	55	0.0039–0.0067	0.0067	0.0006 (0.0014)	Area	
HEPA vacuum/wet wiping dust/debris	17	0.029–0.304	0.098	0.026 (0.073)	Personal	
HEPA vacuum/wet wiping dust/debris	19	0.0023–0.027	0.0068	0.0031 (0.0074)	Area	
Wet wipe cleaning	25	0.018–0.048	0.031	0.0092 (0.024)	Personal	
Office environment	10	0.0016–0.057	0.0091	0.0032 (0.025)	Area	
TOTAL (range)	302	0.0030–3.5	0.020–0.35	0.0042–0.030 (0.018–0.21)	Personal	
TOTAL (range)	102	0.0016–0.062	0.0067–0.027	0.0006–0.0032 (0.0014–0.025)	Area	
Spay-buffing tile (poor)	5	0.008–0.015	0.012		Personal	Kominsky et al 1998a
Spay-buffing tile (medium)	5	0.003–0.008	0.006		Personal	
Spay-buffing tile (good)	5	0.015–0.030	0.019		Personal	
Wet-stripping tile (medium)	5	0.006–0.016	0.010		Personal	
Wet-stripping tile (good)	5	0.004–0.010	0.006		Personal	

Table 6-7. Exposure to Airborne Asbestos During Building Maintenance or Repair[a] *(continued)*

Material abated	Number of samples	Concentration range[b] (f/mL)	Arithmetic mean (SD) (f/mL)	TWA mean (Max) (f/mL)	Type[b]	Reference
Spay-buffing tile (poor)	5	0.046–0.081[c]	0.059[c]		Personal	
Spay-buffing tile (medium)	5	0.001–0.032[c]	0.014[c]		Personal	
Spay-buffing tile (good)	5	0.004–0.046[c]	0.024[c]		Personal	
Wet-stripping tile (medium)	5	0.055–2.58[c]	0.978[c]		Personal	
Wet-stripping tile (good)	5	0.010–0.128[c]	0.041[c]		Personal	
UHS burnishing tile (poor)	5	0.046–0.081[c]	0.024[c]		Personal	Kominsky et al 1998b
UHS burnishing tile (good)	5	0.004–0.046[c]	0.017[c]		Personal	
Wet-stripping tile (poor)	5	0.055–2.58[c]	0.019[c]		Personal	
Wet-stripping tile (good)	5	0.010–0.128[c]	0.015[c]		Personal	
UHS burnishing tile (poor)	5	0.872–1.692		0.133–0.275[d]	Personal	
UHS burnishing tile (good)	4	0.670–1.016		0.113–0.145[d]	Personal	
Wet-stripping tile (poor)	8	0.004–0.018		0.001–0.004[d]	Personal	
Wet-stripping tile (good)	8	0.006–0.014		0.001–0.003[d]	Personal	

[a]Analysis by PCM, NIOSH method 7400, unless otherwise indicated.
[b]8-Hour TWA concentrations assume exposure only during sample periods. TWA levels refer to mean concentrations.
[c]Analysis by TEM.
[d]Range of individual measurements, exceedance of OSHA PEL (0.1 f/mL) due to nonasbestos-containing powder generated during the burnishing operation.

ACM = asbestos-containing material; HEPA = high efficiency particulate air; HVAC = Heating, Ventilation and Air Conditioning; NIOSH = National Institute of Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PCM = phase contrast microscopy; PEL = permissible exposure limit; SD = standard deviation; TEM = transmission electron microscopy; TWA = time-weighted average

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).

Children may be exposed to asbestos in the same ways that adults are exposed outside the workplace–from asbestos in air especially near emission sources or in buildings with deteriorating asbestos-containing material. Differences in breathing patterns, airflow velocity, and airway geometry between adults and children can result in age-related differences in deposition of inhaled particles in the respiratory tract (Phalen et al. 1985). Deposition of particles in various regions of the respiratory tract in children may be higher or lower than in adults depending on particle size, but for particles with diameters <1 μm, fractional deposition in the alveolar, tracheobronchial, and nasopharyngeal regions in 2-year-old children has been estimated to be about 1.5 times higher than in adults (Xu and Yu 1986). This information may be relevant to inhalation exposure to asbestos fibers, but direct information regarding age-related differences in deposition of inhaled fibers was not located. Studies that have been conducted on asbestos levels in schools have stressed the low fiber counts in the air even when the buildings contained asbestos-containing material (Mossman et al. 1990a). As mentioned in Section 6.4.4, the release of asbestos fibers from ACM is sporadic and episodic, and human activity and traffic may facilitate release of asbestos fibers and stir up asbestos-containing dust. Monitoring of buildings are frequently performed at night or on weekends may therefore underestimate human exposure to asbestos in the buildings. Historically, children have been exposed to asbestos while playing near mining or processing facilities using materials containing asbestos, or from contact with asbestos-laden clothing of family members employed in asbestos-related industries. Although studies quantifying this type of exposure of children were not located, its existence is known based on reports of the development of asbestos-related respiratory diseases in adults who were "paraoccupationally " exposed as children, but had no occupational exposure to asbestos during adulthood (Anderson et al. 1976; Inase et al. 1991; Magee et al. 1986; Voisin et al. 1994; Wagner et al. 1960). Children may also be exposed from drinking water containing asbestos fibers or from ingesting asbestos-containing dust or soil. Asbestos fibers are not expected to undergo significant transformation in soil, and it is well documented that young children

ingest more soil than adults. Studies that examined levels of childhood exposure to asbestos through soil ingestion, however, were not located.

A few small studies have assessed the lung asbestos fiber content of children. In one, a small number of asbestos fibers were found in 10 of 41 infants aged 1–27 months (Haque and Kanz 1988). In another (Case et al. 1988), asbestos fiber levels in 10 of 15 children under the age of 19 were as high those seen in older, presumably more exposed, age groups; however, all but 2 of the children were over the age of 15 and could have been exposed in jobs. A survey of the lung fiber content of 60 American children aged 8–15 years who died between 1983 and 1987 was conducted by TEM to assess fiber burdens and exposure in children (Case et al. 1994). The preliminary results indicate that asbestos bodies and lung fiber concentrations were one to two orders of magnitude lower than found by the same laboratory in a study of a sample of general population adults. Asbestos bodies were absent in 57 of the children and below 100 asbestos bodies/g in 2 more, both of whom were rural residents. Thirty-eight percent of the subjects had 1 or more long (>5 μm) asbestos fibers. Thirty-three percent of the subjects had long chrysotile fibers and 5% or less contained long amphibole fibers. Short chrysotile fibers were present in twice as many subjects as the long fibers (63 vs. 33%). Short tremolite fibers were observed in 37 subjects. The geometric mean asbestos fiber concentration for the 60 subjects was 0.10×10^6 f/g dry lung tissue.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The people most likely to have high exposure to asbestos are workers who come into contact with asbestos while on the job. This includes people involved in the mining of asbestos and asbestos-containing minerals and manufacture of asbestos-containing products, and also people who install, service, remove, or use these products. The presence of asbestiform minerals is widespread in mining areas, and people employed in the mining and processing of other ores may therefore be exposed to asbestos (Rogers et al. 1997). Workers engaged in the demolition of buildings with asbestos-containing materials are also potentially exposed. Although recent regulations have resulted in a marked decrease in airborne exposure levels in the workplace, the currently acceptable upper limit in workplace air (0.1 f/mL) is still considerably higher than levels found outside the workplace (usually <0.001 f/mL). In the past, workers may have carried asbestos home on their clothing or in their hair, resulting in exposure of family members (Anderson et al. 1979; Case and Sebastien 1989). However, this is not likely to be of concern at the present.

People who live near an asbestos-related industry or near an asbestos-containing waste site may encounter elevated levels of asbestos in air and accumulate it in their lungs (Case 1991; Case and Sebastien 1987, 1989). People may also be exposed to asbestos from a variety of asbestos-containing products, from poorly performed asbestos removal, or from living or working in a building with deteriorating asbestos insulation. Working in a building with asbestos-containing material that is in good condition has not been shown to result in significantly elevated levels of asbestos in air (HEI 1991).

Some people may also be exposed to elevated levels of asbestos in drinking water, particularly where there are widespread natural deposits of asbestos (e.g., San Francisco Bay area), disposal of asbestos-containing ore tailings (e.g., Duluth, Minnesota), or the use of asbestos-containing cement pipes in drinking water distribution systems with low pH and low hardness (Craun et al. 1977; Kanarek et al. 1981; Webber et al. 1989).

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 asbestos 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 asbestos.

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

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of asbestos are well characterized (see Chapter 4), and there does not appear to be a need for further research in this area.

Production, Import/Export, Use, Release, and Disposal. Asbestos is widely used by humans in a variety of products, and exposures are likely from a number of sources. Extensive data are available on current production, import, and use of asbestos (U.S. Bureau of Mines 1992). Releases to the environment may occur either to air or to soil and water, with releases to air being of greatest health concern. Waste friable asbestos is regulated as a hazardous substance, so disposal is permitted only in authorized waste sites. Methods of handling friable asbestos are prescribed to minimize dust release. However, data are lacking on the amount of asbestos disposed in waste sites, and on the location and status of these sites.

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. TRI, which contains this information for 1999, became available in 2001. This database is updated yearly and provides a list of industrial facilities producing, processing, and using friable asbestos and their emissions.

Environmental Fate. Asbestos fibers are fundamentally rather inert and are not considered to undergo transport or degradative processes in the environment analogous to organic pollutants. Additional studies on the behavior of fibers in water (processes such as change in metal ion and hydroxyl ion composition, adsorption to organic materials, flocculation and precipitation, etc.) would be helpful in evaluating water-based transport of fibers, as well as in improving methods for removal of fibers from water. Transport of fibers in air is governed by processes and forces which apply to all particulate matter (EPA 1977, 1979c), and these processes are reasonably well understood.

Bioavailability from Environmental Media. Asbestos fibers are insoluble and are not absorbed in the usual sense after inhalation, oral, or dermal exposure. Most exposures occur either to fibers in air or water, so the effect of matrices such as soil or food are largely unknown. It is possible that adsorption of fibers onto other dust particles could influence the location of deposition in the lung, and might even influence the cellular response to the fibers. Research to determine if this occurs and is of biological significance would be helpful.

Food Chain Bioaccumulation. No data were located on asbestos levels in the tissues of edible organisms. However, it is not expected that either aquatic or terrestrial organisms will accumulate a significant number of fibers in their flesh. Consequently, food chain bioaccumulation or biomagnification does not appear to be of concern.

Exposure Levels in Environmental Media. There have been extensive surveys of asbestos levels in water and air (both outside air and inside air) (Chesson et al. 1990; EPA 1979b, 1991b, 1992c; HEI 1991, 1992; Howe et al. 1989; IARC 1977; Kanarek et al. 1980, 1981; NRC 1984; Spengler et al. 1989). These studies have revealed that wide ranges of asbestos levels may be encountered, indicating that human exposures can only be estimated on a site-specific basis. By converting exposures levels from TEM f/mL to PCM f/mL using a global conversion factor, the benefit of increased sensitivity of TEM and its ability to identify fiber type is diminished. However, further studies on the sources of the fibers and key determinants of exposure level would be valuable. It is especially important that further studies of asbestos levels in environmental media investigate and report on the size distribution of the fibers, because this is important in evaluating the resultant risk. Few data exist on asbestos levels in soil, especially near waste sites. Reliable and recent monitoring data for the levels of asbestos in contaminated media at hazardous waste sites and in soil at mining and other sites with naturally elevated levels of asbestos are needed so that the information obtained on levels of asbestos in the environment can be used in combination with the known body burdens to assess the potential risk of adverse health effects in populations living in these areas. Also, techniques for estimating air levels of asbestos from soil concentrations and activity scenarios would enable screening level estimations of asbestos exposure in advance of activities or disturbances occurring at contaminated sites, without extensive air monitoring.

Several key factors have been recently identified by the European Respiratory Society Working Group regarding the analysis of mineral fibers in biological samples (De Vuyst et al. 1998). These include adequate sampling, comparable analytical procedures and expression of results, and the use of well-defined reference populations. It is important to obtain agreement on guidelines for these types of studies and work to get them adopted by investigators.

Exposure Levels in Humans. The best available methods to measure human exposure levels involve measuring retained fibers in lung tissue (Case 1994; Churg 1982; Churg and Warnock 1981; Churg and Wright 1994; Dufrense et al. 1995, 1996a, 1996b; Dodson et al. 1999; Gylseth et al. 1985; Sebastien et al. 1989; Wagner et al. 1986). Uses of concentrations of asbestos bodies and uncoated fibers in bronchoalveolar lavage and sputum samples as biomarkers of exposure also have been examined in several studies, but these approaches have not been fully developed as quantitative indicators of exposure (see Section 3.8.1). Fibers can also be detected in urine and feces (Cook and Olson 1979; Finn and Hallenback 1984), but these methods would likely reflect only recent exposures (within the last several days) and not the cumulative tissue burden. As discussed in Section 3.12, efforts to develop a noninvasive method for measuring fiber levels in tissue (especially in the lung) would be particularly

valuable in assessing human exposure to asbestos. Future studies of asbestos fiber concentrations in samples of biopsied or autopsied lung tissue from residents living near waste sites or other sites known to contain elevated levels of asbestos also would be helpful in estimating the magnitude of nonoccupational exposure associated with these sites.

Exposures of Children. Only a few small studies have assessed the lung asbestos fiber content of children (Case et al. 1988, 1994). Preliminary results from the most comprehensive of these studies indicate that asbestos bodies and lung fiber concentrations in children are one to two orders of magnitude lower than those found in adults. More data are needed on the levels of asbestos in children, and attempts should be made when these data are acquired to link the body burden with possible sources of exposure (e.g., residing in places with naturally elevated soil concentrations, in areas with mining or hazardous waste sites, or in housing with crumbling asbestos).

Children may be exposed to asbestos in the same ways that adults are exposed outside the workplace, from asbestos in the air especially near emission sources or in buildings with deteriorating asbestos-containing material. Children may also be exposed from drinking water containing asbestos fibers or from ingesting asbestos-containing dust or soil. However, there are factors, such as breathing rate and lung physiology, that may affect the deposition of fibers in lung tissue of children, and these factors need to be explored. These factors would be age-related, and may affect where and to what extent fibers are deposited. Just as children are exposed to asbestos in the same way as nonoccupationally-exposed adults, there are no childhood-specific means to decrease exposure.

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 asbestos were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

Many industries and researchers interested in studying the health effects of asbestos in exposed workers maintain registries of individuals who were exposed to asbestos on the job.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2001) 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.

No information was located regarding ongoing studies on the stability and migration of asbestos in the environment. The EPA and many state and local agencies are continuing to make measurements of asbestos levels in air and in water, in order to identify locations where significant health concerns may be warranted.

M.B. Schenker of Institute of Toxicology, University of California Davis; in Davis, California is leading a multidisciplinary study supported by National Cancer Institute (NCI). This study will examine whether environmental asbestos deposits in California are associated with increased rates of mesothelioma. The study will address geological occurrence of asbestos and potential human exposure based on population patterns and known occupational exposure, and epidemiological characteristics of the disease in the state. The project will plan a case-control study to rigorously test the hypothesis that mesothelioma in California is independently associated with environmental asbestos exposure.

7. ANALYTICAL METHODS

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

As discussed in Chapter 4, asbestos is not a single chemical entity, but is the name for a group of six hydrated fibrous polysilicates. Because the toxicity of asbestos appears to be related primarily to fiber size, modern analytical methods focus on providing information on these parameters, as well as on total number of fibers and mineral type. At present, the number and size distribution of fibers in a sample can only be determined by direct microscopic examination. This may be performed using either light or electron microscopy, as discussed below. It should be noted that OSHA regulations on asbestos refer to the six asbestiform minerals and a fiber is defined as having a minimum length, 5 μm, as aspect ratio of 3:1 (OSHA 1992). NIOSH methods for determining fiber concentrations are geared to counting fibers of these dimensions. In addition, these methods give detailed rules as to how to count different objects (e.g., objects with split ends or attached particles) (NIOSH 1989a, 1989b).

Light Microscopic Method. Phase contrast microscopy (PCM) accurately assesses fiber exposure levels for fibers 5 μm in length and >0.25 μm in diameter. Furthermore, PCM cannot differentiate between asbestos and nonasbestos fibers. Currently, the standard method for the determination of airborne asbestos particles in the workplace is NIOSH Method 7400, Asbestos by Phase Contrast Microscopy (NIOSH 1994a). OSHA considers that sampling and analytical procedures contained in OSHA Method ID-160 and NIOSH Method 7400 are essential for obtaining adequate employee exposure monitoring. Therefore, all employers who are required to conduct monitoring are required to use these or equivalent methods to collect and analyze samples (OSHA 1994). In NIOSH Method 7400, asbestos is collected on a 25 mm cellulose ester filter (cassette-equipped with a 50 mm electrically-conductive cowl). The filter is treated to make it transparent and then is analyzed by microscopy at 400–450x magnification, with phase-

contrast illumination, using a Walton-Beckett graticule. A fiber is defined as any particle with a length >5 μm and a length-to-diameter ratio of 3:1. Although the PCM method is relatively fast and inexpensive, it does not distinguish between asbestos and nonasbestos fibers, and it cannot detect fibers thinner than 0.25 μm. Consequently, this method is most useful for the analysis of samples that are composed mainly of asbestos, but only where a significant fraction of the fibers are large enough to be counted. If samples are grossly contaminated by nonasbestiform fibers, then transmission electron microscopy (NIOSH Method 7402) should be used for positive identification. For fibers greater than 1 μm in diameter, then polarized light microscopy (NIOSH Method 7403) may be useful in identifying polymorphs (NIOSH 1987). Concentrations are reported as fibers/mL or fibers/cm^3. Recent improvements in filter preparation procedures now allow for viewing at higher magnification (1250x), resulting in a several-fold improvement in sensitivity for these fibers (Pang et al. 1989). Polarized light microscopy is frequently used for determining the asbestos content of bulk samples of insulation or other building materials (see, for example, NIOSH Method 9002 [NIOSH 1989c] and OSHA method ID-191 [OSHA 1994]); however, this approach is not used for measuring asbestos in environmental media. Method 9002 also enables one to qualitatively identify asbestos types using fiber morphology, color, and refractive index.

In summary, PCM is a useful tool in assessing occupational exposure to workers engaged in activities that generate airborne asbestos fibers. However, in nonoccupational settings where large proportions of other fibers (e.g., wool, cotton, glass) are present, PCM will overestimate the asbestos fiber concentration. In addition, the sensitivity of PCM is approximately 0.01 f/mL, an asbestos level higher than that generally found in nonoccupational environments.

Electron Microscopic Methods. Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) methods can detect smaller fibers than PCM and also fiber type, but fiber counting accuracy is unacceptably poor. This is a result of the small area that can be scanned at high magnification. Accuracy is more limited with long (>5 μm) fibers. NIOSH Method 7402, Asbestos by TEM, is used to determine asbestos fibers in the optically visible range and is intended to complement NIOSH Method 7400. Examination of a fiber sample by either TEM or SEM allows the detection of much smaller fibers than light microscopy, and so more thorough data can be collected on fiber length and diameter distribution. Of these two methods, TEM has greater sensitivity for small fibers, and is the most common method for measuring asbestos in ambient air or inside schools or other buildings. SEM analysis usually images fibers that are more than 0.2 μm in diameter because of contrast limitations, while TEM can visualize fibers of all sizes. In addition, most modern transmission electron microscopes are

equipped with instrumentation that allows examination of individual fibers by electron diffraction or energy-dispersive x-ray analysis. This permits determination of the crystalline and elemental composition of the fiber. Thus, reliable distinctions can be made not only between asbestos and nonasbestos fibers, but also between different asbestos mineral classes (NIOSH 1994b). SEM may also incorporate energy-dispersive x-ray analysis devices. Although TEM clearly provides the most information about a fiber sample, TEM methods are relatively slow and costly compared to PCM methods.

Two different procedures are used for preparation of samples for TEM analysis (HEI 1991). Direct transfer methods retain particles in the same relative position during analysis as they were on the original filter with a minimum of change to the airborne particles. Indirect methods involve dispersing the particulate matter from the original filter into a liquid and capturing the suspended particles particulates onto intermediate filters that are used to prepare the TEM specimens. By varying the proportion of liquid, one is able to concentrate or dilute the sample analyzed. In addition, one is able to remove organic and other unwanted particulate matter by ashing or dissolution, thereby selectively concentrating the asbestos. In dispersing the particles in water the sample may be gently sonicated. In the process, fiber bundles may be separated into individual fibrils or fibers broken.

Application of either PCM or TEM methods to the determination of asbestos fibers in biological or environmental media (air or water) requires that the fibers be separated from interfering material and collected on appropriate supports. Methods for preparing biological and environmental samples for microscopy are described below.

7.1 BIOLOGICAL SAMPLES

Asbestos fibers are particularly resistant to chemical and thermal degradation, and this property is used to the advantage in the analysis of biological materials for asbestos. In most cases, the bulk of the biological material is solubilized by digesting the tissue in strong base (e.g., KOH) or a powerful oxidant (e.g., hypochlorite). The insoluble residue (including the asbestos fibers) is collected by ultracentrifugation or filtration, and may be further cleared of biological material by ashing. In some cases, biological material may be removed by ashing without prior digestion. Residual material is then dispersed and transferred to a suitable support for microscopy. Sample handling during sample preparation and dispersal onto a support for microscopy can break fibers or result in the breakup of fiber aggregates. If fiber breakage results in fibers shorter than 5 μm, a lower fiber count would result.

Conversely, if aggregates are separated, a higher fiber count could result. Tissue samples are often embedded in paraffin for sectioning and to preserve the sample for retrospective analysis.

In collecting and preparing samples for fiber analysis by electron microscopy, care must be taken to avoid contamination. Asbestos contamination of laboratory materials, including paraffin (Lee et al 1995), grids (Case 1994; Rogers 1984), and especially cross-contamination by tissues themselves (Case 1994) must be accounted for. While good laboratory practice required that all reagents and materials used in asbestos analysis be tested for the presence of asbestos, paraffin used to embed tissue has generally avoided scrutiny, being viewed by the laboratory as part of the tissue sample, rather than a reagent. Lee et al. (1995) observed that paraffin used to embed tissue of a mesothelioma victim was contaminated with asbestos. Both the surface and portions cut from the washed paraffin blocks contained chrysotile and amphibole fibers. These finding led to an investigation of asbestos structures in raw paraffin and paraffin from tissue blocks from several sources in different parts of the country. Asbestos was present in 24 of 27 cases; of these 24 cases, 11 had levels that could be considered above background and 4 were severely contaminated. While asbestos was observed in some samples of raw paraffin, the highest levels were seen in prepared blocks. Therefore, it is not clear whether contamination was present in the wax or introduced in the reagents used or during the embedding process. These results raises questions about the validity of tissue analyses by electron microscopy for asbestos unless blank control blocks were part of the procedure.

A recent report (Rogers et al. 1999) has demonstrated that *in situ* confocal laser scanning microscopy (CLSM) can provide three dimensional views of fibers retained, undisturbed, in lung tissue tens or hundreds of microns below the surface of the specimen. This allows the three-dimensional location of fibers relative to cells and surrounding tissue to be studied and understood. Tissue samples prepared for asbestos by analysis by TEM are generally digested and ashed. While TEM has been used to image fibers within lung tissue, the process of obtaining 60–70 nm thick tissue sections would be expected to cut apart asbestos fibers and introduce artifacts. While SEM permits intact fibers to be studied, images show primarily the surface of fibers and tissue closest to the observer. There are no standard methods for the analysis of asbestos in biological materials. Table 7-1 summarizes several methods that have been applied for analyzing asbestos fibers in a variety of biological materials.

Table 7-1. Analytical Methods for Determining Asbestos in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Bronchoalveolar fluid	Mix with sodium hypochlorite; membrane filter; dry	PCM	1 AB/mL	No data	Spurny 1994
Urine	Mix with hydrogen peroxide; digest for 20 hours; collect residue on filter	TEM	$0.1\text{-}0.3 \times 10^{-6}$ f/L	No data	Boatman et al. 1983
Urine	Filter through polycarbonate filter; ash filter; wash; collect residue on second filter	TEM	5×0^{3} f/mL	No data	Finn and Hallenbeck 1984
Feces	Dry, ash, dissolve residue in hydrochloric acid; filter; ash filter; transfer residue to grid	TEM	0.15×10^{6} f/g	85.5	Cunningham et al. 1976
Lung tissue	Dry to constant weight;digest with sodium hyroxide (90 C); ash residue; collect on nucleopore filter	TEM	0.1×10^{6} f/g	No data	Wagner et al. 1982a
Lung tissue	Digest wet tissue in potassium hydroxide; wash residue with water; transfer residue to slide	PCM	5,000 f/g	No data	Whitwell et al. 1977
Tissue sections	Ash on slide; transfer	TEM	No data	No data	Pooley 1976
Tissue specimens	Predigest in 10% potassium hydroxide; collect residue by ultra-centrifugation; ash residue; transfer to carbon grids	TEM	0.2×10^{5} f/g	13–70	Carter and Taylor 1980

f/g = fibers per gram; f/L = fibers per liter; f/mL = fibers per milliliter; PCM = phase contrast microscopy; TEM = transmission electron microscopy

7.2 ENVIRONMENTAL SAMPLES

For the analysis of asbestos fibers in air, a sample of air is drawn through a filter by a vacuum pump (usually at a flow-rate of around 1–2 L/minute), and the fibers retained on the filters are examined microscopically. The sensitivity of the methods depends on the volume of air drawn through the filter and the microscopic method employed. In the workplace, where PCM is the standard method, the theoretical detection limit for a short-term sample (15 minutes) is around 0.04 PCM f/mL, but may be reduced to 0.001 f/mL using an 8-hour sample (NIOSH 1976). In practice, such low detection limits are not readily achievable, and measured values below 0.1 PCM f/mL should not usually be considered reliable (ASTM 1988). Sensitivity of TEM methods for ambient or indoor air are usually around 0.1–1 ng/m^3.

A similar approach is used for measuring asbestos in water. A known volume (generally, at least 1 L) is drawn through a filter, and the filter is then prepared for examination, usually by TEM. Table 7-2 summarizes several representative methods for the analysis of asbestos in air and water. No methods were located for the analysis of asbestos in soil.

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 asbestos 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 asbestos.

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.

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Pump air through filter membrane; convert to optically transparent gel	PCM	<0.5 f/mL	±35	ASTM 1988
Air	Filter	NIOSH 7400; PCM	<0.01 f/mL	No data	NIOSH 1994a
Air	Filter; mount on	NIOSH 7402; TEM	<0.01 f/mL	No data	NIOSH 1994b
Air	Measured volume of air collected on 25 mm diameter, 0.45 m MCE filter, Both direct and indirect specimen preparation	Superfund Method. TEM at 20,000X, EXDA, Separate examination of structures of all sizes (0.5 m) and those with a length 5 m. Structures have mean aspect ratios 5:1.	Sensitivity >0.5 s/L and 0.02 s/L for all structures and those	No Data	EPA 1990c, 1990d
Water (drinking)	Filter, carbon coat and wash	APHA Method 2570-B; TEM	No data	No data	EMMIWIN 1997
Water	Filter; mount on carbon	TEM at 20,000X	0.01 MFL	100±35	Anderson and Long 1980
Water	Extract into isooctane from water containing anionic surfactant	Microscope or color spot test	0.1 MFL	No data	Melton et al. 1978

Water	Filter; mount on carbon film	TEM	No data	No data	WHO 1986

Table 7-2. Analytical Methods for Determining Asbestos in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Place in ultrasonic bath (15 minutes); filter; dry and collapse filter; plasma etch; mount on carbon film	TEM	No data	No data	Brackett et al. 1992

f/mL = fibers per milliliter; MCE=mixed cellulose ester; MFL = million fibers per liter; PCM = phase contrast microscopy; TEM = transmission electron microscopy; EXDA=energy dispersive x-ray analysis

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Reliable methods exist for measuring asbestos fibers in biological tissues and fluids (Boatman et al. 1983; Carter and Taylor 1980; Wagner et al. 1982b). These methods (based on microscopic examination of fibers remaining after ashing and digestion) are sufficiently sensitive to quantify fiber burden in samples from both control (background) and exposed populations. However, there is considerable variability in the details of sample preparation, and this makes inter-study comparisons difficult. For this reason, it would be helpful to develop a standardized method or group of methods for analysis of asbestos in biological materials, similar to the standardized methods for asbestos in air and water. A major limitation to current methods is that lung retained fibers can only be measured by examining excised lung tissue (see Section 3.8.1). Concentrations of fibers or asbestos bodies in broncho-alveolar lavage or sputum samples may provide indications of exposure to asbestos fibers. Consequently, it is not possible to estimate retained fiber in lung tissue of living persons except by fiber analysis of these samples that are, to various degrees, invasively obtained. Development of some noninvasive method that would permit accurate estimation of asbestos content *in vivo* would be especially valuable.

Effect. There are no chemical analytical methods recognized for measuring asbestos-induced health effects in humans. Clinical methods (x-ray, spirometry) for evaluating effects are discussed in Chapter 3. Development of sensitive and specific chemical or biochemical tests for asbestos-induced effects would be very valuable, especially if preclinical changes could be detected.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Standardized methods have been established in the United States for measurement of asbestos in air by PCM and TEM, the media most likely to lead to human exposure (NIOSH 1989a, 1989b), Standard TEM methods are also available for measuring asbestos in water (WHO 1986). These methods are sufficiently sensitive to quantify asbestos both at background levels and at levels of health concern. There are variations in both sampling conditions and counting rules in PCM methods used in other countries that lead to significant differences in results (Dion and Perrault 1994). Improved comparability would be achieved if an international consensus could be reached to resolve these differences. However, the electron microscopic techniques that give the greatest amount of useful data are also the slowest and most costly. TEM equipment allows fiber type to be identified and finer fibers to be counted. Fiber size,

shape, and mineralogy are important factors for assessing risk. Improved analytical methods for screening samples and determining the chemical structure of asbestos fibers would be useful. Further efforts to reduce the time and cost per analysis would also be helpful.

7.3.2 Ongoing Studies

Given the need and financial incentives for improved, faster asbestos analysis, studies are ongoing to improve these areas. Intense activity is underway in the areas of automation and computerization, especially with TEM and analytical electron microscopy. Another area of investigation is to identify the fiber types and sizes most closely identified with risk of lung cancer and mesothelioma and develop methodology that will give results that are most closely correlated with risk (Berman et al. 1995).

A major area of concern is the possibility that asbestos fibers adsorb carcinogens in smoke, such as benzidine, N,N-dimethylanaline, and benzo(a)pyrene, and carry them to cells. Investigations are being carried out to detect such chemical impurities on asbestos fiber surfaces by a technique known as laser microprobe mass analysis (Warner 1988).

Reliability of asbestos analysis should be improved by new regulations requiring accreditation of asbestos-testing laboratories. The National Institute of Science and Technology (formerly the National Bureau of Standards) is conducting programs for accreditation of polarized light microscopy and TEM laboratories.

8. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, numerous regulations and advisories have been established for asbestos by various international, national, and state agencies. Such regulations and advisories control asbestos in various media, such as air and water, and also how it is contained, handled, disposed, etc.

Major regulations and advisories pertaining to asbestos are summarized in Table 8-1. Most states have adopted and enforce the regulations and guidelines set by national agencies. For example, with regard to emissions standards, most states follow the National Emission Standards for Hazardous Air Pollutants established by EPA (in Volume 40, Part 61 of the Code of Federal Regulations) for asbestos emissions. States may establish their own standards, but they are comparable to or more stringent than the ones set forth by EPA, OSHA, etc. (CELDS 1994). In addition, states may establish regulations for asbestos when federal regulations do not exist for a particular scenario (Kaplan 1993).

Table 8-1. Regulations and Guidelines Applicable to Asbestos[a]

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenic classification	Group 1[b]	IARC 2001
NATIONAL			
Regulations and guidelines			
a. Air			
ACGIH	TLV–TWA	0.1 f/mL	ACGIH 2000
EPA	Carcinogenic inhalation unit risk	2.3×10^{-1} $(f/mL)^{-1}$	IRIS 2001
	Carcinogenic classification	Group A[c]	
	NESHAP—HAP		EPA 2000c 40CFR61.01(a)
NIOSH	REL (100-minute TWA in a 400 L sample); f>5 µm in length	0.1 f/mL	NIOSH 2001
OSHA	PEL (8-hour TWA)	0.1 f/mL	OSHA 2001a 29CFR1910.1001
	PEL (8-hour TWA) for construction	0.1 f/mL	OSHA 2001b 29CFR1926.1101
	PEL (excursion limit) averaged over a 30-minute sampling period for construction	1.0 f/mL	OSHA 2001b 29CFR1926.1101
	PEL (8-hour TWA) for shipyard	0.1 f/mL	OSHA 2001c 29CFR1915.1001
	PEL (excursion limit) averaged over a 30-minute sampling period for shipyard	1.0 f/mL	OSHA 2001c 29CFR1915.1001
USC	HAP		USC 2001c 42USC7412
b. Water			
EPA	Concentration at cancer risk of 10^{-4} for drinking water	700 MFL	EPA 2000a
	Human health for consumption of: Water and organism	7 MFL	EPA 1999a

Table 8-1. Regulations and Guidelines Applicable to Asbestos[a] *(continued)*

Agency	Description	Information	References
NATIONAL *(cont.)*			
EPA	MCL (f>10 μm in length) MCLG (f>10 μm in length)	7 MFL 7 MFL	EPA 2001a
USC	Clean Water Act—National Standards of Performance		USC 2001a 33USC1316
c. Food			
FDA	Indirect food additives: Adhesives and components of coatings		FDA 2000a 21CFR175.105 (c)(5)
	Indirect food additives: Polymers		FDA 2000b 21CFR177.2420 (b)
	Indirect food additives: Polymers —phenolic resins in molded articles		FDA 2000c 21CFR177.2410 (b)
d. Other			
ACGIH	Carcinogenic classification	A1[d]	ACGIH 2000
CPSC	Test results on crayons—manufacturers will reformulate crayons using substitute ingredients to eliminate fibers within one year		CPSC 2001a
	Testing finds no asbestos fibers in children's chalk		CPSC 2001b
EPA	Asbestos—containing materials in schools; Asbestos abatement project		EPA 2000b 40CFR763
	CERCLA—reportable quantity	1 pound	EPA 1999b 40CFR302.4
	Toxic chemical release reporting; Community Right-to-Know—effective date	01/01/87	EPA 2001c 40CFR372.65(a)
USC	Congressional findings and purpose—implementation of appropriate response actions with respect to asbestos-containing material in the Nation's schools		USC 2001b 15USC2641

Table 8-1. Regulations and Guidelines Applicable to Asbestos[a] *(continued)*

Agency	Description	Information	References
DHHS	Carcinogen classification	Known to be a human carcinogen	NTP 2001
STATE			
Regulations and Guidelines			
a. Air			
Alabama	HAP		BNA 2001
Arizona	Research HAPs List		ADEQ 2001
California	Toxic air contaminant		Environmental Defense 2001
Colorado	HAP		BNA 2001
Hawaii	HAP		BNA 2001
Illinois	Toxic air contaminant		BNA 2001
Kansas	HAP		BNA 2001
Kentucky	HAP		BNA 2001
Louisiana	Toxic air pollutant Minimum emission rate	 25.0 pounds/year	BNA 2001
Maryland	Toxic air pollutant		BNA 2001
Minnesota	HAP threshold De minimis level (tons/year)	 Zero	BNA 2001
Missouri	Air contaminant De minimis emission level	 0.007 tons/year	BNA 2001
Nebraska	HAP		BNA 2001
New York	HAP		BNA 2001
Rhode Island	HAP		BNA 2001
Vermont	Hazardous air contaminant		BNA 2001
	Hazardous ambient air standards Annual average Action level	 1.2×10^{-4} µg/m^3 1×10^{-5} pounds/ 8 hours	BNA 2001
Washington	HAP—threshold level	4×10^{-5} f/mL	BNA 2001
Wyoming	HAP		BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Asbestos[a] *(continued)*

Agency	Description	Information	References
STATE *(cont.)*			
b. Water			
Alabama	Primary drinking water standard MCL (f>10 μm in length)	 7 MFL	BNA 2001
Alaska	Drinking water standard MCL (f>10 μm in length)	 7 MFL	BNA 2001
Arizona	Safe drinking water MCL (f>10 μm in length)	 7 MFL	BNA 2001
California	Primary MCL	7 MFL	California DHS 1999
Colorado	Groundwater standard	7 MFL	BNA 2001
	Primary drinking water regulation MCL (f>10 μm in length)	 7 MFL	BNA 2001
Connecticut	Public drinking water standard MCL (f>10 μm in length)	 7 MFL	BNA 2001
Florida	Drinking water standard MCL	 7 MFL	BNA 2001
Georgia	Safe drinking water MCL (f>10 μm in length)	 7 MFL	BNA 2001
Hawaii	MCL (f>10 μm in length)	7 MFL	CDC 1999
Illinois	Primary drinking water standard MCL	 7 MFL	BNA 2001
Indiana	MCL	7 MFL	IDEM 2001a
Kansas	Surface water quality criteria Domestic water supply	 7 MFL	BNA 2001
Kentucky	Surface water standards Domestic water supply use	 7 MFL	BNA 2001
Maryland	Drinking water MCL (f>10 μm in length)	 7 MFL	BNA 2001
Massachusetts	Water quality standard (f>10 μm in length)	7 MFL	FSTRAC 1999
Michigan	Drinking water standard MCL (f>10 μm in length) Effective date	 7 MFL 07/30/92	BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Asbestos[a] *(continued)*

Agency	Description	Information	References
STATE *(cont.)*			
Montana	Public water supply requirement MCL (f>10 μm in length)	 7 MFL	BNA 2001
Nebraska	Drinking water standard MCL (f>10 μm in length)	 7 MFL	BNA 2001
Nebraska	Water quality standard Water supply (f>10 μm in length)	 7 MFL	BNA 2001
New Hampshire	Drinking water rule MCL (f>10 μm in length) MCLG (f>10 μm in length)	 7 MFL 7 MFL	BNA 2001
	Surface water quality regulation Water and fish ingestion	 7 MFL	BNA 2001
New Mexico	Drinking water MCL (f>10 μm in length)	 7 MFL	BNA 2001
New York	Drinking water supplies MCL (f>10 μm in length)	 7 MFL	BNA 2001
North Dakota	Public water supply systems MCL (f>10 μm in length)	 7 MFL	BNA 2001
Rhode Island	Groundwater quality standard Preventive action limit	7 MFL 3.5 MFL	BNA 2001
South Carolina	Drinking water MCL (f>10 μm in length)	 7 MFL	BNA 2001
	Water quality criteria Organism consumption	 7 MFL	BNA 2001
South Dakota	Surface water quality standard Human health value concentration	 7 MFL	BNA 2001
Tennessee	Groundwater quality criteria	7 MFL	BNA 2001
	Public water systems MCL (f>10 μm in length)	 7 MFL	BNA 2001
Utah	Primary drinking water standard MCL (f>10 μm in length)	 7 MFL	BNA 2001
Vermont	Drinking water quality requirement MCL (f>10 μm in length) MCLG (f>10 μm in length)	 7 MFL 7 MFL	BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Asbestos[a] *(continued)*

Agency	Description	Information	References
STATE *(cont.)*			
Vermont	Groundwater quality standard Enforcement standard Preventive action limit	 7 MFL 3.5 MFL	BNA 2001
Washington	Public water supplies MCL (f>10 μm in length)	 7 MFL	BNA 2001
Wisconsin	Groundwater quality standard Enforcement standard Preventive action limit	 7 MFL 0.7 MFL	BNA 2001
c. Food		No data	
d. Other			
California	Chemical known to cause cancer or reproductive toxicity Effective date	 02/27/87	BNA 2001
	Hazardous substance		BNA 2001
	Identification and listing of hazardous waste —characteristics of toxicity TTLC (wet-weight mg/kg)	 1.0 (as a percent)	BNA 2001
Florida	Toxic substances in the workplace		BNA 2001
Indiana	Regulations for asbestos hazards to the atmosphere and disposal of asbestos-containing waste; licenses asbestos personnel		IDEM 2001b
Maine	Emissions standard	200 pounds	BNA 2001
Massachusetts	Oil and hazardous material		BNA 2001
	Toxic substance		BNA 2001
New Jersey	Hazardous substance		BNA 2001
New York	Occupation lung disease		BNA 2001
	Hazardous substance—reportable quantity Air Land and water	 1 pound 1 pound	BNA 2001
Ohio	Toxic chemical list		Ohio EPA 2001
Oregon	Toxic substance		BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Asbestos[a] *(continued)*

Agency	Description	Information	References
STATE *(cont.)*			
Pennsylvania	Hazardous substance		BNA 2001
South Carolina	Toxic pollutant		BNA 2001

[a]Includes: Actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite
[b]Group 1: Carcinogenic to humans
[c]Group A: Human carcinogen
[d]A1: Confirmed human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; ADEQ = Arizona Department of Environmental Quality; BNA = Bureau of National Affairs; CDC = Center for Disease Control; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; CPSC = Consumer Product Safety Commission; DHS = Department of Health Services; DHHS = Department of Health and Human Services; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FSTRAC = Federal–State Toxicology Risk Analysis Committee; HAP = Hazardous Air Pollutant; IARC = International Agency for Research on Cancer; IDEM = Indiana Department of Environmental Management; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; MFL = million fibers per liter; NESHAP = National Emission Standards for Hazardous Air Pollutants; NIOSH = National Institute of Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; TLV = threshold limit value; TTLC = total threshold limit concentration; TWA = time-weighted average; USC = United States Code

9. REFERENCES

*Aberle DR, Gamsu G, Ray CS, et al. 1988a. Asbestos-related pleural and parenchymal fibrosis: Detection with high-resolution CT. Radiology 166:729-734.

*Aberle DR, Gamsu G, Ray CS. 1988b. High-resolution CT of benign asbestos-related diseases: Clinical and radiographic correlation. Am J Radiol 151:883-891.

*Abidi P, Afaq F, Arif JM, et al. 1999. Chrysotile-mediated imbalance in the glutathione redox system in the development of pulmonary injury. Toxicol Lett 106:31-39.

ACGIH. 1986. Documentation of the threshold limit values and biological exposure indices. 5th ed. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

ACGIH. 1991. Documentation of the threshold limit values and biological exposure indices 6th ed American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

ACGIH. 1992. 1992-1993 Threshold limit values for chemical substances in the work environment. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

ACGIH. 1993. 1993-1994 Threshold limit values for chemical substances and physical agents and biological exposure indices. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

*ACGIH. 1998. Documentation of the threshold limit values and biological exposure indices. 6th Ed. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

*ACGIH. 2000. 2000 TLVs and BEIs. Threshold limit values for chemical substances and physical agents and biological exposure indices. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

*Acheson ED, Gardner MJ, Pippard EC, et al. 1982. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: A 40-year follow-up. Br J Ind Med 39:344-348.

Adachi S, Kawamura K, Kimura K, et al. 1992b. Tumor incidence was not related to the thickness of visceral pleural in female Syrian hamsters intratracheally administered amphibole asbestos or manmade fibers. Environ Res 58:55-65.

*Adachi S, Kawamura K, Yoshida S, et al. 1992a. Oxidative damage on DNA induced by asbestos and man-made fibers in vitro. Int Arch Occup Environ Health 63:553-557.

Adachi S, Yoshida S, Kawamura K, et al. 1994. Inductions of oxidative DNA damage and mesothelioma by crocidolite, with special reference to the presence of iron inside and outside of asbestos fiber. Carcinogenesis 15(4):753-758.

---

*Cited in text

9. REFERENCES

Adamson IYR. 1997. Early mesothelial cell proliferation after asbestos exposure: In vivo and in vitro studies. Environ Health Perspect Suppl 5:1205-1208.

*Adamson IY, Bowden DH. 1987a. Response of mouse lung to crocidolite asbestos. 1. Minimal fibrotic reaction to short fibres. J Pathol 152:99-107.

*Adamson IY, Bowden DH. 1987b. Response of mouse lung to crocidolite asbestos. 2. Pulmonary fibrosis after long fibres. J Pathol 152:109-117.

Adamson IYR, Bowden DH. 1990. Pulmonary reaction to long and short asbestos fibers is independent of fibroblast growth factor production by alveolar macrophages. Am J Pathol 137:523-529

Addison J, Browne K, Davis JM, et al. 1993. Asbestos fibers in parenteral medication. Regul Toxicol Pharmacol 18(3):371-380.

*ADEQ. 2001. List of HAPs research compounds. Arizona Department of Environmental Quality. Http://www.adeq.state.az.us/comm/download/air.html. January 19,2001.

*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.

*Afaq F, Abidi P, Matin R, et al. 1998. Activation of alveolar macrophages and peripheral red blood cells in rats exposed to fibers/particles. Toxicol Lett 99:175-182.

Ahmad I, Krishnamurthi K, Arif JM, et al. 1995. Augmentation of chrysotile-induced oxidative stress by BHA in mice lungs. Food Chem Toxicol 33:209-215.

Ahrens W, Joeckel K-H, Patzak W, et al. 1991. Alcohol smoking and occupational factors in cancer of the larynx: A case-control study. Am J Ind Med 20(4):477-493.

Aisner J. 1989. Therapeutic approach to malignant mesothelioma. Chest 96(Suppl 1):95S-97S

*Akira M, Yokoyama K, Yamamoto S, et al. 1991. Early asbestosis: Evaluation with high resolution CT. Thoracic Radiology 409-416.

Albin M, Engholm G, Hallin N, et al. 1998. Impact of exposure to insulation wool on lung function and cough in Swedish construction workers. Occup Environ Med 55:661-667.

*Albin M, Horstmann V, Jakobsson K, et al. 1996. Survival in cohorts of asbestos cement workers and controls. Occup Environ Med 53:87-93.

*Albin M, Jakobsson K, Attewell R, et al. 1990a. Mortality and cancer morbidity in cohorts of asbestos cement workers and referents. Br J Ind Med 47:602-610.

*Albin M, Johansson L, Pooley FD, et al. 1990b. Mineral fibres, fibrosis, and asbestos bodies in lung tissue from deceased asbestos cement workers. Br J Ind Med 47:767-774.

9. REFERENCES

*Albin M, Pooley FD, Stromberg U, et al. 1994. Retention patterns of asbestos fibres in lung tissue among asbestos cement workers. Occup Environ Med 51:205-211.

*Alden HS, Howell WM. 1944. The asbestos corn. Archives of Dermatology and Syphilology 49:312-314.

Alderisio M, Giovagnoli MR, Cenci M, et al. 1996. Asbestos bodies in the sputum of workers exposed to environmental pollution. Anticancer Res 16:2965-2968.

Al Jarad N, Carroll MP, Laroche C, et al. 1994. Respiratory muscle function in patients with asbestos-related pleural disease. Resp Med 88:115-120.

*Al Jarad N, Macey M, Uthayakumar S, et al. 1992. Lymphocyte subsets in subjects exposed to asbestos: Changes in circulating natural killer cells. Br J Ind Med 49(11) 811-814.

Al Jarad N, Poulakis N, Pearson MC, et al. 1991. Assessment of asbestos-induced pleural disease by computer tomography - correlation with chest radiograph and lung function. Resp Med 85:203-208.

*Al Jarad N, Strickland B, Bothamley G, et al. 1993. Diagnosis of asbestosis by a time expanded wave form analysis, auscultation and high resolution computed tomography: A comparative study. Thorax 48(4)347-353.

*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.

*Amandus HE, Wheeler R. 1987. The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actimolite: Part II. Mortality. Am J Med 11:15-26.

*Amandus HE, Althouse R, Morgan WKC, et al. 1987. The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part III. Radiographic findings. Am J Ind Med 11:27-37.

*American Thoracic Society. 1986. The diagnosis of nonmalignant diseases related to asbestos. Am Rev Resp Dis 134:363-368.

*American Thoracic Society. 1990. Health effects of tremolite. Am Rev Respir Dis 142(6):1453-1458.

*Andersen A, Glattre E, Johansen BV. 1993. Incidence of cancer among lighthouse keepers exposed to asbestos in drinking water. Am J Epidemiol 138(9):682-687.

*Andersen ME, Kirshnan 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 ME, Clewell HJ 3rd, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87:185-205.

*Anderson HA, Lilis R, Daum SM, et al. 1976. Household-contact asbestos neoplastic risk. Ann NY Acad Sci 271:311-323.

9. REFERENCES

*Anderson HA, Lilis R, Daum SM, et al. 1979. Asbestosis among household contacts of asbestos factory workers. Ann NY Acad Sci 271:387-399.

Andersson E, Toren K. 1995. Pleural mesotheliomas are underreported as occupational cancer in Sweden. Am J Ind Med 27:577-580.

*Andrion A, Bosia S, Paoletti L, et al. 1994. Malignant peritoneal mesothelioma in a 17-year-old boy with evidence of previous exposure to chrysotile and tremolite asbestos. Hum Pathol 25(6):617-622.

Anjilvel S, Asgharian B. 1995. A multiple-path model of particle deposition in the rat lung. Fundam Appl Toxicol 28:41-50.

Anonymous. 1997. Asbestos, asbestosis, and cancer: The Helsinki criteria for diagnosis and attribution. Scand J Work Environ Health 23:311-316.

*Anonymous. 2000. The WTO speaks: Chrysotile is bad for you! British Asbestos Newsletter. Issue 39. Http://www.1kaz.demon.co.uk/ban39.htm. April 19, 2001.

*Anton-Culver H, Culver BD, Kurosaki T. 1988. Immune response in shipyard workers with x-ray abnormalities consistent with asbestos exposure. Br J Ind Med 45:464-468.

*Anton-Culver H, Culver BD, Kurosaki T. 1989. An epidemiologic study of asbestos-related chest x-ray changes to identify work areas of high risk in a shipyard population. Appl Ind Hyg 4:110-118.

Anttila S, Luostarinen L, Hirvonen A, et al. 1995. Pulmonary expression of glutathione S-transferase M3 in lung cancer patients: Association with GSTM1 polymorphism, smoking, and asbestos exposure. Cancer Res 55:3305-3309.

Apostolou S, De Rienzo A, Murthy SS, et al. 1999. Absence of *BCL10* mutations in human malignant mesothelioma. Cell 97:684-686.

Appel JD, Fasy TM, Kohtz JD, et al. 1988. Asbestos fibers mediate transformation of monkey cells by exogenous plasmid DNA. Proc Natl Acad Sci USA 85:7670-7674.

Arden MG, Adamson IYR. 1992. Collagen synthesis and degradation during the development of asbestos-induced pulmonary fibrosis. Exp Lung Res 18:9-20.

Arenas-Huertero FJ, Salazar-Flores M, Osornio-Vargas AR. 1994. Ferruginous bodies as markers of environmental exposure to inorganic particles: Experience with 270 autopsy cases in Mexico. Environ Res 64:10-17.

Arif JM, Khan SG, Ahmad I, et al. 1997. Effect of kerosene and its soot on the chrysotile-mediated toxicity to the rat alveolar macrophages. Environ Res 72:151-161.

Arif JM, Khan SG, Aslam M, et al. 1992. Diminution in kerosene-mediated induction of drug metabolizing enzymes by asbestos in rat lungs. Pharmacol Toxicol 71:37-40.

Arif JM, Khan SG, Mahmood N, et al. 1994. Effect of coexposure to asbestos and kerosene soot on pulmonary drug-metabolizing enzyme system. Environ Health Perspect Suppl 102:181-183.

9. REFERENCES

*Armstrong BK, DeKlerk NH, Musk AW, et al. 1988. Mortality in miners and millers of crocidolite in Western Australia. Br J Ind Med 45:5-13.

Ascoli V, Facciolo F, Rahimi S, et al. 1996. Concomitant malignant mesothelioma of the pleura, peritoneum, and tunica vaginalis testis. Diagn Cytopathol 14:243-248.

Ascoli V, Scalxo CC, Facciolo F, et al. 1996. Malignant mesothelioma in Rome, Italy 1980-1995. A retrospective study of 79 patients. Tumori 82:526-532.

*Asgharian B, Anjilvel S. 1998. A multiple-path model of fiber deposition in the rat lung. Toxicol Sci 44:80-86.

*Asgharian B, Wood R, Schlesinger RB. 1995. Empirical modeling of particle deposition in the alveolar region of the lungs: A basis for interspecies extrapolation. Fundam Appl Toxicol 27:232-238.

Ashcroft T, Heppleston AG. 1973. The optical and electron microscopic determination of pulmonary asbestos fibre concentration and its relation to the human pathological reaction. J Clin Pathol 26:224-234.

*ASTM. 1988. Standard test method for airborne asbestos concentration in workplace atmosphere - method D 4240-83. In: 1988 annual book of ASTM standards. Vol 11.03. Atmospheric analysis, occupational safety and health. Philadelphia, PA: American Society for Testing and Materials, 300-308.

*ATSDR. 1989. Agency for Toxic Substances and Disease Registry. Federal Register 54:37619-37633.

Attanoos RL, Gibbs AR. 1997. Pathology of malignant mesothelioma. Histopathology 30:403-417.

Auerbach O, Conston AS, Garfinkel L, et al. 1980. Presence of asbestos bodies in organs other than the lung. Chest 77:133-137.

Aufderheide M, Knebel JW, Schulte P. 1996. Differences in the sensitivity of hamster and rat lung cells exposed in vitro to natural and man-made fibres. Exp Toxicol Pathol 48:505-507.

*Ault JG, Cole RW, Jensen CG, et al. 1995. Behavior of crocidolite asbestos during mitosis in living vertebrate lung epithelial cells. Cancer Res 55:792-798.

*Awadalla FT, Habashi F, Page M. 1990. Reaction of chrysotile asbestos with phosphate ion in relation to toxicity. J Chem Tech Biotechnol 49:183-196.

*Babu KA, Lakkad BC, Nigam SK, et al. 1980. *In vitro* cytological and cytogenetic effects of an Indian variety of chrysotile asbestos. Environ Res 21:416-422.

*Baker EL, Dagg T, Greene RE. 1985. Respiratory illness in the construction trades. I. The significance of asbestos-associated pleural disease among sheet metal workers. J Occup Med 27:483-489.

Balmes JR, Daponte A, Cone JE. 1991. Asbestos-related disease in custodial and building maintenance workers from a large municipal school district. Ann NY Acad Sci 540-549.

*Balsara BR, Bell DW, Sonoda G, et al. 1999. Comparative genomic hybridization and loss of heterozygosity analyses identify a common region of deletion at 15q11.1-15 in human malignant mesothelioma. Cancer Res 59:450-454.

9. REFERENCES

Band PR, Le ND, Fang R, et al. 1997. Cohort mortality study of pulp and paper mill workers in British Columbia, Canada. Am J Epidemiol 146:186-194.

Barbers RG, Abraham JL. 1989. Asbestosis occurring after brief inhalation exposure: Usefulness of bronchoalveolar lavage in diagnosis. Br J Ind Med 46:106-110.

Barbers RG, Oishi J. 1987. Effects of *in vitro* asbestos exposure on natural killer and antibody-dependent cellular cytotoxicity. Environ Res 43:217-226.

*Barchowsky A, Roussel RR, Krieser RJ, et al. 1998. Expression and activity of urokinase and its receptor in endothelial and pulmonary epithelial cells exposed to asbestos. Toxicol Appl Pharmacol 152:388-396.

Baris I, Simonato L, Artivinli M, et al. 1987. Epidemiological and environmental evidence of the health effects of exposure to erionite fibres: A four-year study in the Cappadocian region of Turkey. Int J Cancer 39:10-17.

*Bariş YI, Artvinli M, Sahin AA, et al. 1988a. Non-occupational asbestos related chest diseases in a small Anatolian village. Br J Ind Med 45:841-842.

*Baris YI, Bilir N, Artvinli M, et al. 1988b. An epidemiological study in an Anatolian village environmentally exposed to tremolite asbestos. Brit J Ind Med 45:838-840.

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

*Barnes PJ. 1997. Nuclear factor-kappa B. Int J Biochem Cell Biol 29:867-870.

Barnhart S, Keogh J, Cullen MR, et al. 1997. The CARET asbestos-exposed cohort: Baseline characteristics and comparison to other asbestos-exposed cohorts. Am J Ind Med 32:573-581.

Barnhart S, Thornquist M, Omenn GS, et al. 1990. The degree of roentgenographic parenchymal opacities attributable to smoking among asbestos-exposed subjects. Am Rev Respir Dis 141:1102-1106.

Barrett JC. 1993. Mechanisms of multistep carcinogenesis and carcinogen risk assessment. Environ Health Perspect 100(4):9-20, 109.

*Barrett JC, Lam PW, Wiseman RW. 1989. Multiple mechanisms for the carcinogenic effects of asbestos and other mineral fibers. Environ Health Perspect 81:81-89.

Barrett JC, Thomassen DG, Hesterberg TW. 1983. Role of gene and chromosomal mutations in cell transformation. Ann NY Acad Sci 407:291-300.

Barroetavena MC, Teschke K, Bates DV. 1996. Unrecognized asbestos-induced disease. Am J Ind Med 29:183-185.

Bateman ED, Benatar SR. 1987. Asbestos-induced diseases: Clinical perspectives. Q J Med 62:183-194.

Bayeux MC, Letourneux M, Brochard P, et al. 1998. Round atelectasis and asbestos: A review of 26 patients. Rev Mal Resp 15:281-286.

9. REFERENCES

Becklake MR. 1976. Asbestos-related disease of the lung and other organs: Their epidemiology and implications for clinical practice. Am Rev Resp Dis 114:187-227.

*Becklake MR, Case BW. 1994. Fiber burden and asbestos-related lung disease: Determinants of dose-response relationships. Am J Respir Crit Care Med 150:1488-1492.

Beer TW. 1998. Cancer among spouses: Review of 195 couples. [Letter]. Cancer 83:591-592.

*Begin R, Boileau R, Peloquin S. 1987a. Asbestos exposure, cigarette smoking, and airflow limitation in long-term Canadian chrysotile miners and millers. Am J Ind Med 11:55-66.

Begin R, Cantin A, Masse S. et al. 1988. Effects of cyclophosphamide treatment in experimental asbestosis. Exp Lung Res 14:823-836.

Begin R, Cantin A, Masse S. 1991. Influence of continued asbestos exposure on the outcome of asbestosis in sheep. Exp Lung Res 17:971-984.

Begin R, Cantin A, Sebastien P. 1990. Chrysotile asbestos exposures can produce an alveolitis with limited fibrosing activity in a subset of high fibre retainer sheep. Eur Respir J 3:81-90.

Begin R, Filion R, Ostiguy G. 1995. Emphysema in silica- and asbestos-exposed workers seeking compensation. Chest 108:647-655.

*Begin R, Martel M, Desmarais Y, et al. 1986. Fibronectin and procollagen 3 levels in bronchoalveolar lavage of asbestos-exposed human subjects and sheep. Chest 89:237-243.

Begin R, Masse S, Rola-Pleszczynski M, et al. 1987b. Asbestos exposure dose-bronchoalveolar milieu response in asbestos workers and the sheep model: Evidences of a threshold for chrysotile-induced fibrosis. Drug Chem Toxicol 10:87-107.

Begin R, Ostiguy G, Filion R, et al. 1992. Recent advances in the early diagnosis of asbestosis. Semin Roentgenol 27:121-139.

Bekkelund SI, Aasebo U, Pierre-Jerome C, et al. 1998. Magnetic resonance imaging of the thorax in the evaluation of asbestosis. Eur Resp J 11:194-197.

Beland FA, Poirier MC. 1991. Biomarkers of human exposure to carcinogens: An overview. Biomed Environ Sci 4(1-2):69-72.

*Bell DW, Jhanwar SC, Testa JR. 1997. Multiple regions of allelic loss from chromosome arm 6q in malignant mesothelioma. Cancer Res 57:4057-4062.

Belli S, Bruno C, Combat P, et al. 1998. [Cause-specific mortality of asbestos-cement workers compensated for asbestosis in the city of Bari.] Epidemiol Prev 22:8-11. (Italian).

Bellmann B, Muhle H. 1994. Investigation of the biodurability of wollastonite and xonotlite. Environ Health Perspect Suppl 102:191-195.

*Bellmann B, Muhle H, Kamstrup O, et al. 1994. Investigation on the durability of man-made vitreous fibers in rat lungs. Environ Health Perspect Suppl 102:185-189.

*Bellmann B, Muhle H, Pott F, et al. 1987. Persistence of man-made mineral fibres (MMMF) and asbestos in rat lungs. Ann Occup Hyg 31:693-709.

*Berger G. 1994. Epidemiology of endometriosis. In: Modern surgical management of endometriosis. New York: Springer-Verlag.

Berger M, de Hazen M, Nejjari M, et al. 1993. Radical oxidation reactions of the purine moiety of 2'-deoxyribonucleosides and DNA by iron-containing minerals. Carcinogenesis 14(1):41-46.

Berkow, R, Talbott, JH. 1977. The Merck index of diagnosis and therapy. 13th ed. Rahway, N.J.: Merck & Co., Inc.

Berlin J, Frumkin H. 1988. Exposure to asbestos and the risk of gastrointestinal cancer [Letter]. Br J Ind Med 45:575.

Berman DW, Crump KS. 1989. Relative potency of asbestos fibers of different lengths. Toxicol Pathol 17:841-842.

*Berman DW, Crump KS, Chatfield EJ, et al. 1995. The sizes, shapes, and mineralogy of asbestos structures that induce lung tumors or mesothelioma in AF/HAN rats following inhalation. (Errata attached). Risk Anal 15:181-195.

Berman J. 1984. Beshada v. Johns-Manville Products Corp.: The function of state of the art evidence in strict products liability. Am J Law Med 10:93-114.

Bermudez E, Everitt J, Walker C. 1990. Expression of growth factor and growth factor receptor RNA in rat pleural mesothelial cells in culture. Exp Cell Res 190:91-98.

Berry G. 1994. Mortality and cancer incidence of workers exposed to chrysotile asbestos in the friction-products industry. Ann Occup Hyg 38:539-546.

Berry G. 1999. Models for mesothelioma incidence following exposure to fibers in terms of timing and duration of exposure and the biopersistence of the fibers. Inhal Toxicol 11:111-130.

*Berry G, Newhouse ML. 1983. Mortality of workers manufacturing friction materials using asbestos. Br J Ind Med 40:1-7.

*Berry G, Gilson JC, Holmes S, et al. 1979. Asbestosis: A study of dose-response relationships in an asbestos textile factory. Br J Ind Med 36:98-112.

*Berry G, Newhouse ML, Antonis P. 1985. Combined effect of asbestos and smoking on mortality from lung cancer and mesothelioma in factory workers. Br J Ind Med 42:12-18.

Berry G, Rogers AJ, Pooley FD. 1989. Mesotheliomas - asbestos exposure and lung burden. IARC Sci Pub 90:486-496.

*Berry M. 1997. Mesothelioma incidence and community asbestos exposure. Environ Res 75:34-40.

Bertrand R, Pezerat H. 1980. Fibrous glass: Carcinogenicity and dimensional characteristics. IARC Sci Publ 30:901-911.

*Berube KA, Quinlan TR, Moulton G, et al. 1996. Comparative proliferative and histopathologic changes in rat lungs after inhalation of chrysotile or crocidolite asbestos. Toxicol Appl Pharmacol 137:67-74.

Bevan DR, Ulman MR. 1991. Examination of factors that may influence disposition of benzo[a]pyrene in vivo: Vehicles and asbestos. Cancer Lett 57:173-179.

Bianchi AB, Mitsunaga S-I, Cheng JQ, et al. 1995. High frequency of inactivating mutations in the neurofibromatosis type 2 gene (*NF2*) in primary malignant mesotheliomas. Proc Natl Acad Sci U S A 92:10854-10858.

Bianchi C, Bittesini L, Brollo A. 1986. Asbestos exposure and Alzheimer disease. Ital J Neurol Sci 7:145-151.

Bianchi C, Brollo A, Ramani L, et al. 1993a. Asbestos-related mesothelioma in Monfalcone, Italy. Am J Ind Med 24(2):149-160.

Bianchi C, Brollo A, Ramani L, et al. 1997. Pleural plaques as risk indicators for malignant pleural mesothelioma: A necropsy-based study. Am J Ind Med 32:445-449.

Bianchi C, Brollo A, Zuch C. 1993b. Asbestos-related familial mesothelioma. Eur J Cancer Prev 2(3):247-250.

*Bianchi C, Giarelli L, Grandi G, et al. 1997. Latency periods in asbestos-related mesothelioma of the pleura. Eur J Cancer Prev 6:162-166.

*Bignon J, Jaurand MC. 1983. Biological *in vitro* and *in vivo* responses of chrysotile versus amphiboles. Environ Health Perspect 51:73-80.

*Bignon J, Sebastien P, DiMenza L, et al. 1979. French mesothelioma registry. Ann NY Acad Sci 330:455-466.

*Bisson G, Lamoureuz G, Begin R. 1987. Quantitative gallium 67 lung scan to assess the inflammatory activity in the pneumoconioses. Semin Nucl Med 17:72-80.

*Bissonnette E, Bubois C, Rola-Pleszczynski M. 1989. Changes in lymphocyte function and lung histology during the development of asbestosis and silicosis in the mouse. Res Commun Chem Pathol Pharmacol 65:211-227.

*Bissonnette E, Carre B, Dubois C, et al. 1990. Inhibition of alveolar macrophage cytotoxicity by asbestos: Possible role of prostaglandins. J Leukoc Biol 47:129-134.

*Blackwell TS, Christman JW. 1997. The role of nuclear factor-kappa B in cytokine gene regulation. Am J Respir Cell Mol Biol 17:3-9.

Blanc P. 1991. Cigarette smoking, asbestos, and parenchymal opacities revisited. Ann NY Acad Sci 133-141.

*Blanc PD, Golden JA, Gamsu G, et al. 1988. Asbestos exposure-cigarette smoking interactions among shipyard workers. JAMA 259:370-373.

Blot WJ, Harrington JM, Toledo A, et al. 1978. Lung cancer after employment in shipyards during World War II. N Engl J Med 299:620-624.

*BNA. 2001. Environmental and Safety Library on the Web States and Territories. Bureau of National Affairs, Inc. Washington, D.C. Http//www.esweb.bna.com/. June 6, 2001.

*Boatman ES, Merrill T, O'Neill A, et al. 1983. Use of quantitative analysis of urine to assess exposure to asbestos fibers in drinking water in the Puget Sound region. Environ Health Perspect 53:131-141.

Boehme DS, Maples KR, Henderson RF. 1992. Glutathione release by pulmonary alveolar macrophages in response to particles in vitro. Toxicol Lett 60:53-60.

Boffetta P, Burdorf A, Goldberg M, et al. 1998. Towards the coordination of European research on the carcinogenic effects of asbestos. Scand J Work Environ Health 24:312-317.

*BOHS. 1968. Hygiene standards for chrysotile asbestos dust. British Occupational Hygiene Society. Ann Occup Hyg 11:47-69.

*BOHS. 1983. A study of the health experience in two U. K. asbestos factories. British Occupational Hygiene Society. Ann Occup Hyg 27:1-13.

Boltin WR, Clark BH, Detter-Hoskin L, et al. 1989. Alternative instrumentation in the analysis for asbestos in various media. American Laboratory (April):15-25.

*Bolton RE, Davis JM, Donaldson K, et al. 1982b. Variations in the carcinogenicity of mineral fibres. Ann Occup Hyg 26:569-582.

*Bolton RE, Davis JM, Lamb D. 1982a. The pathological effects of prolonged asbestos ingestion in rats. Environ Res 29:134-150.

*Bolton RE, Vincent JH, Jones AD, et al. 1983. An overload hypothesis for pulmonary clearance of UICC amosite fibres inhaled by rats. Br J Ind Med 40:264-272.

*Bonneau L, Malard C, Pezerat H. 1986. Studies on surface properties of asbestos: II. Role of dimensional characteristics and surface properties of mineral fibers in the induction of pleural tumors. Environ Res 41:268-275.

Bonner JC, Goodell AL, Coin PG, et al. 1993. Chrysotile asbestos upregulates gene expression and production of alpha-receptors for platelet-derived growth factor (PDGF-AA) on rat lung fibroblasts. J Clin Invest 92(1):425-430.

Booth SJ, Weaver EJ. 1986. Malignant pleural mesothelioma five years after domestic exposure to blue asbestos [Letter]. Lancet 1:435.

*Boraschi P, Neri S, Braccini G, et al. 1999. Magnetic resonance appearance of asbestos-related benign and malignant pleural diseases. Scand J Work Environ Health 25:18-23.

Borron SW, Forman SA, Lockey JE, et al. 1997. An early study of pulmonary asbestosis among manufacturing workers: Original data and reconstruction of the 1932 cohort. Am J Ind Med 31:324-334.

9. REFERENCES

*Both K, Henderson DW, Turner DR. 1994. Asbestos and erionite fibres can induce mutations in human lymphocytes that result in loss of heterozygosity. Int J Cancer 59:538-542.

*Both K, Turner DR, Henderson DW. 1995. Loss of heterozygosity in asbestos-induced mutations in a human mesothelioma cell line. Environ Mol Mutagen 26:67-71.

Botta M, Magnani C, Terracini B, et al. 1991. Mortality from respiratory and digestive cancers among asbestos cement workers in Italy. Cancer Detect Prev 15:445-447.

Bourbeau J, Ernst P, Chrome J, et al. 1988. Relationship between respiratory impairment and asbestos related pleural disease in an active workforce [Abstract]. Am Rev Respir Dis 137 (Suppl): 92.

*Bourbeau J, Ernst P, Chrome J, et al. 1990. The relationship between respiratory impairment and asbestos-related pleural abnormality in an active work force. Am Rev Respir Dis 142:837-842.

*Boutin C, Dumortier P, Rey F, et al. 1996. Black spots concentrate oncogenic asbestos fibers in the parietal pleura. Am J Resp Crit Care Med 153:444-449.

*Boutin G, Viallat JR, Steinbauer J, et al. 1989. Bilateral pleural plaques in Corsica: A marker of non-occupational asbestos exposure. IARC Sci Publ 90:406-410.

*Boylan AM, Ruegg C, Kim JK, et al. 1992. Evidence of a role for mesothelial cell-derived interleukin 8 in the pathogenesis of asbestos-induced pleurisy in rabbits. J Clin Invest 89:1257-1267.

*Brackett KA, Clark PJ, Millette JR. 1992. Method for the analysis of asbestos fibers in water using MCE filters. Microscope 40(3):159-163.

*Branchaud RM, Garant LJ, Kane AB. 1993. Pathogenesis of mesothelial reactions to asbestos fibers. Monocyte recruitment and macrophage activation. Pathobiology 61(3-4):154-163.

Branchaud RM, MacDonald JL, Kane AB. 1989. Induction of angiogenesis by intraperitoneal injection of asbestos fibers. FASEB J 3:1747-1752.

Brass DM, Hoyle G, Liu JY, et al. 1997. Asbestos-induced lung fibrosis and expression of TNF-alpha in two strains of mice. FASEB J 11:A227.

*Brass DM, Hoyle GW, Poovey HG, et al. 1999. Reduced tumor necrosis factor-α and transforming growth factor-β1 expression in the lungs of inbred mice that fail to develop fibroproliferative lesions consequent to asbestos exposure. Am J Pathol 154:853-862.

*Bravo MP, Del Rey-Calero J, Conde M. 1988. Bladder cancer and asbestos in Spain. Rev Epidemol Med Soc Sante Publique 36:10-14.

*Bresnitz EA, Gilman MJ, Gracely EJ, et al. 1993. Asbestos-related radiographic abnormalities in elevator construction workers. Am Rev Respir Dis 147(6):1341-1344.

*Britton MG. 1982. Asbestos pleural disease. Br J Dis Chest 76:1-10.

*Broaddus VC, Yang L, Scavo LM, et al. 1996. Asbestos induces apoptosis of human and rabbit pleural mesothelial cells via reactive oxygen species. J Clin Invest 98:2050-2059.

*Broaddus VC, Yang L, Scavo LM, et al. 1997. Crocidolite asbestos induces apoptosis of pleural mesothelial cells: Role of reactive oxygen species and poly (ADP-ribosyl) polymerase. Environ Health Perspect Suppl 105:1147-1152.

Brodkin CA, McCullough J, Stover B, et al. 1997. Lobe of origin and histologic type of lung cancer associated with asbestos exposure in the carotene and retinol efficacy trial (CARET). Am J Ind Med 32:582-591.

*Brody AR. 1986. Pulmonary cell interactions with asbestos fibers *in vivo* and *in vitro*. Chest 89(Suppl 3):155S-159S.

*Brody AR. 1993. Asbestos-induced lung disease. Environ Health Perspect 100(4):21-30.

Brody AR, Hill LH. 1982. Interstitial accumulation of inhaled chrysotile asbestos fibers and consequent formation of microcalcifications. Am J Pathol 109:107-114.

Brody AR, Hill LH, Adkins B, et al. 1981. Chrysotile asbestos inhalation in rats: Deposition pattern and reaction of alveolar epithelium and pulmonary macrophages. Am Rev Respir Dis 123:670-679.

Brody AR, Hoyle G, Liu J-Y, et al. 1999. Reduced growth factor expression in mice resistant to developing fibroproliferative lesions after lung injury. Chest 116(1)(Suppl.):97.

Brody AR, Liu J-Y, Brass D, et al. 1997. Analyzing the genes and peptide growth factors expressed in lung cells in vivo consequent to asbestos exposure in vitro. Environ Health Perspect Suppl 105:1165-1171.

Broser M, Zhang Y, Aston C, et al. 1996. Elevated interleukin-8 in the alveolitis of individuals with asbestos exposure. Int Arch Occup Environ Health 68:109-114.

Brown A. 1974. Lymphohematogenous spread of asbestos [Commentary]. Environ Health Perspect 9:203-204.

*Brown DM, Fisher C, Donaldson K. 1998. Free radical activity of synthetic vitreous fibers: Iron chelation inhibits hydroxy radical generation by refractory ceramic fiber. J Toxicol Environ Health 53:545-561.

*Brown DP, Dement JM, Okun A. 1994. Mortality patterns among female and male chrysotile asbestos textile workers. J Occup Med 36:882-888.

*Brown RC, Carthew P, Hoskins JA, et al. 1990. Surface modification can affect the carcinogenicity of asbestos. Carcinogenesis 11:1883-1885.

*Brown RC, Poole A, Fleming GTA. 1983. The influence of asbestos dust on the oncogenic transformation of C3HlOT1/2 cells. Cancer Letters 18:221-227.

*Brown RC, Sara EA, Hoskins JA, et al. 1991. Factors affecting the interaction of asbestos fibres with mammalian cells: a study using cells in suspension. Ann Occup Hyg 35:25-34.

Browne K. 1983. Asbestos-related mesothelioma: Epidemiological evidence for asbestos as a promoter. Arch Environ Health 38:261-266.

*Browne K. 1986a. A threshold for asbestos related lung cancer. Br J Ind Med 43:556-558.

*Browne K. 1986b. Is asbestos or asbestosis the cause of increased risk of lung cancer in asbestos workers [Editorial]? Br J Ind Med 43:145-149.

*Browne K, Gee JBL. 2000. Asbestos exposure and laryngeal cancer. Ann Occup Hyg 44(4):239-250.

Browne KA. 1991. Asbestos related malignancy and the Cairns hypothesis [Letter]. Br J Ind Med 48:73-76.

Brownson RC, Alavanja MCR, Chang JC. 1993. Occupational risk factors for lung cancer among nonsmoking women a case-control study in Missouri, United States. Cancer Causes Control 4(5):449-454.

Brownson RD. 1998. Current and historical American asbestos regulations. Monaldi Arch Chest Dis 53:181-185.

Buckley SE, Aust AE. 1997. Role of vitronectin in regulation of intracellular glutathione concentrations in human lung epithelial cells. FASEB J 11:A1335.

Burdett G. 1998. A comparison of historic asbestos measurements using a thermal precipitator with the membrane filter-phase contrast microscopy method. Ann Occup Hyg 42:21-31.

Burdett GJ, Jaffrey SAMT, Rood AP. 1989. Airborne asbestos fibre levels in buildings: A summary of UK measurements. IARC Sci Pub 90:277-290.

*California DHS. 1999. California drinking water standards, action levels, and unregulated chemicals requiring monitoring. California Department of Health Services. Http://www.dhs.cahwnet.gov/ps/ddwem/chemicals/mcl/mclindex.htm. May 7, 1999.

Callahan KS, Griffith DE, Garcia JGN. 1990. Asbestos exposure results in increased lung procoagulant activity in vivo and in vitro. Chest 98:112-119.

*Camus M, Siematycki J, Meek B. 1998. Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. N Engl J Med 338:1565-1571.

*Cantin A, Dubois F, Begin R. 1988. Lung exposure to mineral dusts enhances the capacity of lung inflammatory cells to release superoxide. J Leukoc Biol 43:299-303.

*Cantin AM, Larivee P, Martel M, et al. 1992. Hyaluronan (hyaluronic acid) in lung lavage of asbestos-exposed humans and sheep. Lung 170:211-220.

*Cantor KP. 1997. Drinking water and cancer. Cancer Causes Control 8:292-308.

Capellaro E, Chiesa A, Villari S, et al. 1996. Asbestos bodies in bronchoalveolar lavage fluid and sputum. Med Lav 88:99-107.

*Carbone M. 1999. Simian virus 40 and human tumors: It is time to study mechanisms. J Cell Biochem 76:189-193.

*Carbone M, Rizzo P, Pass H. 2000. Simian virus 40: The link with human malignant mesothelioma is well established. Anticancer Res 20:875-878.

*Carter RE, Taylor WF. 1980. Identification of a particular amphibole asbestos fiber in tissues of persons exposed to a high oral intake of the mineral. Environ Res 21:85-93.

Carthew P, Edwards RE, Dorman BM, et al. 1993. A reappraisal of the carcinogenicity of surface modified asbestos fibers. Carcinogenesis 14(11):2413-2414.

Carthew P, Hill RJ, Edwards RE, et al. 1992. Intrapleural administration of fibers induces mesothelioma in rats in the same relative order of hazard as occurs in man after exposure. Hum Exp Toxicol 11(6):530-534.

*Case BW. 1991. Health effects of tremolite. Now and in the future. Ann NY Acad Sci 491-504.

*Case BW. 1994. Biological indicators of chrysotile exposure. Ann Occup Hyg 38:503-518.

Case BW. 1998. [Letter]. N Engl J Med 339:1001.

*Case BW, Dufresne A. 1997. Asbestos, asbestosis, and lung cancer: Observations in Quebec chrysotile workers. Environ Health Perspect Suppl 105:1113-1119.

Case BW, Oliver LC. 1992. Asbestos bodies are absent from sputum of school custodial workers [Abstract]. Am Rev Respir Dis 145:332.

*Case BW, Sebastien P. 1987. Environmental and occupational exposures to chrysotile asbestos: A comparative microanalytic study. Arch Environ Health 42(4):185-191.

*Case BW, Sebastien P. 1989. Fibre levels in lung and correlation with air samples. In: Bignon J, Peto J, Saracci R, eds. Non-occupational exposure to mineral fibres, 207-218.

*Case BW, Dufresne A, McDonald AD, et al. 2000. Asbestos fiber type and length in lungs of chrysotile textile and production workers: Fibers longer than 18 μm. Inhal Toxicol 12:411-418.

*Case BW, Ip MPC, Padilla M, et al. 1986. Asbestos effects on superoxide production: An *in vitro* study of hamster alveolar macrophages. Environ Res 39:299-306.

*Case BW, Kuhar M, Harrigan M, et al. 1994. Lung fibre content of American children aged 8-15 years: Preliminary findings. Ann Occup Hyg 38:639-645.

Case BW, Monaghan LA, Giguère M. 1991. Sputum asbestos bodies in female residents of two chrysotile mining towns [Abstract]. Am Rev Respir Dis 143:266.

*Case BW, Sebastien P, McDonald JC. 1988. Lung fiber analysis in accident victims: A biological assessment of general environmental exposure. Arch Environ Health 43:178-179.

*Casey G. 1983. Sister-chromatid exchange and cell kinetics in CHO-Kl cells, human fibroblasts and lymphoblastoid cells exposed *in vitro* to asbestos and glass fibre. Mutat Res 116:369-377.

Castellan RM, Sanderson WT, Petersen MR. 1985. Prevalence of radiographic appearance of pneumoconiosis in an unexposed blue collar population. Am Rev Respir Dis 131:684-686.

*Cavalleri A, Gobba F, Bacchella L, et al. 1991. Evaluation of serum aminoterminal propeptide of type III procollagen as an early marker of the active fibrotic process in asbestos-exposed workers. Scand J Work Environ Health 17:139-144.

Cazzadori A, Malesani F, Romeo L. 1992. Malignant pleural mesothelioma caused by non-occupational childhood exposure to asbestos. Br J Ind Med 49:599

CCRIS. 1992. Chemical Carcinogenesis Research Information System. National Library of Medicine, Bethesda, MD. November 2, 1992.

CCTTE. 1988. Computerized Listing of Chemicals Being Tested for Toxic Effects. United Nations Environment Programme, International Programme on Chemical Safety, International Register of Potentially Toxic Chemicals. Geneva, Switzerland.

*CDC. 1999. Centers for Disease Control and Prevention. Http://search.cdc.gov/shd/search2.html. May 25, 1999.

CDC/ATSDR. 1990. Biomarkers of organ damage or dysfunction for the renal, hepatobiliary and immune systems. Atlanta, GA: CDC/ATSDR Subcommittee on Biomarkers of Organ Damage and Dysfunction, Centers for Disease Control, Agency for Toxic Substances and Disease Registry. Summary report, August 27, 1990.

*CELDS. 1994. Computer-Environmental Legislative Data Systems. University of Illinois, Urbana, IL. August 1994.

Chailleux E, Pioche D, Chopra S, et al. 1995. [The epidemiology of malignant pleural mesothelioma in the Nantes-Saint-Nazaire region. Evolution between 1956 and 1992]. Rev Mal Resp 12:353-357. (French)

Chamberlain M, Brown RC. 1978. The cytotoxic effects of asbestos and other mineral dust in tissue culture cell lines. Br J Exp Pathol 59:183-189.

*Chamberlain M, Tarmy EM. 1977. Asbestos and glass fibres in bacterial mutation tests. Mutat Res 43:159-164.

Chan CK, Gee JB. 1988. Asbestos exposure and laryngeal cancer: An analysis of the epidemiologic evidence. J Occup Med 30:23-27.

*Chang H-Y, Chen C-R, Wang J-D. 1999. Risk assessment of lung cancer and mesothelioma in people living near asbestos-related factories in Taiwan. Arch Environ Health 54(3):194-201.

*Chang L-Y, Overby LH, Brody AR, et al. 1988. Progressive lung cell reactions and extracellular matrix production after a brief exposure to asbestos. Am J Pathol 131:156-170.

*Chang MJ, Joseph LB, Stephens RE, et al. 1990. Modulation of biological processes by mineral fiber adsorption of macromolecules *in vitro*. JEPTO 10:89-93.

*Chao CC, Aust AE. 1994. Effect of long-term removal of iron from asbestos by desferrioxamine B on subsequent mobilization by other chelators and induction of DNA single-strand breaks. Arch Biochem Biophys 308(1):64-69.

*Chao C-C, Park S-H, Aust AE. 1996. Participation of nitric oxide and iron in the oxidation of DNA in asbestos-treated human lung epithelial cells. Arch Biochem Biophys 326:152-157.

Chen CR, Chang HY, Suo J, et al. 1992. Occupational exposure and respiratory morbidity among asbestos workers in Taiwan. J Formos Med Assoc 91(12):1138-1142.

*Cheng JQ, Jhanwar SC, Klein WM, et al. 1994. *p16* alterations and deletion mapping of 9p21-p22 in malignant mesothelioma. Cancer Res 54:5547-5551.

*Cheng JQ, Jhanwar SC, Lu YY, et al. 1993. Homozygous deletions within 9p21-p22 identify a small critical region of chromosomal loss in human malignant mesotheliomas. Cancer Res 53:4761-4763.

Cheng JQ, Lee W-C, Klein MA, et al. 1999a. Frequent mutations of NF2 and allelic loss from chromosome band 22q12 in malignant mesothelioma: Evidence for a two-hit mechanism of *NF2* inactivation. Genes Chromosomes Cancer 24:238-242.

*Cheng N, Shi X, Ye J, et al. 1999b. Role of transcription factor NF-κB in asbestos-induced TNFα response from macrophages. Exp Mol Pathol 66:201-210.

Cheng WN, Kong J. 1992. A retrospective mortality cohort study of chrysotile asbestos products workers in Tianjin 1972-1987. Environ Res 59(1):271-278.

*Cherubini M, Fornaciai G, Mantelli F, et al. 1998. Results of survey on asbestos fibre contamination of drinking water in Tuscany, Italy. J Wat SRT 47:1-8.

*Chesson J, Hatfield J, Schultz B, et al. 1990. Airborne asbestos in public buildings. Environ Res 51:100-107.

*Chissick SS. 1985. Asbestos. In: Gerhartz W, Yamamoto YS, Campbell FT, et al., ed. Ullmann's encyclopedia of industrial chemistry. Weinheim: VCH, 151-167.

Choe N, Tanaka S, Kagan E. 1998. Asbestos fibers and interleukin-1 upregulate the formation of reactive nitrogen species in rat pleural mesothelial cells. Am J Respir Cell Mol Biol 19:226-236.

Choe N, Tanaka S, Xia W, et al. 1997. Pleural macrophage recruitment and activation in asbestos-induced pleural injury. Environ Health Perspect Suppl 105:1257-1260.

Choe N, Zhang J, Iwagaki A, et al. 1999. Asbestos exposure upregulates the adhesion of pleural leukocytes to pleural mesothelial cells via VCAM-1. Am J Physiol 277(2):292-300.

*Choi I, Smith RW. 1972. Kinetic study of dissolution of asbestos fibers in water. J Colloid Interface Sci 40:253-262.

Choudhary G. 1996. Human health perspectives on environmental exposure to benzidine: A review. Chemosphere 32:267-291.

Chouroulinkov I. 1989. Experimental studies on ingested fibres. IARC Sci Publ 90:112-126.

*Churg A. 1982. Fiber counting and analysis in the diagnosis of asbestos-related disease. Hum Pathol 13(4):381-392.

*Churg A. 1986a. Nonneoplastic asbestos-induced disease. Mt Sinai J Med (NY) 53:409-415.

*Churg A. 1986b. Lung asbestos content in long-term residents of a chrysotile mining town. Am Rev Respir Dis 134:125-127.

*Churg A. 1988. Chrysotile, tremolite, and malignant mesothelioma in man. Chest 93:621-628.

*Churg A. 1989. The diagnosis of asbestosis. Hum Pathol 20(2):97-99.

*Churg A. 1993. Asbestos-related disease in the workplace and the environment: Controversial issues. Monogr Pathol 36:54-77.

*Churg A. 1994. Deposition and clearance of chrysotile asbestos. Ann Occup Hyg 38:625-633.

*Churg A. 1998. Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer [Letter]. N Engl J Med 339:999.

*Churg A, DePaoli L. 1988. Environmental pleural plaques in residents of a Quebec chrysotile mining town. Chest 94(1):58-60.

Churg A, Stevens B. 1993. Absence of amosite asbestos in airway mucosa of non-smoking long term workers with occupational exposure to asbestos. Br J Ind Med 50(4):355-359.

*Churg A, Stevens B. 1995. Enhanced retention of asbestos fibers in the airways of human smokers. Am J Resp Crit Care Med 151:1409-1413.

*Churg AM, Warnock ML. 1981. Asbestos and other ferruginous bodies: Their formation and clinical significance. Am J Pathol 102:447-456.

Churg A, Wiggs B. 1986. Fiber size and number in workers exposed to processed chrysotile asbestos, chrysotile miners, and the general population. Am J Ind Med 9:143-152.

*Churg A, Wright JL. 1989. Fibre content of lung in amphibole- and chrysotile-induced mesothelioma: Implications for environmental exposure. IARC Sci Pub 90:314-318.

*Churg A, Wright JL. 1994. Persistence of natural mineral fibers in human lungs: An overview. Environ Health Perspect 102(Suppl. 5):229-233.

*Churg A, Brauer M, Keeling B. 1996. Ozone enhances the uptake of mineral particles by tracheobronchial epithelial cells in organ culture. Am J Resp Crit Care Med 153:1230-1233.

*Churg A, Sun J-P, Zay K. 1998. Cigarette smoke increases amosite asbestos fiber binding to the surface of tracheal epithelial cells. Am J Physiol 275(19):L502-L508.

*Churg A, Wright JL, Depaoli L, et al. 1989a. Mineralogic correlates of fibrosis in chrysotile miners and millers. Am Rev Respir Dis 139:891-896.

*Churg A, Wright JL, Gilks B, et al. 1989b. Rapid short-term clearance of chrysotile compared with amosite asbestos in the guinea pig. Am Rev Respir Dis 139:885-890.

*Churg A, Wright JL, Hobson J, et al. 1992. Effects of cigarette smoke on the clearance of short asbestos fibres from the lung and a comparison with the clearance of long asbestos fibres. Int J Exp Path 73:287-297.

*Churg A, Wright JL, Vedal S. 1993. Fiber burden and patterns of asbestos-related disease in chrysotile miners and millers. Am Rev Respir Dis 148:25-31.

*Churg A, Wright JL, Wiggs B, et al. 1990. Mineralogic parameters related to amosite asbestos-induced fibrosis in humans. Am Rev Respir Dis 142:1331-1336.

*Chuwers P, Barnhart S, Blanc P, et al. 1997. The protective effect of beta-carotene and retinol on ventilatory function in an asbestos-exposed cohort. Am J Resp Crit Care Med 155:1066-1071.

Cicioni C, London SJ, Garabrant DH, et al. 1991. Occupational asbestos exposure and mesothelioma risk in Los Angeles county: Application of an occupational hazard survey job-exposure matrix. Am J Ind Med 20:371-379.

Clansky KB, ed. 1986. Chemical guide to the OSHA hazard communication standard. Burlingame, CA: Roytech Publications, Inc., 100, B-3, C-3, E-3.

CLC. 1988. Coordinated List of Chemicals. Washington, DC: U. S. Environmental Protection Agency, Office of Research and Development.

*Clewell HJ III, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1:111-113.

Clouter A, Houghton CE, Bowskill CA, et al. 1996. An in vitro/in vivo study into the short term effects of exposure to mineral fibres. Exp Toxicol Pathol 48:484-486.

Cocco P, Dosemeci M. 1999. Peritoneal cancer and occupational exposure to asbestos: Results from the application of a job-exposure matrix. Am J Ind Med 35:9-14.

Cocco P, Palli D, Buiatti E, et al. 1994. Occupational exposures as risk factors for gastric cancer in Italy. Cancer Causes Control 5:241-248.

*Cocco P, Ward MH, Buiatti E. 1996. Occupational risk factors for gastric cancer: An overview. Epidemiol Rev 18:218-234.

Cocco P, Ward MH, Dosemeci M. 1998. Occupational risk factors for cancer of the gastric cardia. J Occup Environ Med 40:855-861.

*Coin PG, Osornio-Vargas AR, Roggli VL, et al. 1996. Pulmonary fibrogenesis after three consecutive inhalation exposures to chrysotile asbestos. Am J Resp Crit Care Med 154:1511-1519.

*Coin PG, Roggli VL, Brody AR. 1992. Deposition, clearance and translocation of chrysotile asbestos from peripheral and central regions of the rat lung. Environ Res 58:97-116.

*Coin PC, Roggli VL, Brody AR. 1994. Persistence of long, thin chrysotile asbestos fibers in the lungs of rats. Environ Health Perspect Suppl 102:197-199.

*Cole RW, Ault JG, Hayden JH, et al. 1991. Crocidolite asbestos fibers undergo size-dependent microtubule-mediated transport after endocytosis in vertebrate lung epithelial cells. Cancer Res 51:4942-4947.

Collegium Ramazzini. 1999a. Call for an international ban on asbestos. Am J Ind Med 36:227-229.

Collegium Ramazzini. 1999b. Call for an international ban on asbestos. Int J Occup Med Environ Health 12(3):285-288.

Collegium Ramazzini. 1999c. Call for an international ban on asbestos. J Occup Environ Med 41(10):830-832.

Colt HG. 1997. Mesothelioma: Epidemiology, presentation, and diagnosis. Am J Resp Crit Care Med 18:353-361.

Comba P, Di Paola M, Martuzzi M, et al. 1997. Asbestos-related mortality in Italy: A geographical approach. Med Lav 88:293-301.

Conforti PM. 1983. Effect of population density on the results of the study of water supplies in five California counties. Environ Health Perspect 53:69-78.

*Conforti PM, Kanarek MS, Jackson LA, et al. 1981. Asbestos in drinking water and cancer in the San Francisco Bay Area: 1969-1974 incidence. J Chronic Dis 34:211-224.

Constantini AS, Chellini E. 1997. The experience of the mesothelioma registry of Tuscany in assessing health hazard associated with asbestos exposure. Med Lav 88:310-315.

*Constantinidis K. 1977. Pneumoconiosis and rheumatoid arthritis (Caplan's syndrome). Br J Clin Pract 31:25-31.

Constantopoulos SH, Dalavanga YA, Sakellariou K, et al. 1992. Lymphocytic alveolitis and pleural calcifications in nonoccupational asbestos exposure: Protection against neoplasia? Am Rev Respir Dis 146(6):1565-1570.

*Constantopoulos SH, Goudevenos JA, Saratzis N, et al. 1985. Metsovo lung: Pleural calcification and restrictive lung function in northwestern Greece. Environmental exposure to mineral fiber as etiology. Environ Res 38:319-331.

*Constantopoulos SH, Malamou-Mitsi VD, Goudevenos JA, et al. 1987a. High incidence of malignant pleural mesothelioma in neighbouring villages of northwestern Greece. Respiration 51:266-271.

*Constantopoulos SH, Saratzis NA, Kontogiannis D, et al. 1987b. Tremolite whitewashing and pleural calcifications. Chest 92(4):709-712.

Cook PM. 1983. Review of published studies on gut penetration by ingested asbestos fibers. Environ Health Perspect 53:121-130.

*Cook PM, Olson GF. 1979. Ingested mineral fibers: Elimination in human urine. Science 204:195-198.

*Cook PM, Palekar LD, Coffin DL. 1982. Interpretation of the carcinogenicity of amosite asbestos and ferroactinolite on the basis of retained fiber dose and characteristics *in vivo*. Toxicol Lett 13:151-158.

Cooper M, Johnson K, Delany DJ. 1996. Case report: Asbestos related pericardial disease. Clin Radiol 51:656-657.

*Çöplü L, Dumortier P, Demir AU, et al. 1996. An epidemiological study in an Anatolian village in Turkey environmentally exposed to tremolite asbestos. J Environ Pathol Toxicol Oncol 15:177-182.

*Cordier S, Lazar P, Brochard P, et al. 1987. Epidemiologic investigation of respiratory effects related to environmental exposure to asbestos inside insulated buildings. Arch Environ Health 42:303-309.

Corhay JL, Delavignette JP, Bury T, et al. 1990. Occult exposure to asbestos in steel workers revealed by bronchoalveolar lavage. Arch Environ Health 45:278-282.

*Corn M. 1994. Airborne concentrations of asbestos in non-occupational environments. Ann Occup Hyg 38:495-502.

*Corn M, McArthur B, Dellarco M. 1994. Asbestos exposures of building maintenance personnel. Appl Occup Environ Hyg 9(11):845-852.

*Corpet DE, Pirot V, Goubet I. 1993. Asbestos induces aberrant crypt foci in the colon of rats. Cancer Letters 74(3):183-187.

*Corsini E, Luster MI, Mahler J, et al. 1994. A protective role for T lymphocytes in asbestos-induced pulmonary inflammation and collagen deposition. Am J Respir Cell Mol Biol 11:531-539.

Cote RJ, Jhanwar SC, Novick S, et al. 1991. Genetic alterations of the p53 gene are a feature of malignant mesotheliomas. Cancer Res 51(19):5410-5416.

*CPSC. 2001a. CPSC release test results on crayons. Consumer Product Safety Commission. Http://cpsc.gov/cpscpub/prerel/prhtml100/00123.html. May 01, 2001.

*CPSC. 2001b. CPSC testing finds no asbestos fibers in children's chalk. Consumer Product Safety Commission. Http://cpsc.gov/cpscpub/prerel/prhtml100/00123.html. May 01, 2001.

Craighead JE. 1987. Current pathogenetic concepts of diffuse malignant mesothelioma. Hum Pathol 18:544-557.

Craighead JE, Mossman BT. 1982. The pathogenesis of asbestos-associated diseases. N Engl J Med 306:1446-1455.

*Craighead JE, Abraham JL, Churg A, et al. 1982. The pathology of asbestos-associated diseases of the lungs and pleural cavities: Diagnostic criteria and proposed grading schema. Arch Pathol Lab Med 106:544-597.

Craighead JE, Mossman BT, Bradley BJ. 1980. Comparative studies on the cytotoxicity of amphibole and serpentine asbestos. Environ Health Perspect 34:37-46.

9. REFERENCES

*Craun GF, Millette JR, Woodhull RS, et al. 1977. Exposure to asbestos fibers in water distribution systems. In: Proceedings of the 97th Annual Conference of the American Waterworks Association, Anaheim, California, May 8-13, 1-13.

CRISP Database. 1994. Computer Retrieval of Information on Scientific Projects. Washington, DC: National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services. December 1992.

Crosignani P, Forastiere F, Petrelli G, et al. 1995. Malignant mesothelioma in thermoelectric power plant workers in Italy. Am J Ind Med 27:573-576.

Crotty TB, Myers JL, Katzenstein A-L, et al. 1994. Localized malignant mesothelioma: A clinicopathologic and flow cytometric study. Am J Surg Pathol 18(4):357-363.

*Cullen MR, Baloyi RS. 1991. Chrysotile asbestos and health in Zimbabwe. I. Analysis of miners and millers compensated for asbestos-related diseases since independence (1980). Am J Ind Med 19(2):161-169.

Cullen RT, Miller BG, Davis JMG, et al. 1997. Short-term inhalation and in vitro tests as predictors of fiber pathogenicity. Environ Health Perspect Suppl 105:1235-1240.

Cullen RT, Searl A, Miller BG, et al. 2000. Pulmonary and intraperitoneal inflammation induced by cellulose fibres. J Appl Toxicol 20:49-60.

Cunningham HM, Pontefract R. 1971. Asbestos fibres in beverages and drinking water. Nature 232:332-333.

*Cunningham HM, Pontefract RD. 1973. Asbestos fibers in beverages, drinking water, and tissues: Their passage through the intestinal wall and movement through the body. J AOAC 56:976-981.

*Cunningham HM, Pontefract RD. 1974. Placental transfer of asbestos. Nature 249:177-178.

*Cunningham HM, Moodie CA, Lawrence GA, et al. 1977. Chronic effects of ingested asbestos in rats. Arch Environ Contam Toxicol 6:507-513.

*Cunningham HM, Pontefract RD, O'Brien RC. 1976. Quantitative relationship of fecal asbestos to asbestos exposure. J Toxicol Environ Health 1:377-379.

Curin K, Saric M. 1995. Cancer of the lung, pleura, larynx, and pharynx in an area with an asbestos-cement plant. Arh Hig Rada Toksikol 46:289-300.

Dai J, Gilks B, Price K, et al. 1998. Mineral dusts directly induce epithelial and interstitial fibrogenic mediators and matrix components in the airway wall. Am J Respir Crit Care Med 158:1907-1913.

Daniel FB. 1983. *In vitro* assessment of asbestos genotoxicity. Environ Health Perspect 53:163-167.

Dave SK, Bhagia LJ, Mazumdar PK, et al. 1996. The correlation of chest radiograph and pulmonary function tests in asbestos miners and millers. Indian J Chest Dis Allied Sci 38:81-89.

*Dave SK, Ghodasara NB, Mohanrao N, et al. 1997. The relation of exposure to asbestos and smoking habit with pulmonary function tests and chest radiograph. Indian J Public Health 41:16-24.

Dave SK, Ghodasara NB, Patel GC, et al. 1995. Correlation of asbestos exposure and cigarette smoking with pulmonary function tests and chest radiography. Indian J Ind Med 41:106-115.

*Davies D, Andrews MI, Jones JS. 1991. Asbestos induced pericardial effusion and constrictive pericarditis. Thorax 46(6):429-432.

*Davis JM. 1970. The long term fibrogenic effects of chrysotile and crocidolite asbestos dust injected into the pleural cavity of experimental animals. Br J Exp Pathol 5:617-627.

*Davis JM. 1972. The fibrogenic effects of mineral dusts injected into the pleural cavity of mice. Br. J Exp Pathol 53:190-201.

Davis JM. 1975. The use of animal experiments in the study of asbestos bioeffects. Hefte Unfallheilkd (Iss 126):564-574.

Davis JM. 1979. The use of animal models for studies on asbestos bioeffects. Ann NY Acad Sci 330:795-798.

Davis JM. 1981. The biological effect of mineral fibres. Ann Occup Hyg 24:227-234.

Davis JM. 1984. The pathology of asbestos related disease. Thorax 39:801-808.

*Davis JMG. 1989. Mineral fibre carcinogenesis: Experimental data relating to the importance of fibre type, size, deposition, dissolution and migration. IARC Sci Publ 90:33-45.

Davis JMG. 1994. Other diseases in animals. Ann Occup Hyg 38:581-587.

Davis JM, Coniam SW. 1973. Experimental studies on the effects of heated chrysotile asbestos and automobile brake lining dust injected into the body cavities of mice. Exp Mol Pathol 19:339-353.

*Davis JM, Cowie HA. 1990. The relationship between fibrosis and cancer in experimental animals exposed to asbestos and other fibers. Environ Health Perspect 88:305-309.

*Davis JM, Jones AD. 1988. Comparisons of the pathogenicity of long and short fibres of chrysotile asbestos in rats. Br J Exp Pathol 69:717-737.

*Davis JM, Addison J, Bolton RE, et al. 1985. Inhalation studies on the effects of tremolite and brucite dust in rats. Carcinogenesis 6:667-674.

*Davis JM, Addison J, Bolton RE, et al. 1986a. The pathogenicity of long versus short fibre samples of amosite asbestos administered to rats by inhalation and intraperitoneal injection. Br J Exp Pathol 67:415-430.

*Davis JM, Beckett ST, Bolton RE, et al. 1980a. The effects of intermittent high asbestos exposure (peak dose levels) on the lungs of rats. Br J Exp Pathol 61:272-280.

*Davis JM, Beckett ST, Bolton RE, et al. 1980b. A comparison of the pathological effects in rats of the UICC reference samples of amosite and chrysotile with those of amosite and chrysotile collected from the factory environment. IARC Sci Publ 30:285-292.

Davis JMG, Beckett ST, Boulton RE, et al. 1978. Mass and number of fibres in the pathogenesis of asbestos-related lung disease in rats. Br J Cancer 37:673-688.

Davis JM, Bolton RE, Brown D, et al. 1986b. Experimental lesions in rats corresponding to advanced human asbestosis. Exp Mol Pathol 44:207-221.

*Davis JM, Bolton RE, Douglas AN, et al. 1988. Effects of electrostatic charge on the pathogenicity of chrysotile asbestos. Br J Ind Med 45:292-299.

*Davis JM, Bolton BG, Niven K. 1991a. Mesothelioma dose response following intraperitoneal injection of mineral fibres. Int J Exp Path 72:263-274.

*Davis JM, Gylseth B, Morgan A. 1986c. Assessment of mineral fibres from human lung tissue. Thorax 41:167-175.

Davis JM, Jones AD, Miller BG. 1991b. Experimental studies in rats on the effects of asbestos inhalation coupled with the inhalation of titanium dioxide or quartz. Int J Exp Path 72:501-525.

Dawson A, Gibbs A, Browne K, et al. 1992. Familial mesothelioma details of 17 cases with histopathologic findings and mineral analysis. Cancer 70(5):1183-1187.

Dawson A, Gibbs AR, Pooley FD, et al. 1993. Malignant mesothelioma in women. Thorax 48(3):269-274.

*de Klerk NH, Armstrong BK, Musk AW, et al. 1989. Cancer mortality in relation to measures of occupational exposure to crocidolite at Wittenoom Gorge in Western Australia. Br J Ind Med 46:529-536.

*de Klerk NH, Musk AW, Ambrosini GL, et al. 1998. Vitamin A and cancer prevention II: Comparison of the effects of retinol and beta-carotene. Int J Cancer 75:362-367.

*de Klerk NH, Musk AW, Armstrong BK, et al. 1991. Smoking, exposure to crocidolite, and the incidence of lung cancer and asbestosis. Br J Ind Med 48:412-417.

de Klerk NH, Musk AW, Armstrong BK, et al. 1994. Diseases in miners and millers of crocidolite from Wittenoom, Western Australia: A further follow-up to December 1986. Ann Occup Hyg 38:647-655.

de Klerk NH, Musk AW, Cookson WO, et al. 1993. Radiographic abnormalities and mortality in subjects with exposure to crocidolite. Br J Ind Med 50(10):902-906.

*de Klerk NH, Musk AW, Williams V, et al. 1996. Comparison of measures of exposure to asbestos in former crocidolite workers from Wittenoon Gorge, W. Australia. Am J Ind Med 30:579-587.

*Delahunty TJ, Hollander D. 1987. Toxic effect on the rat small intestine of chronic administration of asbestos in drinking water. Toxicol Lett 39:205-209.

Delfino RJ, Anton-Culver H, Saltzstein SL. 1995. Gender-related differences in the distribution of throacic versus abdominal malignant mesothelioma. Cancer Detect Prev 19:301-307.

Dell L, Teta MJ. 1995. Mortality among workers at a plastics manufacturing and research and development facility: 1946-1988. Am J Ind Med 28:373-384.

Dement JM. 1991. Carcinogenicity of chrysotile asbestos: A case control study of textile workers. Cell Biol Toxicol 7:59-65.

*Dement JM, Brown DP. 1994. Lung cancer mortality among asbestos textile workers: A review and update. Ann Occup Hyg 38:525-532.

*Dement JM, Brown DP, Okun A. 1994. Follow-up study of chrysotile asbestos textile workers: Cohort mortality and case-control analyses. Am J Ind Med 26:431-447.

*Dement JM, Harris RL, Symons MJ, et al. 1983. Exposures and mortality among chrysotile asbestos workers. Part II: Mortality. Am J Ind Med 4:421-433.

*Dement JM, Hensley L, Kieding S, et al. 1998. Proportionate mortality among union members employed at three Texas refineries. Am J Ind Med 33:327-340.

*Demers PA, Stellman SD, Colin D, et al. 1998. Nonmalignant respiratory disease mortality among woodworkers participating in the American Cancer Society cancer prevention study-II (CPS-II). Am J Ind Med 34:238-243.

Demers RY, Burns PB, Swanson GM. 1994. Construction occupations, asbestos exposure, and cancer of the colon and rectum. J Occup Med 36:1027-1031.

*Demyanek ML, Lee RJ, Allison KA, et al. 1994. Air, surface, and passive measurements in a building during spray-buffing of vinyl-asbestos floor tile. Appl Occup Environ Hyg 9:869-875.

*deShazo RD, Morgan J, Bozelka B, et al. 1988. Natural killer cell activity in asbestos workers: Interactive effects of smoking and asbestos exposure. Chest 94:482-485.

De Stafani E, Kogevinas M, Boffetta P, et al. 1996. Occupation and the risk of lung cancer in Uruguay. Scand J Work Environ Health 22:346-352.

*De Vuyst P, Dumortier P, Gevenois PA. 1997. Analysis of asbestos bodies in BAL from subjects with particular exposure. Am J Ind Med 31:699-704.

De Vuyst P, Dumortier P, Jacobovitz D, et al. 1994. Environmental asbestosis complicated by lung cancer. Chest 105:1593-1595.

*De Vuyst P, Dumortier P, Moulin E, et al. 1988. Asbestos bodies in bronchoalveolar lavage reflect lung asbestos body concentration. Eur Resp J 1:362-367.

*De Vuyst P, Jedwab J, Dumortier P, et al. 1982. Asbestos bodies in bronchoalveolar lavage. Am Rev Resp Dis 126:972-976.

*De Vuyst P, Karjalainen A, Dumortier P, et al. 1998. Guidelines for mineral fibre analyses in biological samples: Report of the ERS Working Group. Eur Resp J 11:1416-1426.

*DHHS. 1985. The health consequences of smoking: Cancer and chronic lung disease in the workplace. U.S. Department of Health and Human Services. Office on Smoking and Health, Rockville, MD, 13-14.

DHHS. 1986. Report on cancer risks associated with the ingestion of asbestos. U.S. Department of Health and Human Services. NTIS No. PB90-B0527.

Di Bonito L, Giarelli L, Stanta G, et al. 1997. [Lung cancer in the Trieste area]. G Ital Med Lav 19:42-43. (Italian).

*Di Lorenzo L, Mele M, Pegorari MM, et al. 1996. Lung cinescintigraphy in the dynamic assessment of ventilation and mucociliary clearance of asbestos cement workers. Occup Environ Med 53:628-635.

*Dion C, Perrault G. 1994. Comparison of four methods for the determination of asbestos fiber concentrations in workplace atmospheres by phase contrast microscopy. Appl Occup Environ Hyg 9(10):707-711.

*DiPaolo JA, DeMarinis AJ, Doniger J. 1983. Asbestos and benzo(a)pyrene synergism in the transformation of Syrian hamster embryo cells. Pharmacology 27:65-73.

Dixon D, Bowser AD, Badgett A, et al. 1995. Incorporation of bromodeoxyuridine (BrdU) in the bronchiolar-alveolar regions of the lungs following two inhalation exposures to chyrsotile asbestos in strain A/J mice. J Environ Pathol Toxicol Oncol 14:205-213.

Dodoli D, Del Nevo M, Fiumalbi C, et al. 1992. Environmental household exposures to asbestos and occurrence of pleural mesothelioma. Am J Ind Med 21:681-687.

Dodson RF, Ford JO. 1991. Tissue reaction following a second exposure to amosite asbestos. Cytobios 68:53-62.

Dodson RF, Hurst GA, Williams MG, et al. 1988. Comparison of light and electron microscopy for defining occupational asbestos exposure in transbronchial lung biopsies. Chest 94:366-370.

Dodson RF, O'Sullivan M, Corn C. 1993. Technique dependent variations in asbestos burden as illustrated in a case of nonoccupational exposed mesothelioma. Am J Ind Med 24(2):235-40.

Dodson RF, O'Sullivan M, Corn CJ, et al. 1995. Quantitative comparison of asbestos and talc bodies in an individual with mixed exposure. Am J Ind Med 27:207-215.

Dodson RF, O'Sullivan M, Corn CJ. 1996. Relationships between ferruginous bodies and uncoated asbestos fibers in lung tissue. Arch Environ Health 51:462-466.

Dodson RF, O'Sullivan M, Corn CJ, et al. 1997. Analysis of asbestos fiber burden in lung tissue from mesothelioma patients. Ultrastruct Pathol 21:321-336.

*Dodson RF, Williams MG, Huang J, et al. 1999. Tissue burden of asbestos in nonoccupationally exposed individuals from east Texas. Am J Ind Med 35:281-286.

*DOL. 1980. Asbestiform and/or fibrous minerals in mines, mills, and quarries. Mine Safety and Health Administration, U.S. Department of Labor.

*Doll R. 1955. Mortality from lung cancer in asbestos workers. Br J Ind Med 12:81-86.

Doll R. 1987. The quantitative significance of asbestos fibres in the ambient air. Experientia (Supp) 51:213-219.

*Doll R. 1989. Mineral fibres in the nonoccupational environment: Concluding remarks. IARC Sci Pub 90:511-518.

*Doll R, Peto J. 1985. Asbestos: Effects on health of exposure to asbestos. A report to the Health and Safety Commission. London, England, Her Majesty's Stationery Office.

*Doll R, Peto J. 1987. Other asbestos-related neoplasms. In: Antman K, Aisner J, ed. Asbestos-related malignancy. New York: Grune & Stratton, Inc., 81-96.

*Donaldson K, Golyasnya N. 1995. Cytogenetic and pathogenic effects of long and short amosite asbestos. J Pathol 177:303-307.

*Donaldson K, Bolton RE, Jones A, et al. 1988a. Kinetics of the bronchoalveolar leucocyte response in rates during exposure to equal airborne mass concentrations of quartz, chrysolite asbestos, or titanium dioxide. Thorax 43:525-533.

Donaldson K, Brown GM, Brown DM, et al. 1989. Inflammation generating potential of long and short fibre amosite asbestos samples. Br J Ind Med 46:271-276.

Donaldson K, Brown RC, Brown GM. 1993. Respirable industrial fibers: Mechanisms of pathogenicity. Thorax 48(4):390-395.

Donaldson K, Slight J, Bolton RE. 1988b. Oxidant production by control and inflammatory bronchoalveolar leukocyte populations treated with mineral dusts in vitro. Inflammation 12:231-243.

*Dong H, Saint-Etienne L, Renier A, et al. 1994. Air samples from a building with asbestos-containing material: Asbestos content and *in vitro* toxicity on rat pleural mesothelial cells. Fundam Appl Toxicol 22:178-185.

*Donham KJ, Berg JW, Will LA, et al. 1980. The effects of long-term ingestion of asbestos on the colon of F344 rats. Cancer (March Suppl) 45:1073-1084.

*Donmez H, Ozkul Y, Ucak R. 1996. Sister chromatid exchange frequency in inhabitants exposed to asbestos in Turkey. Mutat Res 361:129-132.

*Dopp E, Schiffmann D. 1998. Analysis of chromosomal alteration induced by asbestos and ceramic fibers. Toxicol Lett 96:155-162.

*Dopp E, Jonas L, Nebe B, et al. 2000. Dielectric changes in membrane properties and cell interiors of human mesothelial cells *in vitro* after crocidolite asbestos exposure. Environ Health Perspect 108(2):153-158.

*Dopp E, Nebe B, Hahnel C, et al. 1995a. Mineral fibers induce apoptosis in Syrian hamster embryo fibroblasts. Pathobiology 63:213-221.

*Dopp E, Saedler J, Stopper H, et al. 1995b. Mitotic disturbances and micronucleus induction in Syrian hamster embryo fibroblast cells caused by asbestos fibers. Environ Health Perspect 103:268-271.

*Dopp E, Schuler M, Schiffmann D, et al. 1997. Induction of micronucleai, hyperdiploidy and chromosomal breakage affecting the centri/pericentric regions of chromosomes 1 and 9 in human amniotic fluid cells after treatment with asbestos and ceramic fibers. Mutat Res 377:77-87.

Dossing M, Groth S, Vestbo J, et al. 1990. Small-airways dysfunction in never smoking asbestos exposed Danish plumbers. Int Arch Occup Environ Health 62:209-212.

*Driscoll KE, Carter JM, Hassenbein DG, et al. 1997. Cytokines and particle-induced inflammatory cell recruitment. Environ Health Perspect Suppl 105:1159-1164.

*Driscoll KE, Carter JM, Howard BW, et al. 1998. Crocidolite activates NF-kB and MIP-2 gene expression in rat alveolar epithelial cells. Role of mitochrondrial-derived oxidants. Environ Health Perspect 106(Suppl. 5):1171-1174.

Drumm K, Buhl R, Kienast K. 1999. Additional NO2 exposure induces a decrease in cytokine specific mRNA expression and cytokine release of particle and fibre exposed human alveolar macrophages. Eur J Med Res 4:59-66.

Dubes GR, Mack LR. 1988. Asbestos-mediated transfection of mammalian cell cultures. *In Vitro* Cellular Devel Biol 24:175-181.

*Dubois CM, Bissonnette E, Rola-Pleszczynski M. 1989. Asbestos fibers and silica particles stimulate rat alveolar macrophages to release tumor necrosis factor. Am Rev Respir Dis 139:1257-1264.

*Dufresne A, Begin R, Churg A, et al. 1996a. Mineral fiber content of lungs in patients with mesothelioma seeking compensation in Quebec. Am J Respir Crit Care Med 153:711-718.

*Dufresne A, Begin R, Masse S, et al. 1996b. Retention of asbestos fibres in lungs of workers with asbestosis, asbestosis and lung cancer, and mesothelioma in Asbestos township. Occup Environ Med 53:801-807.

*Dufresne A, Harrigan M, Masse S, et al. 1995. Fibers in lung tissues of mesothelioma cases among miners and millers of the township of Asbestos, Quebec. Am J Ind Med 27:581-592.

Dujic Z, Eterovic D, Tocilj J. 1993. Association between asbestos-related pleural plaques and resting hyperventilation. Scand J Work Environ Health 19(5):346-351.

*Dujic Z, Tocilj J, Boshi S, et al. 1992. Biphasic lung diffusing capacity: Detection of early asbestos induced changes in lung function. Br J Ind Med 49:260-267.

Dujic Z, Tocilj J, Saric M. 1991. Early detection of interstitial lung disease in asbestos exposed non-smoking workers by mid-expiratory flow rate and high resolution computed tomography. Br J Ind Med 48(10):663-664.

Dumortier P, Rey F. 1998. RE main asbestos type in pleural mesothelioma [Letter]. Am J Ind Med 33:94-95.

*Dumortier P, Cöplü L, de Maertelaer V, et al. 1998. Assessment of environmental asbestos exposure in Turkey by bronchoalveolar lavage. Am J Respir Crit Care Med 158:1815-1824.

*Dumotier P, De Vuyst P, Strauss P, et al. 1990. Asbestos bodies in bronchoalveolar lavage fluids of brake lining and asbestos cement workers. Br J Ind Med 47:91-98.

*Dupre JS, Mustard JF, Uffen RJ, et al. 1984. Report of the Royal Commission on matters of health and safety arising from the use of asbestos in Ontario. Ontario, Canada: Ontario Ministry of the Attorney General, Publ., 73-112.

Eastes W, Hadley JG. 1995. Dissolution of fibers inhaled by rats. Inhal Toxicol 7:179-196.

*Eastes W, Hadley JG. 1996. A mathematical model of fiber carcinogenicity and fibrosis in inhalation and intraperitoneal experiments in rats. Inhal Toxicol 8:323-343.

*Edelman DA. 1988a. Exposure to asbestos and the risk of gastrointestinal cancer: A reassessment. Br J Ind Med 45:75-82.

Edelman DA. 1988b. Exposure to asbestos and the risk of gastrointestinal cancer [Letter]. Br J Ind Med 45:574-576.

*Edelman DA. 1988c. Asbestos exposure, pleural plaques and the risk lung cancer. Int Arch Occup Environ Health 60:389-393.

*Edelman DA. 1989. Laryngeal cancer and occupational exposure to asbestos. Int Arch Occup Environ Health 61:223-227.

Edelman DA. 1992. Does asbestos exposure increase the risk of urogenital cancer? Int Arch Occup Environ Health 63:469-475.

*Edward AT, Whitaker D, Browne K, et al. 1996. Mesothelioma in a community in the north of England. Occup Environ Med 53:547-552.

Egilman D, Reinert A. 1996. Lung cancer and asbestos exposure: Asbestosis is not necessary. Am J Ind Med 30:398-406.

Egilman DS, Reinert A. 2000. Corruption of previously published asbestos research. Arch Environ Health 55(1):75-76.

Egilman DA, Goldin AS, Golding GA. 1996. Mesothelioma: An unwarranted causal model. J Occup Environ Med 38:239-240.

Ehrenreich T, Selikoff IJ. 1981. Asbestos fibers in human lung: Forensic significance. Am J Forensic Med Pathol 2:67-74.

Ehrlich A, Gordon RE, Dikman SH. 1991. Carcinoma of the colon in asbestos-exposed workers: Analysis of asbestos content in colon tissue. Am J Ind Med 19:629-636.

*Ehrlich R, Lilis R, Chan E, et al. 1992. Long term radiological effects of short term exposure to amosite asbestos among factory workers. Br J Ind Med 49:268-275.

Elferink JGR. 1989. Chrysotile asbestos-induced cytotoxicity and calcium-dependent exocytosis in polymorphonuclear leukocytes. Res Commun Chem Pathol Pharmacol 65:361-372.

Elferink JGR, Kelters I. 1991. Chrysotile asbestos-induced membrane damage in human erythrocytes. Res Commun Chem Pathol Pharmacol 73:355-365.

*Ellenhorn MJ, Schonwald S, Ordog G et al., eds. 1997. Ellenhorn's medical toxicology: Diagnosis and treatment of human poisoning. 2nd ed. Baltimore, MD: Williams & Wilkins.

Elmes P. 1994. Mesotheliomas and chrysotile. Ann Occup Hyg 38:547-553.

Elmes P, Browne K. 1986. Mesothelioma shortly after brief exposure to asbestos [Letter]. Lancet 1:746.

Elstner EF, Schueltz W, Vogl G. 1988. Cooperative stimulation by sulfite and crocidolite asbestos fibres of enzyme catalyzed production of reactive oxygen species. Arch Toxicol 62:424-427.

*Emerit I, Jaurand MC, Saint-Etienne L, et al. 1991. Formation of a clastogenic factor by asbestos-treated rat pleural mesothelial cells. Agents Actions 34(3-4):410-415.

*EMMIWIN. 1997. Environmental monitoring methods index, Ver 1.1 Environ Dynamics, Inc. McLean, VA.

*Enarson DA, Embree V, MacLean L, et al. 1988. Respiratory health in chrysotile asbestos miners in British Columbia: A longitudinal study. Br J Ind Med 45:459-463.

Englund A. 1995. Recent data on cancer due to asbestos in Sweden. Med Lav 86:435-439.

*Enterline PE, Henderson VL. 1987. Geographic patterns for pleural mesothelioma deaths in the United States, 1968-81. J Natl Cancer Inst 79:31-37.

Enterline PE, Kendrick MA. 1967. Asbestos-dust exposures at various levels and mortality. Arch Environ Health 15:181-186.

*Enterline PE, Hartley J, Henderson V. 1987. Asbestos and cancer: A cohort followed up to death. Br J Ind Med 44:396-401.

*Environmental Defense. 2001. Asbestos. CalEPA Air Resources Board Toxic Air Contaminant Summary, Environmental Defense. Http://www.scorecard.org/chemical-profiles/html/asbesots.html. January 19, 2001.

*EPA. 1976. Asbestos fibers in natural runoff and discharges from sources manufacturing asbestos products. Pt II Non-point sources and point sources manufacturing asbestos products. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA-560/6-76-020. NTIS No. PB-263746.

*EPA. 1977. Movement of selected metals, asbestos, and cyanide in soil: Applications to waste disposal problems. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/2-77-020. NTIS No. PB-266905.

EPA. 1978a. Development of a rapid analytical method for determining asbestos in water. Report to U.S. Environmental Protection Agency, Office of Research and Development, Health Effects Research Laboratory, Athens, GA, by Battelle Columbus Laboratories. EPA-600/4-78-066.

EPA. 1978b. Fate of ingested chrysotile asbestos fiber in the newborn baboon. Report to U.S. Environmental Protection Agency, Office of Research and Development, Health Effects Research Laboratory, Cincinnati, OH, by University of Illinois, School of Public Health. EPA-600/1-78-069. NTIS PB 291686.

EPA. 1979a. Effects of selected asbestos fibers on cellular and molecular parameters. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/1-79-021. NTIS No. PB-299199.

*EPA. 1979b. Exposure to asbestos from drinking water in the United States. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/1-79-028. NTIS No. PB-300444.

*EPA. 1979c. 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 Standards. EPA-440/4-79-029a. NTIS No. PB80-204373.

*EPA. 1980a. Ambient water quality criteria for asbestos. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. EPA 440/5-80-022. PB81-117335.

EPA. 1980b. Interim method for determining asbestos in water. Atlanta, GA: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/4-80-005.

EPA. 1980c. Chemical contaminants in nonoccupationally exposed U.S. residents. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/1-80-001. NTIS No. PB80-192339.

EPA. 1982. Intermedia priority pollutant guidance documents. Washington, DC: U.S. Environmental Protection Agency, Office of Toxics Integration, Office of Pesticides and Toxic Substances.

EPA. 1983. Treatability manual. Vol I. Treatability data. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/2-82-001a.

EPA. 1984a. Health effects for asbestos. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. EPA 540/1-86/049.

EPA. 1984b. Final report: Asbestos in buildings: National survey of asbestos-containing friable materials. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances.

EPA. 1984c. Evaluation of turbidometric methods for monitoring of asbestos fibers in water. Athens, GA: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/4-84-071. NTIS PB84-232511.

*EPA. 1985a. Drinking water criteria document for asbestos. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment office. EPA 600/X-84-199-1.

*EPA. 1985b. U.S. Environmental Protection Agency. Federal Register 50:13456-13522.

EPA. 1985c. U.S. Environmental Protection Agency. Federal Register 50:46936-47022.

EPA. 1985d. Environmental release of asbestos from commercial product shaping. Cincinnati, OH: U.S. Environmental Protection Agency, Water Engineering Research Laboratory. EPA/600/S2-85/044.

*EPA. 1986a. Airborne asbestos health assessment update. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environment Assessment. EPA/600/8-84/003F.

EPA. 1986b. U.S. Environmental Protection Agency. Federal Register 51:3738-3759.

EPA. 1986c. Reference values for risk assessment. Final draft. Cincinnati OH: U.S. Environmental Protection Agency, Office of Solid Waste. ECAO-CIN-477.

EPA. 1986d. U.S. Environmental Protection Agency. Federal Register 51:15722-15733.

EPA. 1987a. U.S. Environmental Protection Agency. Federal Register 52:8140-8171.

EPA. 1987b. U.S. Environmental Protection Agency. Federal Register 52:41826-41835.

EPA. 1987c. Toxic air pollutant/source crosswalk: A screening tool for locating possible sources emitting toxic air pollutants. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. EPA-450/4-87-023a.

*EPA. 1987d. Asbestos-containing materials in schools. U.S. Environmental Protection Agency. Federal Register 40CFR 763.

EPA. 1987e. Reference dose (RfD): Description and use in health risk assessments. Vol. I. Appendix A: Integrated risk information system supportive documentation. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA/600/8-86/032a.

EPA. 1988a. U.S. Environmental Protection Agency. Federal Register 53:38642-38654.

EPA. 1988b. U.S. Environmental Protection Agency. Federal Register 53:4500-4539.

*EPA. 1988c. EPA study of asbestos-containing materials in public buildings: A report to Congress. Washington, DC: U.S. Environmental Protection Agency.

EPA. 1988d. Assessing asbestos exposure in public buildings. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA 560/5-88-002.

EPA. 1988e. U.S. Environmental Protection Agency. Federal Register 53:40615.

EPA. 1988f. Comparative mesothelioma induction in rats by asbestos and nonasbestos mineral fibers: possible correlation with human exposure data. Research Triangle Park, NC: U.S. Environmental Protection Agency, Health Effects Research Laboratory. NTIS No. PB88-250246.

EPA. 1988g. Additional analysis of EPA's 1984 asbestos survey data. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA 560/5-88-010.

EPA. 1988h. General pretreatment regulations for existing and new sources of pollution. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 403 (plus Appendix B).

*EPA. 1988i. Asbestos exposure assessment. Revised report. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances.

*EPA. 1988j. Chromosomal changes associated with tumorigenic mineral fibers. Research Triangle Park, NC: U.S. Environmental Protection Agency, Health Effects Research Laboratory, Office of Research and Development. EPA/600/D-88/222. NTIS No. PB89-124739.

EPA. 1989a. Exposure factors handbook. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA/600/8-89/043.

EPA. 1989b. Interim methods for development of inhalation references doses. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA 600/8-88/066F.

*EPA. 1989c. U.S. Environmental Protection Agency. Federal Register 54:36315-36316, 38436.

EPA. 1989d. U.S. Environmental Protection Agency. Federal Register 54:912-937.

*EPA. 1989e. U.S. Environmental Protection Agency. Federal Register 54:22062-22160.

*EPA. 1989f. U.S. Environmental Protection Agency. Federal Register 54:29460-29513.

EPA. 1989g. U.S. Environmental Protection Agency. Federal Register 54:32430, 33449-33450.

EPA. 1989h. Guidelines for conducting the AHERA TEM clearance test to determine completion of an asbestos abatement project. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances, NTIS No. PB90-171778.

EPA. 1989i. U.S. Environmental Protection Agency. Federal Register 54:15622-15627.

*EPA. 1990a. U.S. Environmental Protection Agency. Federal Register 55:48406-48433.

EPA. 1990b. U.S. Environmental Protection Agency. Federal Register 55:5144-5162, 20522-20523.

*EPA. 1990c. Environmental asbestos assessment manual: Superfund method for the determination of asbestos in ambient air: Part 2: Technical background document. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. EPA-540/2-90/005b.

*EPA. 1990d. Environmental asbestos assessment manual: Method for the Determination of Asbestos in Ambient Air, Part 1: Method. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. EPA/540/2-90/005a. NTIS No. PB90-274283.

EPA. 1991a. U.S. Environmental Protection Agency. Federal Register 56:3526-3528, 3536, 3548, 3565, 11421-11422.

*EPA. 1991b. Indoor-air assessment: Indoor concentrations of environmental carcinogens. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA/600/8-90/042. NTIS No. PB91-193847.

*EPA. 1992a. U.S. Environmental Protection Agency. Federal Register 57:11364-11365.

*EPA. 1992b. U.S. Environmental Protection Agency. Federal Register 57:31576-31592.

*EPA. 1992c. Asbestos concentrations two years after abatement in seventeen schools. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA 600/R-92/027.

EPA. 1992d. U.S. Environmental Protection Agency. Federal Register 57:11412-11413.

EPA. 1993a. Test method for the determination of asbestos in bulk building materials. Washington, DC: U.S. Environmental Protection Agency. EPA 600/R-93/116.

EPA. 1993b. Quantitative evaluation of HEPA filtration systems at asbestos abatement sites. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development, Risk Reduction Engineering Laboratory. EPA/600/J-93/498. NTIS PB94-136116.

EPA. 1994. Drinking water regulations and health advisories. Washington, DC: U.S. Environmental Protection Agency. May 1994.

EPA. 1995. Final decision not to issue new regulations for asbestos processing facilities under the air toxics provision of the Clean Air Act Amendments of 1990. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. Http://www.epa.gov/ttnuatw1/fsasbes.html. May 11, 1999.

EPA. 1996. Drinking water regulations and health advisories. Washington DC: U.S. Environmental Protection Agency, Office of Water. EPA 822-B-96-002.

*EPA. 1997. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency. EPA/630/R-96/012.

*EPA. 1998a. Technical drinking water and health contaminant specific fact sheets. Washington, DC: U.S. Environmental Protection Agency, Office of Water. Http://www.epa.gov/ogwdw000/dwh/t-ioc/asbestos.htm. April 29, 1999.

*EPA. 1998b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4.

*EPA. 1998c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 763 Subpart G.

EPA. 1998d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65.

EPA. 1998e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.30.

*EPA. 1999a. National recommended water quality criteria - Correction. Washington, DC: U. S. Environmental Protection Agency, Office of Water. EPA 822-Z-99-001.

*EPA. 1999b. Toxic chemical release inventory reporting forms and instructions. U. S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. EPA 745-K-99-001.

EPA. 1999c. Designation of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations, National Archives and Records Administration. 40 CFR 302.4. Http:www.access.gpo.gov.nara/cfr/cfr-table-search.html. January 15, 2001.

*EPA. 2000a. Asbestos-containing materials in schools. U.S. Environmental Protection Agency. Code of Federal Regulations, National Archives and Records Administration. 40 CFR 763. Http://www.access.gpo.gov/nara/cfr/cfr-table-search.html. January 23, 2001.

*EPA. 2000b. Drinking water standards and health advisories. Washington, DC: U. S. Environmental Protection Agency, Office of Water. Http://www.epa.gov/ow/search.html. January 18, 2001.

*EPA. 2000c. National emission standards for hazardous air pollutants. U.S. Environmental Protection Agency. Code of Federal Regulations, National Archives and Records Administration. 40 CFR 61.01. Http://www.access.gpo.gov/nara/cfr/cfr-table-search.html. January 23,2001.

*EPA. 2000d. Sampling and analysis of consumer garden products that contain vermiculite. Washington, DC: U.S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances. EPA 744-R-00-010.

*EPA. 2001a. Asbestos: Hazard summary. Washington, DC: U. S. Environmental Protection Agency, Office of Air and Radiation. Http://www.epa.gov/ttnuatw1/hlthef/asbestos.html. January 18,2001.

*EPA. 2001b. Technical drinking water and health: Contaminant specific fact sheets for consumers. Washington, DC: U. S. Environmental Protection Agency, Office of Water. Http://www.epa.gov/safewater/dwh/c-ioc/asbestos.html. January 18, 2001.

*EPA. 2001c. Toxic chemical release reporting: Community right-to-know. Chemicals and chemical categories to which this part applies. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65. Http://www.access.gpo.gov/nara/cfr/cfrhtml_00/Title_40/40cfr20_00.html. May 01, 2001.

Epstein PE. 1992. Asbestos inhalation and nonmalignant abnormalities of the chest. Semin Roentgenol 27:85-93.

Erdogdu G, Hasirci V. 1998. An overview of the role of mineral solubility in silicosis and asbestosis. Environ Res 78:38-42.

Erdreich LS. 1983. Comparing epidemiologic studies of ingested asbestos for use in risk assessment. Environ Health Perspect 53:99-104.

*Ernst P, Dales RE, Nunes F, et al. 1989. Relation of airway responsiveness to duration of work in a dusty environment. Thorax 44:116-120.

Erren TC, Jacobsen M, Piekarski C. 1999. Synergy between asbestos and smoking on lung cancer risks. Epidemiology 10(4):405-411.

*Erzen C, Eryilmaz M, Kalyoncu F, et al. 1991. CT findings in malignant pleural mesothelioma related to nonoccupational exposure to asbestos and fibrous zeolite (erionite). J Comput Assist Tomogr 15:256-260.

*Esmen NA, Corn M. 1998. Airborne fiber concentrations during splitting open and boxing bags of asbestos. Toxicol Ind Health 14(6):843-856.

*Evans JC, Evans RJ, Holmes A, et al. 1973. Studies on the deposition of inhaled fibrous material in the respiratory tract of the rat and its subsequent clearance using radioactive tracer techniques. 1. UICC crocidolite asbestos. Environ Res 6:180-201.

EXICHEM Data Base. 1989. Organization for Economic Cooperation and Development.

*Fasske E. 1988. Experimental lung tumors following specific intrabronchial application of chrysotile asbestos. Longitudinal light and electron microscopic investigations in rats. Respir 53:111-127.

Fasy TM. 1991. Asbestos fibers are mutagenic after all: New signs of orthodoxy for a paradoxical group of carcinogens. Ann NY Acad Sci 271-279.

*Fatma N, Jain AK, Rahman Q. 1991. Frequency of sister chromatid exchange and chromosomal aberrations in asbestos cement workers. Br J Ind Med 48:103-105.

*Fatma N, Khan SG, Aslam M, et al. 1992. Induction of chromosomal aberrations in bone marrow cells of asbestotic rats. Environ Res 57:175-180.

*Faux SP, Howden PJ. 1997. Possible role of lipid peroxidation in the induction of NF-KB and AP-1 in RFL-6 cells by crocidolite asbestos: Evidence following protection by vitamin E. Environ Health Perspect Suppl 105:1127-1130.

*Faux SP, Howden PJ, Levy LS. 1994. Iron-dependent formation of 8-hydroxydeoxyguanosine in isolated DNA and mutagenicity in salmonella typhimurium TA102 induced by crocidolite. Carcinogenesis 15:1749-1751.

FDA. 1994. Indirect food additives: Adhesives and components of coatings. U.S. Department of Health and Human Services, U.S. Food and Drug Administration. Code of Federal Regulations 21 CFR 175.

FDA. 1998. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 175.105.

*FDA. 2000a. Food and drugs: Indirect food additives: Adhesives and components of coatings. U.S. Food and Drug Administration. Code of Federal Regulations, National Archives and Records Administration. 21 CFR 175.105. Http://frwebgate.access.gpo.gov/cgi...175&SECTION=105&YEAR=2000&TYPE=TEXT. January 18, 2001.

*FDA. 2000b. Food and drugs: Indirect food additives: Polymers. U.S. Food and Drug Administration. Code of Federal Regulations, National Archives and Records Administration. 21 CFR 177.2410. Http://frwebgate.access.gpo.gov/cgi...77&SECTION=2410&YEAR=2000&TYPE=TEXT. January 23, 2001.

*FDA. 2000c. Food and drugs: Indirect food additives: Polymers. U.S. Food and Drug Administration. Code of Federal Regulations, National Archives and Records Administration. 21 CFR 177.2420. Http://frwebgate.access.gpo.gov/cgi...77&SECTION=2420&YEAR=2000&TYPE=TEXT. January 23, 2001.

Fear NT, Roman E, Carpenter LM, et al. 1996. Cancer in electrical workers: An analysis of cancer registrations in England, 1981-87. Br J Cancer 73:935-939.

FEDRIP. 1994. Federal Research in Progress [database]. Dialog Information Retrieval System, CA.

FEDRIP. 1999. Federal Research in Progress [database]. Dialog Information Retrieval System, CA.

*FEDRIP. 2000. Federal Research in Progress [database]. Dialog Information Retrieval System, CA.

*FEDRIP. 2001. Federal Research in Progress [database]. Dialog Information Retrieval System, CA.

Feige MA, Clark PJ, Brackett KA. 1993. Guidance and clarification for the current U.S. EPA test method for asbestos in drinking water. Environmental Choices Technical Supplement Fall 1993. Cincinnati, OH: IT Corp. NTIS publication no. PB94-126108.

Felton JS, Sargent EN, Gordonson JS. 1980. Radiographic changes following asbestos exposure: Experience with 7,500 workers. J Occup Med 22(1):15-20.

*Finkelstein M. 1986. Pulmonary function in asbestos cement workers: A dose-response study. Br J Ind Med 43:406-413.

*Finkelstein MM. 1983. Mortality among long-term employees of an Ontario asbestos-cement factory. Br J Ind Med 40:138-144.

Finkelstein MM. 1989. Mortality among employees of an Ontario factory that manufactured construction materials using chrysotile asbestos and coal tar pitch. Am J Ind Med 16:281-287.

Finkelstein MM. 1991. Analysis of the exposure-response relationship for mesothelioma among asbestos-cement factory workers. Ann NY Acad Sci 85-89.

*Finkelstein MM. 1995. Potential pitfall in using cumulative exposure in exposure-response relationships: Demonstration and discussion. Am J Ind Med 28:41-47.

Finkelstein MM. 1996. Asbestos-associated cancer in the Ontario refinery and petrochemical sector. Am J Ind Med 30:610-615.

*Finkelstein MM, Dufresne A. 1999. Inferences on the kinetics of asbestos deposition and clearance among chrysotile miners and millers. Am J Ind Med 35:401-412.

Finkelstein MM, Vingilis JJ. 1984. Radiographic abnormalities among asbestos-cement workers: An exposure-response study. Am Rev Respir Dis 129:17-22.

*Finn MB, Hallenbeck WH. 1984. Detection of chrysotile asbestos in workers' urine. Am Ind Hyg Assoc J 45:752-759.

Fischbein A, Luo J-C, Lacher M, et al. 1993. Respiratory findings among millwright and machinery erectors: Identification of health hazards from asbestos in place at work. Environ Res 61(1):25-35.

Fischbein A, Luo J-C, Pinkston GR. 1991a. Asbestosis, laryngeal carcinoma, and malignant peritoneal mesothelioma in an insulation worker. Br J Ind Med 48(5):338-341.

Fischbein A, Luo J-C, Rosenfeld S, et al. 1991b. Respiratory findings among ironworkers: Results from a clinical survey in the New York metropolitan area and identification of health hazards from asbestos in place at work. Br J Ind Med 48(6):404-411.

Fisher CE, Brown DM, Shae J, et al. 1998. Respirable fibres: Surfactant coated fibres release more Fe3+ than native fibres at both pH 4.5 and 7.2. Ann Occup Hyg 42:337-345.

Fisher CE, Rossi AG, Shaw J, et al. 2000. Release of TNFα in response to SiC fibres: Differential effects in rodent and human primary macrophages, and in macrophage-like cell lines. Toxicol in Vitro 14:25-31.

Fisher GL, Mossman BT, McFarland AR, et al. 1987. A possible mechanism of chrysotile asbestos toxicity. Drug Chem Toxicol 10:109-131.

Fitzgerald EF, Stark AD, Vianna N, et al. 1991. Exposure to asbestiform minerals and radiographic chest abnormalities in a talc mining region of upstate New York. Arch Environ Health 46:151-154.

*Flejter WL, Li FP, Antman KH, et al. 1989. Recurring loss involving chromosomes 1, 3, and 22 in malignant mesothelioma: Possible sites of tumor suppressor genes. Genes Chromosomes Cancer 1:148-154.

*Fligiel Z, Kaneko M. 1976. Malignant mesothelioma of the tunica vaginalis propria testis in a patient with asbestos exposure. Cancer 37:1478-1484.

Fogel P, Morsheidt C, Hanton D, et al. 1998. A formula for predicting the tumor incidence in intraperitoneal experiments with mineral fibers. Inhal Toxicol 10:875-893.

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

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

*Fontecave M, Jaouen M, Mansuy D, et al. 1990. Microsomal lipid peroxidation and oxy-radicals formation are induced by insoluble iron-containing minerals. Biochem Biophys Res Commun 173:912-918.

*Fowler DP. 2000. Exposures to asbestos arising from bandsawing gasket material. Appl Occup Environ Hyg 15(5):404-408.

*Fraire AE, Cooper S, Greenberg SD, et al. 1988. Mesothelioma of childhood. Cancer 62:838-847.

Frank AL. 1982. The epidemiology and etiology of lung cancer. Clin Chest Med 3:219-228.

*Frank AL, Dodson RF, Williams MG. 1998. Carcinogenic implications of the lack of tremolite in UICC reference chrysotile. Am J Ind Med 34:314-317.

Freed JA, Miller A, Gordon RE, et al. 1991. Desquamative interstitial pneumonia associated with chrysotile asbestos fibers. Br J Ind Med 48(5):332-337.

*Friedman AC, Fiel SB, Fisher MS, et al. 1988. Asbestos-related pleural disease and asbestosis: A comparison of CT and chest radiography. Am J Roentgenol 150:269-275.

Friemann J, Mueller KM, Pott F. 1990. Mesothelial proliferation due to asbestos and man-made fibres. Path Res Pract 186:117-123.

*Froom P, Lahat N, Kristal-Boneh E, et al. 2000. Circulating natural killer cells in retired asbestos cement workers. J Occup Environ Med 42:19-24.

*Frumkin H, Berlin J. 1988. Asbestos exposure and gastrointestinal malignancy review and meta-analysis. Am J Ind Med 14:79-95

FSTRAC. 1990. Summary of state and federal drinking water standards and guidelines. Washington, DC: Federal-State Toxicology and Regulatory Alliance Committee, Chemical Communication Subcommittee.

*FSTRAC. 1999. Federal-State Toxicology and Risk Analysis Committee. U. S. Environmental Protection Agency, Office of Water. May 20, 1999. Http://www.epa.gov/ostwater/fstrac/states.html. May 20, 1999.

Fubini B. 1997. Surface reactivity in the pathogenic response to particulates. Environ Health Perspect Suppl 105:1013-1020.

*Fung H, Kow YW, Van Houten B, et al. 1997a. Patterns of 8-hydroxydeoxyguanosine formation in DNA and indications of oxidative stress in rat and human pleural mesothelial cells after exposure to crocidolite asbestos. Carcinogenesis 18:825-832.

Fung H, Kow YW, Van Houten B, et al. 1998. Asbestos increases mammalian AP-endonuclease gene expression, protein levels, and enzyme activity in mesothelial cells. Cancer Res 58:189-194.

*Fung H, Quinlan TR, Janssen YMW, et al. 1997b. Inhibition of protein kinase C prevents asbestos-induced c-fos and c-jun proto-oncogene expression in mesothelial cells. Cancer Res 57:3101-3105.

Gabrielson EW, Rosen GM, Grafstrom RC, et al. 1986. Studies on the role of oxygen radicals in asbestos-induced cytopathology of cultured human lung mesothelial cells. Carcinogenesis 7:1161-1164.

Gabrielson EW, Van der Meeren A, Reddel RR, et al. 1992. Human mesothelioma cells and asbestos-exposed mesothelial cells are selectively resistant to amosite toxicity: A possible mechanism for tumor promotion by asbestos. Carcinogenesis 13:1359-1363.

Gaensler EA. 1992. Asbestos exposure in buildings. Occup Lung Diseases 13:231-242.

Gaensler EA, Jederlinic PJ, Churg A. 1991. Idiopathic pulmonary fibrosis in asbestos-exposed workers. Am Rev Respir Dis 144(3):689-696.

*Gamble JF. 1994. Asbestos and colon cancer: A weight-of-the-evidence review. Environ Health Perspect 102:1038-1050.

*Gamsu G, Aberle DR, Lynch D. 1989. Computed tomography in the diagnosis of asbestos-related thoracic disease. J Thorac Imag 4:61-67.

*Garabrant DH, Peters RK, Homa DM. 1992. Asbestos and colon cancer: Lack of association in a large case-control study. Am J Epidemiol 135:843-853.

*Garcia JGN, Gray LD, Dodson RF, et al. 1988. Asbestos-induced endothelial cell activation and injury. Demonstration of fiber phagocytosis and oxidant-dependent toxicity. Am Rev Respir Dis 138:958-964.

*Garcia JGN, Griffith DE, Cohen AB, et al. 1989. Alveolar macrophages from patients with asbestos exposure release increased levels of leukotriene B_4. Am Rev Respir Dis 139:1494-1501.

Garcia-Closas M, Christiano DC. 1995. Asbestos-related diseases in construction carpenters. Am J Ind Med 27:115-125.

Gardner MJ, Powell CA, Gardner AW, et al. 1988. Continuing high lung cancer mortality among ex-amosite asbestos factory workers and a pilot study of individual anti-smoking advice. J Soc Occup Med 38:69-72.

*Gaumer HR, Doll NJ, Kaimal J, et al. 1981. Diminished suppressor cell function in patients with asbestosis. Clin Exp Immunol 44:108-116.

*Gefter WB, Conant EF. 1988. Issues and controversies in the plain-film diagnosis of asbestos-related disorders in the chest. J Thorac Imaging 3:11-28.

Geisler O. 1991. Occupational health and hygiene following a fire in a warehouse with an asbestos cement roof [Letter; Comment]. J Soc Occup Med 41(3):143.

Geist LJ, Powers LS, Monick MM, et al. 2000. Asbestos stimulation triggers differential cytokine release from human monocytes and alveolar macrophages. Exp Lung Res 26:41-56.

*Gendek EG, Brody AR. 1990. Changes in lipid ordering of model phospholipid membranes treated with chrysotile and crocidolite asbestos. Environ Res 53:152-167.

Gennaro V, Ceppi M, Boffetta P, et al. 1994. Pleural mesothelioma and asbestos exposure among Italian oil refinery workers. Scand J Work Environ Health 20:213-215.

*Gerhardsson de Verdier M, Plato N, Steineck G, et al. 1992. Occupational exposures and cancer of the colon and rectum. Am J Ind Med 22(3):291-303.

Gevenous PA, de Maertelaer V, Madani A, et al. 1998. Asbestosis, pleural plaques and diffuse pleural thickening: Three distinct benign responses to asbestosis exposure. Eur Resp J 11:1021-1027.

Ghio AJ, Crumbliss AL. 1992. Surface complexation of Fe^{3+} by silica and silicate dusts increases *in vitro* oxidant generation but diminishes *in vitro* cytotoxicity. Durham, NC: Duke University Medical Center, Division of Allergy, Critical Care, and Respiratory Medicine, Department of Medicine.

*Ghio AJ, Kadiiska MB, Xiang QH, et al. 1998. In vivo evidence of free radical formation after asbestos instillation: An ESR spin trapping investigation. Free Radic Biol Med 24:11-17.

Ghio AJ, Kennedy TP, Schapira RM, et al. 1990. Hypothesis: Is lung disease after silicate inhalation caused by oxidant generation? Lancet 336:967-969.

*Ghio AJ, LeFrugey A, Roggli VL. 1997. In vivo accumulation of iron on crocidolite is associated with decrements in oxidant generation by the fiber. J Toxicol Environ Health 50:125-142.

Giarelli L, Bianchi C, Grandi G. 1992. Malignant mesothelioma of the pleura in Trieste, Italy. Am J Ind Med 22(4):521-530.

Giaroli C, Bruno C, Candela S, et al. 1994. Mortality study of asbestos cement workers. Int Arch Occup Environ Health 66(1):7-11.

Gibbs AR, Gardner MJ, Pooley FD, et al. 1994. Fiber levels and disease in workers from a factory predominantly using amosite. Environ Health Perspect Suppl 102:261-263.

Gibbs AR, Griffiths DM, Pooley FD, et al. 1990. Comparison of fibre types and size distributions in lung tissues of paraoccupational and occupational cases of malignant mesothelioma. Br J Ind Med 47:621-626.

Gibbs AR, Jasani B, Pepper C, et al. 1998. SV40 DNA sequences in mesotheliomas. In: Brown F, Lewis AM, ed. Simian virus 40 (SV40): A possible human polyomavirus. Basel: Karger, 41-45.

Gibbs AR, Stephens M, Griffiths DM, et al. 1991. Fibre distribution in the lungs and pleura of subjects with asbestos related diffuse pleural fibrosis. Br J Ind Med 48:762-770.

*Gibbs GW. 1979. Etiology of pleural calcification: A study of Quebec chrysotile asbestos miners and millers. Arch Environ Health 34:76-83.

Gibbs GW. 1994. The assessment of exposure in terms of fibres. Ann Occup Hyg 38(4):477-487.

Gillam JD, Dement JM, Lemen RA, et al. 1976. Mortality patterns among hard rock gold miners exposed to an asbestiform mineral. Ann NY Acad Sci 271:336-344.

Gilmour PS, Brown DM, Beswick PH, et al. 1997. Free radical activity of industrial fibers: Role of iron in oxidative stress and activation of transcription factors. Environ Health Perspect Suppl 105:1313-1317.

Gilson JC. 1971. Asbestos. In: Encyclopedia of occupational health and safety. New York, NY: McGraw Hill, 120-124.

*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 101:65-71.

Glass W, Kawachi I, Pearce N. 1991. Lung cancer, smoking and exposure to asbestos in New Zealand. Journal of Occupational Health and Safety of Australia and New Zealand 7(1):43-47.

*Glencross PM, Weinberg JM, Ibrahaim JG, et al. 1997. Loss of lung function among sheet metal workers: Ten-year study. Am J Ind Med 32:460-466.

Gold J, Amandusson H, Krozer A, et al. 1997. Chemical characterization and reactivity of iron chelator-treated amphibole asbestos. Environ Health Perspect Suppl 5:1021-1030.

Goldberg P, Luce D, Billon-Galland MA, et al. 1995. Potential role of environmental and domestic exposure to tremolite in pleural cancer in New Caledonia. Rev Epidemiol Sante Publique 43:444-450.

*Goldfrank LR, Flomenbaum NE, Lewin NA et al., eds. 1998. Goldfrank's toxicologic emergencies. 6th ed. Stanford, CT: Appleton & Lange.

*Goldstein B, Coetzee FSJ. 1990. Experimental malignant mesothelioma in baboons. South Africa J Sci 86:89-93.

Gonzalez S, Friemann J, Mueller KM, et al. 1991. Ultrastructure of mesothelial regeneration after intraperitoneal injection of asbestos fibres on rat omentum. Path Res Pract 187:931-935.

*Goodglick LA, Kane AB. 1990. Cytotoxicity of long and short crocidolite asbestos fibers *in vitro* and *in vivo*. Cancer Res 50:5153-5163.

*Goodglick LA, Pietras LA, Kane AB. 1989. Evaluation of the causal relationship between crocidolite asbestos-induced lipid peroxidation and toxicity to macrophages. Am Rev Respir Dis 139:1265-1273.

Goodman GE, Omenn GS. 1992. Carotene and retinol efficacy trial: Lung cancer chemoprevention trial in heavy cigarette smokers and asbestos-exposed workers. CARET Coinvestigators and Staff. Adv Exp Med Biol 320:137-40.

*Goodman M, Morgan RW, Ray R, et al. 1999. Cancer in asbestos-exposed occupational cohorts: a meta-analysis. Cancer Causes Control 10:453-465.

Gormley IP, Bolton RE, Brown GM, et al. 1983. Some observations on the *in vitro* cytotoxicity of chrysotile prepared by the wet dispersion process. Environ Health Perspect 51:35-39.

Gosselin RE, Smith RP, Hodge HC. 1984. Toxicity information about selected ingredients. In: Clinical toxicology of commercial products. 5th ed. Baltimore, MD: Williams and Wilkins, II-94.

Governa M, Amati M, Fontana S, et al. 1999. Role of iron in asbestos-body-induced oxidant radical generation. J Toxicol Environ Health A 58:279-287.

Governa M, Amati M, Valentino M, et al. 2000. In vitro cleavage by asbestos fibers of the fifth component of human complement through free-radical generation and kallikrein activation. J Toxicol Environ Health A 59:539-552.

*Graceffa P, Weitzman SA. 1987. Asbestos catalyzes the formation of the 6-oxobenzo[a]pyrene radical from 6-hydroxybenzo[a]pyrene. Arch Biochem Biophysics 257:481-484.

*Greaves IA. 1979. Rheumatoid "pneumoconiosis" (Caplan's syndrome) in an asbestos worker: A 17 years' follow-up. Thorax 34:404-405.

*Green FH, Harley R, Vallyathan V, et al. 1986. Pulmonary fibrosis and asbestos exposure in chrysotile asbestos textile workers: Preliminary results. In: Accomplishments in oncology. The biological effects of chrysotile. Vol. 1, No. 2, 59-68.

*Green FHY, Harley R, Vallyathan V, et al. 1997. Exposure and mineralogical correlates of pulmonary fibrosis in chrysotile asbestos workers. Occup Environ Med 54:549-559.

Greenberg M. 1994. Dust exposure and mortality in chrysotile mining, 1910-76. Occup Environ Med 51:431.

Greenberg M. 1997. History of mesothelioma. Eur Resp J 10:2690-2691.

Greenberg M. 1998. The priority for recognizing asbestos as a multicentre carcinogen, and problems in categorizing asbestos tumours. Eur Resp J 11:996.

Greenberg M. 1999. A study of lung cancer mortality in asbestos workers: Doll, 1955. Am J Ind Med 36:331-347.

Greenblatt J. 1984. Evaluation of the EPA asbestos-in-schools identification and notification rule. Report to Battelle Columbus Laboratories, Washington, DC, by Westat, Inc., Rockville, MD.

Greene R, Boggis C, Jantsch H. 1982. Asbestos-related pleural thickening: Effect of threshold criteria on interpretation. Radiology 152:569-573.

Greene R, Schaefer CM, Oliver LC. 1991. Improved detection of asbestos-related pleural plaques with digital radiography. Ann NY Acad Sci 643(12):90-96.

*Griffis LG, Pickrell JA, Carpenter PR, et al. 1983. Deposition of crocidolite asbestos and glass microfibers inhaled by the beagle dog. Amer Ind Hyg Assoc J 44(3):216-222.

*Griffith DE, Miller EJ, Gray LD, et al. 1994. Interleukin-1-mediated release of interleukin-8 by asbestos-stimulated human pleural mesothelial cells. Am J Respir Cell Mol Biol 10(3):245-52.

Grimson RC. 1987. Apportionment of risk among environmental exposures: Application to asbestos exposure and cigarette smoking. J Occup Med 29:253-255.

Gross P, Harley RA. 1988. Asbestos-induced intrathoracic tissue reactions. Pittsburgh, PA: Industrial Health Foundation, Inc. PB88-248380.

*Gross P, deTreville RT, Tolker EB, et al. 1967. Experimental asbestosis: The development of lung cancer in rats with pulmonary deposits of chrysotile asbestos dust. Arch Environ Health 15:343-355.

*Gross P, Harley RA, Swinburne LM, et al. 1974. Ingested mineral fibers: Do they penetrate tissue or cause cancer? Arch Environ Health 29:341-347.

Guillemin B, Zhang Y, Lee TC, et al. 1991. Role of peptide growth factors in asbestos-related human lung cancer. Ann NY Acad Sci 245-257.

Guillemin MP, Madelaine P, Litzistorf G, et al. 1989. Asbestos in buildings. Aerosol Sci Technol 11:221-243.

*Guinee DGJ, Travis WD, Trivers GE, et al. 1995. Gender comparisons in human lung cancer: Analysis of p53 mutations, anti-p53 serum antibodies and C-erB-2 expression. Carcinogenesis 16:993-1002.

Gulumian M. 1999. The role of oxidative stress in diseases caused by mineral dusts and fibres: Current status and future of prophylaxis and treatment. Mol Cell Biochem 196:69-77.

Gulumian M, Bhoolia DJ, Du Toit RS, et al. 1993. Activation of UICC crocidolite: The effect of conversion of some ferric ions to ferrous ions. Environ Res 60(2):193-206.

Gun RT. 1995. Mesothelioma: Is asbestos exposure the only cause? Med J Aust 162:429-432.

Gustavsson P, Jakobsson R, Johansson H, et al. 1998. Occupational exposures and squamous cell carcinoma of the oral cavity, pharynx, larynx, and oesophagus: A case-control study in Sweden. Occup Environ Med 55:393-400.

Guthrie GD. 1997. Mineral properties and their contributions to particle toxicity. Environ Health Perspect Suppl 5:1003-1011.

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

Gylseth B, Skaug V. 1986. Relation between pathological grading and lung fibre concentration in a patient with asbestosis. Br J Ind Med 43:754-759.

*Gylseth B, Churg A, Davis JM, et al. 1985. Analysis of asbestos fibers and asbestos bodies in tissue samples from human lung: An international interlaboratory trial. Scand J Work Environ Health 11:107-110.

*Habashi F, Awadalla FT, Page M. 1991. Surface modification of chrysotile asbestos with organic reagents: A preliminary *in vitro* toxicological study. CIM Bulletin 84:67-79.

Hahon N, Booth JA, Flowers L. 1990. Coinhibition of viral interferon induction by benzo[a]pyrene in association with occupation-related particles. Environ Res 52:83-98.

Hall EJ, Hei TK. 1985. Oncogenic transformation with radiation and chemicals. Int J Radiat Biol 48:1-18.

Hall NEL, Rosenmann KD. 1991. Cancer by industry: Analysis of a population-based cancer registry with an emphasis on blue-collar workers. Am J Ind Med 19(2):145-159.

Hallenbeck WH. 1983. Asbestos penetration of the gastrointestinal tract [Commentary]. Environ Health Perspect 53:153-154.

Hallenbeck WH. 1988. Can we really evaluate the health risks due to exposure to airborne asbestos? The Environmental Professional 10:333-340.

*Hallenbeck WH, Patel-Mandlik KJ. 1979. Presence of fibers in the urine of a baboon gavaged with chrysotile asbestos. Environ Res 20:335-340.

*Hallenbeck WH, Chen EH, Hesse CS. 1978. Is chrysotile asbestos released from asbestos-cement pipe into drinking water? J AWWA (February):97-102.

Hammar SP. 1992. Controversies and uncertainties concerning the pathologic features and pathologic diagnosis of asbestosis. Sem Diag Path 9:102-109.

*Hammond EC, Selikoff IJ, Seidman H. 1979. Asbestos exposure, cigarette smoking and death rates. Ann NY Acad Sci 330:473-490.

Hansen J, de Klerk NH, Eccles JL, et al. 1993. Malignant mesothelioma after environmental exposure to blue asbestos. Int J Cancer 54(4):578-581.

*Hansen J, de Klerk NH, Musk AW, et al. 1998. Environmental exposure to crocidolite and mesothelioma: Exposure-response relationships. Am J Respir Crit Care Med 157:69-75.

*Hansen K, Mossman BT. 1987. Generation of superoxide ($O_2^{\cdot}$-) from alveolar macrophages exposed to asbestiform and nonfibrous particles. Cancer Res 47:1681-1686.

*Hansteen I-L, Hilt B, Lien JT, et al. 1993. Karyotypic changes in the preclinical and subsequent stages of malignant mesothelioma: A case report. Cancer Genet Cytogenet 70(2):94-98.

*Haque AK, Kanz, MF. 1988. Asbestos bodies in children's lungs. Arch Pathol Lab Med 112:514-518.

*Haque AK, Vrazel DM. 1998. Transplacental transfer of asbestos in pregnant mice. Bull Environ Contam Toxicol 60:620-625.

*Haque AK, Kanz MF, Mancuso MG, et al. 1991. Asbestos in the lungs of children. Ann NY Acad Sci 419-429.

*Haque AK, Mancugo MG, Williams MG, et al. 1992. Asbestos in organs and placenta of 5 stillborn infants suggests transplacental transfer. Environ Res 58(2):163-175.

*Haque AK, Vrazel DM, Burau KD, et al. 1996. Is there transplacental transfer of asbestos? A study of 40 stillborn infants. Pediatr Pathol Lab Med 16:877-892.

*Haque AK, Vrazel DM, Uchida T. 1998. Assessment of asbestos burden in the placenta and tissue digets of stillborn infants in South Texas. Arch Environ Contam Toxicol 35:532-538.

*Hardy RJ, Highsmith VR, Costa DL, et al. 1992. Indoor asbestos concentrations associated with the use of asbestos-contaminated tap water in portable home humidifiers. Environ Sci Technol 26:680-689.

Harington JS. 1981. Fiber carcinogenesis: Epidemiologic observations and the Stanton hypothesis. J Natl Cancer Inst 67:977-989.

Harington JS. 1991. The carcinogenicity of chrysotile asbestos. Ann NY Acad Sci 465-472.

Harkin TJ, McGuinness G, Goldring R, et al. 1996. Differentiation of the ILO boundary chest roentgenograph (0/1 to 1/0) in asbestosis by high-resolution computed tomography scan, alveolitis, and respiratory impairment. J Occup Environ Med 38:46-52.

Harrington JM, Craun GF, Meigs JW, et al. 1978. An investigation of the use of asbestos cement pipe for public water supply and the incidence of gastrointestinal cancer in Connecticut, 1935-1973. Am J Epidemiol 107:96-103.

Harrison PT, Health JC. 1988. Apparent synergy between chrysotile asbestos and *N*-nitrosoheptamethyleneimine in the induction of pulmonary tumours in rats. Carcinogenesis 9:2165-2171.

Harrison PTC, Levy LS, Patrick G, et al. 1999. Comparative hazards of chrysotile asbestos and its substitutes: A European perspective. Environ Health Perspect 107(8):607-611.

Hatch GE, Boykin E, Graham JA, et al. 1985. Inhalable particles and pulmonary host defense: *In vivo* and *in vitro* effects of ambient air and combustion particles. Environ Res 36:67-80.

*Hayashi I, Konishi N, Matsuda H, et al. 1996. Comparative analysis of p16/CDKN2, p53 and ras gene alterations in human non-small cell lung cancers, with and without associated pulmonary asbestosis. Int J Oncol 8:85-90.

*Hayes AA, Mullan B, Lovegrove FT, et al. 1989. Gallium lung scanning and bronchoalveolar lavage in crocidolite-exposed workers. Chest 96:22-26.

*Hayes AA, Venaille TJ, Rose AH, et al. 1990. Asbestos-induced release of a human alveolar macrophage-derived neutrophil chemotactic factor. Exp Lung Res 16:121-130.

HazDat. 1994. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA.

HazDat. 1999. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA. May 1999.

HazDat. 2000. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA. May 2000.

*HazDat. 2001. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA. Http://atsdr.cdc.gov/hazdat.html. June 13, 2001.

*HEI. 1991. Health Effects Institute. Asbestos in public and commercial buildings: A literature review and synthesis of current knowledge. Report of the asbestos literature review panel. Cambridge, MA: Health Effects Institute.

*HEI. 1992. Health Effects Institute. Asbestos in public and commercial buildings: Supplementary analyses of selected data previously considered by the literature review panel. Cambridge, MA: Health Effects Institute.

*Hei TK, Hall EJ, Osmak RS. 1984. Asbestos, radiation, and oncogenic transformation. Br J Cancer 50:717-720.

*Hei TK, Piao CQ, He ZY, et al. 1992. Chrysotile fiber is a strong mutagen in mammalian cells. Cancer Res 52:6305-6309.

Heineman EF, Bernstein L, Stark AD, et al. 1996. Mesothelioma, asbestos, and reported history of cancer in first-degree relatives. Cancer 77:549-554.

*Heintz NH, Janssen YM, Mossman BT. 1993. Persistent induction of c- *fos* and c- *jun* expression by asbestos. Proc Natl Acad Sci U S A 90:3299-3303.

Heler DS, Gordon RE, Turnnir R, et al. 1998. Presence of asbestos in peritoneal mesothelioma [Abstract]. Lab Invest 78:104A.

Heller DS, Gordon RE, Westhoff C, et al. 1996. Asbestos exposure and ovarian fiber burden. Am J Ind Med 29:435-439.

Henderson DW, Attwood HD, Constance TJ, et al. 1988. Lymphohistiocytoid mesothelioma: A rare lymphomatoid variant of predominantly sarcomatoid mesothelioma. Ultrastruct Pathol 12:367-384.

*Henderson VL, Enterline PE. 1979. Asbestos exposure: Factors associated with excess cancer and respiratory disease mortality. Ann NY Acad Sci 330:117-126.

Hessel PA, Sluis-Cremer GK. 1989. X-ray findings, lung function, and respiratory symptoms in black South African vermiculite workers. Am J Ind Med 15:21-29.

*Hesterberg TW, Barrett JC. 1984. Dependence of asbestos- and mineral dust-induced transformation of mammalian cells in culture on fiber dimension. Cancer Res 44:2170-2180.

*Hesterberg TW, Axten C, McConnell EE, et al. 1997. Chronic inhalation study of fiber glass and amosite asbestos in hamsters: Twelve-month preliminary results. Environ Health Perspect Suppl 105:1223-1229.

Hesterberg TW, Butterick CJ, Oshimura M, et al. 1986. Role of phagocytosis in Syrian hamster cell transformation and cytogenetic effects induced by asbestos and short and long glass fibers. Cancer Res 46:5795-5802.

*Hesterberg TW, Chase G, Axten C, et al. 1998a. Biopersistence of synthetic vitreous fibers and amosite asbestos in the rat lung following inhalation. Toxicol Appl Pharmacol 151:262-275.

*Hesterberg TW, Hart GA, Chevalier J, et al. 1998b. The importance of fiber biopersistence and lung dose in determining the chronic inhalation effects of X607, RCF1, and chrysotile asbestos in rats. Toxicol Appl Pharmacol 153:68-82.

*Hesterberg TW, Miller WC, Musselman RP, et al. 1996. Biopersistence of man-made vitreous fibers and crocidolite asbestos in the rat lung following inhalation. Fundam Appl Toxicol 29:267-279.

*Hesterberg TW, Miller WC, Thevenaz P, et al. 1995. Chronic inhalation studies of man-made vitreous fibres: Characterization of fibres in the exposure aerosol and lungs. Ann Occup Hyg 39:637-653.

*Higashi T, Hori H, Sakurai H, et al. 1994. Work environment of plants manufacturing asbestos-containing products in Japan. Ann Occup Hyg 38:489-494.

Hill RJ, Edwards RE, Carthew P. 1990. Early changes in the pleural mesothelium following intrapleural inoculation of the mineral fibre erionite and the subsequent development of mesotheliomas. J Exp Path 71:105-118.

Hillerdal G. 1978. Pleural plaques in a health survey material: Frequency, development and exposure to asbestos. Scand J Respir Dis 59:257-263.

*Hillerdal G. 1980. The pathogenesis of pleural plaques and pulmonary asbestosis: Possibilities and impossibilities. Eur J Respir Dis 61:129-138.

Hillerdal G. 1983. Malignant mesothelioma 1982: Review of 4710 published cases. Br J Dis Chest 77:321-343.

Hillerdal G. 1991. Pleural plaques in the general population. Ann NY Acad Sci 430-437.

*Hillerdal G. 1994. Pleural plaques and risk for bronchial carcinoma and mesothelioma: A prospective study. Chest 105(1):144-150.

*Hillerdal G, Henderson DW. 1997. Asbestos, asbestosis, pleural plaques and lung cancer. Scand J Work Environ Health 23:93-103.

Hillerdal G, Musk AW. 1990. Pleural lesions in crocidolite workers from Western Australia. Br J Ind Med 47:782-783.

Hillerdal G, Lee J, Blomkvist A, et al. 1997. Pleural disease during treatment with bromocriptine in patients previously exposed to asbestos. Eur Resp J 10:2711-2715.

Hilt B, Andersen A, Rosenber J, et al. 1991. Cancer incidence among asbestos-exposed chemical industry workers: An extended observation period. Am J Ind Med 20:261-264.

Hilt B, Lien JT, Lund-Larsen PG, et al. 1986. Asbestos-related findings in chest radiographs of the male population of the county of Telemark, Norway - a cross-sectional study. Scand J Work Environ Health 12:567-573.

Hirano S, Ono M, Aimoto A. 1988. Functional and biochemical effects on rat lung following instillation of crocidolite and chrysotile asbestos. J Toxicol Environ Health 24:27-39.

Hiraoka K, Horie A, Kido M. 1990. Study of asbestos bodies in Japanese urban patients. Am J Ind Med 18:547-554.

Hiraoka T, Ohkura M, Morinaga K, et al. 1998. Anthophyllite exposure and endemic pleural plaques in Kumamoto, Japan. Scand J Work Environ Health 24:392-397.

Hiroshima K, Murai Y, Suzuki Y, et al. 1993. Characterization of asbestos fibers in lungs and mesotheliomatous tissues of baboons following long-term inhalation. Am J Ind Med 23(6):883-901.

Hirvone A, Saarikoski ST, Linnainmaa K, et al. 1996. Glutathion S-transferase and N-acetyltransferase genotypes and asbestos-associated pulmonary disorders. J Natl Cancer Inst 88:1853-1856.

*Hirvonen A. 1997. Combinations of susceptible genotypes and individual responses to toxicants. Environ Health Perspect Suppl 105:755-758.

Hirvonen A, Mattson K, Karjalainen A, et al. 1999. Simian virus 40 (SV40)-like DNA sequences not detectable in Finnish mesothelioma patients not exposed to SV40-contaminated polio vaccines. Mol Carcinog 26:93-99.

*Hirvonen A, Pelin K, Tammilehto L, et al. 1995. Inherited GSTM1 and NAT2 defects as concurrent risk modifiers in asbestos-related human malignant mesothelioma. Cancer Res 55:2981-2983.

*Hirvonen A, Saarikoski ST, Linnainmaa K, et al. 1996. Glutathione-S-transferase and N-acetyltransferase genotypes and asbestos-associated pulmonary disorders. J Natl Cancer Inst 88:1853-1856.

*Hnizdo E, Sluis-Cremer GK. 1988. Effect of tobacco-smoking on the presence of asbestosis at postmortem and on the reading of irregular opacities on roentgenograms in asbestos-exposed workers. Am Rev Respir Dis 138:1207-1212.

*Hobson J, Gilks B, Wright J, et al. 1988. Direct enhancement by cigarette smoke of asbestos fiber penetration and asbestos-induced epithelial proliferation in rat tracheal explants. J Natl Cancer Inst 80:518-521.

*Hobson J, Wright JL, Churg A. 1990. Active oxygen species mediate asbestos fiber uptake by tracheal epithelial cells. FASEB J 4:3135-3139.

*Hodgson JT, Darnton A. 2000. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg 44(8):565-601.

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

*Hofmann W, Koblinger L, Martonen TB. 1989. Structural differences between human and rat lungs: Implications for Monte Carlo modeling of aerosol deposition. Health Phys 57:41-47.

*Holian A, Uthman MO, Goltsova T, et al. 1997. Asbestos and silica-induced changes in human alveolar macrophage phenotype. Environ Health Perspect Suppl 105:1139-1142.

*Holt PF. 1974. Small animals in the study of pathological effects of asbestos. Environ Health Perspect 9:205-211.

*Holt PF. 1983. Translocation of inhaled dust to the pleura. Environ Res 31:212-220.

Holtz G, Bresnick E. 1988. Ascorbic acid inhibits the squamous metaplasia that results from treatment of tracheal explants with asbestos or benzo[a]pyrene-coated asbestos. Cancer Lett 42:23-28.

*Homa DM, Garabrant DH, Gillespie BW. 1994. A meta-analysis of colorectal cancer and asbestos exposure. Am J Epidemiol 139:1210-1222.

Hooper K, Ladou J, Resenbaum JS, et al. 1992. Regulation of priority carcinogens and reproductive or developmental toxicants. Am J Ind Med 22(6):793-808.

Horii H, Nagasaka Y, Yamada Y. 1992. Asbestos-related pleural thickenings in Japanese sake brewers. Int Arch Occup Environ Health 64(5):315-319.

*Howe HL, Wolfgang PE, Burnett WS, et al. 1989. Cancer incidence following exposure to drinking water with asbestos leachate. Public Health Reports 104:251-256.

Howel D, Arblaster L, Swinburne L, et al. 1997. Routes of asbestos exposure and the development of mesothelioma in an English region. Occup Environ Med 54:403-409.

HSDB. 1994. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

HSDB. 1999a. Asbestos. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. June 16, 1999.

HSDB. 1999b. Tremolite asbestos. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. June 16, 1999.

HSDB. 1999c. Chrysotile asbestos. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. June 16, 1999.

HSDB. 1999d. Amosite asbestos. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. June 16, 1999.

*HSDB. 2001a. Asbestos. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. January 23, 2001.

*HSDB. 2001b. Tremolite asbestos. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. January 23, 2001.

*HSDB. 2001c. Chrysotile asbestos. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. January 23, 2001.

*HSDB. 2001d. Amosite asbestos. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. January 23, 2001.

*Hsiao TM, Ho CK, Su WP, et al. 1993. Asbestos related pleural plaques in retired boiler room workers. Kao Hsiung I Hsueh Ko Hsueh Tsa Chih 9(2):74-79.

*Huang SL. 1979. Amosite, chrysotile and crocidolite asbestos are mutagenic in Chinese hamster lung cells. Mutat Res 68:265-274.

Hubbard R. 1997. The aetiology of mesothelioma: Are risk factors other than asbestos exposure important? [Letter]. Thorax 52:496-497.

*Hughes JM. 1994. Human evidence: Lung cancer mortality risk from chrysotile exposure. Ann Occup Hyg 38(4):555-560.

*Hughes J, Weill H. 1980. Lung cancer risk associated with manufacture of asbestos-cement products. IARC Sci Publ 30:627-635.

Hughes JM, Weill H. 1991. Asbestosis as a precursor of asbestos related lung cancer: Results of a prospective mortality study. Br J Ind Med 48(4):229-233.

*Hughes JM, Weill H, Hammad YY. 1987. Mortality of workers employed in two asbestos cement manufacturing plants. Br J Ind Med 44:161-174.

*Huilan Z, Zhiming W. 1993. Study of occupational lung cancer in asbestos factories in China. Br J Ind Med 50(11):1039-1042.

Huncharek M. 1986. The biomedical and epidemiological characteristics of asbestos-related diseases: A review. Yale J Biol Med 59:435-451.

Huncharek M. 1994. Asbestos and cancer: Epidemiological and public health controversies. Cancer Invest 12(2):214-222.

Huncharek M, Muscat J. 1991. Metastatic laryngeal carcinoma mimicking pleural mesothelioma. Respiration 58(3-4):204-206.

*Huncharek M, Kelsey K, Muscat J, et al. 1996. Parental cancer and genetic predisposition in malignant pleural mesothelioma: A case-control study. Cancer Lett 102:205-208.

*Huncharek M, Klassen M, Christian D. 1995. Mesothelioma of the tunica vaginalis testis with possible occupational asbestos exposure. Br J Urol 75:673-685.

Hunting KL, Welch LS. 1993. Occupational exposure to dust and lung disease among sheet metal workers. Br J Ind Med 50(5):432-442.

Hurbankova M. 1994. One-year follow-up of the phagocytic activity of leukocytes after exposure of rats to asbestos and basalt fibers. Environ Health Perspect Suppl 102:201-203.

*Hurbankova M, Kaiglova A. 1993. The changes of some immunological parameters in subjects exposed to asbestos in dependence on age, duration of exposure, radiological findings, and smoking habits. Zentralbl Hyg Umweltmed 195(1):55-65.

Hurbankova M, Kaiglova A. 1997. Some bronchoalveolar lavage parameters and leukocyte cytokine release in response to intratracheal instillation of short and long asbestos and wollastonite fibres in rats. Physiol Res 46:459-466.

*Hurlbut CS Jr, Klein C. 1977. Manual of mineralogy. 19th ed. New York, NY: John Wiley and Sons, 338-339.

Husgafvel-Pursiainen K, Kannio A, Oksa P, et al. 1997. Mutations, tissue accumulations, and serum levels of p53 in patients with occupational cancers from asbestos and silica exposure. Environ Mol Mutagen 30:224-230.

Husgafvel-Pursiainen K, Ridanpaa M, Anttila S, et al. 1995. p53 and ras Gene mutations in lung cancer: Implications for smoking and occupational exposures. J Occup Environ Med 37:69-76.

*IARC. 1977. IARC monographs on the evaluation of the carcinogenic risk of chemicals to man: Asbestos. Vol 14. World Health Organization, Lyon, France, 33-35.

IARC. 1982. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol 1-29 (Supplement 4): Chemicals, industrial processes and industries associated with cancer in humans. World Health Organization, Lyon, France, 33-35.

*IARC. 1987. Asbestos and certain asbestos compounds. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Chemicals, industrial processes and industries associated with cancer in humans. IARC monographs, Vol 1 to 42. IARC monographs supplement 7. Lyon, France: World Health Organization, International Agency for Research on Cancer, 29-33,56-58.

*IARC. 2001. Asbestos. IARC Monographs Database on Carcinogenic Risks to Humans, International Agency for Research on Cancer. Http://www.iarc.fr/pageroot/top1.html. January 17, 2001.

*IARC Expert Panel. 1996. Consensus Report. In: Kane AB, Boffetta P, Saracci R et al., eds. Mechanisms of fibre carcinogenesis. Lyon: International Agency for Research on Cancer. IARC Scientific Publications No. 140, 1-9.

*ICRP. 1994. Human respiratory tract model for radiological protection. ICRP Publ.66:1-482.

*IDEM. 2001a. Demolition and renovation: Asbestos. Indiana Department of Environmental Management. Http://www.state.in.us/idem/ctap/asbestos.pdf. January 19, 2001.

*IDEM. 2001b. Water pollution control board: Proposed rule as preliminarily adopted. Indiana Department of Environmental Management. Http://www.state.in.us/idem/owm/planbr/rules/dwspropr.pdf. January 23, 2001.

*Iguchi H, Kojo S. 1989. Possible generation of hydrogen peroxide and lipid peroxidation of erythrocyte membrane by asbestos: Cytotoxic mechanism of asbestos. Biochem Int 18:981-990.

*Iguchi H, Kojo S, Ikeda M. 1993. Lipid peroxidation and disintegration of the cell membrane structure in cultures of rat lung fibroblasts treated with asbestos. J Appl Toxicol 13(4):269-275.

Ilg AGS, Bignon J, Valleron AJ. 1998. Estimation of the past and future burden of mortality from mesothelioma in France. Occup Environ Med 55:760-765.

Ilgren EB, Browne K. 1991. Asbestos-related mesothelioma: Evidence for a threshold in animals and humans. Regul Toxicol Pharmacol 13:116-132.

ILO. 1980. International Labour Office. Guidelines for the use of the ILO international classification of radiographs of pneumoconiosis, revised edition. Geneva, Switzerland: ILO Occupational Safety and Health Series. No. 22.

Imbernon E, Goldberg M, Bonenfant S, et al. 1995. Occupational respiratory cancer and exposure to asbestos: A case-control study in a cohort of workers in the electricity and gas industry. Am J Ind Med 28:339-352.

*Inase N, Takayama S, Nakayama M, et al. 1991. Pleural mesothelioma after neighborhood exposure to asbestos during childhood. Jpn J Med 30(4):343-345.

*International Expert Meeting on Asbestos. 1997. Asbestos, asbestosis, and cancer: The Helsinki criteria for diagnosis and attribution. Scand J Work Environ Health 23:311-316.

IRIS. 1993. Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. July 1, 1993.

IRIS. 1999. Asbestos. Integrated Risk Information System, U.S. Environmental Protection Agency.

*IRIS. 2001. Asbestos. Integrated Risk Information System, U.S. Environmental Protection Agency. Http://www.epa.gov/iris/subst/0371.htm. January 23,2001.

IRPTC. 1989. IRPTC data profile: Asbestos. International Register of Potentially Toxic Chemicals, United Nations Environment Programme, Geneva, Switzerland. January 1989.

Irvine HDV. 1995. Mesotheliom. Lancet 345:1233-1234.

Irvine HD, Lemont DW, Hole DJ, et al. 1993. Asbestos and lung-cancer in Glasgow and the west of Scotland. BMJ 306(6891):1503-1506.

*Irwig LM, du Toit RS, Sluis-Cremer GK, et al. 1979. Risk of asbestosis in crocidolite and amosite mines in South Africa. Ann NY Acad Sci 330:35-52.

Ishihara Y, Kohyama N, Kagawa J. 1998. Contribution of human pulmonary macrophage-derived cytokines to asbestos-induced lung inflammation and fibrosis. Inhal Toxicol 10:205-225.

*Ishizaki T, Yano E, Evans PH. 1997. Cellular mechanisms of reactive oxygen metabolite generation from human polymorphonuclear leukocytes induced by crocidolite asbestos. Environ Res 75:135-140.

*Israbian VA, Weitman SA, Kamp DW. 1994. Dibutyryl cAMP attenuates asbestos-induced pulmonary epithelial cell cytotoxicity and decline in ATP levels. Am J Physiol 267(11):L518-L525.

*Iwatsubo Y, Pairon JC, Boutin C, et al. 1998. Pleural mesothelioma: Dose-response relation at low levels of asbestos exposure in a French population-based case-control study. Am J Epidemiol 148:133-142.

Jabbour AJ, Holian A, Scheule RK. 1991. Lung lining fluid modification of asbestos bioactivity for the alveolar macrophage. Toxicol App Pharmacol 110:283-294.

Jackson JH, Schraufstatter IU, Hyslop PA, et al. 1987. Role of oxidants in DNA damage: Hydroxyl radical mediates the synergistic DNA damaging effects of asbestos and cigarette smoke. J Clin Invest 80:1090-1095.

*Jacobs R, Humphrys J, Dodgson KS, et al. 1978a. Light and electron microscope studies of the rat digestive tract following prolonged and short-term ingestion of chrysotile asbestos. Br J Exp Pathol 59:443-453.

*Jacobs R, Weinzweig M, Dodgson KS, et al. 1978b. Nucleic acid metabolism in the rat following short-term and prolonged ingestion of chrysotile asbestos or cigarette-smoke condensate. Br J Exp Pathol 59:594-600.

*Jaenicke R. 1980. Natural aerosols. Ann NY Acad Sci 338:317-325.

Jagirdar J, Lee TC, Reibman J, et al. 1997. Immunohistochemical localization of transforming growth factor beta isoforms in asbestos-related diseases. Environ Health Perspect Suppl 105:1197-1203.

*Jakobsson K, Albin M, Hagmar L. 1994. Asbestos, cement, and cancer in the right part of the colon. Occup Environ Med 51(2):95-101.

*Jakobsson K, Rannug A, Alexandrie AK, et al. 1995a. Radiographic changes and lung function in relation to activity of the glutathione transferases theta and mu among asbestos cement workers. Toxicol Lett 77:363-369.

*Jakobsson K, Stromberg U, Albin M, et al. 1995b. Radiological changes in asbestos cement workers. Occup Environ Med 52:20-27.

*Janssen YMW, Sen CK. 1999. Nuclear factor kappa B activity in response to oxidants and antioxidants. Methods Enzymol 300:363-374.

Janssen YMW, Driscoll KE, Howard B, et al. 1997. Asbestos causes translocation of p65 protein and increase NF-KB DNA binding activity in rat lung epithelial and pleural mesothelial cells. Am J Pathol 151:389-401.

*Janssen YMW, Heintz NH, Mossman BT. 1995. Induction of c-*fos* and c-*jun* proto-oncogene expression by asbestos is ameliorated by N-acetyl-L-cysteine in mesothelial cells. Cancer Res 55:2085-2089.

*Janssen YMW, Marsh JP, Absher MP, et al. 1992. Expression of antioxidant enzymes in rat lungs after inhalation of asbestos or silica. J Biol Chem 267:10625-10630.

Jarvholm B, Brisman J. 1988. Asbestos associated tumours in car mechanics. Br J Ind Med 45:645-646.

*Jarvholm B, Larsson S. 1988. Do pleural plaques produce symptoms? A brief report. J Occup Med 30:345-347.

Jarvholm B, Sanden A. 1988. Asbestos-associated diseases in Swedish shipyard workers. Arh Hig Rada Toksikol 39:437-440.

Jarvholm B, Sanden A. 1998. Lung cancer and mesothelioma in the pleura and peritoneum among Swedish insulation workers. Occup Environ Med 55:766-770.

*Jarvholm B, Arvidsson, H, Bake B, et al. 1986. Pleural plaques -asbestos - ill-health. Eur J Respir Dis Suppl 68(Suppl 145):1-59.

Jarvholm B, Larsson S, Hagberg S, et al. 1993. Quantitative importance of asbestos as a cause of lung cancer in a Swedish industrial city: A case-referent study. Eur Respir J 6(9):1271-1275.

Jarvholm B, Malker H, Malker B, et al. 1988. Pleural mesotheliomas and asbestos exposure in the pulp and paper industries: A new risk group identified by linkage of official registers. Am J Ind Med 13:561-567.

Jaurand MC. 1991. Observations on the carcinogenicity of asbestos fibers. Ann NY Acad Sci 258-270.

Jaurand MC. 1997. Mechanisms of fiber-induced genotoxicity. Environ Health Perspect Suppl 105:1073-1084.

*Jaurand MC, Fleury J, Monchaux G, et al. 1987. Pleural carcinogenic potency of mineral fibers (asbestos, attapulgite) and their cytotoxicity on cultured cells. J Natl Cancer Inst 79:797-804.

*Jaurand MC, Gaudichet A, Halpern S, et al. 1984. *In vitro* biodegradation of chrysotile fibers by alveolar macrophages and mesothelial cells in culture: Comparison with a pH effect. Br J Ind Med 41:389-395.

Jaurand MC, Magne L, Bignon J. 1979. Inhibition by phospholipids of haemolytic action of asbestos. Br J Ind Med 36:113-116.

Jaurand MC, Renier A, Gaudichet A, et al. 1988. Short-term tests for the evaluation of potential cancer risk of modified asbestos fibers. Ann NY Acad Sci 741-753.

*Jensen CG, Watson M. 1999. Inhibition of cytokinesis by asbestos and synthetic fibres. Cell Biol Int 23(12):829-840.

Jessurun GAJ, Crijns HJGM, van Wijngaarden J. 1996. An unusual case of cardiac tamponade following electrical cardioversion. Int J Cardiol 53:317-320.

Jimenez LA, Zanella C, Fung H, et al. 1997. Role of extracellular signal-regulated protein kinases in apoptosis by asbestos and H2O2. Am J Physiol 273(17):L1029-L1035.

Jockel K-H, Ahrens W, Bolm-Audorff U. 1994. Lung cancer risk and welding-Preliminary results from an ongoing case-control study. Am J Ind Med 25:805-812.

Jockel K-H, Ahrens W, Bolm-Audorff U, et al. 1997. Estimation of the dose-response between risk of lung cancer and cumulative dose of asbestos exposure in fibre-year [Abstract]. Eur Resp J 10:434S.

Jockel K-H, Ahrens W, Jan I, et al. 1998. Occupational risk factors for lung cancer: A case-control study in West Germany. Int J Epidemiol 27:549-560.

Johansen C, Olsen Jorgen H. 1998. Risk of cancer among Danish utility workers-A nationwide cohort study. Am J Epidemiol 147:548-555.

*Johanson CE. 1980. Permeability and vascularity of the developing brain: Cerebellum vs cerebral cortex. Brain Res 190:3-16.

Johansson L, Albin M, Jakobsson K, et al. 1992. Histological type of lung carcinoma in asbestos cement workers and matched controls. Br J Ind Med 49(9):626-30.

Johnson NF. 1994. Phagosomal pH and glass fiber dissolution in cultured nasal epithelial cells and alveolar macrophages: A preliminary study. Environ Health Perspect Suppl 102(5):97-102.

*Johnson NF, Jaramillo RJ. 1997. p53, Cip1, and Gadd153 expression following treatment of A549 cells with natural and man-made vitreous fibers. Environ Health Perspect Suppl 105:1143-1145.

Johnson NF, Carpenter TR, Jaramillo RJ, et al. 1997. DNA damage-inducible genes as biomarkers for exposures to environmental agents. Environ Health Perspect Suppl 105:913-918.

Johnson NF, Edwards RE, Munday DE, et al. 1984. Pluripotential nature of mesotheliomata induced by inhalation of erionite in rats. Br J Exp Pathol 65:377-388.

Johnson NF, Haslam PL, Dewar A, et al. 1988. Identification of inorganic dust particles in bronchoalveolar lavage macrophages by energy dispersive X-ray microanalysis. Arch Environ Health 41:133-144.

Johnson NF, Hoover MD, Thomassen DG, et al. 1992. In vitro activity of silicon carbide whiskers in comparison to other industrial fibers using four cell culture systems. Am J Ind Med 21:807-823.

Johnson NF, Wagner JC, Brown DG, et al. 1982. The ultrastructure of asbestos induced rat pleural mesotheliomas following transplantation into syngeneic animals [Abstract]. J Pathol 137:80.

Johnson NF, Wagner JC, Wills HA. 1980a. Endocrine cell proliferation in the rat lung following asbestos inhalation. Lung 158:221-228.

Johnson NF, Wagner JC, Wills HA. 1980b. Neuroendocrine cell proliferation in the rat lung following asbestos inhalation [Abstract]. J Pathol 131:261-262.

Jolicoeur C, Poisson D. 1987. Surface physico-chemical studies of chrysotile asbestos and related minerals. Drug Chem Toxicol 10:1-47.

*Jolicoeur CR, Alary JF, Sokov A. 1992. Asbestos. In: Kroschwitz JI, Howe-Grant M, ed. Kirk-Othmer encyclopedia of chemical technology. New York: John Wiley & Sons, 659-688.

*Jones AD, McMillan CH, Johnston AM, et al. 1988a. Pulmonary clearance of UICC amosite fibres inhaled by rats during chronic exposure at low concentration. Br J Ind Med 45:300-304.

*Jones AD, Vincent JH, Addison J, et al. 1994. The fate and effect of inhaled chrysotile asbestos fibres. Ann Occup Hyg 38:619-629.

Jones AD, Vincent JH, McIntosh C, et al. 1989. The effect of fibre durability on the hazard potential of inhaled chrysotile asbestos fibres. Exp Pathol 37:98-102.

*Jones JS, Pooley FD, Smith PG, et al. 1980a. The consequences of exposure to asbestos dust in a wartime gas-mask factory. IARC Sci Publ 30:637-653.

Jones RN, Diem JE, Ziskand MM, et al. 1984. Radiographic evidence of asbestos effects in American marine engineers. J Occup Med 26(4):281-284.

*Jones JS, Pooley FD, Clark NJ, et al. 1980b. The pathology and mineral content of lungs in cases of mesothelioma in the United Kingdom in 1976. IARC Sci Publ 30:187-199.

Jones RN, Hughes JM, Weill H. 1996. Asbestos exposure, asbestosis, and asbestos-attributable lung cancer. Thorax 51:S9-S15.

*Jones RN, McLoud T, Rockoff SD. 1988b. The radiographic pleural abnormalities in asbestos exposure: Relationship to physiologic abnormalities. J Thoracic Imaging 3:57-66.

Joubert L, Seidman H, Selikoff IJ. 1991. Mortality experience of family contacts of asbestos factory workers. Ann NY Acad Sci 416-418.

Jung M, Davis WP, Taatjes DJ, et al. 2000. Asbestos and cigarette smoke cause increased DNA strand breaks and necrosis in bronchiolar epithelial cells in vivo. Free Radic Biol Med 28(8):1295-1299.

Jung T, Burkart W. 1997. Assessment of risks from combined exposures to radiation and other agents at environmental levels. In: Wei L, Sugarhara T, Tao Z, ed. High levels of natural radiation 1996: Radiation dose and health effects. New York, NY: Elsevier Science, 167-178.

Juntunen J, Oksa P, Pukkala E, et al. 1997. Neurological signs in relation to cancer in patients with asbestosis. Occup Environ Med 54:746-749.

Kagamimori S, Scott MP, Brown DG, et al. 1980. Effects of chrysotile asbestos on mononuclear cells *in vitro*. Br J Exp Pathol 61:55-60.

*Kagan E. 1988. Current issues regarding the pathobiology of asbestosis: A chronologic perspective. J Thorac Imaging 3:1-9.

*Kagan E, Solomon A, Cochrane JC, et al. 1977. Immunological studies of patients with asbestosis: I. Studies of cell-mediated immunity. Clin Exp Immunol 28:261-267.

*Kaiglová A, Kovácíková Z, Hurbánková M. 1999. Impact of acute and subchronic asbestos exposure on some parameters of antioxidant defense system and lung tissue injury. Ind Health 37:348-351.

*Kamal AA, El Khafif M, Koraah S, et al. 1992. Blood superoxide dismutase and plasma malondialdehyde among workers exposed to asbestos. Am J Ind Med 21:353-361.

*Kamal AA, Gomaa A, El Khafif M, et al. 1989. Plasma lipid peroxides among workers exposed to silica or asbestos dusts. Environ Res 49:173-180.

*Kambic V, Radsel Z, Gale N. 1989. Alterations in the laryngeal mucosa after exposure to asbestos. Br J Ind Med 46:717-723.

*Kamp DW, Weitzman SA. 1997. Asbestosis: Clinical spectrum and pathogenic mechanisms. Proc Soc Exp Biol Med 214:12-26.

*Kamp DW, Weitzman SA. 1999. The molecular basis of asbestos induced lung injury. Thorax 54:638-652.

Kamp DW, Dunne M, Dykewicz MS, et al. 1993. Asbestos-induced injury to cultured human pulmonary epithelial-like cells: Role of neutrophil elastase. J Leukoc Biol 54(1):73-80.

*Kamp DW, Graceffa P, Pryor WA, et al. 1992. The role of free radicals in asbestos-induced diseases. Free Rad Biol Med 12:293-315.

*Kamp DW, Greenberger MJ, Sbalchierro JS, et al. 1998. Cigarette smoke augments asbestos-induced alveolar epithelial cell injury: Role of free radicals. Free Radic Biol Med 25:728-739.

Kamp DW, Israbian VA, Presusen SE, et al. 1995a. Asbestos causes DNA strand breaks in cultured pulmonary epithelial cells: Role of iron-catalyzed free radicals. Am J Physiol 268(12):L471-L480.

Kamp DW, Israbian VA, Yeldandi AV, et al. 1995b. Phytic acid, an iron chelator, attenuates pulmonary inflammation and fibrosis in rats after intratracheal instillation of asbestos. Toxicol Pathol 23:689-695.

Kanarek MS. 1983. The San Francisco Bay epidemiology studies on asbestos in drinking water and cancer incidence: Relationship to studies in other locations and pointers for further research [Commentary]. Environ Health Perspect 53:105-106.

*Kanarek MS. 1989. Epidemiological studies on ingested mineral fibers: Gastric and other cancers. IARC Sci Pub 90:428-437.

*Kanarek MS, Conforti PM, Jackson LA, et al. 1980. Asbestos in drinking water and cancer incidence in the San Francisco Bay Area. Am J Epidemiol 112:54-72.

*Kanarek MS, Conforti PM, Jackson LA, et al. 1981. Chrysotile asbestos fibers in drinking water from asbestos-cement pipe. Environ Sci Technol 15:923-925.

Kanazawa K, Birbeck MS, Carter RL, et al. 1969. Migration of asbestos fibers from subcutaneous injection sites in mice. Br J Cancer 24:96-106.

Kane AB. 1992. Environmental pathology: The pathologist's responsibility? Hum Pathol 23:1093-1094.

Kane AB. 1996. Mechanisms of mineral fibre carcinogenesis. In: Kane AB, Bofetta P, Saracci R, et al., eds. Mechanisms of fibre carcinogenesis. Lyon, France: International Agency for Research on Cancer. IARC Scientific Publications No. 140, 11-34.

Kane MJ, Chahinian AP, Holland JF. 1990. Malignant mesothelioma in young adults. Cancer 65:1449-1455.

*Kang S-K, Burnett CA, Freund E, et al. 1997. Gastrointestinal cancer mortality of workers in occupations with high asbestos exposures. Am J Ind Med 31:713-718.

Kannerstein M. 1979. Recent advances and perspectives relevant to the pathology of asbestos-related diseases in man. IARC Sci Publ 30:149-162.

Kannio A, Ridanpaa M, Koskinen H, et al. 1996. A molecular and epidemiological study on bladder cancer: P53 mutations, tobacco smoking, and occupational exposure to asbestos. Cancer Epidemiol Biomarkers Prev 5:33-39.

*Kaplan DE. 1993. Unregulated disposal of asbestos contaminated shower water effluent: A question of public health risk. J Environ Health 55(6):6-8.

*Kaplan H, Renier A, Javrand MG, et al. 1980. Sister chromatid exchanges in mesothelial cells cultured with chrysotile fibers. In: Brown et al., eds. The *in vitro* effects of mineral dusts. London, England: Acad. Press, 251.

Karjalainen A, Anttila S, Heikkila L, et al. 1993a. Asbestos exposure among Finnish lung cancer patients: Occupational history and fiber concentration in lung tissue. Am J Ind Med 23(3):461-471.

Karjalainen A, Anttila S, Heikkila L. 1993b. Lobe of origin of lung cancer among asbestos-exposed patients with or without diffuse interstitial fibrosis. Scand J Work Environ Health 19(4):102-107.

*Karjalainen A, Banhala E, Karhunen PJ, et al. 1994a. Asbestos exposure and pulmonary fiber concentrations of 300 Finnish urban men. Scand J Work Environ Health 20:34-41.

Karjalainen A, Karhunen PJ, Lalu K, et al. 1951. Pleural plaques and exposure to mineral fibres in a male urban necropsy population. Occup Environ Med 51:456-460.

Karjalainen A, Meurman LO, Pukkala E. 1994b. Four cases of mesothelioma among Finnish anthophyllite miners. Occup Environ Med 51(3):212-215.

*Karjalainen A, Nurminen M, Vanhala E, et al. 1996a. Pulmonary asbestos bodies and asbestos fibers as indicators of exposure. Scand J Work Environ Health 22:34-38.

*Karjalainen A, Piipari R, Mantyla T, et al. 1996b. Asbestos bodies in bronchoalveolar lavage in relation to asbestos bodies and asbestos fibres in lung parenchyma. Eur Resp J 9:1000-1005.

Karjalainen A, Pukkala E, Mattson K, et al. 1997. Trends in mesothelioma incidence and occupational mesotheliomas in Finland in 1960-1995. Scand J Work Environ Health 23:266-270.

Karjalainen A, Taikina-Aho O, Anttila S, et al. 1994c. Asbestos exposure among Finnish lung cancer patients. Comparison of scanning and transmission electron microscopy in the analysis of lung burden. Ann Occup Hyg 38:657-663.

Karjalainen A, Vanhala E, Karhunen PJ, et al. 1994d. Asbestos exposure and pulmonary fiber concentrations of 300 Finnish urban men. Scand J Work Environ Health 20(1):34-41.

Karn CM, Socinski MA, Fletcher JA, et al. 1994. Cardiac synovial sarcoma with translocation (X;18) associated with asbestos exposure. Cancer 73(1):74-78.

*Karnak Corporation. 1998. The U.S. Court of Appeals for the Fifth Circuit overturns EPA's ban rule on asbestos. Http://www.karnakcorp.com/faq/faq-aiaruling.htm. April 19, 2001.

Kauffer E, Vigneron JC, Fabries JF, et al. 1996. The use of a new static device based on the collection of the thoracic fraction for the assessment of the airborne concentration of asbestos fibres by transmission electron microscopy. Ann Occup Hyg 40:311-319.

Kawai A, Nagasaka Y, Muraki M, et al. 1997. Brain metastasis in malignant pleural mesothelioma. Intern Med 36:591-594.

Kayser K, Seemann C, André S, et al. 2000. Association of concentration of asbestos and asbestos-like fibers with the patient's survival and the binding capacity of lung parenchyma to galectin-1 and natural α-galactoside- and α-mannoside-binding immunoglobulin G subfractions from human serum. Pathol Res Pract 196:81-87.

Kazan-Allen L. 2000. The international ban asbestos secretariat. Int J Occup Environ Health 6(2):164.

*Keane MJ, Stephens JW, Zhong B-Z, et al. 1999. A study of the effect of chrysotile fiber surface composition on genotoxicity in vitro. J Toxicol Environ Health A 57:529-541.

Kee ST, Gamsu G, Blanc P. 1996. Causes of pulmonary impairment in asbestos-exposed individuals with diffuse pleural thickening. Am J Respir Crit Care Med 154:789-793.

Kehrer JP, Mossman BT, Sevanian A, et al. 1988. Free radical mechanisms in chemical pathogenesis. Toxicol App Pharmacol 95:349-362.

Kelley J. 1998. Occupational lung disease caused by asbestos, silica, and other silicates. In: Baum GL, Crapo JD, Celli BR, et al., ed. Textbook pulmonary diseases. Philadelphia, PA: Lippincott-Raven, 659-682.

*Kelsey KT, Nelson HH, Wiencke JK, et al. 1997. The glutathione s-transferase theta and mu deletion polymorphisms in asbestosis. Am J Ind Med 31:274-279.

*Kelsey KT, Yano E, Liber HL, et al. 1986. The *in vitro* genetic effects of fibrous erionite and crocidolite asbestos. Br J Cancer 54:107-114.

*Kenne K, Ljungquist S, Ringertz NR. 1986. Effects of asbestos fibers on cell division, cell survival, and formation of thioguanine-resistant mutants in Chinese hamster ovary cells. Environ Res 39:448-464.

Kennedy SM, Vedal S, Mueller N, et al. 1991. Lung function and chest radiograph abnormalities among construction insulators. Am J Ind Med 20:673-684.

*Kennedy TP, Dodson R, Rao NV, et al. 1989. Communication. Dusts causing pneumoconiosis generate OH and produce hemolysis by acting as Fenton catalysts. Arch Biochem Biophys 269:359-364.

Khan SG, Ali S, Rahman Q. 1990. Protective role of ascorbic acid against asbestos induced toxicity in rat lung: *In vitro* study. Drug Chem Toxicol 13:249-256.

*Khan SG, Ali S, Rahman Q. 1992. Interaction of mineral fibres with lung cytochrome P-450 system: Impairment of drug metabolizing enzyme activities. Chemosphere 24:959-968.

*Kienast K, Kaes C, Drumm K, et al. 2000. Asbestos-exposed blood monocytes - deoxyribonucleic acid strand lesions in co-cultured bronchial epithelial cells. Scand J Work Environ Health 26(1):71-77.

Kilanowicz A, Czerski B, Sapota A. 1999. The disposition and metabolism of naphthalene in rats. Int J Occup Med Environ Health 12(3):209-219.

Kilburn KH. 2000. Prevalence and features of advanced asbestosis: (ILO profusion scores above 2/2). Arch Environ Health 55(2):104-108.

Kilburn KH, Warshaw RH. 1992a. Irregular opacities in the lung, occupational asthma, and airways dysfunction in aluminum workers. Am J Ind Med 21:845-853.

Kilburn KH, Warshaw RH. 1992b. Severity of pulmonary asbestosis as classified by international labour organization profusion of irregular opacities in 8749 asbestos-exposed American workers: Those who never smoked compared with those who ever smoked. Arch Intern Med 152(2):325-327.

*Kilburn KH, Warshaw RH. 1994. Airways obstruction from asbestos exposure: Effects of asbestosis and smoking. Chest 106:1061-1070.

*Kilburn KH, Warshaw RH, Thornton JC. 1995. Do radiographic criteria for emphysema predict physiologic impairment? Chest 107:1225-1231.

Kimizuka G, Azuma M, Ishibashi M, et al. 1993. Co-carcinogenic effect of chrysotile and amosite asbestos with benzo(*a*)pyrene in the lung of hamsters. Acta Pathol Jpn 43(4):149-153.

*Kimizuka G, Shinozaki K, Hayashi Y. 1992. Comparison of the pulmonary responses to chrysotile and amosite asbestos administered intratracheally. I. Early phase of cellular reactions. Acta Pathol Jpn 42(10):707-711.

King JA, Wong SW. 1996. Autopsy evaluation of asbestos exposure: Retrospective study of 135 cases with quantitation of ferruginous bodies in digested lung tissue. South Med J 89:380-385.

King JAC, Tucker JA, Wong SW. 1997. Mesothelioma: A study of 22 cases. South Med J 90:199-205.

*Kinnula VL. 1999. Oxidant and antioxidant mechanisms of lung disease caused by asbestos fibres. Eur Resp J 14:706-716.

Kinnula VL, Linnala A, Viitala E, et al. 1998. Tenascin and fibronectin expression in human mesothelial cells and pleural mesothelioma cell-line cells. Am J Respir Cell Mol Biol 19:445-452.

Kiritani EW. 1990. Asbestos and stomach cancer in Japan - a connection? Med Hypotheses 33:159-160.

Kishimoto T. 1992a. Cancer due to asbestos exposure. Chest 101:58-63.

Kishimoto T. 1992b. Coexistence of a malignant fibrous histiocytoma and asbestos exposure. Brief report. Pathobiology 60(6):332-334.

Kishimoto T. 1992c. Intensity of exposure to asbestos in metropolitan Kure City as estimated by autopsied cases. Cancer 69(10):2598-2602.

Kishimoto T, Ishikura M. 1991. Intensities of asbestos exposure in patients admitted to Kure Kyosai Hospital, Japan. Jpn J Chest Dis 50(8):637-641.

Kishimoto T, Okada K. 1988. The relationship between lung cancer and asbestos exposure. Chest 94:486-490.

*Kishimoto T, Hashimoto H, Ono T, et al. 1992. Synchronous double malignancy: Adenocarcinoma of lung and malignant astrocytoma induced by asbestos exposure. Cancer Invest 10(2):129-133.

Kishimoto T, Ono T, Okada K, et al. 1989. Relationship between number of asbestos bodies in autopsy lung and pleural plaques on chest x-ray film. Chest 95:549-552.

*Kitamura F, Araki S, Tanigawa T, et al. 1998. Assessment of mutations of Ha and Ki-ras oncogenes and the p53 suppressor gene in seven malignant mesothelioma patients exposed to asbestos - PCR-SSCP and sequencing analyses of paraffin-embedded primary tumors. Ind Health 36:52-56.

*Klaas VE. 1993. A diagnostic approach to asbestosis, utilizing clinical criteria, high resolution computed tomography, and gallium scanning. Am J Ind Med 23(5):801-809.

Kleinfeld M, Messite J, Kooyman O, et al. 1967. Mortality among talc miners and millers in New York State. Arch Environ Health 14:663-667.

*Kleinfeld M, Messite J, Zaki H. 1974. Mortality experiences among talc workers: A follow-up study. J Occup Med 16:345-349.

Kleymenova EV, Bianchi AA, Kley N, et al. 1997. Characterization of the rat neruofibromatosis 2 gene and its involvement in asbestos-induced mesothelioma. Mol Carcinog 18:54-60.

Klockars M, Savolainen H. 1992. Tumour necrosis factor enhances the asbestos-induced production of reactive oxygen metabolites by human polymorphonuclear leucocytes (PMN). Clin Exp Immunol 90(1):68-71.

*Koerten HK, de Bruijn JD, Daems WT. 1990a. The formation of asbestos bodies by mouse peritoneal macrophages. Am J Pathol 137:121-134.

*Koerten HK, Hazekamp J, Kroon M. et al. 1990b. Asbestos body formation and iron accumulation in mouse peritoneal granulomas after the introduction of crocidolite asbestos fibers. Am J Pathol 136:141-157.

*Kokkola K, Huuskonen MS. 1979. Electrocardiographic signs of cor pulmonale in asbestosis. Int Arch Occup Environ Health 43:167-175.

*Kominsky JR, Freyberg RW, Clark PJ, et al. 1998a. Asbestos exposures during routine floor tile maintenance. Part 1: Spray-buffing and wet-stripping. Appl Occup Environ Hyg 13(2):101-106.

*Kominsky JR, Freyberg RW, Clark PJ, et al. 1998b. Asbestos exposures during routine floor tile maintenance. Part 2: Ultra high speed burnishing and wet-stripping. Appl Occup Environ Hyg 13(2):107-112.

*Komori M, Nishio K, Kitada M, et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human liver. Biochemistry 29:4430-4433.

*Korkina LG, Durnev AD, Suslova TB, et al. 1992. Oxygen radical-mediated mutagenic effect of asbestos on human lymphocytes: suppression by oxygen radical scavengers. Mutat Res 265:245-253.

Koshi K, Kohyama N, Myojo, et al. 1991. Cell toxicity, hemolytic action and clastogenic activity of asbestos and its substitutes. Ind Health 29:37-56.

Koskinen K, Rinne J-P, Zitting A, et al. 1996. Screening for asbestos-induced disease in Finland. Am J Ind Med 30:241-251.

Koskinen K, Zitting A, Tossavainen A, et al. 1998. Radiographic abnormalities among Finnish construction, shipyard and asbestos industry workers. Scand J Work Environ Health 24:109-117.

*Kostyuk VA, Potapovich AI, Speransky SD, et al. 1996. Protective effect of natural flavonoids on rat peritoneal macrophages injury caused by asbestos fibers. Free Radic Biol Med 21:487-493.

Koustas RN. 1991. Control of incidental asbestos exposure at hazardous waste sites. J Air Waste Manage Assoc 41:1004-1009.

Kramer JR. 1976. Fibrous cummingtonite in Lake Superior. Can Mineral 14:91-98.

*Kraus T, Drexler H, Weber A, et al. 1995. The association of occupational asbestos dust exposure and laryngeal carcinoma. Isr J Med Sci 31:540-548.

*Kravchenko IV, Furalyov VA, Vasylieva LA, et al. 1998. Spontaneous and asbestos-induced transformation of mesothelial cells in vitro. Teratog Carcinog Mutagen 18:141-151.

*Krishnan K, Andersen ME. 1994. Physiologically-based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. Principles and methods of toxicology. New York, NY: Raven Press, Ltd., 149-188.

*Krishnan K, Andersen ME, Clewell H 3rd, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang R, ed. Toxicology of chemical mixtures. New York: Academic Press, 399-437.

Kronenberg RS, Levin JL, Dodson RF, et al. 1991. Asbestos-related disease in employees of a steel mill and a glass bottle-manufacturing plant. Ann NY Acad Sci 397-403.

*Kubota M, Ksgamimori S, Yokoyama K, et al. 1985. Reduced killer cell activity of lymphocytes from patients with asbestosis. Br J Ind Med 42:276-280.

Kurumatani N, Natori Y, Mizutani R, et al. 1999. A historical cohort mortality study of workers exposed to asbestos in a refitting shipyard. Ind Health 37:9-17.

Kuwahara M, Kuwahara M, Verma K, et al. 1994. Asbestos exposure stimulates pleural mesothelial cells to secrete the fibroblast chemoattractant, fibronectin. Am J Respir Cell Mol Biol 10:167-176.

Lakshmi VM, Zenser TV, Davis BB. 1994. Mechanism of 3-(glutathion-S-yl)-benzidine formation. Toxicol Appl Pharmacol 125:256-263.

Landrigan PJ. 1991. A population of children at risk of exposure to asbestos in place. Ann NY Acad Sci 283-286.

*Landrigan PJ. 1998. Asbestos–still a carcinogen [Editorial]. New Engl. J. Med. 338:1618-1619.

Landrigan PJ, Nicholson WJ, Suzuki Y, et al. 1999. The hazards of chrysotile asbestos: A critical review. Ind Health 37:271-280.

*Lange A, Garncarek D, Tomeczko J, et al. 1986. Outcome of asbestos exposure (lung fibrosis and antinuclear antibodies) with respect to skin reactivity: An 8-year longitudinal study. Environ Res 41:1-13.

Lange A, Karabon L, Tomeczko J. 1995. Interleukin-6- and interleukin-4-related proteins (C-reactive protein and IgE) are prognostic factors of asbestos-related cancer. Ann N Y Acad Sci 762:435-438.

*Lange A, Smolik R, Zatonski W, et al. 1974. Autoantibodies and serum immunoglobulin levels in asbestos workers. Int Arch Arbeitsmed 32:313-325.

Lange JH. 1999. A statistical evaluation of asbestos air concentrations. Indoor Built Environ 8:293-303.

*Lange JH, Thomulka KW. 2000a. Air sampling during asbestos abatement of floor tile and mastic. Bull Environ Contam 64:497-501.

*Lange JH, Thomulka KW. 2000b. An evaluation of personal airborne asbestos exposure measurements during abatement of dry wall and floor tile/mastic. Int J Environ Health Res 10:5-19.

*Lange JH, Thomulka KW. 2000c. Area and personal airborne exposure during abatement of asbestos-containing roofing material. Bull Environ Contam Toxicol 64:673-678.

*Lange JH, Lange PR, Reinhard TK, et al. 1996. Ann Occup Hyg 40(4):449-466.

Langer AM, Nolan RP. 1994. Chyrsotile biopersistence in the lungs of persons in the general population and exposed workers. Environ Health Perspect Suppl 102:235-239.

Langer AM, Nolan RP. 1997. Asbestos disease in foundrymen [Letter]. J Occup Environ Med 39:699-700.

*Langer AM, Nolan RP. 1998. Asbestos in the lungs of persons exposed in the USA. Monaldi Arch Chest Dis 53:168-180.

Langer AM, Pooley FD. 1973. Identification of single asbestos fibres in human tissue. IARC Sci Publ 8:119-125.

*Langer AM, Nolan RP, Constantopoulos SH, et al. 1987. Association of Metsovo lung and pleural mesothelioma with exposure to tremolite-containing whitewash. Lancet 1(8539):965-967.

*Lanphear BP, Buncher CR. 1992. Latent period for malignant mesothelioma of occupational origin. J Occup Med 34:718-721.

*Lash TL, Crouch EAC, Green LC. 1997. A meta-analysis of the relation between cumulative exposure to asbestos and relative risk of lung cancer. Occup Environ Med 54:254-263.

Lasky JA, Bonner JC, Brody AR. 1991. The pathobiology of asbestos-induced lung disease: A proposed role for macrophage-derived growth factors. Ann NY Acad Sci 239-244.

*Lasky JA, Bonner JC, Tonthat B, et al. 1996. Chrysotile asbestos induces PDGF-A chain-dependent proliferation in human and rat lung fibroblasts in vitro. Chest 109:26S-28S.

Lasky JA, Tonthat B, Liu J-Y, et al. 1998. Upregulation of the PDGF-alpha receptor precedes asbestos-induced lung fibrosis in rats. Am J Respir Crit Care Med 157:1652-1657.

Laug EP, Nelson AA, Fitzhugh OG, et al. 1950. Liver cell alteration and DDT storage in the fat of the rat induced by dietary levels of 1 to 50 ppm DDT. J Pharmacol Exp Ther 98:268-273.

*Lavappa KS, Fu MM, Epstein SS. 1975. Cytogenetic studies on chrysotile asbestos. Environ Res 10:165-173.

Le Bouffant L, Martin JC, Durif S, et al. 1973. Structure and composition of pleural plaques. IARC Sci Publ 8:249-257.

*Lechner JF, Haugen A, Trump BF, et al. 1983. Effects of asbestos and carcinogenic metals on cultured human bronchial epithelium. In: Harris CC, Autrup HN, eds. Human carcinogenesis. New York, NY: Academic Press, Inc., 561-585.

Lee BW, Wain JC, Kelsey KT, et al. 1998a. Association between diet and lung cancer location. Am J Respir Crit Care Med 158:1197-1203.

Lee BW, Wain JC, Kelsey KT, et al. 1998b. Association of cigarette smoking and asbestos exposure with location and histology of lung cancer. Am J Respir Crit Care Med 157:748-755.

Lee DH. 1974. Biological effects of ingested asbestos: Report and commentary. Environ Health Perspect 9:113-122.

*Lee RJ, Florida RG, Stewart IM. 1995. Asbestos contamination in paraffin tissue blocks. Arch Pathol Lab Med 119:528-532.

*Lee RJ, Van Orden DR, Corn M, et al. 1992. Exposure to airborne asbestos in buildings. Regul Toxicol Pharmacol 16:93-107.

*Lee S-H, Shin M, Lee K-J, et al. 1999. Frequency of sister chromatid exchange in chrysotile-exposed workers. Toxicol Lett 108:315-319.

Lee TC, Gold LI, Reibman J, et al. 1997. Immunohistochemical localization of transforming growth factor-beta and insulin-like growth factor-I in asbestosis in the sheep model. Int Arch Occup Environ Health 69:157-164.

*Lee W-C, Testa JR. 1999. Somatic genetic alterations in human malignant mesothelioma (Review). Int J Oncol 14:181-188.

*Lee W-C, Balsara B, Liu Z, et al. 1996. Loss of heterozygosity analysis defines a critical region in chromosome 1p22 commonly deleted in human malignant mesothelioma. Cancer Res 56:4297-4301.

*Leeder JS, Kearns GL. 1997. Pharmcogenetics in pediatrics: Implications for practice. Pediatr Clin North Am 44:55-77.

Leigh J, Corvalan CF, Grimwood A, et al. 1991. The incidence of malignant mesothelioma in Australia 1982-1988. Am J Ind Med 20:643-655.

Lemaire I. 1991. Selective differences in macrophage populations and monokine production in resolving pulmonary granuloma and fibrosis. Am J Pathol 138:487-495.

Lemaire I, Gingras D, Lemaire S. 1986. Effects of chrysotile asbestos on DNA synthesis and growth of human embryonic lung fibroblasts. J Environ Pathol Toxicol Oncol 6:169-180.

Le Marchadour F, Peoch M, Pasquier B, et al. 1994. Cardiac synovial sarcoma with translocation (X;18) associated with asbestos exposure [Letter]. Cancer 74:986.

*Lemen R, Becking GC, Cantor K, et al. 1987. Report on cancer risks associated with the ingestion of asbestos. Environ Health Perspect 72:253-265.

*Lemen RA, Dement JM, Wagoner JK. 1980. Epidemiology of asbestos-related diseases. Environ Health Perspect 34:1-11.

*Lerman Y, Selikoff IJ, Lilis R, et al. 1986. Clinical findings among asbestos workers in V.S.: Influences of cigarette smoking. Am J Ind Med 10:449-458.

Lesage S. 1993. Methods for the analysis of hazardous wastes. J Chromatogr 642(1-2):65-74.

Lesur O, Bernard AM, Begin RO. 1996. Clara cell protein (CC-16) and surfactant-associated protein A (SP-A) in asbestos-exposed workers. Chest 109:467-474.

*Leung H-W. 1993. Physiologically-based pharmacokinetic modelling. In: Ballentine B, Marro T, Turner P, ed. General and applied toxicology. New York: Stockton Press, 153-164.

*Levin JL, Mclarty JW, Hurst GA, et al. 1998. Tyler asbestos workers: Mortality experience in a cohort exposed to amosite. Occup Environ Med 55:155-160.

Levin SM, Selikoff IJ. 1991. Radiological abnormalities and asbestos exposure among custodians of the New York City board of education. Ann NY Acad Sci 530-539.

*Levy BS, Sigurdson E, Mandel J, et al. 1976. Investigating possible effects of asbestos in city water: Surveillance of gastrointestinal cancer incidence in Duluth, Minnesota. Am J Epidemiol 103:362-368.

*Lew F, Tsang P, Holland JF, et al. 1986. High frequency of immune dysfunctions in asbestos workers and in patients with malignant mesothelioma. J Clin Immunol 6:225-233.

Lewitus Z, Guttmann S, Anbar M. 1962. Effect of thyroid-stimulating hormone (TSH) on the accumulation of perchlorate and fluoroborate ions in the thyroid glands of rats. Endocrinology 70:295-297.

*Lezon-Geyda K, Jaime CM, Godbold JH, et al. 1996. Chrysotile asbestos fibers mediate homologous recombination in rat2 delta fibroblasts: Implications for carcinogenesis. Mutat Res 361:113-120.

Li XY, Lamb D, Donaldson K. 1992. Intratracheal injection of crocidolite asbestos depresses the secretion of tumor necrosis factor by pleural leukocytes in vitro. Exp Lung Res 18:359-372.

Li XY, Lamb D, Donaldson K. 1994. Mesothelial cell injury caused by pleural leukocytes from rats treated with intratracheal instillation of crocidolite asbestos or *Corynebacterium parvum*. Environ Res 64(2):181-191.

*Libbus BL, Illenye SA, Craighead JE. 1989. Induction of DNA strand breaks in cultured rat embryo cells by crocidolite asbestos as assessed by nick translation. Cancer Res 49:5713-5718.

Liddell D. 1994. Cancer mortality in chrysotile mining and milling: Exposure-response. Ann Occup Hyg 38:519-523.

Liddell FDK. 1994. Mining and milling. Ann Occup Hyg 38:412.

Liddell FD, Hanley JA. 1985. Relations between asbestos exposure and lung cancer SMRS in occupational cohort studies. Br J Ind Med 42:389-396.

Liddell FDK, McDonald JC. 1980. Radiological findings as predictors of mortality in Quebec asbestos workers. Br J Ind Med 37:257-267.

*Liddell FDK, McDonald AD, McDonald JC. 1997. The 1891-1920 birth cohort of Quebec chrysotile miners and millers: Development from 1904 and mortality to 1992. Ann Occup Hyg 41:13-36.

*Liddell FDK, McDonald AD, McDonald JC. 1998. Dust exposure and lung cancer in Quebec chyrsotile miners and millers. Ann Occup Hyg 42:7-20.

Lilienfeld DE. 1991a. Asbestos-associated pleural mesothelioma in school teachers: A discussion of four cases. Ann NY Acad Sci 643:454-486.

Lilienfeld DE. 1991b. The silence: The asbestos industry and early occupational cancer research--a case study. Am J Public Health 81(6):791-800.

Lilienfeld DE, Mandel JS, Coin P, et al. 1988. Projection of asbestos related diseases in the United States, 1985-2009 I. Cancer. Br J Ind Med 45:283-291.

Lilis R, Miller A, Godbold J, et al. 1991. Radiographic abnormalities in asbestos insulators: Effects of duration from onset of exposure and smoking. Relationships of dyspnea with parenchymal and pleural fibrosis. Am J Ind Med 20:1-15.

*Lim Y, Kim S-H, Kim K-A, et al. 1997. Involvement of protein kinase C, phospholipase C, and protein tyrosine kinase pathways in oxygen radical generation by asbestos-stimulated alveolar macrophage. Environ Health Perspect Suppl 105:1325-1327.

Lindroos PN, Coin PG, Badgett A, et al. 1997. Alveolar macrophages stimulated with titanium dioxide, chrysotile asbestos, and residual oil fly ash upregulate the PDGF receptor-alpha on lung fibroblasts through an IL-1 beta-dependent mechanism. Am J Respir Cell Mol Biol 16:283-292.

Linnalnmaa K, Pelin K, Vanhala E, et al. 1993. Gap junctional intercellular communication of primary and asbestos-associated malignant human mesothelial cells. Carcinogenesis 14(8):1597-1602.

*Lippmann M. 1988. Review: Asbestos exposure indices. Environ Res 46:86-106.

*Lippmann M. 1990. Effects of fiber characteristics on lung deposition, retention, and disease. Environ Health Perspect 88:311-317.

*Lippmann M. 1994. Deposition and retention of inhaled fibres: Effects on incidence of lung cancer and mesothelioma. Occup Environ Med 51:793-798.

Lippmann M, Schlesinger RB. 1983. Interspecies comparisons of particle deposition and mucociliary clearance in tracheobronchial airways. J Toxicol Environ Health :441-463.

Lison D, Knoops B, Lauwerys R. 1989. Effect of retinoic acid on asbestos induced plasminogen activator activity of peritoneal macrophages. Br J Ind Med 46:496-497.

Little DN. 1995. Children and environmental toxins. Prim Care 22:69-79.

*Liu J-Y, Brass DM, Hoyle GW, et al. 1998. TNF-α receptor knockout mice are protected from the fibroproliferative effects of inhaled asbestos fibers. Am J Pathol 153(6):1839-1847.

Liu JY, Morris GF, Lei WH, et al. 1997. Rapid activation of PDGF-A and -B expression at sites of lung injury in asbestos-exposed rats. Am J Respir Cell Mol Biol 17:129-140.

*Livingston, AL. 1978. Forage plant estrogens. J Toxicol Environ Health 4:301.

*Livingston GK, Rom WN, Morris MV. 1980. Asbestos-induced sister chromatid exchanges in cultured Chinese hamster ovarian fibroblast cells. J Environ Pathol Toxicol 3:373-382.

*Lockey JE, Brooks SM, Jarabek AM, et al. 1984. Pulmonary changes after exposure to vermiculite contaminated with fibrous tremolite. Am Rev Respir Dis 129(6):952-958.

Longo WE, Rigler MW, Slade J. 1995. Crocidolite asbestos fibers in smoke from original Kent cigarettes. Cancer Res 55:2232-2235.

Lotan R. 1999. Lung cancer promotion by beta-carotene and tobacco smoke: Relationship to suppression of retinoic acid receptor-beta and increased activator protein-1? J Natl Cancer Inst 91:7-9.

Lozewicz S, Reznek RH, Herdman M, et al. 1989. Role of computed tomography in evaluating asbestos related lung disease. Br J Ind Med 46:777-781.

*Lu J, Keane MJ, Ong T, et al. 1994a. *In vitro* genotoxicity studies of chrysotile asbestos fibers dispersed in simulated pulmonary surfactant. Mutat Res 320(4):253-259.

*Lu YY, Jhanwar SC, Cheng JQ, et al. 1994b. Deletion mapping of the short arm of chromosome 3 in human malignant mesothelioma. Genes Chromosomes Cancer 9:76-80.

*Luce D, Bugel I, Goldberg P, et al. 2000. Environmental exposure to tremolite and respiratory cancer in New Caledonia: A case-control study. Am J Epidemiol 151(3):259-265.

*Lund LG, Aust AE. 1991a. Iron-catalyzed reactions may be responsible for the biochemical and biological effects of asbestos. BioFactors 3:83-89.

*Lund LG, Aust AE. 1991b. Mobilization of iron from crocidolite asbestos by certain chelators results in enhanced crocidolite-dependent oxygen consumption. Arch Biochem Biophys 287:91-96.

*Lund LG, Aust AE. 1992. Iron mobilization from crocidolite asbestos greatly enhances crocidolite-dependent formation of DNA single-strand breaks in X174 RFI DNA. Carcinogenesis 13:637-642.

Lund LG, Williams MG, Dodson RF, et al. 1994. Iron associated with asbestos bodies is responsible for the formation of single strand breaks in φ X174 RFI DNA. Occup Environ Med 51(3):200-204.

Luo J-C, Zehab R, Anttila S, et al. 1994. Detection of serum p53 protein in lung cancer patients. J Occup Med 36:155-160.

*Luo SQ, Liu XZ, Wang CJ. 1992. An investigation of crocidolite contamination and experimental study in southwestern China. J Hyg Epidemiol Microbiol Immunol 36(2):223-224.

*Luster MI, Simeonova PP. 1998. Asbestos induces inflammatory cytokines in the lung through redox sensitive transcription factors. Toxicol Lett 102-103:271-275.

Lutz W, Krajewska B, Pilacic B. 1997. Determination of tissue polypeptide antigens (TPA) and carcinoembryonic antigen (CEA) in serum: Its value in the preliminary cancer risk assessment in asbestos exposed workers. Int J Occup Med Environ Health 10:259-265.

MacDonald JL, Kane AB. 1997. Mesothelial cell proliferation and biopersistence of wollastonite and crocidolite asbestos fibers. Fundam Appl Toxicol 38:173-183.

MacRae KD. 1988. Asbestos in drinking water and cancer. J R Coll Physicians Lond 22:7-10.

*Magee F, Wright JL, Chan N, et al. 1986. Malignant mesothelioma caused by childhood exposure to long-fiber low aspect ratio tremolite. Am J Ind Med 9:529-533.

*Magnani C, Leporati M. 1998. Mortality from lung cancer and population risk attributable to asbestos in an asbestos cement manufacturing town in Italy. Occup Environ Med 55:111-114.

Magnani C, Borgo G, Betta GP, et al. 1991. Mesothelioma and non-occupational environmental exposure to asbestos [Letter]. Lancet 338(50):8758.

Magnani C, Ivaldi C, Botta M, et al. 1997. Pleural malignant mesothelioma and environmental asbestos exposure in Casale Monferrato, Piedmont. Preliminary analysis of a case-control study. Med Lav 88:302-309.

Magnani C, Mollo F, Paoletti L, et al. 1998. Asbestos lung burden and asbestosis after occupational and environmental exposure in an asbestos cement manufacturing area: A necropsy study. Occup Environ Med 98:840-846.

*Magnani C, Terracini B, Ivaldi C, et al. 1993. A cohort study on mortality among wives of workers in the asbestos cement industry in Casale Monferrato, Italy. Br J Ind Med 50(9):779-784.

Magnani C, Terracini B, Ivaldi C, et al. 1995. Pleural malignant mesothelioma and non-occupational exposure to asbestos in Casale Monferrato, Italy. Occup Environ Med 52:362-367.

Maguire GP, Meggs LG, Addonizio J, et al. 1991. Association of asbestos exposure, retroperitoneal fibrosis, and acute renal failure. NY State J Med 91(8):357-359.

*Mahmood N, Khan SG, Ali S, et al. 1993. Asbestos induced oxidative injury to DNA. Ann Occup Hyg 37(3):315-319.

Maier H, Tisch M. 1997. Epidemiology of laryngeal cancer. In: Kleinasser O, Glanz H, Olofsson J, ed. Advances in larynogology in Europe. Elsevier Science, 129-133.

*Malorni W, Iosi F, Falchi M, et al. 1990. On the mechanism of cell internalization of chrysotile fibers: An immunocytochemical and ultrastructural study. Environ Res 52:164-177.

Maltoni C. 1999. Call for an international ban on asbestos. Toxicol Ind Health 15:529-531.

Maltoni C, Minardi F. 1989. Recent results of carcinogenicity bioassays of fibres and other particulate materials. Bologna, Italy: Institute of Oncology, 46-53.

Maltoni C, Pinto C. 1997. Mesotheliomas in some selected Italian population groups. Med Lav 88:321-332.

Maltoni C, Pinto C, Carnuccio R, et al. 1995. Mesotheliomas following exposure to asbestos used in railroads: 130 Italian cases. Med Lav 86:461-477.

Maltoni C, Pinto C, Mobiglia A. 1991. Mesotheliomas following exposure to asbestos used in railroads: The Italian cases. Toxicol Ind Health 7:1-45.

Maltoni C, Pinto C, Valenti D, et al. 1994. Mesotheliomas following exposure to asbestos used in sugar refineries: Report of the eleven Italian cases. J Occup Med Toxicol 3:233-238.

Manavoglu O, Orhan B, Evrensel T, et al. 1996. Malignant peritoneal mesothelioma following asbestos exposure. J Environ Pathol Toxicol Oncol 15:191-194.

Mandel JS, McLaughlin JK, Schlehofer B, et al. 1995. International renal-cell cancer study. IV. Occupation. Int J Cancer 61:601-605.

Manning LS, Davis MR, Robinson BWS. 1991. Asbestos fibres inhibit the *in vitro* activity of lymphokine-activated killer (LAK) cells from healthy individuals and patients with malignant mesothelioma. Clin Exp Immunol 83:85-91.

Manos CG, Patel-Mandlik KJ, Lisk DJ. 1992. Prevalence of asbestos in composted waste from 26 communities in the United States. Arch Environ Contam Toxicol 23 (2):266-269.

*Manos CG, Patel-Mandlik KJ, Lisk DJ. 1993. Asbestos in yard or sludge composts from the same community as a function of time-of-waste-collection. Chemosphere 26(8):1537-1540.

*Manos CG, Patel-Mandlik KJ, Ross BJ, et al. 1991. Prevalence of asbestos in sewage sludges from 51 large and small cities in the united states. Chemosphere 22:963-973.

Manzini VDP, Brollo A, Franceschi S, et al. 1993. Prognostic factors of malignant mesothelioma of the pleura. Cancer 72:410-417.

Maples KR, Johnson NF. 1992. Fiber-induced hydroxyl radical formation: Correlation with mesothelioma induction in rats and humans. Carcinogenesis 13(11):2035-2039.

*Marczynski B, Czuppon AB, Marek W, et al. 1994a. Increased incidence of DNA double-strand breaks and anti-ds DNA antibodies in blood of workers occupationally exposed to asbestos. Hum Exp Toxicol 13(1):3-9.

*Marczynski B, Kerenyi T, Czuppon AB, et al. 1994b. Increased incidence of DNA double-strand breaks in lung and liver of rats after exposure to crocidolite asbestos fibers. Inhal Toxicol 6:395-406.

*Marczynski B, Kerenyi T, Marek W, et al. 1994c. Induction of DNA - damage after rats exposure to crocidolite asbestos fibers. In: Davis JMG, Jaurand MC, ed. Cellular and molecular effects of mineral and synthetic dusts and fibres. Berlin: Springer-Verlag, 227-232.

*Marczynski B, Kraus T, Rozynek P, et al. 2000a. Association between 8-hydroxy-2'-deoxyguanosine levels in DNA of workers highly exposed to asbestos and their clinical data, occupational and non-occupational confounding factors, and cancer. Mutat Res 468:203-212.

*Marczynski B, Rozynek P, Kraus T, et al. 2000b. Levels of 8-hydroxy-2'-deoxyguanosine in DNA of white blood cells from workers highly exposed to asbestos in Germany. Mutat Res 468:195-202.

*Markowitz SB, Morabia A, Lilis R, et al. 1997. Clinical predictors of mortality from asbestosis in the North American insulator cohort, 1981 to 1991. Am J Respir Crit Care Med 156:101-108.

Marsella JM, Liu BL, Vaslet CA, et al. 1997. Susceptibility of p53-deficient mice to induction of mesothelioma by crocidolite asbestos fibers. Environ Health Perspect Suppl 105:1069-1972.

*Marsh GM. 1983. Critical review of epidemiologic studies related to ingested asbestos. Environ Health Perspect 53:49-56.

*Marsh JP, Mossman BT. 1991. Role of asbestos and active oxygen species in activation and expression of ornithine decarboxylase in hamster tracheal epithelial cells. Cancer Res 51:167-173.

Martuzzi M, Comba P, De Santis M, et al. 1998. Asbestos-related lung cancer mortality in Piedmont, Italy. Am J Ind Med 33:565-570.

Masson TJ, McKay FW, Miller RW. 1974. Asbestos-like fibers in Duluth water supply: Relation to cancer mortality. JAMA 228:1019-1020.

*Mast RW, Hesterberg TW, Glass LR, et al. 1994. Chronic inhalation and biopersistence of refractory ceramic fiber in rats and hamsters. Environ Health Perspect Suppl 102:207-209.

*Mast RW, McConnell EE, Anderson R, et al. 1995. Studies on the chronic toxicity (inhalation) of four types of refractory ceramic fiber in male Fischer 344 rats. Inhal Toxicol 7:425-467.

*Mayne ST, Redlich CA, Cullen MR. 1998. Dietary vitamin A and prevalence of bronchial metaplasia in asbestos-exposed workers. Am J Clin Nutr 68:630-635.

*Mayr U, Butsch A and Schneider S. 1992. Validation of two in vitro test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. Toxicology 74:135-149.

Mays CW, Spiess H. 1984. Bone sarcomas in patients given radium-224. In: Boice JD Jr, Fraumeni JF Jr, eds. Radiation carcinogenesis: Epidemiology and biological significance. New York, NY: Raven Press, 241-252.

McCaughey WT. 1986. Neoplastic asbestos-induced disease. Mt Sinai J Med (NY) 53:416-420.

McClellan RO. 1997. Use of mechanistic data in assessing human risks from exposure to particles. Environ Health Perspect Suppl 105:1363-1372.

*McConnell EE, Chevalier HJ, Hesterberg TW, et al. 1994. Comparison of the effects of chrysotile and crocidolite asbestos in rats after inhalation for 24 months. In: Mohr U, Dungworth DL, Mauderly JL, et al., ed. Toxic and carcinogenic effects of solid particles in the respiratory tract. Washington, DC: ILSI Press, 461-467.

McConnell EE, Rutter HA, Ulland BM, et al. 1983a. Chronic effects of dietary exposure to amosite asbestos and tremolite in F344 rats. Environ Health Perspect 53:27-44.

McConnell EE, Shefner AM, Rust JH, et al. 1983b. Chronic effects of dietary exposure to amosite and chrysotile asbestos in Syrian golden hamsters. Environ Health Perspect 53:11-25.

*McConnochie K, Simonato L, Mayrides P, et al. 1987. Mesothelioma in Cyprus: The role of tremolite. Thorax 42:342-347.

*McDonald AD, McDonald JC. 1980. Malignant mesothelioma in North America. Cancer 46:1650-1656.

*McDonald AD, Case BW, Churg A, et al. 1997. Mesothelioma in Quebec chrysotile miners and millers: Epidemiology and aetiology. Ann Occup Hyg 41:707-719.

*McDonald AD, Fry JS, Woolley AJ, et al. 1982. Dust exposure and mortality in an American factory using chrysotile, amosite, and crocidolite in mainly textile manufacture. Br J Ind Med 39:368-374.

*McDonald AD, Fry JS, Woolley AJ, et al. 1983. Dust exposure and mortality in an American chrysotile textile plant. Br J Ind Med 40:361-367.

*McDonald AD, Fry JS, Wooley AJ, et al. 1984. Dust exposure and mortality in an American chrysotile asbestos friction products plant. Br J Ind Med 41:151-157.

*McDonald JC. 1998a. Mineral fibre persistence and carcinogenicity. Ind Health 36:372-375.

*McDonald JC. 1998b. Unfinished business: The asbestos textiles mystery. Ann Occup Hyg 42:3-5.

*McDonald JC, McDonald AD. 1997. Chrysotile, tremolite and carcinogenicity. Ann Occup Hyg 41:699-705.

*McDonald JC, Armstrong B, Case B, et al. 1989. Mesothelioma and asbestos fiber type. Evidence from lung tissue analysis. Cancer 63:1544-1547.

*McDonald JC, Liddell FD, Dufresne A, et al. 1993. The 1891-1920 birth cohort of Quebec chrysotile miners and millers: Mortality 1976-88. Br J Ind Med 50(12):1073-1081.

*McDonald JC, Liddell FD, Gibbs GW, et al. 1980. Dust exposure and mortality in chrysotile mining, 1910-75. Br J Ind Med 37:11-24.

*McDonald JC, McDonald AD, Armstrong B, et al. 1986a. Cohort study of mortality of vermiculite miners exposed to tremolite. Br J Ind Med 43:436-444.

*McDonald JC, McDonald AD, Hughes JM. 1999. Chrysotile, tremolite and fibrogenicity. Ann Occup Hyg 43(7):439-442.

*McDonald JC, McDonald AD, Sebastien P, et al. 1988. Health of vermiculite miners exposed to trace amounts of fibrous tremolite. Br J Ind Med 45:63-634.

*McDonald JC, Sebastien P, Armstrong B. 1986b. Radiological survey of past and present vermiculite miners exposed to tremolite. Br J Ind Med 43:445-449.

*McDonald JC, Sebastien P, Case B. 1992. Ferruginous body counts in sputum as an index of past exposure to mineral fibers. Ann Occup Hyg 36(3):271-82.

*McFadden D, Wright J, Wiggs B, et al. 1986. Cigarette smoke increases the penetration of asbestos fibers into airway walls. Am J Pathol 123:95-99.

McGavin C, Hughes P. 1998. Finger clubbing in malignant mesotheliom and benign asbestos pleural disease. Resp Med 92:691-692.

*McGavin CR, Sheers G. 1984. Diffuse pleural thickening in asbestos workers: Disability and lung function abnormalities. Thorax 39:604-607.

*McGavran PD, Butterick CJ, Brody AR. 1989. Tritiated thymidine incorporation and the development of an interstitial lesion in the bronchiolar-alveolar regions of the lungs of normal and complement deficient mice after inhalation of chrysotile asbestos. JEPTO 9:377-391.

McLachlan MS, Wagner JC. 1974. Radiological diagnosis of crocidolite induced pleural mesotheliomata in the rat. Br J Exp Pathol 55:164-168.

McLarty JW, Holiday DB, Girard WM, et al. 1995. Beta-carotene, vitamin A, and lung cancer chemoprevention: Results of an intermediate endpoint study. Am J Clin Nutr 62:1431S-14318S.

McLean AN, Patel KR. 1997. Clinical features and epidemiology of malignant pleural mesothelioma in west Glasgow 1987-1992. Scott Med J 42:37-39.

McMillan CH, Jones AD, Vincent JH, et al. 1989. Accumulation of mixed mineral dusts in the lungs of rats during chronic inhalation exposure. Environ Res 48:218-237.

McMillan GHG. 1983. The risk of asbestos-related diseases occurring in welders. J Occup Med 25(10):727-730.

McNeill KR, Waring S. 1992. Vitrification of contaminated soils. In: Rees JF, ed. Contamination and land treatment technology (International Public Conference), 143-159.

MDEQE. 1989. Summary of Massachusetts' methodology for developing allowable ambient limits. Boston, MA: Massachusetts Department of Environmental Quality Engineering. Written Communication (May 8).

Meek ME. 1983. Transmigration of ingested asbestos. Environ Health Perspect 53:149-152.

*Menard H, Noel L, Khorami J, et al. 1986. The adsorption of polyaromatic hydrocarbons on natural and chemically modified asbestos fibers. Environ Res 40:84-91.

Meranger JC, Davey ABC. 1989. Non-asbestos fibre content of selected consumer products. Ottawa, Ontario, Canada: Environmental Health Directorate, Health and Welfare Canada, 347-353.

Meredith SK, McDonald JC. 1994. Work-related respiratory disease in the United Kingdom, 1989-1992: Report on the SWORD project. Occup Med 44:183-189.

Merler E. 1998. A cross-sectional study on asbestos workers carried out in Italy in 1940: A forgotten study. Am J Ind Med 33:90-93.

Merler E, Buiatti E, Vainio H. 1997. Surveillance and intervention studies on respiratory cancers in asbestos-exposed workers. Scand J Work Environ Health 23:83-92.

Merler E, Ricci P, Silvestri S. 1996. Crocidolite and not chrysotile was mainly used by the Italian railroad system. Med Lav 87:268-269.

Metintas M, Gibbs AR, Harmanci E, et al. 1997. Malignant localized fibrous tumor of the pleura occurring in a person environmentally exposed to tremolite asbestos. Respiration 64:236-239.

*Metintas M, Özdemir n, Hillerdal G, et al. 1999. Environmental asbestos exposure and malignant pleural mesothelioma. Resp Med 93:349-355.

*Meurman LO, Kiviluoto R, Hakama M. 1974. Mortality and morbidity among the working population of anthophyllite asbestos miners in Finland. Br J Ind Med 31:105-112.

*Meurman LO, Pukkala E, Hakama M. 1994. Incidence of cancer among anthrophyllite asbestos miners in Finland. Occup Environ Med 51(6):421-425.

Miller A, Miller JA. 1993. Diffuse thickening superimposed on circumscribed pleural thickening related to asbestos exposure. Am J Ind Med 23(6):859-871.

*Miller A, Lilis R, Godbold J. 1992. Relationship of pulmonary function to radiographic interstitial fibrosis in 2,611 long-term asbestos insulators: An assessment of the International Labour Office profusion score. Am Rev Respir Dis 145(2):263-270.

*Miller A, Lilis R, Godbold J, et al. 1994. Spirometric impairments in long-term insulators: Relationships to duration of exposure, smoking, and radiographic abnormalities. Chest 105:175-182.

*Miller A, Lilis R, Godbold J, et al. 1996. Relation of spirometric function to radiographic interstitial fibrosis in two large workforces exposed to asbestos: An evaluation of the ILO profusion score. Occup Environ Med 53:808-812.

*Miller A, Teirstein AS, Selikoff I. 1983. Ventilatory failure due to asbestos pleurisy. Am J Med 75:911-919.

Miller BG, Jones AD, Searl A, et al. 1999a. Influence of characteristics of inhaled fibres on development of tumours in the rat lung. Ann Occup Hyg 43(3):167-179.

Miller BG, Searl A, Davis JMG, et al. 1999b. Influence of fibre length, dissolution and biopersistence on the production of mesothelioma in the rat peritoneal cavity. Ann Occup Hyg 43(3):155-166.

Miller K. 1985. Immunotoxicology. Clin Exp Immunol 61:219-223.

Miller K, Brown RC. 1985. The immune system and asbestos-associated disease. In: Dean J et al., eds. Immunotoxicology and immunopharmacology. New York, NY: Raven Press, 429-440.

*Miller K, Webster I, Handfield RI, et al. 1978. Ultrastructure of the lung in the rat following exposure to crocidolite and asbestos and quartz. J Pathol 124:39-44.

*Millette JR, Clark PJ, Pansing MF. 1980. Concentration and size of asbestos in water supplies. Environ Health Perspect 34:13-25.

Millette JR, Clark PJ, Stober J, et al. 1983a. Asbestos in water supplies of the United States. Environ Health Perspect 53:45-48.

Millette JR, Craun GF, Stober JA, et al. 1983b. Epidemiology study of the use of asbestos-cement pipe for the distribution of drinking water in Escambia County, Florida. Environ Health Perspect 53:91-98.

Milosevic M, Petrovic L. 1988. Environmental exposure to chrysotile asbestos and cancer epidemiology. Arh Hig Rada Toksikol 39:489-498.

Minardi F, Maltoni C. 1988. Results of recent experimental research on the carcinogenicity of natural and modified asbestos. Ann NY Acad Sci 754-761.

Minowa M, Hatano S, Ashizawa, et al. 1991. A case-control study of lung cancer with special reference to asbestos exposure. Environ Health Perspect 94:39-42.

Mishra A, Liu J-Y, Brody AR, et al. 1997. Inhaled asbestos fibers induce p52 expression in the rat lung. Am J Respir Cell Mol Biol 16:479-485.

*Mlynarek S, Corn M, Blake C. 1996. Asbestos exposure of building maintenance personnel. Regul Toxicol Pharmacol 23:213-224.

*Moatmed F, Lockey JE, Parry WT. 1986. Fiber contamination of vermiculites: A potential occupational and environmental health hazard. Environ Res 41:207-218.

*Molinini R, Paoletti L, Albrizio M, et al. 1992. Occupational exposure to asbestos and urinary bladder cancer. Environ Res 58(2):176-183.

Mollo F, Magnani C. 1995. European multicentric case control study on risk for mesothelioma after non-occupational (domestic and environmental) exposure to asbestos. Med Lav 86:496-500.

Mollo F, Andrion A, Pira E, et al. 1983. Indicators of asbestos exposure in autopsy routine. 2. Pleural plaques and occupation. Med Lav 74:137-142.

Mollo F, Piolatto G, Bellis D, et al. 1990. Asbestos exposure and histologic cell types of lung cancer in surgical and autopsy series. Int J Cancer 46:576-580.

Mollo F, Pira E, Piolatto G, et al. 1995. Lung adenocarcinoma and indicators of asbestos exposure. Int J Cancer 60:289-293.

Monchaux G, Chameaud J, Morlier JP, et al. 1989. Translocation of subcutaneously injected chrysotile fibres: potential cocarcinogenic effect on lung cancer induced in rats by inhalation of radon and its daughters. IARC Sci Pub 90:161-166.

*Mongan LC, Jones T, Patrick G. 2000. Cytokine and free radical responses of alveolar macrophages in vitro to asbestos fibres. Cytokine 12(8):1243-1247.

Moniewska A, Szyba K, Jazwiec B, et al. 1989. Chrysotile A affects YAC-1 cytolytic activity of spleen cells. Arch Imm Et Therap 37:61-68.

Monso E, Texido A, Lopex D, et al. 1995. Asbestos bides in normal lung of western Mediterranean populations with no occupational exposure to inorganic dust. Arch Environ Health 50:305-311.

Moran EM. 1996. Environment, cancer, and molecular epidemiology: Air pollution. J Environ Pathol Toxicol Oncol 15:97-104.

Morgan A. 1994. The removal of fibres of chrysotile asbestos from lung. Ann Occup Hyg 38:643-646.

Morgan A. 1995. Deposition of inhaled asbestos and man-made mineral fibers in the respiratory tract. Ann Occup Hyg 39:747-758.

Morgan A, Holmes A. 1983. Distribution and characteristics of amphibole asbestos fibres, measured with the light microscope, in the left lung of an insulation worker. Br J Ind Med 40:45-50.

*Morgan A, Holmes A. 1986. Solubility of asbestos and man-made mineral fibers *in vitro* and *in vivo*: Its significance in lung disease. Environ Res 39:475-484.

Morgan A, Collier CG, Morris KJ, et al. 1993. A radioactive tracer technique to determine *in vivo* the number of fibers in the lungs of rats following their administration by intratracheal instillation. Environ Res 63(2):182-190.

Morgan A, Davies P, Wagner JC, et al. 1977. The biological effects of magnesium-leached chrysotile asbestos. Br J Exp Pathol 58:465-473.

*Morgan A, Evans JC, Evans RJ, et al. 1975. Studies on the deposition of inhaled fibrous material in the respiratory tract of the rat and its subsequent clearance using radioactive tracer techniques: II. Deposition of the UICC standard reference samples of asbestos. Environ Res 10:196-207.

*Morgan A, Talbot RJ, Holmes A. 1978. Significance of fiber length in the clearance of asbestos fibres from the lung. Br J Ind Med 35:146-153.

*Morgan RW. 1991. Re: Meta-analysis of asbestos and gastrointestinal cancer. Am J Ind Med 19:407-408.

Morgan RW, Goodman M. 1998. [Letter]. N Engl J Med 339:1001.

*Morgan RW, Foliart DE, Wong O. 1985. Asbestos and gastrointestinal cancer. West J Med 143:60-65.

Morimoto Y, Kido M, Tanaka I, et al. 1993. Synergistic effects of mineral fibers and cigarette smoke on the production of necrosis factor by alveolar macrophages of rats. Br J Ind Med 50(10):955-960.

Morimoto Y, Tsuda T, Nakamura H, et al. 1997. Expression of matrix metalloproteinases, tissue inhibitors of metalloproteinases, and extracellular matrix mRNA following exposure to mineral fibers and cigarette smoke in vivo. Environ Health Perspect Suppl 105:1247-1251.

Morris GF, Brody AR. 1999. Stressing fibrogenesis in cell culture. Am J Respir Cell Mol Biol 21:447-448.

*Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants. Clin Pharmacokin 5:485-527.

Mossman BT. 1983. *In vitro* approaches for determining mechanisms of toxicity an carcinogenicity by asbestos in the gastrointestinal and respiratory tracts. Environ Health Perspect 53:155-161.

Mossman BT. 1988. Carcinogenic potential of asbestos and nonasbestos fibers. J Environ Sci Health 6:151-195.

Mossman BT. 1990. *In vitro* studies on the biologic effects of fibers: Correlation with *in vivo* bioassays. Environ Health Perspect 88:319-322.

*Mossman BT, Churg A. 1998. Mechanisms in the pathogenesis of asbestosis and silicosis. Am J Resp Crit Care Med 157:1666-1680.

Mossman BT, Craighead JE. 1979. Use of hamster tracheal organ cultures for assessing the cocarcinogenic effects of inorganic particulates on the respiratory epithelium. Prog Exp Tumor Res 24:37-47.

Mossman BT, Marsh JP. 1989. Evidence supporting a role for active oxygen species in asbestos-induced toxicity and lung disease. Environ Health Perspect 81:91-94.

*Mossman BT, Bignon J, Corn M, et al. 1990a. Asbestos: Scientific developments and implications for public policy. Science 247:294-301.

*Mossman BT, Eastman A, Bresnick E. 1984. Asbestos and benzo[a]pyrene act synergistically to induce squamous metaplasia and incorporation of [^{3}H]thymidine in hamster tracheal epithelium. Carcinogenesis 5:1401-1405.

*Mossman BT, Eastman A, Landesman JM, et al. 1983a. Effects of crocidolite and chrysotile asbestos on cellular uptake and metabolism of benzo(a)pyrene in hamster epithelial cells. Environ Health Perspect 51:331-335.

*Mossman BT, Faux S, Janssen Y, et al. 1997. Cell signaling pathways elicited by asbestos. Environ Health Perspect Suppl 105:1121-1125.

*Mossman B, Light W, Wei E. 1983b. Asbestos: Mechanisms of toxicity and carcinogenicity in the respiratory tract. Ann Rev Pharmacol Toxicol 23:595-615.

*Mossman BT, Marsh JP, Sesko A, et al. 1990b. Inhibition of lung injury, inflammation, and interstitial pulmonary fibrosis by polyethylene glycol-conjugated catalase in a rapid inhalation model of asbestosis. Am Rev Respir Dis 141:1266-1271.

Moulin JJ. 1997. A meta-analysis of epidemiologic studies of lung cancer in welders. Scand J Work Environ Health 23:104-113.

Mukhtar M-SR, Rao GMM. 1996. Respiratory effects of occupational exposure to asbestos. Indian J Physiol Pharmacol 40:98-102.

Murai Y, Kitagawa M. 1992. Asbestos fiber analysis in 27 malignant mesothelioma cases. Am J Ind Med 22(2):193-207.

Murai Y, Kitagawa M, Hiraoka T. 1995a. Asbestos body formation in the human lung: Distinctions, by type and size. Arch Environ Health 50:19-25.

Murai Y, Kitagawa M, Hiraoka T. 1997. Fiber analysis in lungs of residents of a Japanese town with endemic pleural plaques. Arch Environ Health 52:263-269.

Murai Y, Kitagawa M, Matsui K, et al. 1995b. Asbestos fiber analysis in nine lung cancer cases with high asbestos exposure. Arch Environ Health 50:320-325.

Murai Y, Kitagawa M, Yasuda M, et al. 1994. Asbestos fiber analysis in seven asbestosis cases. Arch Environ Health 49:67-72.

*Murray KA, Gamsu G, Webb WR, et al. 1995. High-resolution computed tomography sampling for detection of asbestos-related lung disease. Acad Radiol 2:111-115.

*Murthy SS, Testa JR. 1999. Asbestos, chromosomal deletions, and tumor suppressor gene alterations in human malignant mesothelioma. J Cell Physiol 180:150-157.

Murthy SS, Shen T, De Rienzo A, et al. 2000. Expression of *GPC3*, an X-linked recessive overgrowth gene, is silenced in malignant mesothelioma. Oncogene 19:410-416.

*Muscat JE, Wynder EL. 1991. Cigarette smoking, asbestos exposure, and malignant mesothelioma. Cancer Res 51:2263-2267.

Muscat JE, Wynder EL. 1992. Tobacco, alcohol, asbestos, and occupational risk factors for laryngeal cancer. Cancer 69:2244-2251.

Muscat JE, Stellman SD, Richie JP, et al. 1998. Lung cancer risk and workplace exposures in black men and women. Environ Res 76:78-84.

Muscat JE, Stellman SD, Wynder EL. 1995. Insulation, asbestos, smoking habits, and lung cancer cell types. Am J Ind Med 27:257-269.

*Musk AW, De Klerk NH, Ambrosimi GL, et al. 1998. Vitamin A and cancer prevention I: Observations in workers previously exposed to asbestos at Wittenoom, western Australia. Int J Cancer 75:355-361.

Musselman R, Miiller W, Eastes W, et al. 1994a. Biopersistence of crocidolite versus man-made vitreous fibers in rat lungs after brief exposures. In: Mohr U, Dungworth DL, Mauderly JL, et al., ed. Toxic and carcinogenic effects of solid particles in the respiratory tract. Washington,DC: ILSI Press, 451-454.

Musselman RP, Miiller WC, Eastes W, et al. 1994b. Biopersistences of man-made vitreous fibers and crocidolite fibers in rat lungs following short-term exposures. Environ Health Perspect Suppl 102:139-143.

Mutsaers SE, Harrison NK, McAnulty RJ, et al. 1998. Fibroblast mitogens in bronchoalveolar lavage (BAL) fluid from asbestos-exposed subjects with and without clinical evidence of asbestosis: No evidence for the role of PDGF, TNF-alpha, IGF-1, or IL-1beta. J Pathol 185:199-203.

Mutti L, De Luca A, Claudio PP, et al. 1998. Simian virus 40-like DNA sequences and large-T antigen-retinoblastoma family protein pRb2/p130 interaction in human mesothelioma. Dev Biol 94:47-53.

Nadeau Denis, Lane DA. 1989. On the cytotoxicity of chrysotile asbestos fibers toward pulmonary alveolar macrophages. Toxicol App Pharmacol 98:144-158.

Nakadate T. 1995. Decline in annual lung function in workers exposed to asbestos with and without pre-existing fibrotic changes on chest radiography. Occup Environ Med 52:368-373.

Narasimhan SR, Yang L, Gerwin BI, et al. 1998. Resistance of pleural mesothelioma cell lines to apoptosis: Relation to expression of Bcl-2 and Bax. Am J Physiol 275:L165-L171.

*NAS. 1977. Drinking water and health. Washington, DC: National Academy of Sciences, 144-168.

*NAS. 1982. Drinking water and health. Vol 4. Washington, DC: National Academy Press, 42-61.

*NAS. 1983. Drinking water and health. Vol 5. Washington, DC: National Academy Press, 123-147.

*NAS/NRC. 1989. Biologic markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.

NATICH. 1988. NATICH data base 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, National Air Toxics Information Clearinghouse. EPA 450/5-88-007. NTIS No. PB89-106983.

NATICH. 1991. NATICH data base report on state, local and EPA air toxics activities. Report to U.S. Environmental Protection Agency, Office of Air Quality Planning Standards, National Air Toxics Information Clearinghouse, Research Triangle Park, NC, by Radian Corporation, Austin, TX. EPA 68/08-0065.

NATICH. 1992. NATICH data base 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, National Air Toxics Information Clearinghouse. September 1992.

*Nelson HH, Christiani DC, Wiencke JK, et al. 1999. k- *ras* mutation and occupational asbestos exposure in lung adenocarcinoma: Asbestos-related cancer without asbestosis. Cancer Res 59:4570-4573.

*Nelson HH, Wiencke JK, Gunn L, et al. 1998. Chromosome 3p14 alterations in lung cancer: Evidence the FHIT exon deletion is a target of tobacco carcinogens and asbestos. Cancer Res 58:1804-1807.

*Neri S, Antonelli A, Falaschi F, et al. 1994. Findings from high resolution computed tomography of the lung and pleura of symptom free workers exposed to amosite who had normal chest radiographs and pulmonary function tests. Occup Environ Med 51:239-243.

*Neri S, Boraschi P, Antonelli A, et al. 1996. Pulmonary function, smoking habits, and high resolution computed tomography (HRCT) early abnormalities of lung and pleural fibrosis in shipyard workers exposed to asbestos. Am J Ind Med 30:588-595.

Nettesheim P, Topping DC, Jamasbi R. 1981. Host and environmental factors enhancing carcinogenesis in the respiratory tract. Ann Rev Pharmacol Toxicol 21:133-163.

Neuberger M, Kundi M. 1990. Individual asbestos exposure: Smoking and mortality-a cohort study in the asbestos cement industry. Br J Ind Med 47:615-620.

*Neuberger M, Frank W, Golob P, et al. 1996. [Asbestos concentrations in drinking water: Asbestos cement pipes and geogen sources in Austria.] Zentralbl Hyg Umeweltmed 198:293-306. (German).

*Neugut AI, Murray TI, Garbowski GC, et al. 1991. Association of asbestos exposure with colorectal adenomatous polyps and cancer. J Natl Cancer Inst 83:1827-1828.

*Newhouse ML, Berry G. 1976. Predictions of mortality from mesothelial tumours in asbestos factory workers. Br J Ind Med 33:147-151.

*Newhouse ML, Berry G. 1979. Patterns of mortality in asbestos factory worker in London. Ann NY Acad Sci 330:53-60.

*Newhouse ML, Sullivan KR. 1989. A mortality study of workers manufacturing friction materials: 1941-86. Br J Ind Med 46:176-179.

Newhouse ML, Berry G, Skidmore JW. 1982. A mortality study of workers manufacturing friction materials with chrysotile asbestos. Ann Occup Hyg 26:899-909.

Newhouse ML, Berry G, Wagner JC, et al. 1972. A study of the mortality of female asbestos workers. Br J Ind Med 29:134-141.

Newhouse ML, Berry G, Wagner JC. 1985. Mortality of factory workers in east London 1933-1980. Br J Ind Med 42:4-11.

Newman HA, Saat YA, Hart RW. 1980. Putative inhibitory effects of chrysotile, crocidolite, and amosite mineral fibers on the more complex surface membrane glycolipids and glycoproteins. Environ Health Perspect 34:103-111.

*Ni Z, Liu Y-Q, Keshava N, et al. 2000. Analysis of K- *ras* and *p53* mutations in mesotheliomas from humans and rats exposed to asbestos. Mutat Res 468:87-92.

Nicholson WJ. 1971. Measurement of asbestos in ambient air. Final report. National Air Pollution Control Administration. [Unpublished study to be peer reviewed].

Nicholson WJ. 1978. Chrysotile asbestos in air samples collected in Puerto Rico. Report to the Consumer Products Safety Commission by the City University of New York. New York, NY: Mount Sinai School of Medicine, Environmental Sciences Laboratory. CPSC 77128000.

*Nicholson WJ. 1987. Airborne levels of mineral fibres in the non-occupational environment. New York, NY: City University of New York, Mount Sinai School of Medicine, Division of Environmental and Occupational Medicine.

Nicholson WJ. 1989. Airborne mineral fibre levels in the non-occupational environment. In: Bignon J, Peto J, Saracci R, eds. Lyon, France: International Agency for Research on Cancer, World Health Organization.

Nicholson WJ. 1991. Comparative dose-response relationships of asbestos fiber types: Magnitude and uncertainties. Ann NY Acad Sci 74-84.

*Nicholson WJ, Landrigan PJ. 1996. Asbestos: A status report. Curr Issues Pub Health 2:118-123.

*Nicholson WJ, Pundsack FL. 1973. Asbestos in the environment. In: Biological effects of asbestos, proceedings of a working conference held at IARC 26 October, 1972. IARC Sci Publ 8:126-132.

*Nicholson WJ, Perkel G, Selikoff IJ. 1982. Occupational exposure to asbestos: Populations at risk and projected mortality--1980-2030. Am J Ind Med 3:259-311.

Nicholson WJ, Rohl AN, Weisman I. 1975. Asbestos contamination of the air in public buildings. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. EPA-450/3-76-004. NTIS No. PB-250980.

*Nicholson WJ, Selikoff IJ, Seidman H, et al. 1979. Long-term mortality experience of chrysotile miners and millers in Thetford Mines, Quebec. Ann NY Acad Sci 330:11-21.

*Nigam SK, Suthar AM, Patel MM, et al. 1993. Humoral immunological profile of workers exposed to asbestos in asbestos mines. Indian J Med Res 98(12):274-7.

NIOSH. 1975. Asbestos exposure during servicing of motor vehicle brake and clutch assemblies. Current intelligence bulletin 5. Rockville, MD: U.S. Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

*NIOSH. 1976. Revised recommended asbestos standard. Washington, DC: U.S. Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. DHEW (NIOSH) Publication No. 77-169.

NIOSH. 1984. Chrysotile asbestos - method 9000. In: NIOSH manual of analytical methods. 3rd ed. Cincinnati, OH: National Institute for Occupational Safety and Health, 9000-1 - 9000-7.

NIOSH. 1985. 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, 54.

*NIOSH. 1987. Fibers - method 7400. In: NIOSH manual of analytical methods. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. Revision 2. August 15, 1987.

NIOSH. 1988a. National occupational exposure survey. Cincinnati, OH: National Institute for Occupational Safety and Health.

NIOSH. 1988b. National occupational hazard survey. Cincinnati, OH: National Institute for Occupational Safety and Health.

NIOSH. 1988c. Asbestos-induced intrathoracic tissue reactions. Cincinnati, OH: National Institute for Occupational Safety and Health, NTIS No. PB88-248380.

*NIOSH. 1989a. Fibers - method 7400. In: NIOSH manual of analytical methods. 3rd ed. Supplement. Cincinnati, OH: National Institute for Occupational Safety and Health, 7400-1 - 7400-13.

*NIOSH. 1989b. Asbestos fibers - method 7402. In: NIOSH manual of analytical methods. 3rd ed. Supplement. Cincinnati, OH: National Institute for Occupational Safety and Health, 7402-1 - 7402-8.

*NIOSH. 1989c. Fibers - method 9002. In: NIOSH manual of analytical methods. 3rd ed. Supplement. Cincinnati, OH: National Institute for Occupational Safety and Health, 9002-1 to 9002-10.

NIOSH. 1989d. Control of asbestos exposure during brake drum service. Cincinnati, OH: National Institute for Occupational Safety and Health, NTIS no. PB90-168501.

NIOSH. 1990a. Asbestos related disease - a community epidemic in the making. Cincinnati, OH: National Institute for Occupational Safety and Health, NTIS no. PB90-155896.

NIOSH. 1990b. National Institute for Occupational Safety and Health. NIOSH pocket guide to chemical hazards. Washington, DC: U.S. Department of Health and Human Services.

NIOSH. 1990c. Testimony of the National Institute for Occupational Safety and Health on the occupational safety of proposed rulemaking on occupational exposure to asbestos, tremolite, anthrophyllite, and actinolite. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. 2 CFR 1910 and 1926. May 9, 1990. NTIS no. PB91-152-439.

NIOSH. 1992. NIOSH recommendations for occupational safety and health. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, iv-vi, 51, 140.

*NIOSH. 1994a. Asbestos and other fibres by PCM. In: Manual of analytical methods, 4th edition. Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

*NIOSH. 1994b. Asbestos by TEM. In: Manual of analytical methods, 4th ed. Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

*NIOSH. 1999. Pocket guide to chemical hazards. Washington D.C.: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

*NIOSH. 2001. Pocket guide to chemical hazards. Washington D.C.: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health. Http://www.cdc.gov/niosh/nioshsrch.html. January 17,2001.

Nishimura SL, Broaddus VC. 1998. Asbestos-induced pleural disease. Clin Chest Med 19:311-329.

NLM. 1988. Chemline. National Library of Medicine, Bethesda, MD. December 1988.

Nokso-Koivisto P, Pukkala E. 1994. Past exposure to asbestos and combustion products and incidence of cancer among Finnish locomotive drivers. Occup Environ Med 51:330-334.

Nolan RP, Langer AM, Addison J. 1994. Lung content analysis of cases occupationally exposed to chrysotile asbestos. Environ Health Perspect Suppl 102:245-250.

Nolan RP, Langer AM, Wilson R. 1999. A risk assessment for exposure to grunerite asbestos (amosite) in an iron ore mine. Proc Natl Acad Sci U S A 96:3412-3419.

*NRC. 1984. National Research Council. Asbestiform fibers: Nonoccupational health risks. Washington, DC: National Academy Press.

*NRC. 1993. National Research Council. Pesticides in the diets of infants and children. Washington, DC: National Academy Press.

*NTP. 1983. National Toxicology Program. Technical report series no. 249. Lifetime carcinogenesis studies of amosite asbestos (CAS no. 121-72-73-5) in Syrian golden hamsters (feed studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH Publication No. 84-2505.

*NTP. 1985. National Toxicology Program. Technical report series no. 295. Toxicology and carcinogenesis studies of chrysotile asbestos (CAS no. 12001-29-5) in F344/N rats (feed studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH Publication No. 86-2551.

*NTP. 1988. National Toxicology Program. Technical report on the toxicology and carcinogenesis studies of crocidolite asbestos (CAS no. 12001-28-4) in F344/N rats (feed studies). Research Triangle Park, NC: U. S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH Publication No. 88-2536.

*NTP. 1990a. National Toxicology Program. Technical report on the carcinogenesis lifetime studies of chrysotile asbestos (CAS no. 12001-29-5) in Syrian golden hamsters (feed studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH Publication No. 90-2502.

*NTP. 1990b. National Toxicology Program. Technical report series no. 279. Toxicology and carcinogenesis studies of amosite asbestos F344/N rats. Report to National Institute of Environmental Health Sciences, Research Triangle Park, NC, by Technical Resources, Inc., Rockville, MD. NTP 91-2535.

*NTP. 1990c. National Toxicology Program. Technical report on the toxicology and carcinogenesis studies of tremolite (CAS no. 14567-73-8) in Fischer 344 rats (feed study). Research Triangle Park, NC: U. S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH Publication No. 90-2531.

NTP. 1991. National Toxicology Program. Sixth annual report on carcinogens 1991 summary. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institute of Health. 27-33.

NTP. 1994. National Toxicology Program. Management status report. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, Division of Toxicology Research and Testing.

*NTP. 2001. National Toxicology Program. Ninth annual report on carcinogens. U.S. Department of Health and Human Services, Public Health Service.

*Nuorva K, Makitaro R, Huhti E, et al. 1994. p53 Protein accumulation in lung carcinomas of patients exposed to asbestos and tobacco smoke. Am J Respir Crit Care Med 150:528-533.

*Nurminen M, Tossavainen A. 1994. Is there an association between pleural plaques and lung cancer without asbestos? Scand J Work Environ Health 20:62-64.

*Nyberg P, Klockars M. 1991. Interferon-γ and immunoglobulin enhance mineral dust-induced production of reactive oxygen metabolites by human macrophages. Clin Immunol Immunopathol 60:128-136.

Nyberg P, Klockars M. 1994. Bacillus Calmette-Guerin (BCG) and immunoglobulins synergistically enhance mineral dust-induced production of reactive oxygen metabolites by human monocytes. Clin Exp Immunol 97:334-337.

Nyberg PW, Nordman SAS, Klockars MLG. 1994. Increased mineral dust-induced production of reactive oxygen species by blood monocytes from patients with malignant diseases. Apmis 102:765-770.

Oehlert GW. 1991. A reanalysis of the Stanton et al. pleural sarcoma data. Environ Res 54:194-205.

*Oettinger R, Drumm K, Knorst M, et al. 1999. Production of reactive oxygen intermediates by human macrophages exposed to soot particles and asbestos fibers and increase in NF-kappa B p50/p105 mRNA. Lung 177:343-354.

*Ogino S, Fukumori N, Yasuno T, et al. 1988. Asbestos fibers in sake. J Food Protection 51:737-739.

*Ohio EPA. 2001. Toxic release inventory rules: Air pollution regulations. Division of Air Pollution Control, Ohio Environmental Protection Agency. Http://www.epa.state.oh.us/cgi-bin/htsearch. January 19, 2001.

*Ohlson C-G, Bodin L, Rydman T, et al. 1985. Ventilatory decrements in former asbestos cement workers: A four year follow up. Br J Ind Med 42:612-616.

*Ohlson C-G, Rydman T, Sundell L, et al. 1984. Decreased lung function in long-term asbestos cement workers: A cross-sectional study. Am J Ind Med 5:359-366.

*Okayasu R, Takahashi S, Yamada S, et al. 1999a. Asbestos and DNA double strand breaks. Cancer Res 59:298-300.

Okayasu R, Wu L, Hei TK. 1999b. Biological effects of naturally occurring and man-made fibres: in vitro cytotoxicity and mutagenesis in mammalian cells. Br J Cancer 79(9/10):1319-1324.

Oksa P, Huuskonen MS, Jarvisalo J, et al. 1998a. Follow-up of asbestosis patients and predictors for radiographic progression. Int Arch Occup Environ Health 71:465-471.

Oksa P, Klockers M, Karjalainen A, et al. 1998b. Progression of asbestosis predicts lung cancer. Chest 113:1517-1521.

Oksa P, Koskinen H, Rinne JP, et al. 1992. Parenchymal and pleural fibrosis in construction workers. Am J Ind Med 21:561-567.

Oksa P, Pukkala E, Karjalainen A, et al. 1997. Cancer incidence and mortality among Finnish asbestos sprayers and in asbestosis and silicosis patients. Am J Ind Med 31:693-698.

*Oksa P, Suoranto H, Koshinen H, et al. 1994. High resolution computed tomography in the early detection of asbestosis. Int Arch Occup Environ Health 65(5):299-304.

Oliver LC, Sprince NL, Greene R. 1991. Asbestos-related abnormalities in school maintenance personnel. Ann NY Acad Sci 521-529.

*Ollikainen T, Linnainmaa K, Kinnula VL. 1999. DNA single strand breaks induced by asbestos fibers in human pleural mesothelial cells in vitro. Environ Mol Mutagen 33:153-160.

*Olofsson K, Mark J. 1989. Specificity of asbestos-induced chromosomal aberrations in short-term cultured human mesothelial cells. Cancer Genet Cytogenet 41:33-39.

Omenn GS. 1991/92. CARET, the beta-carotene and retinal efficacy trial to prevent lung cancer in high-risk populations. Public Health Rev 19(1-4):205-208.

Omenn GS, Goodman G, Grizzle J, et al. 1992. Recruitment for the β-carotene and retino efficacy trial (caret) to prevent lung cancer in smokers and asbestos-exposed workers. West J Med 156:540-544.

Omenn GS, Goodman GE, Thornquist MD, et al. 1993. The carotene and reinol efficacy trial (CARET) to prevent lung-cancer in high risk populations--pilot study with asbestos-exposed workers. Cancer Epidemiol Biomarkers Prev 2(4):381-387.

Omenn GS, Goodman G, Thornquist M, et al. 1994. The beta-carotene and retinol efficacy trial (CARET) for chemoprevention of lung cancer in high risk populations: Smokers and asbestos-exposed workers. Cancer Res 54(Suppl 7):2038s-2043s.

*Omenn GS, Goodman GE, Thornquist MD, et al. 1996a. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 334:1150-1155.

*Omenn GS, Goodman GE, Thornquist MD, et al. 1996b. Risk factors for lung cancer and for intervention effects in CARET, the beta-carotene and retinol efficacy trial. J Natl Cancer Inst 88:1550-1559.

Orlowski E, Pairon JC, Ameille J, et al. 1994. Pleural plaques, asbestos exposure, and asbestos bodies in bronchoalveolar lavage fluid. Am J Ind Med 26:349-358.

*Osgood C, Sterling D. 1991. Chrysotile and amosite asbestos induce germ-line aneuploidy in Drosophila. Mutat Res 261:9-13.

*OSHA. 1986. U.S. Department of Labor, Occupational Safety and Health Administration. Federal Register 51:22612-22790.

OSHA. 1988. U.S. Department of Labor, Occupational Safety and Health Administration. Federal Register 53:35610-35629.

*OSHA. 1990. U.S. Department of Labor, Occupational Safety and Health Administration. Federal Register 55:29712-29753.

*OSHA. 1992. U.S. Department of Labor, Occupational Safety and Health Administration. 57:7877-7878, 24310-24331, 49657-49661.

*OSHA. 1994. Occupational exposure to asbestos. U.S. Department of Labor, Occupational Safety and Health Administration. Federal Register 59(153):40964-41162.

OSHA. 1995. Occupational exposure to asbestos; corrections; final rule. U.S. Department of Labor, Occupational Safety and Health Administration. Federal Register 60(125):33973-34002.

OSHA. 1996. Occupational exposure to asbestos, tremolite, anthophyllite and actinolite. U.S. Department of Labor, Occupational Safety and Health Administration. Federal Register 61:43454-43459.

*OSHA. 1998a. U. S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1001.

*OSHA. 1998b. U. S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.1101.

*OSHA. 1998c. U. S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1001.

*OSHA. 2001a. OSHA Regulations: Asbestos. U. S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1001. Http://www.osha-slc.gov/OshStd_data/1910_1001.html. January 18,2001.

*OSHA. 2001b. OSHA Regulations: Asbestos. U. S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.1101. Http://www.osha-slc.gov/OshStd_data/1926_1101.html. January 18,2001.

*OSHA. 2001c. OSHA Regulations: Asbestos. U. S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1001. Http://www.osha-slc.gov/OshStd_data/1915_1001.html. January 18,2001.

*Oshimura M, Hesterberg TW, Barrett JC. 1986. An early, nonrandom karyotypic change in immortal Syrian hamster cell lines transformed by asbestos: Trisomy of chromosome 11. Cancer Genet Cytogenet 22:225-237.

Oshimura M, Hesterberg TW, Tsutsui T, et al. 1984. Correlation of asbestos-induced cytogenetic effect with cell transformation of Syrian hamster embryo cells in culture. Cancer Res 44:5017-5022

Osinubi OYO, Gochfeld M, Kipen HM. 2000. Health effects of asbestos and nonasbestos fibers. Environ Health Perspect 108(Suppl. 4):665-674.

Ostergaard G, Knudsen I. 1998. The applicability of the ADI (acceptable daily intake) for food additives to infants and children. Food Addit Contam 15:63-74.

OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment, U.S. Congress. OTA-BA-436. April 1990.

*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.

Ozdemir N, Metintas M, Uefun I, et al. 1996. Environmental asbestos exposure and malignant pleural mesothelioma. Eur Resp J 9:248S.

Ozdemir T, Cöplü L, Dincer N, et al. 1997. Environmental tremolite exposure in a village located in southwest of Turkey [Abstract]. Eur Resp J 10:230s.

Pache JC, Janssen YMW, Walsh ES, et al. 1998. Increased epidermal growth factor-receptor protein in a human mesothelial cell line in response to long asbestos fibers. Am J Pathol 152:333-340.

Paci E, Zappa M, Paoletti L, et al. 1991. Further evidence of an excess of risk of pleural malignant mesothelioma in textile workers in Prato [Italy]. Br J Cancer 64(2):377-378.

Pailes WH, Judy DJ, Resnick H, et al. 1984. Relative effects of asbestos and wollastonite on alveolar macrophages. J Toxicol Environ Health 14:497-510.

Pairon JC, Martinon L, Iwatsubo Y, et al. 1994. Retention of asbestos bodies in the lungs of welders. Am J Ind Med 25:793-804.

Pairon JC, Orlowski E, Iwatsubo Y, et al. 1994. Pleural mesothelioma and exposure to asbestos: Evaluation from work histories and analysis of asbestos bodies in bronchoalveolar lavage fluid or lung tissue in 131 patients. Occup Environ Med 51(4):244-249.

*Palekar LD, Eyre JF, Most BM, et al. 1987. Metaphase and anaphase analysis of V79 cells exposed to erionite, UICC chrysotile and UICC crocidolite. Carcinogenesis 8:553-560.

*Palekar LD, Most BM, Coffin DL. 1988. Significance of mass and number of fibers in the correlation of V79 cytotoxicity with tumorigenic potential of mineral fibers. Environ Res 46:142-152.

*Pang TW, Schonfeld-Starr FA, Patel K. 1989. An improved membrane filter technique for evaluation of asbestos fibers. Am Ind Hyg Assoc J 50:174-180.

*Pang ZC, Zhang Z, Wang Y, et al. 1997. Mortality from a Chinese asbestos plant: Overall cancer mortality. Am J Ind Med 32:442-444.

*Paoletti L, Caiazza S, Donnelli G, et al. 1984. Evaluation by electron microscopy techniques of asbestos contamination in industrial, cosmetic, and pharmaceutical talcs. Regul Toxicol Pharmacol 4:222-235.

Park SH, Aust AE. 1998. Participation of iron and nitric oxide in the mutagenicity of asbestos in hgprt-, gpt+ Chinese hamster V79 cells. Cancer Res 58:1144-1148.

Parkin DM, Wahrendorf J, Demaret E, et al. 1987. Directory of on-going research in cancer epidemiology. Lyon, France: International Agency for Research on Cancer.

*Parnes SM. 1990. Asbestos and cancer of the larynx: Is there a relationship? Laryngoscope 100:254-261.

Parnes SM, Sherman M. 1991. Head and neck surveillance program for factory personnel exposed to asbestos. Ann Otol Rhinol Laryngol 100(9 Pt 1):731-736.

Parry WT. 1985. Calculated solubility of chrysotile asbestos in physiological systems. Environ Res 37:410-418.

Partanen R, Hemminki K, Brandt-Rauf P, et al. 1994a. Serum levels of growth factor receptors, EGFR and neu in asbestosis patients: A follow-up study. Int J Oncol 4:1025-1028.

Partanen R, Hemminki K, Koskinen H, et al. 1994b. The detection of increased amounts of the extracellular domain of the epidermal growth factor receptor in serum during carcinogenesis in asbestosis patients. J Occup Med 36:1324-1328.

Partanen R, Koskinen H, Oksa P, et al. 1995. Serum oncoproteins in asbestosis patients. Clin Chem 41:1844-1847.

Pasqualetti P, Casale R, Colantonio D, et al. 1991. Occupational risk for hematological malignancies. Am J Hematol 38(2):147-149.

Pasqualetti P, Collacciani A, Casale R. 1996. Risk of monoclonal gammopathy of undetermined significance: A case-referent study. Am J Hematol 52:217-220.

Pass HI. 1994. Contemporary approaches in the investigation and treatment of malignant pleural mesothelioma. Chest Surg Clin N Am 4:497-515.

Pass HI, Mew DJY. 1996. In vitro and in vivo studies of mesotheliom. J Cell Biochem 24:142-151.

*Patel-Mandlik KJ, Millette JR. 1983. Chrysotile asbestos in kidney cortex of chronically gavaged rats. Arch Environ Contam Toxicol 12:247-255.

*Patel-Mandlik K, Manos CG, Johnson KEB, et al. 1994. Prevalence of asbestos in sludges from 16 sewage plants in large American cities in 1993. Chemosphere 29:1369-1372.

*Patel-Mandlik KJ, Manos CG, Lisk DJ, et al. 1988. Identification of asbestos and glass fibers in sewage sludges of small New York state cities. Chemosphere 17:1025-1032.

Pearce N. 1988. Multistage modeling of lung cancer mortality in asbestos textile workers. Int J Epidemiol 17:747-752.

Pele JP, Calvert R. 1983. Hemolysis by chrysotile asbestos fibers. I. Influence of the sialic acid content in human, rat, and sheep red blood cell membranes. J Toxicol Environ Health 12:827-840.

*Pelin K, Hirvonen A, Taavitsainen M, et al. 1995a. Cytogenic response to asbestos fibers in cultured human primary mesothelial cells from 10 different donors. Mutat Res 334:225-233.

*Pelin K, Kivipensas P, Linnainmaa K. 1995b. Effects of asbestos and man-made vitreous fibers on cell division in cultured human mesothelial cells in comparison to rodent cells. Environ Mol Mutagen 25:118-125.

*Pelin-Enlund K, Husgafvel-Pursiainen K, Tammilehto L, et al. 1990. Asbestos-related malignant mesothelioma: Growth, cytology, tumorigenicity and consistent chromosome findings in cell lines from five patients. Carcinogenesis 11:673-681.

Perderiset M, Marsh JP, Mossman BT. 1991. Activation of protein kinase C by crocidolite asbestos in hamster tracheal epithelial cells. Carcinogenesis 12:1499-1502.

*Perkins RC, Scheule RK, Hamilton R, et al. 1993. Human alveolar macrophage cytokine release in response to *in vitro* and *in vivo* asbestos exposure. Exp Lung Res 19(1):55-65.

*Pernis B, Vigliani EC, Selikoff IJ. 1965. Rheumatoid factor in serum of individuals exposed to asbestos. Ann NY Acad Sci 132:112-120.

Peterson JT Jr, Greenberg SD, Buffler PA. 1984. Non-asbestos-related malignant mesothelioma: A review. Cancer 54 (September 1):951-960.

*Peterson MW, Kirschbaum J. 1998. Asbestos-induced lung epithelial permeability: Potential role of nonoxidant pathways. Am J Physiol 275:L262-L268.

*Peterson MW, Walter ME, Gross TJ. 1993. Asbestos directly increases lung epithelial permeability. Am J Physiol 265(3 Pt 1):L308-L317.

*Peto J. 1980. The incidence of pleural mesothelioma in chrysotile asbestos textile workers. IARC Sci Pub 30:703-711.

Peto J. 1989. Fibre carcinogenesis and environmental hazards. IARC Sci Pub 90:457-470.

*Peto J, Decarli A, La Vecchhia C, et al. 1999. The European mesothelioma epidemic. Br J Cancer 79:666-672.

*Peto J, Doll R, Hermon C, et al. 1985. Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. Ann Occup Hyg 29:305-345.

*Peto J, Hodgson JT, Matthews FE, et al. 1995. Continuing increase in mesothelioma mortality in Britain. Lancet 345:535-539.

*Peto J, Seidman H, Selikoff IJ. 1982. Mesothelioma mortality in asbestos workers: Implications for models of carcinogenesis and risk assessment. Br J Cancer 45:124-135.

Petrini MF. 1998. Cigarette smoking, asbestos exposure, lung cancer, and sample size [Letter]. Am J Respir Crit Care Med 158:1688.

*Petruska JM, Leslie KO, Mossman BT. 1991. Enhanced lipid peroxidation in lung lavage of rats after inhalation of asbestos. Free Radical Biol Med 11:425-432.

Pettinari A, Mengucci R, Belli S, et al. 1994. [Mortality of workers employed at an asbestos cement manufacturing plant in Senigallia.] Med Lav 85:223-230. (Italian)

*Phalen RF, Cuddihy RG, Fisher GL, et al. 1991. Main features of the proposed NCRP respiratory tract model. Radiat Prot Dosim 38:159-184.

*Phalen RF, Oldham MJ, Beaucage CB, et al. 1985. Postnatal enlargement of human tracheobronchial airways and implications for particle deposition. Anat Rec 212:368-380.

PHRED. 1988. Public Health Risk Evaluation Database. Washington, DC: U. S. Environmental Protection Agency. March 1988.

*Pietarinen-Runtti P, Raivio KO, Linnainmaa K, et al. 1996. Differential effects of tumor necrosis factor and asbestos fibers on manganese superoxide dismutase induction and oxidant-induced cytotoxicity in human mesothelial cells. Cell Biol Toxicol 12:167-175.

Piirila P, Sovijarvi ARA. 1995. Crackles: Recording, analysis and clinical significance. Eur Resp J 8:2139-2148.

*Pinkerton KE, Brody AR, Miller FJ, et al. 1989. Exposure to low levels of ozone results in enhanced pulmonary retention of inhaled asbestos fibers. Am Rev Respir Dis 140:1075-1081.

*Pinkerton KE, Plopper CG, Mercer RR, et al. 1986. Airway branching patterns influence asbestos fiber location and the extent of tissue injury in the pulmonary parenchyma. Lab Invest 55:688-695.

*Pinkerton KE, Pratt PC, Brody AR, et al. 1984. Fiber localization and its relationship to lung reaction in rats after chronic inhalation of chrysotile asbestos. Am J Pathol 117:484-498.

*Pitt R. 1988. Asbestos as an urban area pollutant. J Water Pollut Control Fed 60:1993-2001.

*Platek SF, Groth DH, Ulrich CE, et al. 1985. Chronic inhalation of short asbestos fibers. Fundam Appl Toxicol 5:327-340.

Plato N, Tornling G, Hogsted C, et al. 1995. An index of past asbestos exposure as applied to car and bus mechanics. Ann Occup Hyg 39:441-454.

*Plowman PN. 1982. The pulmonary macrophage population of human smokers. Ann Occup Hyg 25:393-405.

*Polissar L, Severson RK, Boatman ES, et al. 1982. Cancer incidence in relation to asbestos in drinking water in the Puget Sound region. Am J Epidemiol 116:314-328.

Polissar L, Severson RK, Boatman ES. 1983. Cancer risk from asbestos in drinking water: Summary of a case-control study in western Washington. Environ Health Perspect 53:57-60.

*Polissar L, Severson RK, Boatman ES. 1984. A case-control study of asbestos in drinking water and cancer risk. Am J Epidemiol 119:456-471.

Pontefract RD. 1974. Penetration of asbestos through the digestive wall in rats [Commentary]. Environ Health Perspect 9:213-214.

*Pontefract RD, Cunningham HM. 1973. Penetration of asbestos through the digestive tract of rats. Nature 243:352-353.

Pontius FW. 1998. New horizons in federal regulation: New requirements and schedules have dramatically accelerated the pace of regulatory activity. J Am Water Works Assoc 90:38-50.

*Pooley FD. 1976. An examination of the fibrous mineral content of asbestos lung tissue from the Canadian chrysotile mining industry. Environ Res 12:281-298.

Pooley FD, Clark NJ. 1979. Quantitative assessment of inorganic fibrous particulates in dust samples with an analytical transmission electron microscope. Ann Occup Hyg 22:253-271.

Pott F. 1987. [The fibre as a carcinogenic agent.] Zentralbl Bakteriol Hyg [B] 184:1-23. (German)

Pott F, Bellman B, Muhle H, et al. 1989a. Proceedings of the First International Conference on Health Related Effects of Phyllosilicates, Paris, France.

Pott F, Roller M, Ziem U, et al. 1989b. Carcinogenicity studies on natural and man-made fibres with the intraperitoneal test in rats. IARC Sci Pub 90:173-179.

Préat B. 2000. Confusion about the precision of asbestos fibres counting by electron microscopy. Ann Occup Hyg 44(1):75.

*Price B. 1997. Analysis of current trends in United States mesothelioma incidence. Am J Epidemiol 145:211-218.

Price B, Crump KS, Baird EC 3d. 1992. Airborne asbestos levels in buildings: Maintenance worker and occupant exposures. J Expo Anal Environ Epidemiol 2(3):357-374.

*Price-Jones MJ, Gubbings G, Chamberlain M. 1980. The genetic effects of crocidolite asbestos: Comparison of chromosome abnormalities and sister-chromatid exchanges. Mutat Res 79:331-336.

Prior AJ, Ball ABS. 1993. Intestinal obstruction complicating malignant mesothelioma of the pleura. Respir Med 87(2):147-148.

Prowse OW, Reddy PP, Barrieras D, et al. 1998. Pediatric genitourinary tumors. Curr Opin Oncol 10:253-260.

Pylev LN. 1987. [The role of modifying factors in the carcinogenic effects of asbestos and asbestos-containing dusts.] Eksp Onkol 9:14-17. (Russian)

Pylev LN, Kogan FM, Kulagina TF. 1988. [Carcinogenic activity of asbestos cement dust.] Gig Tr Prof Zabol (July):55-57 (Russian)

Quinlan TR, Berube KA, Hacker MP, et al. 1998. Mechanisms of asbestos-induced nitric oxide production by rat alveolar macrophages in inhalation and in vitro models. Free Radic Biol Med 24:778-788.

*Quinlan TR, Berube KA, Marsh JP, et al. 1995. Patterns of inflammation, cell proliferation, and related gene expression in lung after inhalation of chrysotile asbestos. Am J Pathol 147:728-739.

*Quinlan TR, Marsh JP, Janssen YMW, et al. 1994. Dose-responsive increases in pulmonary fibrosis after inhalation of asbestos. Am J Resp Crit Care Med 150:200-206.

*Raffn E, Lynge E, Juel K, et al. 1989. Incidence of cancer and mortality among employees in the asbestos cement industry in Denmark. Br J Ind Med 46:90-96.

Raffn E, Villadsen E, Engholm G, et al. 1996a. Lung cancer in asbestos cement workers in Denmark. Occup Environ Med 53:399-402.

*Raffn E, Villadsen E, Lynge E. 1996b. Colorectal cancer in asbestos cement workers in Denmark. Am J Ind Med 30:267-272.

Rafnsson V, Jahannesdottir SG, Oddsson H, et al. 1988. Mortality and cancer incidence among marine engineers and machinists in Iceland. Scand J Work Environ Health 14:197-200.

*Rahman Q, Khan SG, Ali S. 1990. Effect of chrysotile asbestos on cytochrome P-450 - dependent monooxygenase and glutathione-s-transferase activities in rat lung. Chem Biol Interactions 75:305-314.

Raithel HJ, Weltle D, Bohlig H, et al. 1989. Health hazards from fine asbestos dusts. Int Arch Occup Environ Health 61:527-541.

Rajan KT, Wagner JC, Evans PH. 1972. The response of human pleura in organ culture to asbestos. Nature 238:346-347.

Rapiti, E, Turi E, Forastiere F, et al. 1992. A mortality cohort study of seamen in Italy. Am J Ind Med 21(6):863-872.

*Reeves AL, Puro HE, Smith RG, et al. 1971. Experimental asbestos carcinogenesis. Environ Res 4:496-511.

*Reeves AL, Puro HE, Smith RG. 1974. Inhalation carcinogenesis from various forms of asbestos. Environ Res 8:178-202.

Reid AS, Causton BE, Jones JS, et al. 1991. Malignant mesothelioma after exposure to asbestos in dental practice [Letter]. Lancet 338(8768):696.

Reiss B, Millette JR, Williams GM. 1980a. The activity of environmental samples in a cell culture test for asbestos toxicity. Environ Res 22:315-321.

*Reiss B, Solomon S, Tong C, et al. 1982. Absence of mutagenic activity of three forms of asbestos in liver epithelial cells. Environ Res 27:389-397.

Reiss B, Solomon S, Weisburger JH, et al. 1980b. Comparative toxicities of different forms of asbestos in a cell culture assay. Environ Res 22:109-129.

Reiss B, Tong C, Telang S, et al. 1983. Enhancement of benzo[a]pyrene mutagenicity by chrysotile asbestos in rat liver epithelial cells. Environ Res 31:100-104.

*Ren H, Lee DR, Hruban RH, et al. 1991. Pleural plaques do not predict asbestosis: High-resolution computed tomography and pathology study. Mod Pathol 4(2):201-209.

Renke W. 1990. Evaluation of pathological changes in respiratory system of workers exposed to asbestos dust. Bull Inst Mar Trop Med Gdynia 41:5-15.

*Rey F, Boutin C, Steinbauer J, et al. 1993. Environmental pleural plaques in an asbestos exposed population of northeast Corsica. Eur Respir J 6(7):978-982.

Rey F, Boutin C, Viallat JR, et al. 1994. Environmental asbestotic pleural plaques in northeast Corsica: Correlations with airborne and pleural mineralogic analysis. Environ Health Perspect Suppl 102:251-252.

Reynolds SJ, Kreiger RA, Bohn JA, et al. 1994. Factors affecting airborne concentrations of asbestos in a commercial building. Am Ind Hyg Assoc J 55:823-828.

Ribak J, Lilis R, Suzuki Y, et al. 1988. Malignant mesothelioma in a cohort of asbestos insulation workers: Clinical presentation, diagnosis, and causes of death. Br J Ind Med 45:182-187.

Ribak J, Lilis R, Suzuki Y, et al. 1991. Death certificate categorization of malignant pleural and peritoneal mesothelioma in a cohort of asbestos insulation workers. J Soc Occup Med 41(3):137-139.

Ribak J, Seidman H, Selikoff IJ. 1989. Amosite mesothelioma in a cohort of asbestos workers. Scan J Work Environ Health 15:106-110.

Richter ED, Berdugo M, Laster R, et al. 1995. Chrysotile and crocidolite asbestos in Israel: Uses, exposures and risks. Med Lav 86:449-456.

*Rickards, AL. 1994. Levels of workplace exposure. Ann Occup Hyg 38(4):469-475.

Riediger G, Rödelsperger K. 2000. Confusion about the precision of asbestos fibres counting by electron microscopy. Ann Occup Hyg 44(1):76.

*Rihn B, Coulais C, Kauffer E, et al. 2000. Inhaled crocidolite mutagenicity in lung DNA. Environ Health Perspect 108(4):341-346.

Rihn B, Kauffer E, Martin P, et al. 1996. Short-term crocidolite inhalation studies in mice: Validation of an inhalation chamber. Toxicology 109:147-156.

Rittmeyer L, Yang P, Schwartz AG, et al. 1995. Genetic and environmental factors in lung cancer susceptibility [Abstract]. Am J Hum Genet 57:A76.

Robb JA, Hammar SP, Yokoo H. 1993. Pseudomesotheliomatous lung carcinoma a rare asbestos-related malignancy readily separable from epithelial pleural mesothelioma. 1993 Annual Meeting of the United States and Canadian 68(1):134A.

Robins TG, Green MA. 1988. Respiratory morbidity in workers exposed to asbestos in the primary manufacture of building materials. Am J Ind Med 14:433-448.

Robinson BWS. 1989. Asbestos and cancer: Human natural killer cell activity is suppressed by asbestos fibers but can be restored by recombinant interleukin-2. Am Rev Respir Dis 139:897-901.

Robinson C, Dtern F, Halperin W, et al. 1995. Assessment of mortality in the construction industry in the United States, 1984-1986. Am J Ind Med 28:49-70.

Robinson CF, Petersen M, Sieber WK, et al. 1996. Mortality of carpenters' union members employed in the US construction or wood products industries, 1987-1990. Am J Ind Med 30:674-694.

*Robledo R, Mossman B. 1999. Cellular and molecular mechanisms of asbestos-induced fibrosis. J Cell Physiol 180:158-166.

Robledo RF, Buder-Hoffmann SA, Cummins AB, et al. 2000. Increased phosphorylated extracellular signal-regulated kinase immunoreactivity associated with proliferative and morphologic lung alterations after chrysotile asbestos inhalation in mice. Am J Pathol 156(4):1307-1316.

Rockley PF, Trieff N, Wagner RF, et al. 1994. Nonsunlight risk factors for malignant melanoma Part I: Chemical agents, physical conditions, and occupation. Int J Dermatol 33:398-406.

Rocskay AZ, Harbut MR, Green MA, et al. 1996. Respiratory health in asbestos-exposed ironworkers. Am J Ind Med 29:459-466.

*Rödelsperger K, Woitowitz H-J. 1995. Airborne fibre concentrations and lung burden compared to the tumour response in rats and humans exposed to asbestos. Ann Occup Hyg 39:715-725.

*Rödelsperger K, Woitowitz H-J, Brückel B, et al. 1999. Dose-response relationship between amphibole fiber lung burden and mesothelioma. Cancer Detect Prev 23(3):183-193.

Roe FJ, Carter RL, Walters MA, et al. 1967. The pathological effects of subcutaneous injections of asbestos fibres in mice: Migration of fibres to submesothelial tissues and induction of mesotheliomata. Int J Cancer 2:628-638.

*Rogan WJ, Gladen BC, Ragan NB, et al. 1987. U.S. prevalence of occupational pleural thickening: A look at chest x-rays from the first National Health And Nutrition Examination Survey. Am J Epidemiol 126:893-900.

Rogers A, Nevill M. 1995. Occupational and environmental mesotheliomas due to crocidolite mining activities in Wittenoon, Western Australia. Scand J Work Environ Health 21:259-264.

*Rogers AJ. 1984. Determination of mineral fibre in human lung tissue by light microscopy and transmission electron microscopy. Ann Occup Hyg 28(1):1-12.

*Rogers AJ, Baker EM, Conaty GJ. 1997. Asbestiform minerals: Worker exposure and risk assessment in some contaminated Australian mines. Appl Occup Environ Hyg 12:867-871.

*Rogers AJ, Leigh J, Berry G, et al. 1991. Relationship between lung asbestos fiber type and concentration and relative risk of mesothelioma. Cancer 67:1912-1920.

*Rogers RA, Antonino JM, Brismar H, et al. 1999. *In situ* microscopic analysis of asbestos and synthetic vitreous fibers retained in hamster lungs following inhalation. Environ Health Perspect 107:367-375.

Roggli VL. 1995. Malignant mesothelioma and duration of asbestos exposure: Correlation with tissue mineral fibre content. Ann Occup Hyg 39:363-374.

Roggli VL, Benning TL. 1990. Asbestos bodies in pulmonary Hilar lymph nodes. Modern Pathol 3:513-517.

*Roggli VL, Longo WE. 1991. Mineral fiber content of lung tissue in patients with environmental exposure: Household contacts vs. building occupants. Ann NY Acad Sci 511-518.

*Roggli VL, Coin PG, MacIntyre NR, et al. 1994a. Asbestos content of bronchoalveolar lavage fluid: A comparison of light and scanning electron microscopic analysis. Acta Cytol 38:502-510.

*Roggli VL, George MH, Brady AR. 1987a. Clearance and dimensional changes of crocidolite asbestos fibers isolated from lungs of rats following short-term exposure. Environ Res 42:94-105.

Roggli VL, Hammar SP, Pratt PC, et al. 1994b. Does asbestos or asbestosis cause carcinoma of the lung? Am J Ind Med 26:835-838.

Roggli VL, Kolbeck J, Sanfilippo F, et al. 1987b. Pathology of human mesothelioma: Etiologic and diagnostic considerations. Pathol Annu 22(Pt 2):91-131.

Roggli VL, Pratt PC, Brody AR. 1986. Asbestos content of lung tissue in asbestos associated diseases: A study of 110 cases. Br J Ind Med 43:18-28.

Roggli VL, Pratt PC, Brody AR. 1993. Asbestos fiber type in malignant mesothelioma: An analytical scanning electron microscopic study of 94 cases. Am J Ind Med 23(4):605-614.

Roller M, Pott F, Kamino K, et al. 1997. Dose-response relationship of fibrous dusts in intraperitoneal studies. Environ Health Perspect Suppl 105:1253-1256.

*Rom WN. 1991. Relationship of inflammatory cell cytokines to disease severity in individuals with occupational inorganic dust exposure. Am J Ind Med 19:15-27

*Rom WN. 1992. Accelerated loss of lung function and alveolitis in a longitudinal study of non-smoking individuals with occupational exposure to asbestos. Am J Ind Med 21:835-844.

*Rom WN, Travis WD. 1992. Lymphocyte-macrophage alveolitis in nonsmoking individuals occupationally exposed to asbestos. Chest 101(3):779-786.

*Rom WN, Livingston GK, Casey KR, et al. 1983. Sister chromatid exchange frequency in asbestos workers. J Natl Cancer Inst 70:45-48.

Rom WN, Travis WD, Brody AR. 1991. Cellular and molecular basis of the asbestos-related diseases. Am Rev Respir Dis 143:408-422.

*Roney PL, Holian A. 1989. Possible mechanism of chrysotile asbestos-stimulated superoxide anion production in guinea pig alveolar macrophages. Toxicol App Pharmacol 100:132-144.

Rosenman KD, Reilly MJ. 1998. Asbestos-related x-ray changes in foundry workers. Am J Ind Med 34:197-201.

Rosenman KD, Zhu Z. 1995. Pneumoconiosis and associated medical conditions. Am J Ind Med 27:107-113.

*Rosenthal GJ, Corsini E, Simeonova P. 1998. Selected new developments in asbestos immunotoxicity. Environ Health Perspect Suppl 106:159-169.

Rosenthal GJ, Simeonova P, Corsini E. 1999. Asbestos toxicity: An immunologic perspective. Rev Environ Health 14(1):11-20.

Rosler JA, Woitowitz HJ, Lange HJ, et al. 1994. Mortality rates in a female cohort following asbestos exposure in Germany. J Occup Med 36:889-893.

Ross D, McDonald JC. 1995. Occupational and geographical factors in the epidemiology of malignant mesothelioma. Monaldi Arch Chest Dis 50:459-462.

*Ross M. 1981. The geologic occurrences and health hazards of amphibole and serpentine asbestos. In: Veblen DR, ed. Reviews in mineralogy: Amphiboles and other hydrous pyriboles-mineralogy. Chelsea, MI: Mineralogical Society of America, BookCrafters, Inc., 279-323.

Rossiter CE, Chase JR. 1995. Statistical analysis of results of carcinogenicity studied of synthetic vitreous fibres at research and consulting company, Geneva. Ann Occup Hyg 39:759-769.

RTECS. 1999a. Tremolite asbestos. Registry of Toxic Effects of Chemical Substances. National Institute for Occupational Safety and Health. April 19, 1999.

RTECS. 1999b. Chrysotile asbestos. Registry of Toxic Effects of Chemical Substances. National Institute for Occupational Safety and Health. April 19, 1999.

Rubin ES. 1999. Toxic releases from power plants. Environ Sci Technol 33:3062-3067.

*Rubino GF, Piolatto G, Newhouse ML, et al. 1979. Mortality of chrysotile asbestos workers at the Balangero Mine, Northern Italy. Br J Ind Med 36:187-194.

*Rudd R. 1989. Malignant mesothelioma. J R Soc Med 82:126-129.

Rudd RM. 1988. Exposure to asbestos and the risk of gastrointestinal cancer [Letter]. Br J Ind Med 45:573-574.

Ryan PJ, Oates JL, Crocker J, et al. 1997. Distinction between pleural mesothelioma and pulmonary adenocarcinoma using MOC31 in an asbestos sprayer. Resp Med 91:57-60.

*Saarikoski ST, Reinikainen M, Antilla S, et al. 2000. Role of *NAT2* deficiency in susceptibility to lung cancer among asbestos-exposed individuals. Pharmacogenetics 10:183-185.

*Sadler TD, Rom WN, Lyon JL, et al. 1984. The use of asbestos-cement pipe for public water supply and the incidence of cancer in selected communities in Utah. J Community Health 9:285-293.

Saffiotii U. 1998. Respiratory tract carcinogenesis by mineral fibres and dusts: Models and mechanisms. Monaldi Arch Chest Dis 53:160-167.

Saffiotti U, Stinson SF. 1988. Lung cancer induction by crystalline silica: Relationships to granulomatous reactions and host factors. J Environ Sci Health 6:197-222.

*Sahin AA, Cöplü L, Selcuk ZT, et al. 1993. Malignant pleural mesothelioma caused by environmental exposure to asbestos or erionite in rural Turkey: CT findings in 84 patients. AJR Am J Roentgenol 161(3):533-537.

Sahu AP. 1989. Effect on choline and mineral fibres (chrysotile asbestos) on guinea-pigs. New Delhi, India: Scientific Commission for Continuing Studies on Effects of Bhopal Gas Leakage on Life Systems, 185-189.

*Sahu AP, Dogra RKS, Shanker R, et al. 1975. Fibrogenic response in murine lungs to asbestos. Exp Pathol 11:21-24.

Sakai K, Hisanaga N, Huang J, et al. 1994. Asbestos and nonasbestos fiber content in lung tissue of Japanese patients with malignant mesothelioma. Cancer 73(7):1825-1835.

*Sakellariou K, Malamou-Mitsi V, Haritou A, et al. 1996. Malignant pleural mesothelioma from nonoccupational asbestos exposure in Metsovo (north-west Greece): Slow end of an epidemic? Eur Resp J 9:1206-1210.

*Sampson C, Hansell DM. 1992. The prevalence of enlarged mediastinal lymph nodes in asbestos-exposed individuals a CT study. Clin Radiol 45(5):340-342.

Samudra AV, Harwood CF. 1977. Electron microscope measurement of airborne asbestos concentrations: A provisional methodology manual. Report to U. S. Environmental Protection Agency, Office of Research and Development, Research Triangle Park, NC, by IIT Research Institute, Chicago, IL. EPA 600/2-77-178. NTIS No. PB-285945.

Sanden A, Jarvholm B, Larsson S, et al. 1992. The risk of lung cancer and mesothelioma after cessation of asbestos exposure: A prospective cohort study of shipyard workers. Eur Respir J 5:281-285.

Sanden A, Jarvholm B, Larsson S. 1993. The importance of lung-function, nonmalignant diseases associated with asbestos, and symptoms as predictors of ischemic heart disease in shipyard workers exposed to asbestos. Br J Ind Med 50(9):785-790.

*Sandhu H, Dehnen W, Roller M, et al. 2000. mRNA expression patterns in different stages of asbestos-induced carcinogenesis in rats. Carcinogenesis 21(5):1023-1029.

*Saracci R. 1987. The interactions of tobacco-smoking and other agents in cancer etiology. Epidemiol Rev 9:175-193.

Saric M, Curin K. 1996. Malignant tumours of the gastrointestinal tract in an area with an asbestos-cement plant. Cancer Lett 103:191-199.

Saric M, Vujovic M. 1994. Malignant tumors in an area with an asbestos processing plant. Public Health Rev 22:293-303.

Sauni R, Oksa P, Jarvenpaa R, et al. 1998. Asbestos exposure: A potential cause of retroperitoneal fibrosis. Am J Ind Med 33:418-421.

Sax NI, Lewis RJ Sr. 1987. Hawley's condensed chemical dictionary. llth ed. New York, NY: Van Nostrand Reinhold Company, 100-101.

Scansetti G, Chiesa A, Capellaro E, et al. 1996. Asbestos bodies in sputum of asbestos exposed workers. Med Lav 87:283-288.

Scatarige JC, Stitik FP. 1988. Induction of thoracic malignancy in inorganic dust pneumoconiosis. J Thorac Imaging 3:67-79.

*Schapira RM, Ghio AJ, Effros RM, et al. 1994. Hydroxyl radicals are formed in the rat lung after asbestos instillation in vivo. Am J Resp Cell Mol Biol 10:573-579.

Schimmelpfeng J, Seidel A. 1991. Cytotoxic effects of quartz and chrysotile asbestos: In vitro interspecies comparison with alveolar macrophages. J Toxicol Environ Health 33:131-140.

*Schneider J, Rödelsperger K, Brückel B, et al. 1998. Environmental exposure to tremolite asbestos: Pleural mesothelioma in two Turkish workers in Germany. Rev Environ Health 13(4):213-220.

Schneider J, Straif K, Woitowitz H-J. 1996. Pleural mesothelioma and household asbestos exposure. Rev Environ Health 11:65-70.

*Schneider U, Maurer RR. 1977. Asbestos and embryonic development. Teratology 15:273-280.

Schoenberger CI, Hunninghake GW, Kawanami O, et al. 1982. Role of alveolar macrophages in asbestosis: Modulation of neutrophil migration to the lung after acute asbestos exposure. Thorax 37:803-809.

Scholze H, Conradt R. 1987. An *in vitro* study of the chemical durability of siliceous fibres. Ann Occup Hyg 31:683-692.

*Schwartz DA, Davis CS, Merchant JA, et al. 1994. Longitudinal changes in lung function among asbestos-exposed workers. Am J Resp Crit Care Med 150:1243-1249.

*Schwartz DA, Fuortes LJ, Galvin JR, et al. 1990. Asbestos-induced pleural fibrosis and impaired lung function. Am Rev Respir Dis 141:321-326.

*Schwartz DA, Galvin JR, Frees KL, et al. 1993. Clinical relevance of cellular mediators of inflammation in workers exposed to asbestos. Am Rev Respir Dis 148(1):68-74.

Schwartz DA, Galvin JR, Merchant RK, et al. 1992. Influence of cigarette smoking on bronchoalveolar lavage cellularity in asbestos-induced lung disease. Am Rev Respir Dis 145(2):400-405.

*Searl A. 1997. A comparative study of the clearance of respirable para-aramid, chrysotile and glass fibres from rat lungs. Ann Occup Hyg 41:217-233.

Searl A, Buchanan D, Cullen RT, et al. 1999. Biopersistence and durability of nine mineral fibre types in rat lungs over 12 months. Ann Occup Hyg 43(3):143-153.

*Sebastien P, Armstrong B, Case BW, et al. 1988a. Estimation of amphibole exposure from asbestos body and macrophage counts in sputum: A survey in vermiculite miners. Ann Occup Hyg 32(Suppl 1):195-201. .

*Sebastien P, Armstrong B, Monchaux G, et al. 1988b. Asbestos bodies in bronchoalveolar lavage fluid and in lung parenchyma. Am Rev Respir Dis 137:75-78.

*Sebastien P, Begin R, Masse S. 1990. Mass, number and size of lung fibres in the pathogenesis of asbestosis in sheep. J Exp Path 71:1-10.

*Sebastien P, Bignon J, Barris YI, et al. 1984. Ferruginous bodies in sputum as an indication of exposure to airborne mineral fibers in the mesothelioma villages of Cappadocia. Arch Environ Health 39:18-23.

*Sebastien P, Janson X, Gaudichet A, et al. 1980a. Asbestos retention in human respiratory tissues: Comparative measurements in lung parenchyma and in parietal pleura. IARC Sci Publ 30:237-246.

*Sebastien P, Masse R, Bignon J. 1980b. Recovery of ingested asbestos fibers from the gastrointestinal lymph in rats. Environ Res 22:201-216.

*Sebastien P, McDonald JC, McDonald AD, et al. 1989. Respiratory cancer in chrysotile textile and mining industries: Exposure inferences from lung analysis. Br J Ind Med 46:180-187.

*Segers K, Ramael M, Singh SK, et al. 1995. Detection of numerical chromosomal aberrations in paraffin-embedded malignant pleural mesothelioma by non-isotopic in situ hybridization. J Pathol 175:219-226.

*Seidman H. 1984. Short-term asbestos work exposure and long-term observation. In: Docket of current rulemaking for revision of the asbestos (dust) standard. Washington, DC: U.S. Department of Labor, Occupational Safety and Health Administration. Available for inspection at: U.S. Department of Labor, OSHA Technical Data Center, Francis Perkins Building; docket no. HO33C, exhibit nos. 261-A and 261-B.

*Seidman H, Selikoff IJ, Gelb SK. 1986. Mortality experience of amosite asbestos factory workers: Dose-response relationships 5 to 40 years after onset of short-term work exposure. Am J Ind Med 10:479-514.

*Seidman H, Selikoff IJ, Hammond EC. 1979. Short-term asbestos work exposure and long-term observation. Ann NY Acad Sci 330:61-89.

Sekhon H, Keeling B, Churg A. 1993. Rat pleural mesotheliomal cells show damage after exposure to external but not internal cigarette smoke. Environ Health Perspect 101(4):326-330.

*Sekhon H, Wright J, Churg A. 1995. Effects of cigarette smoke and asbestos on airway, vascular and mesothelial cell proliferation. Int J Exp Pathol 76:411-418.

Selby TW. 1996. Method for converting asbestos to non-carcinogenic compounds. Application: USA 278,487, 21 Jul 1994. USA Patent 5,543,120, issued 6 Aug 1996.

*Selcuk ZT, Cöplü L, Emri S, et al. 1992. Malignant pleural mesothelioma due to environmental mineral fiber exposure in Turkey: Analysis of 135 cases. Chest 102(3):790-796.

Selikoff IJ. 1965. The occurrence of pleural calcification among asbestos insulation workers. Ann N Y Acad Sci 132:351-367.

Selikoff IJ. 1990. Historical developments and perspectives in inorganic fiber toxicity in man. Environ Health Perspect 88:269-276.

*Selikoff IJ, Lee DHK, eds. 1978. Asbestos and disease. New York, NY: Academic Press, 143-187, 357-375, 377-392.

Selikoff IJ, Lilis R. 1991. Radiological abnormalities among sheet-metal workers in the construction industry in the United States and Canada: Relationship to asbestos exposure. Arch Environ Health 46:30-36.

*Selikoff IJ, Hammond EC, Churg J. 1968. Asbestos exposure, smoking and neoplasia. JAMA 204:104-110.

*Selikoff IJ, Hammond EC, Seidman H. 1979. Mortality experience of insulation workers in the United States and Canada, 1943-1976. Ann NY Acad Sci 330:91-116.

Selikoff IJ, Lilis R, Levin G. 1990. Asbestotic radiological abnormalities among United States merchant marine seamen. Br J Ind Med 47:292-297.

*Selikoff IJ, Nicholson WJ, Langer AM. 1972. Asbestos air pollution. Arch Environ Health 25:1-13.

*Selikoff IJ, Seidman H, Hammond EC. 1980. Mortality effects of cigarette smoking among amosite asbestos factory workers. J Natl Cancer Inst 65:507-513.

*Serio G, Ceppi M, Fonte A, et al. 1992. Malignant mesothelioma of the testicular tunica vaginalis. Eur Urol 21(2):174-176.

*Seshan K. 1983. How are the physical and chemical properties of chrysotile asbestos altered by a 10-year residence in water and up to 5 days in simulated stomach acid? Environ Health Perspect 53:143-148.

*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.

Shabad LM, Pylev LN, Krivosheeva LV, et al. 1974. Experimental studies on asbestos carcinogenicity. J Natl Cancer Inst 52:1175-1180.

*Shatos MA, Doherty JM, Marsh JP, et al. 1987. Prevention of asbestos-induced cell death in rat lung fibroblasts and alveolar macrophages by scavengers of active oxygen species. Environ Res 44:103-116.

Sheehan MJ, Reynolds JW. 1992. Airborne asbestos analysis of low fiber density samples: A comparison of the A and B counting rules of the NIOSH method 7400. Applied Occupational Environmental Hygiene 7(1):38-41.

*Shepherd JR, Hillerdal G, McLarty J. 1997. Progression of pleural and parenchymal disease on chest radiographs of workers exposed to amosite asbestos. Occup Environ Med 54:410-415.

Shepherd KE, Oliver LC, Kazemi H. 1989. Diffuse malignant pleural mesothelioma in an urban hospital: Clinical spectrum and trend in incidence over time. Am J Ind Med 16:373-383.

Shih JF, Wilson JS, Broderick A, et al. 1994. Asbestos-induced pleural fibrosis and impaired exercise physiology. Chest 105:1370-1376.

Shin DM, Fossella FV, Umsawasdi T, et al. 1995. Prospective study of combination chemotherapy with cyclophosphamide, doxorubicin, and cisplatin for unresectable or metastatic malignant pleural mesothelioma. Cancer 76:2230-2236.

Shivapurkar N, Wiethege T, Wistuba II, et al. 1999. Presence of simian virus 40 sequences in malignant mesotheliomas and mesothelial cell proliferations. J Cell Biochem 76:181-188.

Siemiatycki J, Boffetta P. 1998. Invited commentary: Is it possible to investigate the quantitative relation between asbestos and mesothelioma in a community-based study. Am J Epidemiol 148:143-147.

Sigurdson EE. 1983. Observations of cancer incidence surveillance in Duluth, Minnesota. Environ Health Perspect 53:61-67.

*Sigurdson EE, Levy BS, Mandel J, et al. 1981. Cancer morbidity investigations: Lessons from the Duluth study of possible effects of asbestos in drinking water. Environ Res 25:50-61.

*Simeonova PP, Luster MI. 1995. Iron and reactive oxygen species in the asbestos-induced tumor necrosis factor-alpha response from alveolar macrophages. Am J Resp Cell Mol Biol 12:676-683.

*Simeonova PP, Luster MI. 1996. Asbestos induction of nuclear transcription factors and interleukin 8 gene regulation. Am J Resp Cell Mol Biol 15:787-795.

*Simeonova PP, Toriumi W, Kommineni C, et al. 1997. Molecular regulation of IL-6 activation by asbestos in lung epithelial cells: Role of reactive oxygen species. J Immunol 159:3921-3928.

*Sincock AM. 1977. Preliminary studies of the *in vitro* cellular effects of asbestos and fine glass dusts. In: Hiatt HH, Watson JD, Winsten JA, eds. Origins of human cancer. Book B: Mechanisms of carcinogenesis. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 941-954.

*Sincock A, Seabright M. 1975. Induction of chromosome changes in Chinese hamster cells by exposure to asbestos fibres. Nature 257:56-58.

*Sincock AM, Delhanty JD, Casey G. 1982. A comparison of the cytogenetic response to asbestos and glass fibre in Chinese hamster and human cell lines: Demonstration of growth inhibition in primary human fibroblasts. Mutat Res 101:257-268.

Sinks T, Hartle R, Boeniger M, et al. 1994. Exposure to biogenic silica fibers and respiratory health in Hawaii sugarcane workers. J Occup Med 36:1329-1334.

Siracusa A, Forcina A, Volpi R, et al. 1988. An 11-year longitudinal study of the occupational dust exposure and lung function of polyvinyl chloride, cement and asbestos cement factory workers. Scand J Work Environ Health 14:181-188.

Sison RF, Hruban RH, Moore GW, et al. 1989. Pulmonary disease associated with pleural "asbestos" plaques. Chest 95(4):831-835.

Sittig M. 1985. Handbook of toxic and hazardous chemicals and carcinogens. 2nd ed. Park Ridge, NJ: Noyes Publications, 92-96.

Skevas AT, Kastanioudakis IG, Constantopoulos SH, et al. 1995. Acquired nasopharyngeal obstruction and "Metsovo lung". Rhinology 33:240-243.

*Skinner HC, Ross M, Frondel C. 1988. Health effects of inorganic fibers. In: Asbestos and other fibrous materials: Mineralogy, crystal chemistry, and health effects. New York, NY: Oxford University Press, 103-162.

*Sluis-Cremer GK. 1991. Asbestos disease at low exposure after long residence time in amphibole miners. Toxicol Ind Health 7:89-95.

Sluis-Cremer GK, Bezuidenhout BN. 1989. Relation between asbestosis and bronchial cancer in amphibole asbestos miners. Br J Ind Med 46:537-540.

*Sluis-Cremer GK, Liddell FDK, Logan WPD, et al. 1992. The mortality of amphibole miners in South Africa 1946-80. Br J Ind Med 49:566-575.

*Sluis-Cremer GK, Thomas RG, Schmaman IB. 1984. The value of computerized axial tomography in the assessment of workers exposed to asbestos. Am J Ind Med 6:27-35.

Smith AH. 1998. Amphibole fibers, chrysotile fibers, and pleural mesothelioma [Letter]. Am J Ind Med 33:96.

*Smith AH, Wright CC. 1996. Chrysotile asbestos is the main cause of pleural mesothelioma. Am J Ind Med 30:252-266.

*Smith AH, Handley MA, Wood R. 1990. Epidemiological evidence indicates asbestos causes laryngeal cancer. J Occup Med 32:499-507.

*Smith AH, Shearn VI, Wood R. 1989. Asbestos and kidney cancer: The evidence supports a causal association. Am J Ind Med 16:159-166.

Smith CM, Batcher S, Catanzaro A, et al. 1987. Sequence of bronchoalveolar lavage and histopathologic findings in rat lungs early in inhalation asbestos exposure. J Toxicol Environ Health 20:147-161.

Smith WE, Miller L, Churg J. 1970. An experimental model for study of cocarcinogenesis in the respiratory tract. In: Nettesheim P, Hanna MG Jr, Deatherage JW Jr, eds. Morphology of experimental respiratory carcinogenesis. Oak Ridge, TN: U.S. Atomic Energy Commission, AEC Symposium Series 21, 299-316.

*Spencer JW, Plisko MJ, Balzer JL. 1999. Asbestos fiber release from the brake pads of overhead industrial cranes. Appl Occup Environ Hyg 14:397-402.

*Spengler JD, Ozkaynak H, McCarthy JF, et al. 1989. Symposium on health aspects of exposure to asbestos in buildings, December 14-16, 1988. Cambridge, MA: Energy and Environmental Policy Center, Harvard University. 1-297.

*Spirtas R, Connelly RR, Tucker MA. 1988. Survival patterns for malignant mesothelioma: The seer experience. Int J Cancer 41:525-530.

*Spirtas R, Heineman EF, Bernstein L, et al. 1994. Malignant mesothelioma: Attributable risk of asbestos exposure. Occup Environ Med 51:804-811.

*Sprince NL, Oliver LC, McLoud TC, et al. 1991. Asbestos exposure and asbestos-related pleural and parenchymal disease. Am Rev Respir Dis 143:822-828.

*Sprince NL, Oliver LC, McLoud TC, et al. 1992. T-cell alveolitis in lung lavage of asbestos-exposed subjects. Am J Ind Med 21:311-319.

Spurny KR. 1989. Asbestos fibre release by corroded and weathered asbestos-cement products. IARC Sci Pub 90:367-371.

*Spurny KR. 1994. Sampling, analysis, identification and monitoring of fibrous dusts and aerosols. Analyst 119(1):41-51.

*Srebro SH, Roggli VL. 1994. Asbestos-related disease associated with exposure to asbestiform tremolite. Am J Ind Med 26:809-819.

Srebro SH, Roggli VL, Samsa GP. 1995. Malignant mesothelioma associated with low pulmonary tissue asbestos burdens: A light and scanning electron microscopic analysis of 18 cases. Mod Pathol 8:614-621.

*SRI. 1982. Chemical economics handbook. Asbestos-salient statistics. Menlo Park, CA: SRI International.

*Stanton MF, Layard M, Tegeris A, et al. 1981. Relation of particle dimension to carcinogenicity in amphibole asbestosis and other fibrous minerals. J Natl Cancer Inst 57:965-975.

STAPPA/ALAPCO. 1999. State and Territorial Air Pollution Program Administrators/Association of Local Air Pollution Control Officials. Washington, DC: Http://www.4cleanair.org/states.html#NorthC. May 6, 1999.

Stayner L, Bailer AJ, Smith R, et al. 1999. Sources of uncertainty in dose-response modeling of epidemiological data for cancer risk assessment. Ann N Y Acad Sci 895:212-222.

*Stayner LT, Dankovic DA, Lemen RA. 1996. Occupational exposure to chrysotile asbestos and cancer risk: A review of the amphibole hypothesis. Am J Public Health 86(2):179-186.

*Stayner L, Smith R, Bailer J, et al. 1997. Exposure-response analysis of risk of respiratory disease associated with occupational exposure to chrysotile asbestos. Occup Environ Med 54:646-652.

Steenland K, Stayner L. 1997. Silica, asbestos, man-made mineral fibers, and cancer. Cancer Causes Control 8:491-503.

*Steenland K, Thun M. 1986. Interaction between tobacco smoking and occupational exposures in the causation on lung cancer. J Occup Med 28:110-118.

*Stephens M, Gibbs AR, Pooley FD, et al. 1987. Asbestos induced diffuse pleural fibrosis: Pathology and mineralogy. Thorax 42:583-588.

*Stober W, McClellan RO. 1997. Pulmonary retention and clearance of inhaled biopersistent aerosol particles: Data-reducing interpolation models and models of physiologically based systems. Crit Rev Toxicol 27:539-598.

Stober W, Morrow PE, Hoover MD. 1989. Compartmental modeling of the long-term retention of insoluble particles deposited in the alveolar region of the lung. Fundam Appl Toxicol 13:823-842.

*Stober W, Morrow PE, Koch W et al. 1994. Alveolar clearance and retention of inhaled insoluble particles in rats simulated by a model inferring macrophage particle load distributions. J Aerosol Sci 25:975-1002.

Stokinger HE. 1981. The halogens and the nonmetals boron and silicon. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology. 3rd ed. Vol. 2B. New York, NY: John Wiley and Sons, 3021-3023.

Storer RD, Cartwright ME, Cook WO, et al. 1995. Short-term carcinogenesis bioassay of genotoxic procarcinogens in PIM transgenic mice. Carcinogenesis 16(2):285-293.

*Storeygard AR, Brown AL Jr. 1977. Penetration of the small intestinal mucosa by asbestos fibers. Mayo Clin Proc 52:809-812.

*Strokova B, Evstatieva S, Dimitrova S, et al. 1998. Study of asbestos exposure in some applications of asbestos materials in the chemical industry. Int Arch Occup Environ Health 71(Suppl.):19-21.

Sturm W, Menze B, Krause J, et al. 1994. Use of asbestos, health risks and induced occupational diseases in the former East Germany. Toxicol Lett 72:317-324.

Sulotto F, Capellero E, Chiesa A, et al. 1997. Relationship between asbestos bodies in sputum and the number of specimens. Scand J Work Environ Health 23:48-53.

Szeszenia-Dabrowska N, Wilczynska U, Szymczak W, et al. 1998. Environmental exposure to asbestos in asbestos cement workers: A case of additional exposure from indiscriminate use of industrial wastes. Int J Occup Med Environ Health 11:171-177.

*Tagesson C, Chabiuk D, Axelson O, et al. 1993. Increased urinary excretion of the oxidative DNA adduct, 8-hydroxydeoxyguanosine, as a possible indicator of occupational cancer hazards in the asbestos, rubber, and azo-dye industries. Pol J Occup Med Environ Health 6(4):357-368.

*Taguchi T, Jhanwar SC, Siegfried JM, et al. 1993. Recurrent deletions of specific chromosomal sites in 1p, 3p, 6q, and 9p in human malignant mesothelioma. Cancer Res 53:4349-4355.

Takagi M. 1991. Histopathological changes in the lung with low-dose asbestos exposure. Acta Med Biol 39(1):11-20.

*Takahashi K, Case BW, Dufresne A, et al. 1994. Relation between lung asbestos fibre burden and exposure indices based on job history. Occup Environ Med 51:461-469.

*Takeuchi T, Nakajima M, Morimoto K. 1999. A human cell system for detecting asbestos cytogenotoxicity in vitro. Mutat Res 438:63-70.

Talcott JA, Thurber WA, Kantor AF, et al. 1989. Asbestos-associated diseases in a cohort of cigarette-filter workers. N Engl J Med 321:1220-1223.

Tammilehto L. 1992. Malignant mesothelioma: Prognostic factors in a prospective study of 98 patients. Lung Cancer (The Netherlands) 8(3-4):175-184.

*Tammilehto L, Tuomi T, Tiainen M, et al. 1992. Malignant mesothelioma: Clinical characteristics, asbestos mineralogy and chromosomal abnormalities of 41 patients. Eur J Cancer 28A:1373-1379.

Tamura M, Tokuyama T, Kasuga JH, et al. 1996. [Study on correlation between chest X-P course findings and change in antinuclear antibody in asbestos plant employees.] J Occup Health 38:138-141. (Japanese)

Tanaka S, Choe N, Hemenway DR, et al. 1998. Asbestos inhalation induces reactive nitrogen species and nitrotyrosine formation in the lungs and pleura of the rat. J Clin Invest 102:445-454.

Tarchi M, Orsi D, Comba P, et al. 1994. Cohort mortality study of rock salt workers in Italy. Am J Ind Med 25(2):251-256.

Tarter ME, Cooper RC, Freeman WR. 1983. A graphical analysis of the interrelationships among waterborne asbestos, digestive system cancer and population density. Environ Health Perspect 53:79-89.

*Teschke K, Ahrens W, Andersen A, et al. 1999. Occupational exposure to chemical and biological agents in the nonproduction departments of pulp, paper, and paper product mills: An international study. Am Ind Hyg Assoc J 60:73-83.

*Teschke K, Morgan MS, Checkoway H, et al. 1997. Mesothelioma surveillance to locate sources of exposure to asbestos. Can J Public Health 88(3):163-168.

*Teschler H, Friedrichs KH, Hoheisel GB, et al. 1994. Asbestos fibers in bronchoalveolar lavage and lung tissue of former asbestos workers. Am J Resp Crit Care Med 149:641-645.

Teschler H, Thompson AB, Dollenkamp R, et al. 1996. Relevance of asbestos bodies in sputum. Eur Resp J 9:680-686.

*Testa JR. 1999. Written communication to the Agency for Toxic Substances and Disease Registry in response to the call for public comments on the draft Toxicological Profile for Asbestos.

Testa JR, Carbone M, Hirvonen A, et al. 1998. A multi-institutional study confirms the presence and expression of Simian virus 40 in human malignant mesotheliomas. Cancer Res 58:4505-4509.

*Teta MJ, Lewinsohn HC, Meigs JW, et al. 1983. Mesothelioma in Connecticut, 1955-1977: Occupational and geographic associations. J Occup Med 25(10):749-756.

*Thomas DC, Whittmore AS. 1988. Methods for testing interactions, with applications to occupational exposures, smoking, and lung cancer. Am J Ind Med 13:131-147.

*Tiainen M, Tammilehto L, Rautonen J, et al. 1989. Chromosomal abnormalities and their correlations with asbestos exposure and survival in patients with mesothelioma. Br J Cancer 60(4):618-626.

Tilkes F, Beck EG. 1989. Cytotoxicity and carcinogenicity of chrysotile fibres from asbestos-cement products. IARC Sci Pub 90:190-196.

Timblin CR, Janssen YMW, Goldberg JL, et al. 1998. GRP78, HSP72/73, and CJUN stress protein levels in lung epithelial cells exposed to asbestos, cadmium, or H2O2. Free Radic Biol Med 24:632-642.

*Timbrell V. 1982. Deposition and retention of fibres in the human lung. Ann Occup Hyg 26:347-369.

Tocilj J, Dujic Z, Boschi S, et al. 1990. Correlation between radiological and functional findings in workers exposed to chrysotile asbestos. Med Lav 81:373-381.

*Toft P, Wigle D, Meranger JC, et al. 1981. Asbestos and drinking water in Canada. Sci Total Environ 18:77-89.

*Tomasini M, Chiappino G. 1981. Hemodynamics of pulmonary circulation in asbestosis: Study of 16 cases. Am J Ind Med 2:167-174.

*Topping DC, Nettesheim P. 1980. Two-stage carcinogenesis studies with asbestos in Fischer 344 rats. J Natl Cancer Inst 65:627-630.

Tossavainen A, Karjalaine A, Karhunen PJ. 1994. Retention of asbestos fibers in the human body. Environ Health Perspect Suppl 102:253-255.

TRI92. 1994. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*TRI96. 1999. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

TRI98. 2000. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*TRI99. 2001. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Offices of Environmental Information. U.S. Environmental Protection Agency. Toxic Release Inventory. Http://www.epa.gov/triexplorer/. April 27, 2001.

*Trosic I, Brumen V, Horbat D. 1997. In vitro assessment of asbestos fibers genotoxicity. Zentralbl Hyg Umeweltmed 199:558-567.

Truhaut R, Chouroulinkov I. 1989. Effect of long-term ingestion of asbestos fibres in rats. IARC Sci Pub 90:127-133.

Tsai SP, Waddell LCJ, Gilstrap EL, et al. 1996. Mortality among maintenance employees potentially exposed to asbestos in a refinery and petrochemical plant. Am J Ind Med 29:89-98.

*Tsang PH, Chu FN, Fischbein A, et al. 1988. Impairments in functional subsets of T-suppressor (CD8) lymphocytes, monocytes, and natural killer cells among asbestos-exposed workers. Clin Immunol Immunopathol 47:323-332.

*Tsuda A, Stringer BK, Mijailovich SM, et al. 1999. Alveolar cell stretching in the presence of fibrous particles induces interleukin-8 responses. Am J Respir Cell Mol Biol 21:455-462.

Tsuda T, Morimoto Y, Yamato H, et al. 1997. Effects of mineral fibers on the expression of genes whose product may play a role in fiber pathogenesis. Environ Health Perspect Suppl 105:1173-1178.

*Tulchinsky TH, Ginsberg GM, Shihab S, et al. 1992. Mesothelioma mortality among former asbestos-cement workers in Israel, 1953-90. Isr J Med Sci 28(8-9):543-547.

Tuomi T. 1992. Fibrous minerals in the lungs of mesothelioma patients: Comparison between data on SEM, TEM and personal interview information. Am J Ind Med 21:155-162.

Tuomi T, Huuskonen MS, Tammilehto L, et al. 1991c. Occupational exposure to asbestos evaluated from work histories and analysis of lung tissues from patients with mesothelioma. Br J Ind Med 48:48-52.

Tuomi T, Huuskonen MS, Virtamo M, et al. 1991a. Relative risk of mesothelioma associated with different levels of exposure to asbestos. Scad J Work Environ Health 17:404-408.

*Tuomi T, Oksa P, Anttila S, et al. 1991b. Fibres and asbestos bodies in bronchoalveolar lavage fluids of asbestos sprayers. Br J Ind Med 49:480-485.

UATW. 1999. Unified Air Toxics Website. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. Http://www.epa.gov/ttnuatw1/uatwn.html. May 6, 1999

Unfried K, Kociok N, Roller M, et al. 1997a. P53 mutations in tumours induced by intraperitoneal injection of crocidolite asbestos and benzo[a]pyrene in rats. Exp Toxicol Pathol 49:181-187.

Unfried K, Roller M, Pott F, et al. 1997b. Fiber-specific molecular features of tumors induced in rat peritoneum. Environ Health Perspect Suppl 105:1103-1108.

Upton AC, Shaikh RA. 1995. Asbestos exposures in public and commercial buildings. Am J Ind Med 27:433-437.

*U.S. Bureau of Mines. 1992. Mineral commodity summaries. Asbestos, 28-29.

*U.S. Bureau of Mines. 1994. Mineral commodity summaries. Asbestos, 26-27.

USC. 1998. United States Code. 42 USC 7412.

*USC. 2001a. Clean Water Act. National standards of performance. U.S. Code. 33 USC 1316. Http://www4.law.cornell.edu/uscode/33/1316.text.html. May 01, 2001.

*USC. 2001b. Congressional findings and purpose. U.S. Code. 15 USC 2641. Http://www4.law.cornell.edu/uscode/15/2641.text.html. May 01, 2001.

*USC. 2001c. Hazardous air pollutants. U.S. Code. 42 USC 4712. Http://www4.law.cornell.edu/uscode/42/7412.text.html. May 01, 2001.

*USGS. 1997. Asbestos. Minerals Yearbook 1997. U.S. Geological Survey. Http://minerals.usgs.gov/minerals/pubs/commodity/asbestos/070497.pdf. April 25, 1997.

*USGS. 1998. Asbestos. Commodity Summaries. U.S. Geological Survey. Http://minerals.usgs.gov/minerals/pubs/commodity/asbestos/070398.pdf. April 29, 1998.

*USGS. 1999a. Asbestos. Commodity Summaries. U.S. Geological Survey. Http://minerals.usgs.gov/minerals/pubs/commodity/asbestos070399.pdf. January 15, 1999.

*USGS. 1999b. Asbestos. Minerals Yearbook 1999. U.S. Geological Survey. Http://minerals.usgs.gov/pubs/commodity/asbestos/070499.pdf. January 15, 1999.

*USGS. 2000. Asbestos. Commodity Summaries. U.S. Geological Survey. Http://minerals.usgs.gov/minerals/commodity/asbestos/070300.pdf. January 23, 2000.

Vacek PM. 1997. Assessing the effect of intensity when exposure varies over time. Stat Med 16:505-513.

Vacek PM. 1998. Effects of the intensity and timing of asbestos exposure on lung cancer risk at two mining areas in Quebec. J Occup Environ Med 40:821-828.

Vainio H, Boffetta P. 1994. Mechanisms of the combined effect of asbestos and smoking in the etiology of lung cancer. Scand J Work Environ Health 20:235-242.

Vainio H, Husgafvel-Pursiainen K, Antilla S, et al. 1993. Interaction between smoking and asbestos in human lung adenocarcinoma. Environ Health Perspect Suppl 101 (3):189-192.

*Valerio F, De Ferrari M, Ottaggio L, et al. 1980. Cytogenetic effect of Rhodesian chrysotile on human lymphocytes *in vitro*. IARC Sci Publ 30:485-489.

Valic F, Beritic-Stahuljak D, Cigula M. 1990. Ventilatory lung function changes in family members of asbestos workers. Acta Med Iug 44:205-209.

Valkila EH, Nieminen MM, Moilanen AK, et al. 1995. Asbestos-induced visceral pleural fibrosis reduces pulmonary compliance. Am J Ind Med 28:363-372.

Vallyathan V, Green FH. 1985. The role of analytical techniques in the diagnosis of asbestos-associated disease. CRC Crit Rev Clin Lab Sci 22:1-42.

Van Der Meeren A, Fleury J, Nebut M, et al. 1992. Mesothelioma in rats following intrapleural injection of chrysotile and phosphorylated chrysotile (chrysophosphate). Int J Cancer 50:937-942.

van Gelder T, Hoogsteden HC, Versnel MA, et al. 1989. Malignant peritoneal mesothelioma: A series of 19 cases. Digestion 43:222-227.

Varga C, Horvath G, Pocsai Z, et al. 1998. On the mechanism of cogenotoxic action between ingested amphibole asbestos fibres and benzo[a]pyrene: I. Urinary and serum mutagenicity studies with rats. Cancer Lett 128:165-169.

*Varga C, Horvath G, Timbrell V. 1996a. In vivo studies on genotoxicity and cogenotoxicity of ingested UICC anthophyllite asbestos. Cancer Lett 105:181-185.

*Varga C, Pocsai Z, Horvath G, et al. 1996b. Studies on genotoxicity of orally administered crocidolite asbestos in rats: Implications for ingested asbestos induced carcinogenesis. Anticancer Res 16:811-814.

Varouchakis G, Velonakis EG, Amfilochiou S, et al. 1991. Asbestos in strange places: Two case reports of mesothelioma among merchant seamen. Am J Ind Med 19(5):673-676.

*Verma DK, Clark NE. 1995. Relationships between phase contrast microscopy and transmission electron microscopy results of samples from occupational exposure to airborne chrysotile asbestos. Am Ind Hyg Assoc J 56:866-873.

Versar. 1988. Final report: Asbestos modeling study. Report to U. S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC, by Versar, Inc., Springfield, VA. EPA 560/3-88/091.

*Viallat JR, Boutin C. 1980. Radiographic changes in chrysotile mine and mill ex-workers in Corsica: A survey 14 years after cessation of exposure. Lung 157:155-163.

*Viallat JR, Raybuad F, Passarel M, et al. 1986. Pleural migration of chrysotile fibers after intratracheal injection in rats. Arch Environ Health 41:282-286.

*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.

Vineis P, Ciccone G, Magnino A. 1993. Asbestos exposure, physical activity and colon cancer: A case-control study. Tumori 79(5):301-303.

Voisin C, Fisekci F, Voisin-Saltiel S, et al. 1995. Asbestos-related rounded atelectasis: Radiologic and mineralogic data in 23 cases. Chest 107:477-481.

*Voisin C, Marin I, Brochard P, et al. 1994. Environmental airborne tremolite asbestos pollution and pleural plaques in Afghanistan. Chest 106:974-976.

*Volkheimer G. 1974. Passage of particles through the wall of the gastrointestinal tract. Environ Health Perspect 9:215-225.

Voytek P, Anver M, Thorslund T, et al. 1990. Mechanism of asbestos carcinogenicity. J Am Coll Toxicol 9:541-550.

*Vu VT. 1993. Regulatory approaches to reduce human health risks associated with exposures to mineral fibers. In: Guthrie GD, Mossman BT, eds. Health Effects of Mineral Dusts. Washington, D.C.: Mineralogical Society of America, 545-554.

Vu V, Barrett JC, Roycroft J, et al. 1996. Chronic inhalation toxicity and carcinogenicity testing of respirable fibrous particles. Regul Toxicol Pharmacol 24:202-212.

Waage HP, Johnson ES, Hilt B, et al. 1994. Asbestosis and pleural changes as risk factors for asbestos-induced lung cancer. Intl J Occup Med Toxicol 3:319-327.

*Waage HP, Vatten LJ, Opedal E, et al. 1996. Lung function and respiratory symptoms related to changes in smoking habits in asbestos-exposed subjects. J Occup Environ Med 38:178-183.

Wagner JC. 1972. Current opinions on the asbestos cancer problem. Ann Occup Hyg 15:61-64.

Wagner JC. 1975. Asbestos carcinogenesis. Br J Cancer 32:258-259.

Wagner JC. 1979. Diseases associated with exposure to asbestos dusts. Practitioner 223:28-33.

Wagner JC. 1983. The risk assessment of asbestos carcinogenicity in the normal population. Animal to human correlations. VDI-Berichte Nr 475:305-308.

Wagner JC. 1984. Mineral fiber carcinogenesis. In: Searle CE, ed. Chemical carcinogens. 2nd ed. Vol 1. Washington, DC: American Chemical Society, 634-641.

Wagner JC, Berry G. 1969. Mesotheliomas in rats following inoculation with asbestos. Br J Cancer 23:567-581.

Wagner JC, Pooley FD. 1986. Mineral fibers and mesothelioma [Editorial]. Thorax 41:161-166.

*Wagner JC, Berry G, Pooley FD. 1982a. Mesotheliomas and asbestos type in asbestos textile workers: A study of lung contents. Br Med J 285:603-606.

*Wagner JC, Berry G, Skidmore JW, et al. 1974. The effects of the inhalation of asbestos in rats. Br J Cancer 29:252-269.

*Wagner JC, Berry G, Skidmore JW, et al. 1980a. The comparative effects of three chrysotiles by injection and inhalation in rats. IARC Sci Publ 30:363-372.

*Wagner JC, Berry G, Timbrell V. 1973. Mesotheliomata in rats after inoculation with asbestos and other materials. Br J Cancer 28:173-185.

*Wagner JC, Chamberlain M, Brown RC, et al. 1982c. Biological effects of tremolite. Br J Cancer 45:352-360.

Wagner JC, Gilson JC, Berry G, et al. 1971. Epidemiology of asbestos cancer. Br Med Bull 27:71-76.

Wagner JC, Griffiths DM, Hill RJ. 1984. The effect of fibre size on the in vivo activity of UICC crocidolite. Br J Cancer 49(4):453-458.

Wagner JC, Hill RJ, Berry G, et al. 1980b. Treatments affecting the rate of asbestos-induced mesotheliomas. Br J Cancer 41:918-922.

*Wagner JC, Moncrieff CB, Coles R, et al. 1986. Correlation between fibre content of the lungs and disease in naval dockyard workers. Br J Ind Med 43:391-395.

*Wagner JC, Pooley FD, Berry G, et al. 1982b. A pathological and mineralogical study of asbestos-related deaths in the United Kingdom in 1977. Ann Occup Hyg 26:423-431.

*Wagner JC, Sleggs CA, Marchand P. 1960. Diffuse pleural mesothelioma and asbestos exposure in the north western Cape Province. Br J Ind Med 17:260-271.

Walach N, Novikov I, Milievskaya I, et al. 1998. Cancer among spouses. Cancer 82:180-185.

Walker C, Bermudez E, Everitt J. 1991a. Growth factor and receptor expression by mesothelial cells: A comparison between rodents and humans. In: Cellular and molecular aspects of fiber carcinogenesis. Cold Spring Harbor Laboratory Press, 149-158.

Walker C, Bermudez E, Stewart W, et al. 1991b. Growth factor and growth factor receptor expression in transformed rat mesothelial cells. In: Brown RC, ed. Mechanisms in fibre carcinogenesis. New York, NY: Plenum Press, 377-383.

Walker C, Bermudez E, Stewart W, et al. 1992a. Characterization of platelet-derived growth factor and platelet-derived growth factor receptor expression in asbestos-induced rat mesothelioma. Cancer Res 52:301-306.

Walker C, Everitt J, Barrett JC. 1992b. Possible cellular and molecular mechanisms for asbestos carcinogenicity. Am J Ind Med 21:253-273.

Walker C, Everitt J, Ferriola PC, et al. 1995. Autocrine growth stimulation by transforming growth factor alpha in asbestos-transformed rat mesothelial cells. Cancer Res 55:530-536.

Walton WH. 1982. The nature, hazards and assessment of occupational exposure to airborne asbestos dust: A review. Ann Occup Hyg 25:117-247.

Wang X, Araki S, Yano E, et al. 1995a. Effects of smoking on respiratory function and exercise performance in asbestos workers. Ind Health 33:173-180.

*Wang X, Christiani DC, Wiencke JK, et al. 1995b. Mutations in the p53 gene in lung cancer are associated with cigarette smoking and asbestos exposure. Cancer Epidemiol Biomarkers Prev 4:543-548.

*Wang X, Yano E, Nonaka K, et al. 1997. Respiratory impairments due to dust exposure: A comparative study among workers exposed to silica, asbestos, and coalmine dust. Am J Ind Med 31:495-502.

*Wang XR, Yano E, Nonaka K, et al. 1998. Pulmonary function of nonsmoking female asbestos workers without radiographic signs of asbestosis. Arch Environ Health 53:292-298.

*Ward JM, Frank AL, Wenk M, et al. 1980. Ingested asbestos and intestinal carcinogenesis in F344 rats. J Environ Pathol Toxicol 3:301-312.

Warheit DB. 1989. Interspecies comparisons of lung responses to inhaled particles and gases. CRC Crit Rev Toxicol 20:1-29.

*Warheit DB, Hartsky MA. 1994. Influences of gender, species, and strain differences in pulmonary toxicological assessments of inhaled particles and/or fibers. In: Mohr U, Dungworth DL, Mauderly JL, et al., ed. Toxic and carcinogenic effects of solid particles in the respiratory tract. Washington, DC: ILSI Press, 253-265.

*Warheit DB, Chang KY, Hill LH, et al. 1984. Pulmonary macrophage accumulation and asbestos-induced lesions at sites of fiber deposition. Am Rev Respir Dis 129:301-310.

*Warheit DB, George G, Hill LH, et al. 1985. Inhaled asbestos activates a complement-dependent chemoattractant for macrophages. Lab Invest 52:505-514.

Warheit DB, Harsky MA, Frame SR. 1996. Pulmonary effects in rats inhaling size-separated chrysotile asbestos fibers or *p*-aramid fibrils: differences in cellular proliferative responses. Toxicol Lett 88:287-292.

Warheit DB, Hartsky MA, McHugh TA, et al. 1994. Biopersistence of inhaled organic and inorganic fibers in the lungs of rats. Environ Health Perspect Suppl 102:151-157.

*Warheit DB, Hill LH, George G, et al. 1986. Time course of chemotactic factor generation and the corresponding macrophage response to asbestos inhalation. Am Rev Respir Dis 134:128-133.

*Warheit DB, Overby LH, George G, et al. 1988. Pulmonary macrophages are attracted to inhaled particles through complement activation. Exp Lung Res 14:51-66.

*Warheit DB, Snajdr SI, Hartsky MA, et al. 1997. Lung proliferative and clearance responses to inhaled para-aramid RFP in exposed hamsters and rats: Comparisons with chrysotile asbestos fibers. Environ Health Perspect Suppl 105:1219-1222.

*Warner M. 1988. Asbestos. Anal Chem 60:395A-396A.

Warnock ML. 1989. Lung asbestos burden in shipyard and construction workers with mesothelioma: Comparison with burdens in subjects with asbestosis or lung cancer. Environ Res 50:68-85.

*Warwick MT, Parkes R, Hanson A, et al. 1973. Immunology and asbestos. IARC Sci Publ 8:258-263.

Watanabe M, Kimura N, Kato M, et al. 1994. An autopsy case of malignant mesothelioma associated with asbestosis. Pathol Int 44:785-792.

Watanabe Y, Yamaguchi M, Kawakami Y, et al. 1993. Human CD4+ CD45RA+ T lymphocytes can be stimulated by crocidolite, anthophyllite and amosite asbestos *in vitro*. Int J Oncol 2(2):209-212.

Weant GE, McCormick GS. 1984. Nonindustrial sources of potentially toxic substances and their applicability to source apportionment methods. Research Triangle Park, NC: U.S. Environmental Protection Agency (MD 14). EPA-450/4-84-003. NTIS No. PB84-231232.

*Webber JS, Covey JR, King MV. 1989. Asbestos in drinking water supplied through grossly deteriorated a-c pipe. J AWWA (February 1989):80-85.

*Webber JS, Syrotynski S, King MV. 1988. Asbestos-contaminated drinking water: Its impact on household air. Environ Res 46:153-167.

*Webster I, Goldstein B, Coetzee FS, et al. 1993. Malignant mesothelioma induced in baboons by inhalation of amosite asbestos. Am J Ind Med 24(6):659-666.

Weidner N. 1991. Malignant mesothelioma of peritoneum. Ultrastruct Pathol 15(4-5):515-520.

*Weill H, Hughes J, Waggenspack C. 1979. Influence of dose and fiber type on respiratory malignancy risk in asbestos cement manufacturing. Am Rev Respir Dis 120:345-354.

Weill H, Hughes JM, Jones RN. 1995. Asbestos: A risk too far? [Letter]. Lancet 346:304-306.

*Weill H, Ziskind MM, Waggenspack C, et al. 1975. Lung function consequences of dust exposure in asbestos cement manufacturing plants. Arch Environ Health 30:88-97.

*Weinzweig M, Richards RJ. 1983. Quantitative assessment of chrysotile fibrils in the bloodstream of rats which have ingested the mineral under dietary conditions. Environ Res 31:245-255.

*Weiss W. 1984. Cigarette smoke, asbestos, and small irregular opacities. Amer Rev Respir Dis 130:293-301.

Weiss W. 1990. Asbestos and colorectal cancer. Gastroenterology 99:876-884.

*Weiss W. 1993. Asbestos-related pleural plaques and lung cancer. Chest 103(6):1854-1859.

*Weiss W. 1995. The lack of causality between asbestos and colorectal cancer. J Occup Environ Med 37:1364-1371.

Weiss W. 1999. Asbestosis: A marker for the increased risk of lung cancer among workers exposed to asbestos. Chest 115:536-549.

*Weitzman SA, Graceffa P. 1984. Asbestos catalyzes hydroxyl and superoxide radical generation from hydrogen peroxide. Arch Biochem Biophysics 228:373-376.

*Weitzman SA, Chester JF, Graceffa P. 1988. Binding of deferoxamine to asbestos fibers *in vitro* and *in vivo*. Carcinogenesis 9:1643-1645.

Welch LS, Michaels D, Zoloth SR, et al. 1994. The national sheet metal workers asbestos disease screening program: Radiologic findings. Am J Ind Med 25:536-648.

*West JB ed. 1985. Physiological basis of medical practice. 11th ed. Baltimore, MD: Williams and Wilkins, 386-389.

*West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J Pediatr 32:10-18.

*Westlake GE, Spjut HJ, Smith MN. 1965. Penetration of colonic mucosa by asbestos particles: An electron microscopic study in rats fed asbestos dust. Lab Invest 14:2029-2033.

White KL Jr, Munson AE. 1986. Suppression of the *in vitro* humoral immune response by chrysotile asbestos. Toxicol Appl Pharmacol 82:493-504.

Whitwell F. 1978. Problems in the pathology of disease caused by asbestos. J R Soc Med 71:919-922.

*Whitwell F, Scott J, Grimshaw M. 1977. Relationship between occupations and asbestos-fibre content of the lungs in patients with pleural mesothelioma, lung cancer, and other diseases. Thorax 32:377-386.

WHO. 1984. Asbestos. In: Guidelines for drinking water quality. Vol. 2. Health criteria and other supporting information. Geneva, Switzerland: World Health Organization, 68-75.

*WHO. 1986. Asbestos and other natural mineral fibers. Environmental health criteria 53. Geneva, World Health Organization, 10-31, 166-167, 178-179.

*WHO. 1998. Chrysotile asbestos: Environmental health criteria. Geneva: Switzerland: World Health Organization.

Whysner J, Covello VT, Kuschner M, et al. 1994. Asbestos in the air of public buildings: A public health risk? Prev Med 23:119-125.

*Widdowson EM, Dickerson JWT. 1964. Chapter 17: 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.

*Wigle DT. 1977. Cancer mortality in relation to asbestos in municipal water supplies. Arch Environ Health 32:185-190.

*Wignall BK, Fox AJ. 1982. Mortality of female gas mask assemblers. Br J Ind Med 39:34-38.

Wilkinson P, Hansell DM, Janssens J, et al. 1995. Is lung cancer associated with asbestos exposure when there are no small opacities on the chest radiograph? Lancet 345:1074-1078.

*Williams V, De Klerk NH, Whitaker D, et al. 1995. Asbestos bodies in lung tissue following exposure to crocidolite. Am J Ind Med 28:489-495.

Windholz M, Budavari S, eds. 1983. The Merck index: An encyclopedia of chemicals, drugs, and biologicals. 10th ed. Rahway, NJ: Merck and Company, Inc., 119.

Woitowitz HJ, Hausmann K. 1995. [Non-Hodgkin's lymphoma of the tonsils following asbestos dust exposure.] Dtsch Med Wochenschr 120:626. (German)

Woitowitz H-J, Rodelsperger K. 1994. Mesothelioma among car mechanics. Ann Occup Hyg 38:635-638.

Wolff H, Saukkonen K, Anttila S, et al. 1998. Expression of cyclooxygenase-2 in human lung carcinoma. Cancer Res 58:4997-5001.

*Wollmer P, Eriksson L, Jonson B, et al. 1987. Relation between lung function, exercise capacity, and exposure to asbestos cement. Br J Ind Med 44:542-549.

*Wortley P, Vaughan TL, Davis S, et al. 1992. A case-control study of occupational risk factors for laryngeal cancer. Br J Ind Med 49(12):837-844.

Wozniak H, Wiecek E, Tossavainen A, et al. 1986. Comparative studies of fibrogenic properties of wollastonite, chrysotile and crocidolite. Med Pr 37:288-296.

Wright A, Cowie H, Gormley IP, et al. 1986. The *in vitro* cytotoxicity of asbestos fibers: I. $P288D_1$ cells. Am J Ind Med 9:371-384.

Wright A, Donaldson K, Davis JM. 1983. Cytotoxic effect of asbestos on macrophages in different activation states. Environ Health Perspect 51:147-152.

Wright JL, Tron V, Wiggs, B, et al. 1988. Cigarette smoke potentiates asbestos-induced airflow abnormalities. Exp Lung Res 14:537-548.

Wright JL, Wiggs B, Churg A. 1991. Pulmonary hypertension induced by amosite asbestos: A physiological and morphologic study in the guinea pig. Lung 169:31-42.

Wunsch-Filho V, Moncau JE, Mirabelli D, et al. 1998. Occupational risk factors of lung cancer in Sao Paulo, Brazil. Scand J Work Environ Health 24:118-124.

Wylie AG, Bailey KF. 1992. The mineralogy and size of airborne chrysotile and rock fragments: Ramifications of using the NIOSH 7400 method. Am Ind Hyg Assoc J 53(7):442-447.

*Wylie AG, Verkouteren JR. 2000. Amphibole asbestos from Libby, Montana: Aspects of nomenclature. Am Mineral 85:1540-1542.

Wylie AG, Bailey KF, Kelse JW, et al. 1993. The importance of width in asbestos fiber carcinogenicity and its implications for public policy. Am Ind Hyg Assoc J 54(5):239-252.

Wylie AG, Skinner HCW, Marsh J, et al. 1997. Mineralogical features associated with cytotoxic and proliferative effects of fibrous talc and asbestos on rodent tracheal epithelial and pleural mesothelial cells. Toxicol Appl Pharmacol 147:143-150.

*Xing Z, Jordana M, Gauldie J, et al. 1999. Cytokines and pulmonary inflammatory and immune disease. Histol Histopathol 14:185-201.

*Xu A, Wu L-J, Santella RM, et al. 1999. Role of oxyradicals in mutagenicity and DNA damage induced by crocidolite asbestos in mammalian cells. Cancer Res 59:5922-5926.

*Xu GB, Yu CP. 1986. Effects of age on deposition of inhaled aerosols in the human lung. Aerosol Sci Technol 5:349-357.

Xu X, Kelsey KT, Wiencke JK, et al. 1996. Cytochrome P450 CYP1A1 MspI polymorphism and lung cancer susceptibility. Cancer Epidemiol Biomarkers Prev 5:687-692.

Yamada H, Hashimoto H, Akiyama M, et al. 1997. Talc and amosite/crocidolite preferentially deposited in the lungs of nonoccupational female lung cancer cases in urban areas of Japan. Environ Health Perspect 105:504-508.

Yamaguchi N, Kido M, Hoshuyama T, et al. 1992. A case-control study on occupational lung cancer risks in an industrialized city of Japan. Jpn J Cancer Res 83(2):134-140.

*Yano E. 1988. Mineral fiber-induced malondialdehyde formation and effects of oxidant scavengers in phagocytic cells. Int Arch Occup Environ Health 61:19-23.

Yates DH, Browne K, Stidolph PN, et al. 1996. Asbestos-related bilateral diffuse pleural thickening: Natural history of radiographic and lung function abnormalities. Am J Resp Crit Care Med 153:301-306.

Yates DH, Corrin B, Stidolph PN, et al. 1997. Malignant mesothelioma in south east England: Clinicopathological experience of 272 cases. Occup Environ Med 52:507-512.

*Yazicioglu S, Ilcayto R, Balci K, et al. 1980. Pleural calcification, pleural mesotheliomas, and bronchial cancers caused by tremolite dust. Thorax 35:564-569.

*Yegles M, Janson X, Dong HY, et al. 1995. Role of fibre characteristics on cytotoxicity and induction of anaphase/telophase aberrations in rat pleural mesothelial cells in vitro: Correlations with in vivo animal findings. Carcinogenesis 16:2751-2758.

*Yegles M, Saint-Etienne L, Renier A, et al. 1993. Induction of metaphase and anaphase/telophase abnormalities by asbestos fibers in rat pleural mesothelial cells *in vitro*. Am J Respir Cell Mol Biol 9(2):186-91.

*Yu CP, Zhang L, Oberdorster G et al. 1994. Deposition modeling of refractory ceramic fibers (RCF) in the rat lung. J Aerosol Sci 25:407-417.

*Yu CP, Zhang L, Oberdorster G et al. 1995. Deposition of refractory ceramic fibers (RCF) in the human respiratory tract and comparison with rodent studies. Aerosol Sci Technol 23:291-300.

*Yu CP, Ding YJ, Zhang L et al. 1996. A clearance model of refractory ceramic fibers (RCF) in the rat lung including fiber dissolution and breakage. J Aerosol Sci 27:151-160.

*Yu CP, Ding YJ, Zhang L, et al. 1997. Retention modeling of refractory ceramic fibers (RCF) in humans. Regul Toxicol Pharmacol 25:18-25.

Yu IJ, Moon YH, Sakai K, et al. 1998. Asbestos and non-asbestos fiber content in lungs of Korean subjects with no known occupational asbestos exposure history. Environ Int 24:293-300.

Zahm SH, Devesa SS. 1995. Childhood cancer: Overview of incidence trends and environmental carcinogens. Environ Health Perspect Suppl 103:177-184.

*Zanella CL, Timblin CR, Cummins A, et al. 1999. Asbestos-induced phosphorylation of epidermal growth factor receptor is linked to c-*fos* and apoptosis. Am J Physiol 277:L684-L693.

Zelen M. 1985. Products liability issues in school asbestos litigation. Am J Law Med 10:467-489.

*Zerva LV, Constantopoulos SH, Moutsopoulos HM. 1989. Humoral immunity alterations after environmental asbestos exposure. Respiration 55:237-241.

*Zhang Y, Lee TC, Guillemin B, et al. 1993. Enhanced IL-1beta tumor necrosis factor-alpha release and messenger RNA expression in macrophages from idiopathic pulmonary fibrosis or after asbestos exposure. J Immunol 150:4188-4196.

Zheng W, Blot WJ, Shu X-O, et al. 1992. Diet and other risk factors for laryngeal cancer in Shanghai China. Am J Epidemiol 136(2):178-191.

Zhu HL, Wang ZM. 1993. Study of occupational lung-cancer in asbestos factories in China. Br J Ind Med 50(11):1039-1042.

*Ziegler EE, Edwards BB, Jensen RL et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12:29-34.

Zitting AJ. 1995. Prevalence of radiographic small lung opacities and pleural abnormalities in a representative adult population sample. Chest 107(1):126-131.

Zitting AJ, Karjalainen A, Impivaara I, et al. 1995. Radiographic small lung opacities and pleural abnormalities as a consequence of asbestos exposure in an adult population. Scand J Work Environ Health 21:470-477.

Zitting AJ, Karjalainen A, Impivaara O, et al. 1996. Radiographic small lung opacities and pleural abnormalities in relation to smoking, urbanization status, and occupational asbestos exposure in Finland. J Occup Environ Med 38:602-609.

Zoller T, Zeller WJ. 2000. Production of reactive oxygen species by phagocytic cells after exposure to glass wool and stone wool fibres - effect of fibre preincubation in aqueous solution. Toxicol Lett 114:1-9.

10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Actinolite— A mineral in the amphibole group, a calcium magnesium (iron) silicate with the chemical formula: $Ca_2(Mg,Fe)_5Si_8O_{22}(OH)_2$. The mineral occurs as a series in which magnesium and iron can freely substitute for each other. Actinolite is the intermediate member; when iron is predominant the mineral is ferro-actinolite and when magnesium is predominant, the mineral is tremolite. The iron produces a green color that darkens as the iron content increases. Actinolite may occur in fibrous form (an asbestos). It is not used commercially, but is a common impurity in chrysotile asbestos.

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 a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Amosite—A type of asbestos in the amphibole group; it is also known as brown asbestos.

Amphibole—The group name for a family of naturally-occurring ferromagnesium silicate minerals, characterized by a double chain of silicate ions (silicon-oxygen tetrahedra). This group includes amosite, actinolite, crocidolite, and tremolite forms of asbestos. However, the amphibole group includes a much broader and larger variety of minerals than the asbestiform ones. Amphibole asbestos particles are generally brittle and often have a rod- or needle-like shape

Anthophyllite—A type of asbestos in the amphibole group; it is also known as azbolen asbestos.

Asbestiform—Possessing the properties of asbestos. Minerals of specific chemical compositions can have asbestiform varieties that are fibrous in nature (e.g., crocidolite and amosite are the asbestiform varieties of the amphibole minerals, reibeckite and grunerite; tremolite and actinolite may be either asbestiform or nonasbestiform)

Asbestos—A general term applied to certain polysilicate fibrous minerals displaying similar physical characteristics although differing in composition. The most common asbestos mineral (over 95% of U.S. production) is chrysotile, a variety of serpentine, a metamorphic mineral.

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.

Bulk Sample—A sample of suspected asbestos-containing material that is obtained from a building to be analyzed microscopically for asbestos content. Bulk sample analysis can be part of a process to assess the hazard from asbestos in a building.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control 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 in workplace air that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Chrysotile Asbestos—A fibrous member of the serpentine group of minerals. Chrysotile asbestos fibers are flexible and have a curved morphology. It is the most common form of asbestos used commercially, also referred to as white asbestos.

Cleavage Fragments—Term used to characterize the form of some nonasbestiform amphiboles. These are microscopic fragments that have the appearance of fibers but are considerably shorter and have smaller length:width ratios (i.e., length >5 μm and a length:width ratio greater than 3:1) than is used by health regulatory agencies to define asbestiform fibers. Cleavage fragments may be formed when nonfibrous amphibole minerals are crushed, as may occur in mining and milling.

Cleavage Plane—Preferred direction along smooth plane surfaces in which a mineral tends to split or cleave. Planes of cleavage are governed by atomic structure and represent direction in which atomic bonds are relatively weak. Amphiboles exhibit prismatic cleavage with an angle of about 55 between cleavage planes.

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.

Crocidolite—A type of asbestos in the amphibole group; it is also known as blue asbestos.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines, at one point in time, the relationship between exposure to a chemical or to chemicals and outcome.

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.

$FEFR_{25-75}$—Forced expiratory flowrate between 25 and 75%.

$FEV_{1.0}$—Forced expiratory volume in 1.0 second.

Fibrogenic—Causing or contributing to the fibrotic response mechanism in tissues; commonly refers to substances that contribute to fibrosis of the lungs or liver.

FVC—Forced vital capacity.

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.

Horticultural Vermiculite —Grade of vermiculite sold for horticultural applications. Such grades of vermiculite have smaller particle size resulting in improved water retention, particle strength, and wettability than coarser grades of vermiculite.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunological Effects—Functional changes in the immune response.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo—Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

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)—A level of exposure to 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 level, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound—A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40 hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

ppbv—Parts per billion by volume.

ppmv—Parts per million by volume.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Proportionate Mortality Ratio (PMR)—The ratio of a cause-specific mortality proportion in an exposed group to the mortality proportion in an unexposed group; mortality proportions may be adjusted for confounding variables such as age. Cause-specific mortality proportions can be calculated when the cohort (the population at risk) cannot be defined due to inadequate records, but the number of deaths and the causes of deaths are known.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and μg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the No-Observed-Adverse-Effect Level (NOAEL- from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Relative Risk (RR)—The risk expressed as a ratio of the incidence of diseased subjects exposed to a particular risk factor to the incidence of diseased subjects in a non-exposed referent group.

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.

Serpentine—A name given to several members of a polymorphic group of magnesium silicate minerals—those having essentially the same chemistry but different structures or forms. Serpentine's structure consists of layers of silicate tetrahedrons linked into sheets with the sheets being separated by layers of $Mg(OH)_2$ called brucite layers. In the asbestos varieties, the brucite and silicate layers bend into tubers that produce the fibers. Chrysotile asbestos is a fibrous member of the serpentine group. "Serpentine" comes from mottled shades of green on massive varieties, suggestive of snake markings.

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 such exposures 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)—The ratio of a cause-specific mortality rate in an exposed cohort during a given period to the mortality rate of an unexposed cohort; mortality rates are often adjusted for age or other confounding variables.

Standardized Proportionate Incidence Ratio (SPIR)—Similar to a Proportionate Mortality Ratio (PMR) in that it is a ratio of a proportion of a specific disease in an exposed group compared with the proportion in an unexposed group.

Talc—A common, extremely soft, basic magnesium silicate mineral; in compact aggregates, it is known as soapstone (steatite) in reference to their soapy feel. It is frequently associated with tremolite.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Tremolite—A mineral in the amphibole group, a calcium magnesium (iron) silicate with the chemical formula: $Ca_2(Mg,Fe)_5Si_8O_{22}(OH)_2$. The mineral occurs as a series in which magnesium and iron can freely substitute for each other. Tremolite is the mineral when magnesium is predominant; otherwise, the mineral is actinolite. Tremolite is sometimes found in forms that are free of iron in which it has a creamy white color; small amounts of iron produces a greenish color. Tremolite may occur in fibrous form (an asbestos). It is not used commercially in the United States, but is a common impurity in chrysotile asbestos and vermiculite mined from deposits in Libby, Montana.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using Lowest-Observed-Adverse-Effect Level (LOAEL) data rather than No-Observed-Adverse-Effect Level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Vermiculite—A chemically inert, lightweight, fire resistant, and odorless magnesium silicate material that is generally used for its thermal and sound insulation in construction and for its absorbent properties in horticultural applications. It is made by a process called exfoliation in which flakes of raw vermiculite concentrate are rapidly heated to a temperature above 870 C. The mica-like flakes of vermiculite concentrate, which contain interlayers of water, then expand into accordion-like particles (originally described as resembling small worms) as the water is converted into steam. Properly speaking, the term vermiculite should be used to apply to the mined, unexfoliated, commercial product (see Vermiculite concentrate). However, the common usage of the term vermiculite as the exfoliated or expanded material is so entrenched in the minds of contractors, retailers, and the general public that it is less confusing to retain the common usage and use descriptors to refer to the raw material. Vermiculite mined from Libby, Montana has been demonstrated to contain various amounts of asbestiform tremolite-like amphibole minerals.

Vermiculite Concentrate (also raw or unexfoliated vermiculite)—The mineralogical name given to hydrated laminar magnesium-aluminum-iron silicate ($Mg,Ca,K,Fe(II)_3(Si,Al,Fe(III)_4O_{10}(OH)_2O_4H_2O$) minerals, which resemble mica in appearance. This mineral has the unusual property of exfoliating or expanding to a low density, bulky material when heated (see Vermiculite).

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 a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 3-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (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 2 "18r" data points in Figure 3-1).

(5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (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 Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in Chapter 9 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1

Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

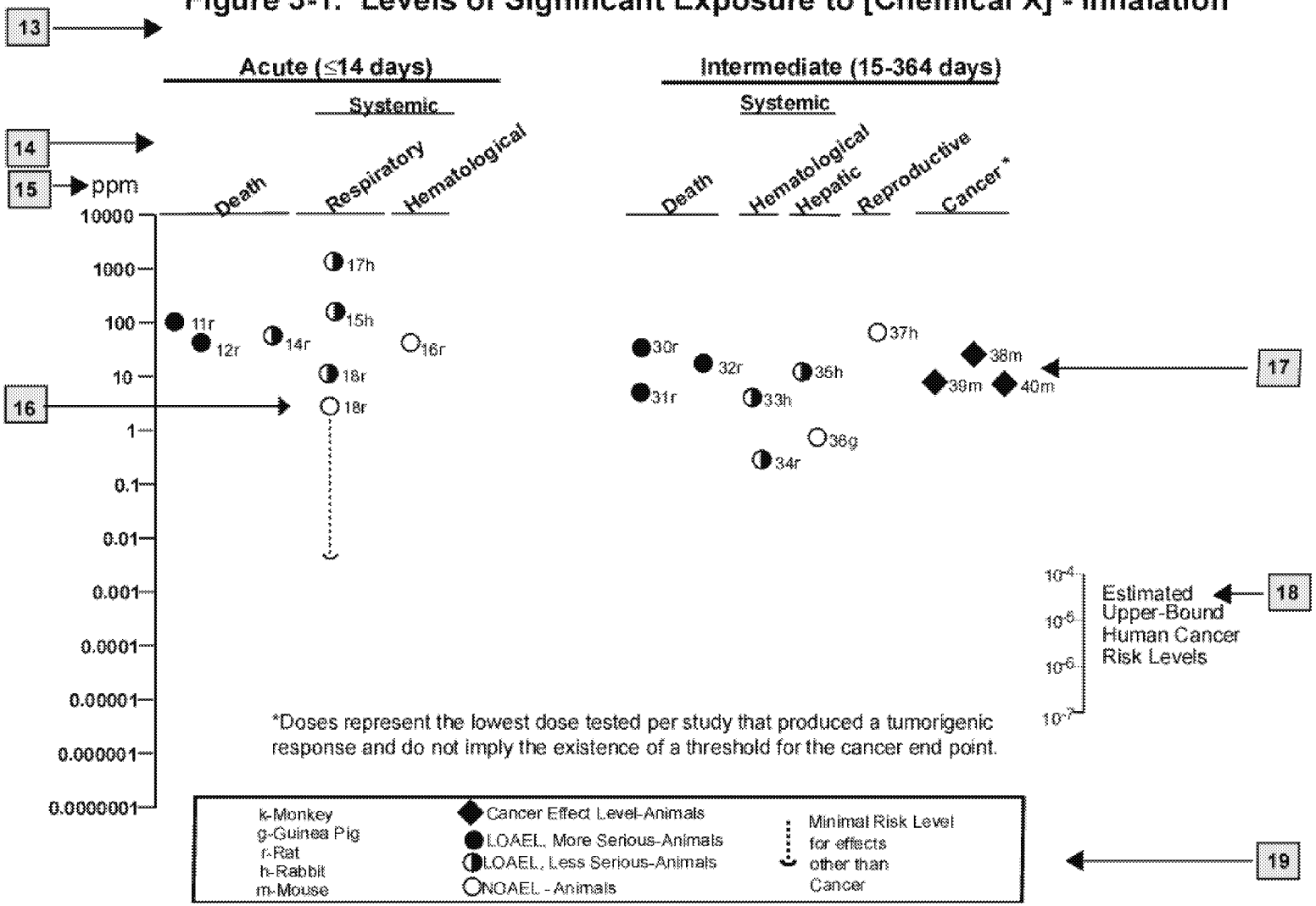
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 Systemic							
4 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
						11	
Cancer							
38	Rat	18 mo 5 d/wk 7 hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

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

12 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AB	Asbestos body
ACGIH	American Conference of Governmental Industrial Hygienists
ACM	Asbestos-containing material
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
APHA	American Public Health Association
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
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	fibers
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
f/m^3	fibers per cubic meter
f/mL	fibers per milliliter
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
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_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie

MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MF	million fibers
MFL	million fibers per liter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
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
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
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
PCM	phase contrast microscopy
PEL	permissible exposure limit
PID	photoionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SEM	scanning electron microscopy
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard 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
TEM	transmission electron microscopy
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week
$>$	greater than
$\geq$	greater than or equal to

=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μg	microgram
μm	micrometer
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D

RISK ASSESSMENT SUMMARY

1.0 LUNG CANCER

Most studies of the risk of asbestos-related lung cancer in occupationally exposed workers indicate that the dose-response relationship is best described by a relative risk model, given by the equation:

$$\text{Relative Risk} = 1.00 + K_L \cdot (\text{cumulative dose})$$

Using this equation, EPA (1986a) calculated the value of K_L (the fractional increase in relative risk of lung cancer per f-yr/mL) for 14 sets of lung cancer mortality data from studies of workers in textile production, friction products manufacture, asbestos mining and milling, insulation products manufacture, and asbestos cement manufacture. The resulting values varied widely, ranging from 0.0006 $(\text{f-yr/mL})^{-1}$ (McDonald et al. 1980) to 0.067 $(\text{f-yr/mL})^{-1}$ (Finkelstein 1983). The geometric mean of all of the studies was 0.065 $(\text{f-yr/mL})^{-1}$. When studies involving mining and milling were excluded (these were judged to be less typical of the risks likely to be encountered in the environment), the resulting geometric mean value was 0.010 $(\text{f-yr/mL})^{-1}$. It is important to stress that this relates to fibers measured by PCM, and not to the total number of fibers measured by TEM.

Since this is a relative risk model, the absolute risk of lung cancer due to asbestos exposure depends not only on cumulative asbestos dose, but also on the underlying risk of lung cancer due to other causes:

$$\text{Absolute Risk} = \text{Relative Risk} \times \text{Underlying Risk}$$

Based on national average lung cancer risk data for male and female smokers and nonsmokers, EPA (1986a) calculated that lifetime exposure to 0.0001 f/mL corresponded to the excess lung cancer risks tabulated in Table D-1.

For the purposes of preparing a simplified graphical display of cancer risk levels for presentation in Figure 3-1, risks from males and females were averaged, both for smokers and nonsmokers, and the cumulative doses corresponding to a lifetime lung cancer risk of 1×10^{-4} were calculated and shown in Table D-1.

2.0 MESOTHELIOMA

Several studies (e.g., Newhouse and Berry 1976; Nicholson et al. 1982; Peto et al. 1982) indicate that the risk of mesothelioma from a given level of exposure to asbestos depends primarily upon the time elapsed since exposure (latency), with risk increasing exponentially with time after a lag period of about 10 years. Based on this, EPA (1986a) fit exposure-incidence data from four studies (Finkelstein 1983; Peto 1980; Peto et al. 1982; Seidman 1984) to the following equation:

Table D-1. Risk Assessment for Asbestos-associated Lung Cancer

	Smokers			Nonsmokers		
Parameter	Male[a]	Female[a]	Average[b]	Male[a]	Female[a]	Average[b]
Lung cancer risk from lifetime exposure to 0.0001 f/mL	2.4×10^{-5}	1.5×10^{-5}	2.0×10^{-5}	0.2×10^{-5}	0.2×10^{-5}	0.2×10^{-5}
Concentration (f/mL) corresponding to lifetime excess risk level of 10^{-4}			0.0005			0.005
Cumulative dose (f·yr/mL) for a 70-year exposure corresponding to 10^{-4} risk level			0.035			0.35

[a]Source: EPA 1986a
[b]Average of males and females

$$\text{Incidence} = K_M \cdot f \cdot [(T-10)^3 - (T-10-d)^3]$$

where:

K_M = empirical constant
f = intensity of exposure (f/mL)
T = latency (years since first exposure)
d = duration of exposure (years)

The resulting values of K_M ranged from 1×10^{-8} to 3×10^{-8} for three of the studies, with one study (Finkelstein 1983) giving a higher value (12×10^{-8}). Based on an analysis of the relative risk of mesothelioma compared to lung cancer in other studies, a value of 1×10^{-8} was identified as the most reasonable estimate for K_M (EPA 1986a). Although this value has considerable uncertainty (about a factor of 10), it can be used to make rough predictions of mesothelioma incidence at low exposure levels, similar to those likely to be encountered in the environment. Assuming lifetime continuous exposure to air containing 0.0001 f/mL, the expected incidence is 2 to 3 mesothelioma deaths per 100,000 persons (EPA 1986a), as shown in Table D-2.

For the purposes of preparing a simple graphical presentation of these risk estimates for inclusion in Figure 3-1, the data from all four groups were combined (since there is little difference between males and females or between smokers and nonsmokers), to yield an average 10^{-4} risk level of 3.1×10^{-2} f-yr/mL.

3.0 COMBINED RISK OF LUNG CANCER AND MESOTHELIOMA

The combined risk of lung cancer and mesothelioma has been estimated by EPA (IRIS 2001), based on the risk calculations presented in EPA (1986a). The average unit risk value was calculated as a composite value for males and females. The epidemiological data show that cigarette smoking and asbestos exposure interact synergistically for production of lung cancer and do not interact with regard to

mesothelioma. The unit risk value is based on risks calculated using U.S. general population cancer rates and mortality patterns without consideration of smoking habits. The risks associated with occupational exposure were adjusted to continuous exposure by applying a factor of 140/50, based on the assumption of 20 m^3/day (140 m^3/week) for total ventilation and 10 m^3/8-hour workday (40 m^3/week) in the occupational setting. The results of these calculations indicate that a concentration of $4x10^{-4}$ f/mL corresponds to a lifetime excess risk level of 10^{-4}. This combined risk estimate was not presented in Figure 3-1, since both the text and the Figure deal with lung cancer and mesothelioma separately.

The Health Effect Institute estimates lifetime cancer risks from lung cancer and mesothelioma combined based on levels of asbestos detected in 198 ACM-containing buildings (HEI 1991). These estimates, presented in Table D-3, should be interpreted with caution because of uncertainty associated with the estimation of average exposure levels and with the risk assessment model. The "high" levels represented in the table are approximately equal to the upper 95th percentile of the exposure levels detected. It should be noted that if the single highest public building sample was excluded from the calculation of the average exposure level, then the average value would be reduced from 0.0002 to 0.00008 TEM f/mL and risk would be similarly reduced by one half. The occupational exposure level of 0.1 f/mL is equivalent to the PEL proposed by OSHA. Actual worker exposures are expected to be lower.

Table D-2. Risk Assessment for Asbestos-related Mesothelioma

	Smokers		Nonsmokers		
Parameter	Male[a]	Female[a]	Male[a]	Female[a]	Average[b]
Risk of mesothelioma from lifetime exposure to 0.0001 f/mL	$1.8x10^{-5}$	$2.5x10^{-5}$	$2.2x10^{-5}$	$2.7x10^{-5}$	$2.2x10^{-5}$
Concentration (f/mL) corresponding to lifetime excess risk level of 10^{-4}					0.00045
Cumulative dose (f·yr/mL) for a 70-year exposure corresponding to 10^{-4} risk level					0.031

[a]Source: EPA 1986a
[b]Average of all four groups

Table D-3. Estimated Lifetime Risks of Lung Cancer and Mesothelioma Combined for Different Scenarios of Exposure to Airborne Asbestos Fibers

Conditions	Premature cancer deaths (lifetime risks) per million exposed persons (male and female)
Lifetime, continuous outdoor exposure	
• 0.00001 TEM f/mL ($2x10^{-7}$ PCM f/mL from birth	4
rural	40
• 0.0001 TEM f/mL ($2x10^{-6}$ PCM f/mL) from birth (high urban)	
Exposure in a school containing ACM, from age 5 to 18 years (180 days/year, 5 hours/day)	6
• 0.0005 TEM f/mL ($8x10^{-6}$ PCM f/mL) (average)	60
• 0.005 TEM f/mL ($8x10^{-5}$ PCM f/mL) (high)	
Exposure in a public building containing ACM age 25 to 45 years (240 days/year, 8 hours/day)	
• 0.0002 TEM f/mL ($3x10^{-6}$ PCM f/mL) (average)	4
• 0.002 TEM f/mL ($3x10^{-5}$ PCM f/mL) (high)	40
Occupational exposure from age 25 to 45	
• 0.1 PCM f/mL (current occupational levels)	2,000
• 10 PCM f/mL (historical industrial exposures)	200,000

Source: HEI 1991

4.0 GASTROINTESTINAL CANCER

4.1 Risk Estimate Based on Animal Data

In a lifetime feeding study in rats, exposure to intermediate length chrysotile fibers led to an increased incidence of intestinal polyps (NTP 1985). Based on these data, EPA (1985b) calculated that the 10^{-4} risk level corresponded to an asbestos concentration of $7.1x10^{8}$ f/L in drinking water.

In order to present this risk estimate in Figure 3-4, the concentration of $7.1x10^{8}$ f/L was converted to a dose of $2.0x10^{7}$ f/kg/day (assuming ingestion of 2 L/day by a 70-kg adult), and this was converted to a dose of 0.16 mg/kg/day by dividing by $0.129x10^{9}$ f/mg (reported in NTP 1985).

4.2 Risk Estimate Based on Human Inhalation Data

Since there are no human studies in which ingestion of a known amount of asbestos can be associated with a clear increase in gastrointestinal cancer risk, NAS (1983) extrapolated data on gastrointestinal risk from epidemiological studies of workers exposed to asbestos by inhalation. These calculations indicated that lifetime ingestion of $1.1x10^{6}$ TEM fibers/liter of water corresponded to an excess gastrointestinal cancer risk of 10^{-4} (NAS 1983).

In order to present this risk estimate in Figure 3-4, the concentration of 1.1×10^{6} f/L was converted to a dose of 3.1×10^{4} f/kg/day (assuming ingestion of 2 L/day by a 70-kg adult), and this was converted to a dose of 1.6×10^{-5} mg/kg/day by multiplying by a factor of 5.0×10^{-10} mg/TEM fiber (NRC 1984).

APPENDIX E

INDEX

ACM 158, 160, 165, 167, 173, 175, 176
actinolite 1, 12, 20, 70, 74, 82, 132, 133, 135, 137, 138, 158, 162-164, 201
acute inhalation exposure 118
adsorption 12, 143, 179
ambient air 13, 18, 155-157, 185, 197
amosite 1, 5, 12, 15, 20, 37, 38, 42, 46, 48, 50-52, 54, 60-62, 64, 68, 70, 73-75, 77, 82, 90, 92, 109, 118, 132, 133, 135, 137, 138, 201
amphibole 1, 3, 5, 12, 20, 37, 50, 51, 53, 81, 91, 92, 104-106, 113, 120, 132, 135, 136, 154, 158, 160, 162, 163, 177, 187
anthophyllite 1, 12, 20, 37, 42, 46, 48, 52, 70, 73, 74, 104, 132, 133, 135, 137, 138, 162-164, 201
asbestos fibers 1-7, 12-15, 17, 19, 21, 22, 36, 37, 40-43, 46-49, 52, 54, 60, 62, 68, 75-84, 87-89, 91-95, 97, 100, 101, 103-106, 108-115, 118-123, 125-127, 135, 136, 140, 146, 148, 151-156, 158-165, 167, 168, 176, 177, 179, 181, 185-187, 189, 192, 193, 196
asbestos minerals 1, 2, 12, 132, 136, 162
asbestosis 4, 5, 14, 15, 17, 18, 22, 36-44, 90, 100, 103, 107-109, 114, 118, 122, 126, 130
asbestos-containing material (see ACM) 6, 143, 148, 175, 176, 178, 181, 196
asbestos-related industries 152, 156, 167, 176
bioaccumulation 179
bioavailability 179
biomagnification 179
biomarker 102, 103
birth weight 62, 102
body weight effects 61
breast milk 6, 176
bronchoalveolar fluid 104, 105, 188
cancer 1, 4, 5, 14-16, 18, 21, 22, 36, 40, 41, 43-49, 51-54, 60, 62, 63, 66-68, 74, 90, 91, 93, 97, 99, 100, 108-111, 113-115, 118-122, 124-126, 128-131, 133, 135, 138, 168, 182, 193, 195, 200
carcinogen 5, 16, 110, 201
carcinogenic 5, 15, 16, 20, 21, 45, 46, 48, 62, 64, 65, 76, 109, 119-121, 124, 195, 196, 201
carcinogenicity 5, 15, 16, 64, 66, 79, 91, 109, 120, 121, 130
carcinoma 53, 64, 69
cardiovascular effects 43
chromosomal abnormalities 74
chronic inhalation exposure 48, 90, 120
chrysotile 1-3, 5, 12, 13, 15, 17, 20, 36-42, 45-48, 50-52, 54, 60-66, 70, 73-77, 80-84, 90-95, 97, 100, 104-106, 109, 113, 120, 130, 132, 133, 135-138, 140, 143, 144, 146, 148, 154-156, 158, 160, 162, 167, 168, 177, 187, 201
cleavage fragments 135, 164
crocidolite 1, 5, 12, 15, 20, 37, 38, 42, 46, 48, 50-52, 54, 60-62, 64, 66, 70, 73-77, 79, 80, 90, 92, 93, 95, 97, 100, 115, 120, 132, 133, 135, 137, 138, 172, 201
Department of Health and Human Services (see DHHS) 5, 16
DHHS 5, 16, 108
DNA 69, 72-74, 76, 92, 93, 103, 108, 109, 113, 130, 131
FDA 8, 196
FEDRIP 131, 182
fetus 62, 98
fiber 1, 2, 4, 5, 13-15, 19-22, 36-38, 40, 41, 46-48, 50, 51, 54, 63, 66, 68, 75-77, 79-83, 87-94, 97, 100, 104-106, 108, 109, 113-115, 119-125, 129, 130, 132, 135, 140, 141, 143, 154-156, 159, 160, 162-164, 167, 168, 172, 176, 177, 180, 181, 184-187, 192, 193
Food and Drug Administration (see FDA) 8
friable 141, 144, 148, 151-153, 158, 179
garden 164
gastrointestinal effects 36, 43, 60
general population 3, 13, 15, 18, 41, 48, 49, 102, 108, 146, 165, 166, 177
grass 6
half-life 83, 102, 154
hydrolysis 76
hydroxyl radical 91, 93, 95

IgA 44
IgG 44
immune system 18, 44, 118, 122, 124
immunological effects 44
inhaled fibers 15, 78, 81, 88, 113, 165, 166, 176
intermediate oral exposure 54
kidney 53, 60, 63, 80, 83
leukemia 64, 71, 75
liver 60, 69, 72, 74, 79, 80, 86, 103
lung 2-5, 7, 14-17, 19, 22, 37, 40-43, 45-48, 51-53, 60, 68, 69, 74, 76, 77, 79-84, 87-97, 100, 101, 103-115, 118-120, 123-127, 129-131, 135, 172, 177, 179-181, 187, 188, 192, 193, 200
lung cancer . . 4, 5, 14-16, 22, 40, 41, 45-48, 51, 52, 68, 74, 90, 91, 93, 97, 100, 108-111, 113-115, 118, 120, 125, 126, 130, 193
lymph 44, 78, 80
lymphatic 53
lymphoreticular effects 18, 44, 61, 68
mesothelioma 4, 5, 14-16, 18, 45, 48-53, 68, 69, 72, 74-76, 90-94, 97, 100, 101, 106, 110-112, 115, 118, 120, 125, 127, 131, 182, 187, 193
midget impinger particle 13
milk 6, 176
MRL 19, 40, 119
NAS/NRC 102, 103
National Priorities List (see NPL) 1, 146
neurobehavioral 98
NIOSH 8, 21, 49, 104, 131, 133, 175, 184-186, 189, 190, 192, 195
NOAEL 21, 36, 60-62
NPL 1, 146, 147, 152, 153
odds ratio 49
PBPD 84
PBPK 84-88
PCM 13, 14, 21, 22, 41, 48, 146, 148, 154-158, 160, 166-168, 172, 175, 180, 184-186, 188-192
PCM fiber 14
Permissible Exposure Level 39
pharmacodynamic 84
pharmacokinetic 84-86, 90
phase contrast microscopy (see PCM) 13, 21, 146, 154, 157, 163, 166, 175, 184, 188, 191
pleural plaques 4, 18, 22, 41, 100, 124
precipitation 153, 179
Public health 1, 4, 8, 12, 14, 19-21, 98, 112, 116, 122, 178, 184, 189
pulmonary fibrosis 37-39, 97, 113, 120, 123, 125-127, 129-131
RCRA 141, 144
regulations 8, 118, 132, 135, 144, 152, 154, 177, 184, 193-197, 200
Resource Conservation and Recovery Act (see RCRA) 141
respiratory effect 127
Richterite 132
Riebeckite 135
scanning electron microscopy 103, 185
sediment 12, 153, 154, 162
serpentine 1, 12, 20, 53, 132, 133, 135, 162
SMR 46, 47, 53
soil 2, 5, 6, 8, 13, 41, 146, 148, 151-154, 162, 163, 176, 177, 179-181, 189
solubility 137
sputum 7, 103-105, 124, 131, 180, 192
Standardized mortality ratio (see SMR) 108
Superfund 190
surface water 12, 152, 198, 199
swallow 3
talc 2, 3, 100, 146, 148, 162, 163
TEM 13, 54, 154-159, 161, 166, 167, 171, 172, 175, 177, 180, 185-193
time-weighted average (see TWA) 169, 171, 175
toxicokinetic 20, 125
Toxics Release Inventory (see TRI) 141, 148
transmission electron microscopy (see TEM) 13, 54, 154, 157, 159, 166, 171, 175, 185, 188, 191

APPENDIX E

tremolite 1, 2, 5, 12, 20, 37, 41, 42, 46, 48, 50, 52, 54, 60-62, 64, 70, 74, 81, 90-92, 100, 104, 105, 120, 132, 133, 135, 137, 138, 146, 148, 158, 162-164, 177, 201
TRI 141, 144, 148, 150-152, 179
tumors 5, 15, 16, 48, 54, 63, 92, 97, 108, 110, 130
TWA 166-175, 195
USDA 131
vermiculite 2, 3, 104, 132, 146, 148, 156, 158, 162-164
Winchite 132

APPENDIX F

CHEMICAL-SPECIFIC HEALTH CONSULTATION: TREMOLITE ASBESTOS AND OTHER RELATED TYPES OF ASBESTOS

APPENDIX F

CHEMICAL-SPECIFIC HEALTH CONSULTATION: TREMOLITE ASBESTOS AND OTHER RELATED TYPES OF ASBESTOS

September, 2001

Prepared by

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Agency for Toxic Substances and Disease Registry
Division of Toxicology
Atlanta, Georgia 30333

ACKNOWLEDGMENTS

The Agency for Toxic Substances and Disease Registry acknowledges Peter R. McClure, Ph.D., DABT, and Gloria W. Sage, Ph.D., from Syracuse Research Corporation for their assistance in developing this consultation.

The agency acknowledges Anne Olin as the editor of this document, and the contributions from the following Division of Toxicology scientific staff: Susan Kess, M.D., M.P. H; Carolyn A. Tylenda, D.M.D., Ph.D.; Rich Nickle; Yee-Wan Stevens, M.S.; Sharon Wilbur, M.A.; Malcolm Williams, D.V.M., Ph.D.; Cassandra Smith, M.S.; Doug Hanley, M.D.; John Wheeler, Ph.D., DABT; and Ed Murray, Ph.D.

APPENDIX F

EXECUTIVE SUMMARY

The U.S. Department of Health and Human Services (DHHS) is addressing public health concerns regarding a fibrous amphibole that occurs in vermiculite ore in the Libby, Montana, area. Scientists agree that exposure to this mineral increased the risk of nonmalignant respiratory and pleural disorders, lung cancer, and mesothelioma in groups of people who worked in the now closed Libby vermiculite mine and mill. These health problems are similar to those experienced by workers exposed to other types of asbestos before modern workplace air regulations were established. The Agency for Toxic Substances and Disease Registry (ATSDR) has prepared this chemical-specific health consultation to provide support for public health decisions regarding individuals exposed to fibrous amphibole from Libby vermiculite or other related asbestos-containing materials. Key technical terms used in discussing asbestos-related health problems are defined after the Introduction.

Physical and Chemical Properties, Occurrence, and Detection: Tremolite Asbestos

Asbestos is the name of a group of highly fibrous minerals with separable, long, and thin fibers. Separated asbestos fibers are strong enough and flexible enough to be spun and woven, are heat resistant, and are chemically inert. Minerals with these asbestos characteristics are said to have an asbestiform habit.

Regulatory agencies such as the U.S. Environmental Protection Agency (EPA) and Occupational Safety and Health Administration (OSHA) recognize six asbestos minerals: chrysotile, a serpentine mineral; and five amphibole minerals, actinolite asbestos, tremolite asbestos, anthophyllite asbestos, crocidolite asbestos, and amosite asbestos. Nonasbestiform amphibole minerals are not included in U.S. health regulations regarding asbestos because there is insufficient evidence that they will produce adverse health effects of the same type and severity produced by chronic exposure to asbestos.

Samples of the fibrous amphibole in the Libby vermiculite ore, popularly referred to as tremolite asbestos, were recently analyzed by U.S. Geological Survey scientists. On the basis of variable chemical composition, several different mineral names were assigned to the samples: winchite, richterite, tremolite, actinolite, ferro-edenite, and magnesio-arfvedsonite. All of these are classified as amphibole minerals. Most of the samples showed both asbestiform and nonasbestiform habits. Since it is known that this mix of fibrous amphibole increased the risk of typical asbestos-related diseases in groups of people who

worked in the Libby, Montana, mine and mill, proposals have been made to consider changing U.S. asbestos regulations to include other asbestiform amphiboles in addition to the five mentioned previously.

Nonasbestiform tremolite is the predominant form of tremolite in the earth's crust, but there are many reports of tremolite asbestos occurring around the world in specific locations (including some locations in Maryland and California) and natural materials. Tremolite asbestos has only rarely been found in commercially mined deposits. It has never been a nationally important commercial source of asbestos in the United States. Two minerals of commercial importance that have been reported to contain tremolite asbestos or other amphibole asbestos are vermiculite and talc.

Before 1990, the now closed mine in Libby, Montana, was a significant source of vermiculite in the United States. In 1998, vermiculite was mined in the United States predominantly in South Carolina and Virginia and was also imported from South Africa and China. A 1984 study reported that the percentage of tremolite asbestos fiber by weight varied from 3.5% to 6.4% in raw vermiculite ore from Libby, Montana. In contrast, several studies of vermiculite mined elsewhere (South Carolina, Virginia, and South Africa) reported that levels of amphibole asbestos were either not detectable or only present at much lower levels than those found in the Libby vermiculite.

Talc ores can also contain a range of other minerals. In the United States, commercial talc is categorized into cosmetic grade, which is free of asbestos, and industrial grade, which may contain other asbestiform or nonasbestiform minerals, depending on intended use. For example, one important U.S. source of industrial-grade talc is a mixture referred to as tremolitic talc. Analysis by OSHA scientists shows that the tremolite in this talc is nonasbestiform.

The combined use of light microscopy, electron microscopy, and energy dispersive x-ray analysis offer the most accurate approach to identify asbestos and estimate concentrations in air samples or bulk samples that may become airborne upon disturbance. For the purposes of counting asbestos fibers in these samples, regulatory agencies commonly count as fibers those particles of asbestos minerals that have lengths 5 μm and length:width ratios 3:1. For other purposes, such as detecting fibers in bulk building materials, asbestos particles with length:width ratios 5:1 are counted. Typical air concentrations of asbestos fibers in ambient air are 0.00001 to 0.0001 fibers per milliliter (fiber/mL). Recent exposure limits for U.S. workplaces are 0.1 to 0.2 fiber/mL.

Exposure Potential: Tremolite Asbestos

Occupational exposure to tremolite asbestos may occur in workers involved in mining, milling, and handling of other ores and rocks that may contain tremolite asbestos (e.g., vermiculite or talc). Residents who live close to mining, milling, or manufacturing sites that involve tremolite asbestos-containing material may be potentially exposed to higher levels of airborne asbestos than levels in general ambient air. EPA, ATSDR, and other agencies currently are investigating past and current exposure to fibrous amphibole found in Libby, Montana, vermiculite. In addition, ATSDR is currently conducting medical testing of individuals who lived close to or worked in the Libby vermiculite mine and mill.

Asbestos can be found in a variety of building materials such as insulation, ceiling or floor tiles, and cement pipes. Amphibole asbestos has been found in some vermiculite sources that have been used as home and building insulation. Workers or homeowners involved in demolition work, maintenance, repair, or remodeling of buildings containing these products can be exposed to higher airborne fibrous amphibole levels than levels in general ambient air. Exposure can occur only when building materials containing asbestos are disturbed in some way to release particles and fibers into the air. When asbestos-containing materials are solidly embedded or contained, exposure will be minimal.

Recently, small amounts of amphibole asbestos have been found in some samples of vermiculite-containing consumer garden products by EPA and in some talc-containing crayons by the U.S. Consumer Product Safety Commission (CPSC). EPA recommended that consumers can reduce possible exposure by limiting the production of dusts when using the garden products. CPSC concluded that the risk is extremely low that children might be exposed to asbestos fibers through inhalation or ingestion of crayons containing asbestos and transitional fibers. The U.S. manufacturers of these crayons, however, have agreed to eliminate talc from their products in the near future.

Health Effects from Asbestos or Tremolite Asbestos

It is known that exposure to any asbestos type (i.e., serpentine or amphibole) will increase the likelihood of lung cancer, mesothelioma (a tumor of the pleura or peritoneum that is rare in the general population), and nonmalignant lung and pleural disorders including interstitial pulmonary fibrosis (asbestosis), pleural plaques, pleural thickening, and pleural effusions. This conclusion is based on observations of these diseases in groups of workers with cumulative exposures ranging from about 5 to 1,200 fiber-year/mL.

Such exposures would result from 40 years of occupational exposure to air concentrations of 0.125 to 30 fiber/mL. The conclusion is supported by results from animal and mechanistic studies.

Based on an analysis of the epidemiologic data, EPA calculated that lifetime continuous exposure to asbestos air concentrations of 0.0001 fiber/mL could result in up to 2-4 cancer deaths (lung cancer or mesothelioma) per 100,000 people. This air concentration is within reported ranges of ambient air levels (0.00001 to 0.0001 fiber/mL). The EPA analysis has been extensively discussed and reviewed in the scientific literature. EPA is in the process of reviewing and possibly updating their cancer risk estimates for asbestos.

Important determinants of asbestos toxicity include exposure concentration, duration, and frequency, and fiber dimensions and durability. Long and thin fibers are expected to reach the lower airways and alveolar regions of the lung, to be retained in the lung longer, and to be more toxic than short and wide fibers or particles. Wide particles are expected to be deposited in the upper respiratory tract and not to reach the lung and pleura, the sites of asbestos-induced toxicity. Short, thin fibers, however, may also play a role in asbestos pathogenesis. Fibers of amphibole asbestos such as tremolite asbestos, actinolite asbestos, and crocidolite asbestos are retained longer in the lower respiratory tract than chrysotile fibers of similar dimension.

Diseases from asbestos exposure take a long time to develop. Most cases of lung cancer or asbestosis in asbestos workers occur 15 or more years after initial exposure to asbestos. Asbestos-exposed tobacco smokers have greater than additive risks for lung cancer than do asbestos-exposed nonsmokers (i.e., the risk is greater than the individual risks from asbestos and smoking added together). The time between diagnosis of mesothelioma and the time of initial occupational exposure to asbestos commonly has been 30 years or more. Cases of mesotheliomas have been reported after household exposure of family members of asbestos workers and in individuals without occupational exposure who live close to asbestos mines.

As with other forms of asbestos, chronic exposure to airborne tremolite asbestos is expected to increase risks of lung cancer, mesothelioma, and nonmalignant lung and pleural disorders. Evidence in humans comes from epidemiologic studies of tremolite asbestos-exposed groups of vermiculite miners and millers from Libby, Montana. This evidence is supported by reports of increased incidences of nonmalignant respiratory diseases, lung cancer, and mesothelioma in villages in various regions of the world that have

traditionally used tremolite-asbestos whitewashes in homes or have high surface deposits of tremolite asbestos and by results from animal studies.

Clinical Diagnosis for Asbestos-Related Diseases

The chest x-ray is the most common and important tool to detect lung and pleural disease caused by chronic exposure to tremolite asbestos or other types of asbestos. Results from pulmonary function tests and high resolution computerized tomography can also be used in the diagnosis.

Biopsy to detect asbestos fibers in pieces of lung tissue, although not needed to make a clinical diagnosis, is the most reliable test to determine asbestos exposure. Less invasive tests can be conducted to detect asbestos fibers or asbestos bodies in bronchoalveolar lavage fluid or in sputum. These tests, however, do not reliably indicate how much asbestos a person may have been exposed to, or predict whether disease will develop.

Treatment Options for Asbestos-Related Diseases

Treatment options for patients diagnosed with nonmalignant lung or pleural disease from chronic exposure to asbestos are few. Preventing of further exposure and ceasing any tobacco smoking activities are the most important steps individuals can take to minimize development of health problems. Once established, these diseases may remain stable or progress in severity in the absence of further exposure. The diseases rarely regress. Treatment options for patients diagnosed with asbestos-related cancer of the lung or pleura are restricted to resection and/or chemotherapy.

Pleural effusions are early manifestations of inhalation exposure to high concentrations of asbestos; the fluid contains varying amounts of red blood cells, macrophages, lymphocytes, and mesothelial cells. Pleural effusions may be an early indication of mesothelioma and warrant further evaluation. Early identification of mesothelioma and intervention may increase chances of survival.

Additional research may help to develop therapeutic methods to interfere with the development of asbestos-induced lung and pleural disorders and to cause the disorders to regress once they are established.

Recommendations

Prevention of exposure and cessation of any tobacco smoking activities are the most important steps that individuals can take to prevent or minimize the development of asbestos-related health problems.

People who were exposed to asbestos and who smoke are expected to be unusually susceptible to asbestos-related lung cancer and asbestosis and are encouraged to cease smoking. Studies of asbestos workers indicate that asbestos-exposed smokers have greater than additive risks for lung cancer and asbestosis than asbestos-exposed nonsmokers.

Individuals residing or working in buildings with insulation or other building materials that may potentially contain asbestiform minerals (for example, vermiculite from the Libby, Montana, mine) are encouraged to ensure that the insulation material is solidly contained and not able to be disturbed and become airborne. If the material is to be removed, special procedures must be followed that minimize the generation of dust and specify appropriate locations for disposal. Individuals can obtain information about asbestos removal and disposal procedures from the 10 regional offices of the EPA.

Further evaluation of the progression of disease associated with exposure to Libby, Montana vermiculite contaminated with asbestos is warranted. EPA, ATSDR, and other agencies currently are investigating exposure levels that Libby, Montana, residents (including children) who were not employed in the vermiculite mines and mills may have and are experiencing. In addition, ATSDR is currently conducting medical testing of individuals potentially exposed to fibrous amphibole associated with vermiculite in Libby, Montana.

APPENDIX F

Introduction

The U.S. Department of Health and Human Services (DHHS) is addressing public health concerns regarding a fibrous amphibole that occurs in vermiculite ore in the Libby, Montana, area. Vermiculite was mined and milled in Libby from 1923 until 1990. In 1963 the mine was acquired from the Zonolite Company by W.R. Grace Company, which marketed the vermiculite as Zonolite®.

The Libby amphibole mineral, popularly known as tremolite asbestos, has been assigned a number of different names by scientists over the years (Meeker et al. 2001; Wylie and Verkouteren 2000); however, scientists agree that exposure to the mineral increased the risk of nonmalignant respiratory and pleural disorders, lung cancer, and mesothelioma in groups of people who worked in the now closed Libby mine and mill.[1] These health problems are similar to those experienced by workers exposed to other types of asbestos before modern workplace air regulations were established.

The Agency for Toxic Substances and Disease Registry (ATSDR) prepared this chemical-specific health consultation to provide support for public health decisions regarding Libby, Montana, and other locations where tremolite asbestos and related asbestos can be found. This document :

- defines terms used to discuss health effects from asbestiform minerals;
- discusses the chemistry of amphibole minerals;
- discusses the occurrence of tremolite asbestos in the earth's crust;
- discusses common methods to detect asbestos in air samples;
- discusses the potential for human exposure to asbestos;
- presents overviews of health effects from asbestos, deposition and clearance of asbestos in the lung, and mechanisms of asbestos toxicity;
- evaluates the weight of evidence that tremolite asbestos can cause mesothelioma, lung cancer, and nonmalignant disorders of the lung and pleura;
- discusses clinical diagnosis for asbestos-related diseases; and
- recommends actions to protect the public from possible health problems from tremolite asbestos and other forms of asbestos.

Evidence that nonasbestiform amphiboles may cause the same effects as amphibole asbestos is outside of the scope of this health consultation. The reader is referred to earlier reports (American Thoracic Society

[1] Epidemiologic studies of Libby, Montana, miners and millers are discussed later in this document.

1990; OSHA 1992) that discuss this issue and to epidemiological studies of workers exposed to mixtures of nonasbestiform amphibole minerals and other nonasbestos minerals including silica, taconite, and talc. For regulatory purposes, the Occupational Safety and Health Administration (OSHA 1992) concluded that there was insufficient evidence that nonasbestiform forms of tremolite, actinolite, and anthophyllite will produce adverse health effects of the same type and severity produced by chronic exposure to amphibole asbestos (OSHA 1992; Vu 1993). Nevertheless, the reader should be aware that repeated exposure to excessive amounts of insoluble dusts of any type can cause adverse health effects including interstitial pulmonary fibrosis (ACGIH 1996; OSHA 1992).

Definitions of Terms Used To Discuss Health Effects from Asbestiform Minerals

Definitions of key technical terms are provided because there has been variable use of some of them in the scientific literature and popular press.

Amphibole: A large group of silicate minerals with more than 40-50 members (Leake 1978; Leake et al. 1997). The molecular structure of all amphiboles consists of two chains of SiO_4 molecules that are linked together at the oxygen atoms. In the earth's crust, amphibole minerals are mostly nonasbestiform; asbestiform amphiboles are relatively rare (Veblen and Wylie 1993; Zoltai 1979, 1981). See definitions of asbestiform, mineral, and mineral habit. Also see the *Chemistry of Amphibole Minerals* section.

Asbestiform: A habit of crystal aggregates displaying the characteristics of asbestos: groups of separable, long, thin, strong, and flexible fibers often arranged in parallel in a column or in matted masses (Veblen and Wylie 1993; Zoltai 1979, 1981). See definitions of mineral and mineral habit. Figure 1 shows a scanning electron micrograph of an asbestiform amphibole mineral showing a parallel arrangement of long fibers. Mineralogists call asbestiform amphibole minerals by their mineral name followed by "asbestos" (Leake 1978). Thus, asbestiform tremolite is called tremolite asbestos.

Asbestos: A group of highly fibrous minerals with separable, long, thin fibers often arranged in parallel in a column or in matted masses (Veblen and Wylie 1993; Zoltai 1979, 1981). Separated asbestos fibers

Figure 1. Scanning electron micrograph of asbestiform amphibole from a former vermiculite mining site near Libby, Montana. Source: U.S. Geological Survey and U.S. Environmental Protection Agency, Region 8, Denver, Colorado.

are generally strong enough and flexible enough to be spun and woven, are heat resistant, and are chemically inert (Veblen and Wylie 1993). See definitions of fibrous and mineral.

Currently, U.S. regulatory agencies, such as the Environmental Protection Agency (EPA) and OSHA, recognize six asbestos minerals: the serpentine mineral, chrysotile; and five asbestiform amphibole minerals, actinolite asbestos, tremolite asbestos, anthophyllite asbestos, amosite asbestos (also known as asbestiform cummingtonite-grunerite), and crocidolite asbestos(also known as asbestiform riebeckite) (ATSDR 2001a; OSHA 1992; Vu 1993). Proposals have been made to update asbestos regulations to include other asbestiform amphibole minerals such as winchite asbestos and richterite asbestos (Meeker et al. 2001; Wylie and Verkouteren 2000). See the *Chemistry of Amphibole Minerals* section.

Asbestosis: Interstitial fibrosis of the pulmonary parenchymal tissue in which asbestos bodies (fibers coated with protein and iron) or uncoated fibers can be detected (American Thoracic Society 1986). Pulmonary fibrosis refers to a scar-like tissue in the lung which does not expand and contract like normal tissue. This makes breathing difficult. Blood flow to the lung may also be decreased, and this causes the heart to enlarge. People with asbestosis have shortness of breath, often accompanied by a persistent cough. Asbestosis is a slow-developing disease that can eventually lead to disability or death in people who have been exposed to high amounts of asbestos over a long period. Asbestosis is not usually of concern to people exposed to low levels of asbestos. For more information, see the *Health Effects from Asbestos: Overview* section.

Cleavage fragment: Microscopic particles formed when large pieces of nonasbestiform amphiboles are crushed, as may occur in mining and milling of ores. Within a population of nonasbestiform amphibole cleavage fragments, a fraction of the particles may fit the definition of a fiber adopted for counting purposes. Populations of asbestos fibers can be readily distinguished from populations of nonasbestiform cleavage fragments, but sometimes it can be difficult to distinguish an isolated nonasbestiform cleavage fragment from an isolated asbestos fiber (Crane 2000; OSHA 1992). See definitions of asbestiform, fiber, fibrous, and mineral habit.

Fiber: Any slender, elongated mineral structure or particle. For the purposes of counting asbestos fibers in air samples, regulatory agencies commonly count particles that have lengths 5 μm and length:width ratios 3:1 as fibers. For detecting asbestos fibers in bulk building materials, particles with length:width ratios 5:1 are counted as fibers. See the *Detection and Analysis of Asbestos in Air Samples* section for more details.

Fiber-year/mL: Epidemiologic studies of groups of asbestos-exposed workers commonly express exposure in cumulative exposure units of fiber-year/mL. This exposure measure is calculated by multiplying a worker's duration of exposure (measured in years) by the average air concentration during the period of exposure (measured in number of fibers/mL of air).

Fibrous: A mineral habit with crystals that look like fibers (Zoltai 1981). A mineral with a fibrous habit is not asbestiform if the fibers are not separable and are not long, thin, strong, and flexible (Veblen and Wylie 1993; Zoltai 1979; 1981).

Interstitial: A term used as an adjective relating to spaces within a tissue or organ. *Pulmonary interstitial fibrosis* refers to fibrosis (scarring) occurring within lung tissue.

Mesothelioma: Cancer of the thin lining surrounding the lung (the pleura) or the abdominal cavity (the peritoneum). Mesotheliomas are rare cancers in general populations. Mesotheliomas annually accounted for an average of 1.75 deaths per million in the U.S. general population for the period 1987-1996 (NIOSH 1999). For U.S. white males (the U.S. group with the highest mortality rate), the rates were 3.61 per million in 1987 and 2.87 per million in 1996 (NIOSH 1999). See the *Health Effects from Asbestos: Overview* section for more information..

Mineral: Any naturally occurring, inorganic substance with a crystal structure. Naturally occurring, inorganic substances without a crystal structure (such as amorphous silica) are called mineraloids (Veblen and Wylie 1993).

Mineral Habit: The shape or morphology that single crystals or crystal aggregates take during crystal formation (Veblen and Wylie 1993). Mineral habit is influenced by the environment during crystal formation. Habits of single crystals include prismatic, acicular, platy, and fiber. Habits of crystal aggregates include asbestiform, fibrous, lamellar, and columnar.

Parenchyma: The functional cells or tissue of a gland or organ; for example, the lung parenchyma. The major lung parenchymal abnormality associated with exposure to asbestos is the development of scar-like tissue referred to as pulmonary interstitial fibrosis or asbestosis.

Pleura: A thin lining or membrane around the lungs or chest cavity. This lining can become thickened or calcified in asbestos-related disease.

Pleural: Having to do with or involving the pleura.

Pleural abnormalities: Abnormal or diseased changes occurring in the pleura. Pleural abnormalities associated with exposure to asbestos include pleural plaques, pleural thickening or calcifications, and pleural effusion.

Pleural calcification: As a result of chronic inflammation and scarring, pleura becomes thickened and can calcify. White calcified areas can be seen on the pleura by X-ray.

Pleural cavity: The cavity, defined by a thin membrane (the pleural membrane or pleura), which contains the lungs.

Pleural effusion: Cells (fluid) can ooze or weep from the lung tissue into the space between the lungs and the chest cavity (pleural space) causing a pleural effusion. The effusion fluid may be clear or bloody. Pleural effusions may be an early sign of asbestos exposure or mesothelioma and should be evaluated.

Pleural plaques: Localized or diffuse areas of thickening of the pleura (lining of the lungs or chest cavity. Pleural plaques are detected by chest x-ray, and appear as opaque, shiny, and rounded lesions.

Pleural thickening: Thickening or scarring of the pleura may be associated with asbestos exposure. In severe cases, the normally thin pleura can become thickened like an orange peel and restrict breathing.

Pulmonary interstitial fibrosis: Scar-like tissue that develops in the lung parenchymal tissue in response to inhalation of dusts of certain types of substances such as asbestos.

Serpentinite: Igneous or metamorphic rock chiefly composed of serpentine minerals such as chrysotile or lizardite (Jackson 1997). Chrysotile, when found, can occur in localities with serpentinite rock (Churchill et al. 2001).

Tremolite asbestos: A special form of the amphibole mineral, tremolite, that displays separable, long, thin fibers often arranged in parallel in a column or in matted masses. The fibers are generally strong enough and flexible enough to be spun and woven, are heat resistant, and are chemically inert.

Ultramafic rock: Igneous rock composed chiefly of dark-colored ferromagnesian silicate minerals (Jackson 1997). Asbestiform amphiboles, when found, can occur in localities with ultramafic rock (Churchill et al. 2001).

Vermiculite: A mineral belonging to the mica group of silicate minerals (Ross et al. 1993). Vermiculite has water molecules located between the silicate layers in the crystal structure. When heated, vermiculite expands to form a light-weight material that has been used for home and building insulation, as a soil amendment, and as a packing material. The process of heating and expanding vermiculite is called exfoliation or "popping". Raw vermiculite ore is processed to produce vermiculite concentrate, which is shipped to exfoliating plants to produce the finished vermiculite product.

The photograph in Figure 2 shows a sample of raw vermiculite ore from Libby, Montana, with asbestiform amphibole fibers mixed in with the vermiculite. Figure 3 shows processed vermiculite concentrate (before expansion) and exfoliated vermiculite (after expansion).

Chemistry of Amphibole Minerals

The molecular structure of all amphiboles consists of two chains of SiO_4 molecules that are linked together at the oxygen atoms (Jolicoeur et al. 1992; Skinner et al. 1988; Veblen and Wylie 1993). The chains are bonded together by cations (e.g. Ca, Mg, Fe) and hydroxyl molecules and stacked together to form crystals. The internal crystal structure of all amphiboles is the same, but there is a wide range of chemical variability within the amphibole group. Four subgroups of amphiboles are currently recognized: the magnesium-iron-manganese-lithium subgroup; the calcic subgroup; the sodic-calcic subgroup; and the sodic subgroup (Leake et al. 1997). Amphibole mineral names are based on ideal chemical compositions. The chemical composition of a specific mineral sample is likely to be close to, but not exactly the same as, the ideal chemical composition of its mineral name, because of natural chemical variability in minerals.

Tremolite ($Ca_2Mg_5Si_8O_{22}[OH]_2$) and ferro-actinolite ($Ca_2Fe_5Si_8O_{22}[OH]_2$) are mineral names currently applied to end members of a series[2] within the calcic amphibole subgroup in which the magnesium and iron content can vary widely (Leake et al. 1997;Verkouteren and Wylie 2000; Wylie and Verkouteren 2000). The ideal chemical composition of tremolite has no iron, ferro-actinolite contains no magnesium, and actinolite contains intermediate amounts of magnesium and iron (Leake et al. 1997). Figure 4 shows two other series within the amphibole group: 1) the tremolite-richterite series in which the calcium and sodium content can vary, and 2) the tremolite-winchite series in which the magnesium, calcium, and iron content vary. Some samples of the Libby amphibole show a chemical composition that is somewhere in the middle of the plane defined by the tremolite, richterite, and winchite corners of the cube in Figure 4.

From a chemical analysis of 30 amphibole samples from Libby mining and milling sites, the U.S. Geological Survey (USGS) assigned several different amphibole names to the samples: winchite, richterite, tremolite, actinolite, ferro-edenite, and magnesio-arfvedsonite (Meeker et al. 2001). These investigators noted that most of the amphibole samples displayed both asbestiform habits and nonasbestiform habits (from which cleavage fragments could be formed).

Occurrence of Tremolite Asbestos

Nonasbestiform tremolite is the predominant form of tremolite that exists in the earth's crust (Veblen and Wylie 1993). There are many reports, however, of tremolite asbestos occurring in specific locations around the world.

Tremolite asbestos has only rarely been found in commercially mined deposits. Some tremolite asbestos has been mined in South Africa, India, Maryland, and South Korea, but it has never been a nationally important commercial source of asbestos in the United States. (Ross 1981). The extent of tremolite asbestos mining was small in Powhatan and Pylesville, Maryland, where it occurs with anthophyllite asbestos in ultramafic rocks (Ross 1981). In South Africa, tremolite asbestos was mined in the early twentieth century, but most amphibole asbestos recently mined in South Africa is amosite or crocidolite (Ross 1981). In contrast, as late as 1996, deposits of anthophyllite and tremolite asbestos were being commercially mined for use in asbestos cement in the South Rajasthan region of India (Mansinghka and Ranawat 1996).

---

[2] Called a solid state solution series by mineralogists.

Figure 2. Photograph of a sample of Libby, Montana, vermiculite ore. Fiber-like structures can be seen along the left edge of the piece of ore on the left. Source: U.S. Geological Survey and U.S. Environmental Protection Agency, Region 8, Denver, Colorado.

Figure 3. Photograph of vermiculite concentrate (on the right) and exfoliated vermiculite (on the left). Source: U.S. Geological Survey and U.S. Environmental Protection Agency, Region 8, Denver, Colorado.

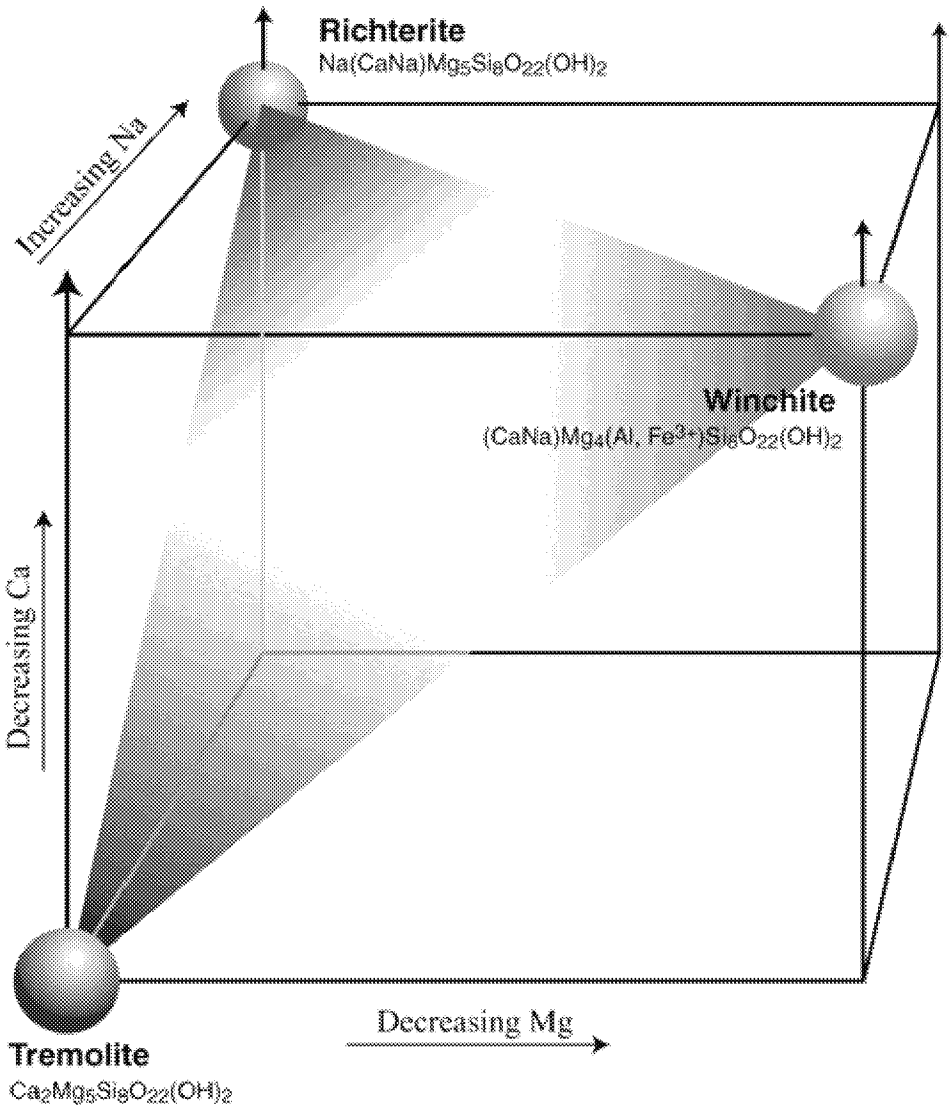


Figure 4. Relationships between magnesium, calcium, and sodium content and three amphibole mineral names: tremolite, winchite, and richterite. All three names have been assigned to various amphibole samples from former vermiculite mining and milling sites near Libby, Montana. Source: U.S. Geological Survey and U.S. Environmental Protection Agency, Region 8, Denver Colorado.

In certain Mediterranean regions, central and eastern Turkey, and New Caledonia in the South Pacific, soil containing tremolite asbestos has been used as stucco and for whitewashing of interior or exterior walls in certain villages (Baris et al. 1988a, 1988b; Bazas 1987; Bazas et al. 1985; Boutin et al. 1989; Constantopoulos et al. 1987a, 1992; Coplu et al. 1996; De Vuyst et al. 1994; Dumortier et al. 1998; Langer et al. 1987; Luce et al. 1994, 2001; McConnochie et al. 1987; Metintas et al. 1999; Sakellariou et al. 1996; Yazicioglu et al. 1980). This practice has declined as the health effects of inhalation exposure to tremolite asbestos have become better known.

Tremolite asbestos and chrysotile occur naturally in California, most commonly in areas of ultramafic rock and serpentinite (Churchill et al. 2001; Renner 2000). The Division of Mines and Geology of the California Department of Conservation has prepared a map identifying areas of ultramafic rock and serpentinite where tremolite asbestos and chrysotile may occur in El Dorado County, California (Churchill et al. 2001).

Occurrence in Vermiculite Before 1990, the now closed mine in Libby, Montana, was a significant source of vermiculite concentrate in the United States. According to a 1998 USGS report, vermiculite concentrate was produced in U.S. mines at Enoree and Woodruff, South Carolina, and in Louisa County, Virginia (USGS 1998b). U.S. imports of vermiculite in 1998 were supplied by South Africa and China (USGS 1998b). Twenty vermiculite exfoliating plants operated in 11 states in 1998.

In an early EPA-supported study, ~21% to 26% of the weight of raw ore samples and 0.3% to 7% of the weight of vermiculite concentrate samples from Libby were accounted for by asbestiform amphibole identified as tremolite-actinolite (Atkinson et al. 1982). In a 1984 study of samples from Libby, Montana, conducted by W.R. Grace, asbestiform amphibole percentage by weight varied from 3.5% to 6.4% in raw ore and from 0.4% to 1.0% in the concentrate (cited in Amandus et al. 1987a).

Amandus et al. (1987a) noted that among 599 fibers counted in eight airborne membrane filter samples from the Libby mine and mill, 96% and 16% had length:width ratios >10 and >50, respectively. Percentages of fibers with lengths >10, >20, and >40 μm were 73%, 36%, and 10%, respectively. McDonald et al. (1986b) reported that fibers in Libby air samples showed ranges for diameter, length, and length:width ratio of 0.1–2 μm, 1–70 μm, and 3–100, respectively. Greater than 60% of fibers were reported to be longer than 5 μm (McDonald et al. 1986b). These data are consistent with the asbestiform habit of the Libby amphibole.

When amphibole asbestos has been detected in vermiculite from other localities, the reported amounts have been lower than those in Libby vermiculite.

Moatamed et al. (1986) analyzed samples of vermiculite ores from Libby, Montana; Louisa County, Virginia; and South Africa for the presence of amphibole. Two samples of Montana unexpanded vermiculite ore were determined to have 0.08% and 2.0% amphibole by weight; two samples of expanded Montana vermiculite both showed 0.6% amphibole content. The South African unexpanded and expanded samples showed 0.4% and 0.0% amphibole content, respectively. The unexpanded and expanded Virginia samples were both determined to be 1.3% amphibole by weight.

The Virginia amphibole (identified as actinolite) and the South African amphibole (identified as anthophyllite) were predominately nonasbestiform, whereas the Montana amphibole (identified as actinolite) was predominately asbestiform (Moatamed et al. 1986). Numbers of fibrous amphibole particles in the Virginia samples were reported to be "extremely low" in comparison to the Montana samples. The infrequent, short fibrous structures were "most likely cleavage fragments." The South African vermiculite samples showed a "near absence of fibers" or "rare, short fibrous structures."

In another investigation, total asbestiform fibers (classified as tremolite-actinolite) represented less than 1% of the weight of samples of raw ore and vermiculite concentrate from Enoree and Patterson, South Carolina, compared with ~21% to 26% and 0.3% to 7% of the weight of raw ore and vermiculite concentrate samples, from Libby, Montana respectively (Atkinson et al. 1982). Concentrations of particles with length > 5 μm in exfoliated vermiculite samples from South Carolina ranged from 0.7 to 11.7 x 10^6 fibers per g, whereas concentrations were higher in exfoliated Libby samples, ranging from 23 to 160 x 10^6 fibers per g (Atkinson et al. 1982). Transmission electron micrographs of nonasbestiform amphibole cleavage fragments from samples of Enoree vermiculite showed dramatic morphological differences from amphibole fibers from Libby vermiculite ore (Ross et al. 1993).

Amphibole (reported as tremolite) was detected in 26 of 57 samples of vermiculite with concentrations ranging from 0.01% to 6.4% in the samples with tremolite (Addison and Davies 1990). It was reported that "most of the amphibole in these samples was non-asbestiform." Further information was not provided in the report concerning where these samples came from and which ones may have contained asbestiform amphibole.

EPA (2000) investigated the occurrence of asbestos in vermiculite-containing garden products purchased in stores in several regions of the United States. These products ranged from products marketed as vermiculite to mixtures of vermiculite with other materials (e.g., soil or other minerals). In an initial investigation, asbestos was detected in 5 of 16 of the products tested, but only three products had sufficient levels that could be quantified. Reported weight concentrations of asbestos (identified as actinolite) were 0.30% and 0.33% for one product, 0.10% to 2.79% for another product, and 0.45% for the third (only one sample concentration was reported for this product). The second investigation detected asbestos in 17 of 36 garden products, but asbestos concentrations (identified predominantly as actinolite) were above 0.1% in only 5 of these products, ranging from 0.13 to 0.7% in an initial sampling. Further sampling showed that the concentrations in these "positive" products varied considerably, but no concentrations higher than the upper end of the initial ranges were reported.

To understand how much asbestos consumers may inhale when using vermiculite-containing garden products, EPA (2000) simulated exposure scenarios in enclosed conditions and in outside open air. From these simulations, EPA (2000) concluded that consumers "face only a minimal health risk from occasionally using vermiculite products at home or in their gardens." To further reduce the low health risk associated with occasional domestic use, EPA (2000) recommended 1) using vermiculite outdoors or in well-ventilated areas; 2) avoiding vermiculite dust by keeping vermiculite damp during use; and 3) avoiding bringing vermiculite dust into the home on clothing.

Occurrence in Chrysotile Amphibole asbestos, identified as tremolite asbestos or actinolite asbestos, has been reported to be a minor contaminant in some deposits of chrysotile in Quebec. Part of the evidence that tremolite asbestos exists in certain chrysotile deposits mined in Quebec comes from observations of higher concentrations of tremolite asbestos fibers than chrysotile fibers in autopsied lung tissues of certain miners and millers who were chronically exposed to chrysotile ores (see Case 1994 for review). Inhaled tremolite asbestos fibers are more persistent in lungs than inhaled chrysotile fibers.

The amount of tremolite asbestos or actinolite asbestos in chrysotile deposits, if present, is expected to vary from region to region and site to site. Tremolite was detected in 3 of 8 samples of commercial chrysotile using a method with detection limits of 0.01% to 0.05% that involved chrysotile digestion and energy-dispersive x-ray analysis (Addison and Davies 1990). Tremolite fibers in these samples were described as generally fine, straight, and needle-like with diameters around 0.2 μm. Weight percentages accounted for by tremolite in the 3 "positive" samples were 0.02%, 0.08%, and 0.20%. The authors concluded, based on a combined analysis of results from this method, electron microscopy, and infrared

spectrophotometry, that the tremolite in only one of the positive samples was asbestiform. In a wider survey of chrysotile samples using the same technique, tremolite was detected in 28 of 81 chrysotile samples; tremolite accounted for weight percentages in positive samples ranging from 0.01% to 0.6% (Addison and Davies 1990). The report did not indicate the extent to which the tremolite samples in the wider survey were asbestiform or nonasbestiform.

Occurrence in Talc Talc occurs in mines along the Appalachian Mountains and in California and Texas; Germany; Florence, Italy; Tyrol, Austria; Transvaal, South Africa; and Shetland, Scotland (Amethyst Galleries 1999). In the United States in 1998, there were 15 talc-producing mines in 7 states. Companies in Montana, New York, Texas, and Vermont accounted for 98% of domestic production (USGS 1999). Industrial use of talc shows the following pattern: ceramics, 37%; paints, 19%; paper, 10%; roofing, 10%; plastics, 7%; cosmetics, 5%; rubber, 3%; and other uses, 9% (NTP 1993). The geological formation of talc may lead to the formation of other mineral phases including amphiboles and serpentines, including some in asbestiform habits. In the United States, commercial talc is categorized into cosmetic grade, which is free of asbestos, and industrial grade, which may contain other asbestiform or nonasbestiform minerals (NTP, 1993; Zazenski et al. 1995). Zazenski et al. (1995) noted that the Cosmetic, Toiletry, and Fragrance Association, the United States Pharmacopeia, and the Food Chemical Codex have established talc quality assurance specifications followed by U.S. cosmetic, pharmaceutical, and food companies that use talc to ensure the purity of their products.

Results of a survey of asbestos fibers in consumer cosmetic talc powders from Italian and international markets using electron microscopy, electron diffraction, and energy dispersive x-ray analysis showed that asbestos was detected in 6 of 14 talc samples from the European Pharmacopeia (Paoletti et al. 1984). Chrysotile was identified in 3 samples, 2 samples contained tremolite asbestos and anthophyllite asbestos, and 1 sample contained chrysotile and tremolite asbestos. The authors noted that, in all talc powders analyzed, fibrous talc particles frequently were present that were morphologically similar to amphibole asbestos fibers. Counting fibers as particles with aspect ratio >3:1 and width < 3 μm, the percentages of particles that were asbestos fibers ranged from <0.03% to 0.13% for 4 samples, and were 18% to 22% for the other 2 samples. Paoletti et al. (1984) noted that the European Pharmacopeia, at that time, had not established analytical quality control of asbestos contamination.

Industrial talc currently mined in New York is called tremolitic talc because it contains significant quantities of nonasbestiform tremolite. Historical references in the scientific literature indicate that these talc deposits and their industrial products may contain asbestos (American Thoracic Society 1990; DOL

1980; NTP 1993; Wagner et al. 1982). In 1992, OSHA noted that the debate over the mineralogical content of the New York tremolitic talc ore was unresolved, but that the presence of asbestiform talc in the ore may have led to the identification of asbestiform tremolite and anthophyllite. More recently, a report from OSHA's Salt Lake Technical Center (Crane 2000) suggests that, in some cases, cleavage fragments of nonasbestiform tremolite and anthophyllite in the talc ore and products may have been inappropriately identified as asbestos. Crane (2000) described the New York talc ore as having nonasbestiform tremolite, mostly nonasbestiform anthophyllite, talc in both massive and asbestiform habits, and minor amounts of other minerals and mineraloids.

Talc has been used in the manufacture of crayons for many years. Recently, it was reported in the U.S. press that tremolite asbestos, anthophyllite asbestos, and chrysotile were detected in some crayons at concentrations ranging from 0.03% to 2.86% (CPSC 2000). In response, the Consumer Product Safety Commission (CPSC 2000) examined crayons from several U.S. manufacturers to determine whether asbestos was present. Trace amounts of anthophyllite asbestos were found in some of the crayons. The CPSC (2000) concluded that the risk that children would be exposed to fibers through inhalation or ingestion of talc-containing crayons is "extremely low," but recommended that, as a precaution, crayons should not contain these fibers. The manufacturers have agreed to reformulate their crayons using substitute materials (CPSC 2000).

Detection and Analysis of Asbestos in Air Samples

The detection and analysis of asbestos in air samples (and in bulk materials that may become airborne) involve both fiber quantification and mineral identification. The distribution of numbers of particles of differing sizes in a sample is determined by microscopic examination, performed using either light or electron microscopy. For counting purposes, a fiber is defined as any particle with a length 5 μm and a length:width ratio 3:1. Concentrations in air are reported as fiber/mL or fiber/cc. For the purposes of determining asbestos content in bulk building material, EPA (2000) uses an operational definition of fiber as any particle with a length:width ratio 5:1. Electron diffraction and energy-dispersive x-ray analysis give information on the chemical content and mineral identity of the particles. The combined use of light microscopy, electron microscopy (transmission and scanning), electron diffraction, and energy-dispersive x-ray methods in analyzing air and/or bulk material samples offers the most accurate approach to estimating airborne asbestos concentrations.

Light Microscopic Methods The current standard method for determining airborne asbestos particles in the U.S. workplace is the National Institute for Occupational Safety and Health (NIOSH) Method 7400 which uses phase contrast light microscopy (PCM) (NIOSH 1994a, 1994b). Fibers are collected on a filter and counted with 400–450x magnification. The method does not accurately distinguish between asbestos and nonasbestos fibers, and cannot detect fibers thinner than about 0.25 μm. Recent improvements in filter preparation allow for viewing at higher magnification (1250x) resulting in a several-fold improvement in sensitivity (Pang et al. 1989).

Phase contrast microscopy methods are widely used to assess occupational exposure to workers engaged in activities known to generate airborne asbestos fibers. However, in settings where large proportions of other particles or fibers (e.g., wool, cotton, glass) are present, the phase contrast microscopy will overestimate the asbestos fiber concentration without additional information.

Polarized light microscopy is frequently used for determining the asbestos content of bulk samples of insulation or other building materials (see, for example, NIOSH Method 9002 [NIOSH 1989] and OSHA method ID-191 [OSHA 1994]). This method also enables qualitative identification of asbestos types using morphology, color, and refractive index.

Electron Microscopic Methods Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) methods can detect smaller fibers than PCM and can be used to determine mineral habit in bulk materials that may become airborne. NIOSH Method 7402, Asbestos by TEM, is used to determine asbestos fibers in the optically visible range and is intended to complement PCM (NIOSH Method 7400). Examination of a sample by either TEM or SEM allows the detection of much smaller fibers than light microscopy, and so more thorough data can be collected on fiber length and diameter distribution. Of these two methods, TEM has greater sensitivity for small fibers, and is the most common method for measuring asbestos in ambient air or inside schools or other buildings. SEM analysis usually images fibers that are more than 0.2 μm in diameter because of contrast limitations, while TEM can visualize fibers of all sizes.

Electron Diffraction and Energy-Dispersive X-ray Methods These methods determine crystal structure and elemental composition and are used to identify the mineral group to which a fiber or particle belongs. Modern transmission electron microscopes are equipped with instrumentation that examines individual particles by both of these methods, but scanning electron microscopy does not measure electron diffraction patterns. To distinguish between a nonasbestiform amphibole cleavage fragment and an

asbestiform amphibole fiber of the same mineral type, information about mineral habit (which comes from light and electron microscopy) is needed.

Conversion Factors Conversion factors are used to compare results from epidemiologic studies that used different methods to measure airborne asbestos levels. Early studies often measured air concentrations in units of mass per volume of air or number of particles per volume of air, whereas more recent studies measure air concentrations in units of number of fibers (particles with lengths 5 μm and aspect ratio 3:1, determined by PCM or electron microscopy) per volume of air.

Older studies of health effects and occupational exposure measured dust exposure in units of million particles per cubic foot (mppcf). This method did not distinguish fibrous from nonfibrous particles and used relatively low magnification, so only the largest fibers were detected. The British Occupational Hygiene Society (BOHS 1968) suggested that an asbestos air concentration of 1 mppcf is roughly equal to 3 fiber/mL (detected by PCM).

To convert from PCM-measured to TEM-measured air concentrations, the National Research Council (NRC 1984) recommended that 1 PCM fiber/mL is roughly equal to 60 TEM fiber/mL, and that 1 PCM fiber/mL and 60 TEM fiber/mL are roughly equal to a mass concentration of 0.03 mg asbestos dust/m^3 (i.e., 1 mg/m^3 is roughly equal to 33 PCM fiber/mL or 2000 TEM fiber/mL). The NRC acknowledged that these conversion factors provide only rough estimates because converting from phase contrast microscopy counts to TEM counts can vary with different sizes of fibers, and converting from mass-per-volume units to fibers-per-volume units can vary with different mineral types and different sizes of fibers.

Epidemiologic studies of groups of asbestos-exposed workers commonly express exposure in cumulative exposure units (fiber-year/mL). This exposure measure is calculated by multiplying a worker's duration of exposure (measured in years) by the average air concentration during the period of exposure (measured in fiber/mL).

Potential for Human Exposure to Asbestos

Occupational exposure to asbestos may occur and has occurred in workers involved in mining, milling, and handling of chrysotile (and other forms of asbestos) and vermiculite ores, in exfoliating vermiculite, and in mining, milling, and handling of other ores and rocks that may contain tremolite asbestos or other

amphibole asbestos. Unless efforts are made to limit dust generation and release, and limit transport of dust on clothes to home environments, there is a probability of exposure to other workers, family members, and area residents.

Residents who live close to mining, milling, or manufacturing sites that involve asbestos-containing material may be potentially exposed to higher levels of airborne tremolite asbestos than levels in general ambient air. EPA, ATSDR, and other agencies currently are investigating levels of amphibole asbestos exposure that residents (including children) who were not employed in the vermiculite mines and mills may have and are experiencing. In addition, ATSDR is conducting medical testing of individuals potentially exposed to asbestiform minerals associated with vermiculite in Libby, Montana (ATSDR 2001b).

Asbestos fibers may be released to indoor or outdoor air by the disturbance of asbestos-containing building materials such as insulation, fire-proofing material, dry wall, and ceiling and floor tile, although the use of asbestos-containing building materials has declined sharply in recent years (HEI 1991). Amphibole asbestos has been found in some vermiculite sources that have been used as home and building insulation. Workers or homeowners involved in demolition work or asbestos removal, or in building or home maintenance, repair, and remodeling, potentially can be exposed to higher levels of airborne asbestos than levels in general ambient air. In general, exposure may occur only when the asbestos-containing material is disturbed in some way to release particles and fibers into the air. Exposure will be greatest when dry, friable (i.e., easily released) material is disturbed. When asbestos-containing materials are solidly embedded or contained, exposure will be negligible (USGS 1998b, 1999).

Typical concentrations of asbestos fibers (with lengths 5 μm) in urban and rural ambient air may be about 0.0001 or 0.00001 fiber/mL, respectively (ATSDR 2001a). In workplace air, recent U.S. regulations have limited asbestos air concentrations to 0.1 to 0.2 fiber/mL to protect against the development of pulmonary fibrosis and cancer (OSHA 1992, 1994). A study of indoor air of homes, schools, and other buildings that contain asbestos materials measured an average asbestos concentration of about 0.0001 fiber/mL (Lee et al. 1992). Most of the fibers in this study were identified as chrysotile; 2% of the fibers were identified as amphibole fibers. Indoor air concentrations are highly variable, however, and depend on the friability of the asbestos-containing material and on activities in which people are engaged.

As discussed in the *Occurrence of Tremolite Asbestos* section, small amounts of amphibole asbestos fibers have been identified in some samples of vermiculite-containing consumer garden products from the United States (EPA 2000). EPA (2000) concluded that consumers may face only a minimal health risk from occasionally using vermiculite products at home, and can reduce any risk by limiting the production of dusts when using the products.

Health Effects from Asbestos: Overview

It is known that exposure to airborne asbestos fibers can increase the risk of lung cancer, malignant mesothelioma, and nonmalignant respiratory effects including pulmonary interstitial fibrosis (asbestosis), pleural plaques, pleural calcification, and pleural thickening. Epidemiologic studies have shown increasing risks for malignant or nonmalignant respiratory disease significantly associated with increasing measures of exposure intensity and duration among groups of occupationally exposed individuals. Results from studies of animals exposed by various routes of exposure and from mechanistic studies are consistent with these findings. Reviews of this evidence include those by the Agency for Toxic Substances and Disease Registry (ATSDR 2001a), the American Conference of Governmental Industrial Hygienists (ACGIH 1998), the American Thoracic Society (1990), Case (1991), Churg and Wright (1994), the Environmental Protection Agency (EPA 1986), the International Agency for Research on Cancer (IARC 1987a), Kamp and Weitzman (1997, 1999), Langer and Nolan (1998), Lippmann (1994), McDonald and McDonald (1997), Mossman and Churg (1998), Mossman et al. (1983, 1990), the National Toxicology Program (NTP 2001), the Occupational Safety and Health Administration (OSHA 1986, 1992), Stayner et al. (1996, 1997), Wylie et al. (1993), and the World Health Organization (WHO 1998).

Consensus Issues and Conclusions

There is general agreement among scientists and health agencies on the following issues and conclusions regarding health effects from asbestos.

(1) *Exposure to any asbestos type (i.e., serpentine or amphibole) can increase the likelihood of lung cancer, mesothelioma, and nonmalignant lung and pleural disorders.*

(2) *Important determinants of toxicity include exposure concentration, exposure duration and frequency, and fiber dimensions and durability.*

(3) *Fibers of amphibole asbestos such as tremolite asbestos, actinolite asbestos, and crocidolite are retained longer in the lower respiratory tract than chrysotile fibers of similar dimension.*

(4) *Pulmonary interstitial fibrosis associated with deposition of collagen, progressive lung stiffening and impaired gas exchange, disability, and death occurred in many asbestos workers.*

(5) *Most cases of asbestosis or lung cancer in asbestos workers occurred 15 or more years after their initial exposure to asbestos.*

(6) *Asbestos-exposed tobacco smokers have greater than additive risks for lung cancer than do asbestos-exposed nonsmokers.*

(7) *The time between diagnosis of mesothelioma and the time of initial occupational exposure to asbestos commonly has been 30 years or more.*

(8) *Cases of mesotheliomas have been reported after household exposure of family members of asbestos workers and in individuals without occupational exposure who live close to asbestos mines.*

Unresolved Issues and Discussions

(1) *Does exposure to asbestos increase the risk for gastrointestinal cancer?*
Results in support of a positive answer to this question include small increases in death rates from gastrointestinal cancer in some groups of asbestos-exposed workers and in some populations with high levels of asbestos fibers in drinking water, and a small but statistically significantly increased incidence of benign intestinal tumors in one National Toxicology Program (NTP) study of male rats exposed to chrysotile in their food for life (see ATSDR 2001a for citation of these studies). However, the increased gastrointestinal mortalities noted in workers and in populations exposed through drinking water were usually quite small, and consistent results were not found across studies. In addition, it is difficult to determine whether the increases were due to asbestos or to other factors (e.g., exposure to other chemicals, misdiagnosis, dietary factors, alcohol intake). The weight of the finding of intestinal tumors in chrysotile-exposed rats is counterbalanced by the facts that the tumors were both infrequent and benign, and that no significant increases in tumors occurred in five other NTP lifetime cancer bioassays of rats exposed to different forms of asbestos in their diet.

The available data do not support a definitive conclusion about whether the increased risk for gastrointestinal cancer observed in some of the epidemiologic studies is real or not. Some scientists believe the available evidence is substantial, others believe the evidence is inadequate to reach a firm conclusion, and still others believe the increased risks are probably due to other factors. ATSDR (2001a) and NTP (2001) concur, however, that it seems only prudent to consider increased risk of gastrointestinal cancer an effect of concern from exposure to asbestos.

(2) *Are chrysotile fibers (or amphibole asbestos fibers) primarily responsible for mesotheliomas in certain groups of workers predominantly exposed to chrysotile?*

Some investigators have proposed that chrysotile fibers may not be the primary cause of mesothelioma in humans exposed predominantly to chrysotile, whereas others have proposed that amphibole fibers are more potent than chrysotile in this regard (see Berman et al. 1995; Case 1991; Churg 1988; Churg and Wright 1994; Frank et al. 1998; Langer and Nolan 1998; Lippmann 1994; McDonald and McDonald 1997; Stayner et al. 1996). Tremolite asbestos fibers have often been detected at higher concentrations than chrysotile fibers in autopsied lung tissues of certain miners and millers who were chronically exposed to chrysotile ores that contained only very small amounts of tremolite asbestos (see Case 1994 for review). Part of the difficulty in ascribing primary responsibility in these mesothelioma cases is that chrysotile fibers are removed from the lung much more quickly than amphibole asbestos fibers, and data on fiber content in pleural or peritoneal tissue in human cases are few.

(3) *Are amphibole asbestos types more potent than chrysotile in inducing asbestosis and lung cancer?*

Some investigators have proposed that amphibole asbestos fibers, such as tremolite asbestos, are more potent than chrysotile fibers in inducing fibrotic lung disease and lung cancer (McDonald 1998; McDonald and McDonald 1997; McDonald et al. 1999; Mossman et al. 1990). Others propose that differences in the potency of chrysotile and amphibole-asbestos fibers in inducing lung cancer cannot be reliably discerned from available data (Berman et al. 1995; Stayner et al. 1996).

Despite the dispute in the scientific literature concerning issues (2) and (3), U.S. and international agencies concur that exposure to any type of asbestos (including chrysotile) can increase the risk for asbestosis, mesothelioma, and lung cancer in humans (e.g., ATSDR 2001a; EPA 1986; IARC 1987a; NTP 2001; WHO 1998).

(4) *Should the U.S. regulatory definition of an asbestos fiber (length 5 μm with aspect ratio 3:1), established for purposes of quantifying exposure levels, be changed?*

This issue has received continued debate since the establishment of the definition (see American Thoracic Society 1990; OSHA 1992, 1994; Wylie et al. 1993, 1997). At least part of the debate has involved uncertainties associated with the relative importance of long and short inhaled fibers in asbestos pathogenicity.

In support of the importance of longer fibers, animal carcinogenic responses to asbestos have been variously reported to be best correlated with the concentration of fibers with lengths 8 μm and diameters 0.25 μm (Stanton et al. 1981) and with the concentration of fibers with lengths 20 μm (Berman et al. 1995). Case-control analyses of fiber concentrations in autopsied lungs of mesothelioma subjects and subjects who died of other causes showed that increased risks for mesothelioma were significantly related to longer fibers. Fibers longer than 5 μm (Rodelsperger et al. 1999), 8 μm (McDonald et al. 1989), or 10 μm (Rogers et al. 1991) were implicated in different studies.

In contrast, analyses of autopsied human lung tissue of asbestos-exposed and nonexposed patients often show greater numbers of short (< 5 μm) than long (> 5 μm) retained fibers (Dodson et al. 1997, 1999), and short chrysotile fibers have been reported to be the most prevalent type of fibers found in parietal pleura tissue from asbestos-exposed autopsy cases (Sebastien et al. 1980). Also, significant inverse relationships have been observed between degree of fibrosis and retained amphibole fiber length in autopsy studies of chrysotile miners and millers (Churg and Wright 1989) and amosite-exposed shipyard and insulation workers (Churg et al. 1990). Significant correlations have also been observed in animal studies between carcinogenic response and concentrations of fibers with lengths shorter than 8 μm (Berman et al. 1995; Stanton et al. 1981). In addition, exceptions to the principle that long and thin structures are required for a carcinogenic response to asbestos or other fibers have been reported in animal studies (Davis et al. 1991; Stanton et al. 1981). For example, carcinogenic responses in rats to two tremolite asbestos samples were markedly higher than the predicted response from Stanton's regression curve relating probability of tumor to the number of particles with lengths 8 μm and diameters 0.25 μm (Stanton et al. 1981). In addition, one of seven talcs tested had high numbers of particles with lengths 8 μm and diameters 0.25 μm, but did not produce tumors (Stanton et al. 1981).

(5) *What are the molecular events involved in the development of asbestos-induced respiratory and pleural effects and how are they influenced by fiber dimensions and mineral type?*

Identification of the molecular and cellular events of asbestos-induced disease has been the subject of extensive research within the past two decades (see *Mechanisms of Asbestos Toxicity: Overview* section). However, much remains unknown, and the precise steps in pathogenic pathways are not fully established.

(6) *What are the actual risks for malignant or nonmalignant respiratory disease that may exist at exposure levels below air concentrations (0.1–0.2 fiber/mL) established as recent occupational exposure limits?*

Asbestosis: Based on its review of available data, a task group convened by the World Health Organization (WHO 1998) concluded that "asbestotic changes are common following prolonged exposure of 5 to 20 fiber/mL" and that "the risk at lower exposure levels is not known."

Alternatively, based on an analysis that extrapolated from data for asbestosis mortalities in a group of asbestos textile workers, Stayner et al. (1997) concluded that there was an excess risk of 2/1,000 for asbestosis mortality for men exposed for 45 years to an airborne asbestos concentration of 0.1 fiber/mL. Other scientists have criticized the applicability of the Stayner analysis to general population environmental exposures, noting that this group of asbestos textile workers displayed higher mortality rates than other groups of asbestos workers (Case et al. 2000; Hodgson and Darnton 2000).

Lung Cancer and Mesothelioma: Based on an analysis of data from epidemiologic studies of workers who were exposed to asbestos before modern occupational exposure limits were established, EPA (1986) calculated by extrapolation that lifetime exposure to asbestos air concentrations of 0.0001 fiber/mL could result in up to 2 to 4 excess cancer deaths (lung cancer or mesothelioma) per 100,000 people. This air concentration is within reported ranges of ambient air levels (0.00001 to 0.0001 fiber/mL). The EPA analysis has been extensively discussed and reviewed in the scientific literature (Camus et al. 1998; Hodgson and Darnton 2000; Hughes 1994; Landrigan 1998; Lash et al. 1997). EPA is in the process of reviewing and possibly updating their cancer risk estimates for asbestos.

(7) *Can lung cancer be attributed to asbestos exposure (regardless of fiber type) in the absence of pulmonary fibrosis?*

Some scientists have supported the hypothesis that asbestosis is a necessary prerequisite for asbestos-induced lung cancer, but there is also evidence that an increased risk for lung cancer occurs in asbestos workers without obvious asbestosis (see Henderson et al. 1997; Hillerdal and Henderson 1997; Hughes and Weill 1991; Jones et al. 1996; Wilkinson et al. 1995). Hillerdal and Henderson (1997) concluded from their review of the data that "there was an increasing body of evidence that, at low exposure levels,

asbestos produces a slight increase in the relative risk of lung cancer even in the absence of asbestosis." In contrast, Jones et al. (1996) concluded from their review that, "While the issue of whether asbestosis is a necessary precursor to asbestos-attributable lung cancer cannot at this time be considered settled, the weight of the available evidence strongly supports this proposition."

Deposition and Clearance of Inhaled Asbestos Fibers: Overview

Human and animal studies indicate that when asbestos fibers are inhaled, thick fibers (diameters greater than 2–5 μm) are deposited in the upper airways, whereas thinner fibers are carried deeper into the alveolar regions of the lung (ATSDR 2001a; Lippman 1994; Wylie et al. 1993). Absorption by epithelial cells and penetration through the epithelial layers of the respiratory tract are thought to be minimal, but some transport of inhaled fibers from the lung to the pleural cavity occurs (ATSDR 2001a; Wylie et al. 1993). Fiber width is a key determinant of access of fibers to the lung and pleural cavity, and thus of fiber toxicity. Wylie et al. (1993) reviewed available evidence from human epidemiology studies, human lung burden studies, and studies of animals implanted or injected with asbestos indicating that fibers with widths greater than 1 μm are unlikely to cause lung cancer or mesothelioma.

Fibers deposited in the respiratory tract are principally removed by mucociliary transport and swallowing, followed by elimination from the gastrointestinal tract via feces. Small numbers of fibers may reach the lymph system or be transported to the pleura and peritoneum. Dissolution of fibers by alveolar macrophages is also thought to play a role in eliminating asbestos fibers from the lung, especially for chrysotile fibers; interstitial macrophages, intravascular macrophages, and pleural macrophages also interact with deposited asbestos fibers (see Oberdorster 1994). In addition, some fibers are not cleared from the lung, leading to a gradual accumulation.

There is evidence in animals that long fibers are retained in the lungs for longer periods than short fibers (e.g., Coin et al. 1992; Davis 1989). This relationship may be associated with the inability of macrophages to engulf and remove fibers that are significantly larger than themselves (Bignon and Jaurand 1983), but analysis of autopsied human lung or parietal tissue for retained fibers often shows higher numbers of short (< 5 μm) fibers than long (> 5 μm) fibers (Dodson et al. 1997, 1999; Sebastien et al. 1980).

There is also evidence that amphibole fibers are retained for longer periods than chrysotile fibers (Albin et al. 1994; Churg 1994; Churg et al. 1993; Davis 1989; Wagner et al. 1974). For example, amphibole

retention in lungs of rats repeatedly exposed to airborne amphibole fibers for 24 months showed a continuous increase throughout exposure, whereas chrysotile lung retention reached a much lower maximum level within about 3 months in rats similarly exposed to chrysotile fibers (Wagner et al. 1974). Tremolite fibers in autopsied lung tissue from workers exposed to airborne chrysotile fibers contaminated with small amounts of tremolite (<1%) accounted for disproportionately large percentages (47–67%), and chrysotile fibers accounted for disproportionately small percentages (19–53%), of the total fibers detected (Churg and Wright 1994). The apparent longer retention of amphibole fibers in lung tissue has been proposed as a partial explanation of why amphibole asbestos appears to be more potent in producing mesothelioma than chrysotile (American Thoracic Society 1990; Mossman et al. 1990).

Mechanisms of Asbestos Fiber Toxicity: Overview

Identification of the molecular and cellular responses leading to the progressive development of asbestos-induced lung cancer, mesothelioma, pulmonary fibrosis, and pleural thickening and effusion has been the subject of extensive research within the past two decades. Published reviews of this work include those by Begin et al. (1992), Kamp and Weitzman (1997, 1999), Kamp et al. (1992), Luster and Simeonova (1998), Mossman and Churg (1998), Mossman et al. (1983, 1996), Rom et al. (1991), and Tanaka et al. (1998). In general, it is recognized that there are multiple cellular and molecular responses to asbestos fibers, that no single mechanism is likely to account for all asbestos-related diseases, that the precise steps in pathogenic pathways leading to asbestos-related disease are not fully established, and that fiber structural and chemical properties (e.g., length, width, iron content, durability, surface areas) are important variables that play a role in the development of lung and pleural injury.

A central working hypothesis proposes that the presence of asbestos fibers in the lung activates alveolar macrophages, pulmonary neutrophils, pulmonary epithelial cells, and pleural mesothelial cells to produce reactive oxygen species (such as hydrogen peroxide, the superoxide anion, and the hydroxyl radical) and/or reactive nitrogen species (such as nitric oxide and peroxynitrite) that can damage cellular macromolecules (e.g., deoxyribonucleic acid [DNA], ribonucleic acid [RNA], signal transduction proteins, and membrane lipids) and lead to cellular dysfunction, cytotoxicity, cellular transformation (to malignancy), and cellular proliferation (see the reviews cited in the previous paragraph for evidence in support of this hypothesis). In addition, iron cations associated with asbestos fibers may augment the production of hydroxyl radicals. The pathogenesis of asbestos-induced lung injury is also thought to involve altered expression of genes involved in oxidation protection (e.g., catalase and superoxide dismutase), other stress responses (e.g., heat shock proteins and ferritin), cellular proliferation (e.g.,

cytokines, cytokine binding proteins, and growth factors), and apoptosis in alveolar macrophages, pulmonary epithelial cells, and/or pleural mesothelial cells. Further understanding of how persistent production of reactive oxygen or nitrogen species and persistent inflammatory cellular responses precisely interact may be useful for developing better approaches to the diagnosis, prevention, and treatment of asbestos-related disease.

Health Effects from Tremolite Asbestos

As with other forms of asbestos, health effects of concern from exposure to inhaled tremolite asbestos are lung cancer, mesothelioma, and nonmalignant lung and pleural disorders. Evidence in humans comes from epidemiologic studies of tremolite asbestos-exposed groups of vermiculite miners and millers from Libby, Montana. This evidence is supported by reports of increased incidences of nonmalignant respiratory diseases, lung cancer, and mesothelioma in villages in various regions of the world that have traditionally used tremolite-asbestos whitewashes or have high surface deposits of tremolite asbestos and by results from animal studies.

Nonmalignant Respiratory Effects: Pulmonary Fibrosis and Pleural Changes. Studies of Libby, Montana vermiculite workers chronically exposed to airborne tremolite asbestos provide evidence that exposure to tremolite asbestos increases the risk of interstitial pulmonary fibrosis, pleural calcification, and pleural wall thickening and the risk of death from these nonmalignant diseases. Supporting evidence comes from observations of 1) high prevalences of pleural calcification among residents of villages where whitewashes containing tremolite asbestos were used or where there are abundant surface deposits of tremolite asbestos and 2) pulmonary fibrogenic reactions in lungs of rats and mice after exposure to tremolite asbestos by inhalation or intratracheal instillation.

In response to a report of 12 cases of pleural effusion within a 12-year period in an Ohio fertilizer plant that processed Libby, Montana vermiculite, 501 workers were surveyed for symptoms of respiratory distress, examined by chest radiography, and tested for pulmonary function (Lockey et al. 1984). Chest radiographs showed 479/501 (95.6%) workers with no significant radiographic changes, 1/501 (0.2%) workers with small irregular parenchymal opacities indicative of pulmonary fibrosis, 10/501 (2.0%) workers with significant pleural changes described as thickening, plaques, and/or calcification, and 11/501(2.2%) workers with costophrenic angle blunting only. Cumulative fiber exposures for the 11 employees with parenchymal or pleural changes ranged from 0.01 to 39.9 fiber-year/mL (mean = 12 fiber-year/mL). Cumulative fiber exposures for the 11 employees with costophrenic angle blunting

ranged from 0.2 to 27.5 fiber-year/mL (mean = 5.4 fiber-year/mL). Increased prevalences of radiographic pleural changes, self-reported pleuritic chest pain, and self-reported shortness of breath were significantly associated with cumulative fiber exposure indices, but exposure-related changes in pulmonary function (spirometric variables and carbon dioxide diffusing capacity) were not found.

Chest radiographs of 184 men employed at the Libby, Montana vermiculite mine and mill for at least 5 years during 1975–1982 were evaluated for parenchymal abnormalities indicative of pulmonary fibrosis (presence of small irregular parenchymal opacities with a profusion International Labor Organization [ILO] category 1/0[3]) and pleural abnormalities including calcification and thickening on the wall (Amandus et al. 1987b). Prevalences for small parenchymal opacities ILO category 1/0, any pleural change, pleural calcification, and pleural wall thickening were 10, 15, 4, and 13%, respectively. Vermiculite workers who were smokers, were of age 45 or greater, and had cumulative fiber exposure indices >100 fiber-year/mL (but not those with exposures <100 fiber-year/mL) showed a significantly higher prevalence of small irregular parenchymal opacities (4/13, 30.8%) than several reference groups of workers of similar age and smoking habits without known fiber exposure (e.g., nonasbestos cement workers). Amandus et al. (1987b) suggested that the finding of higher prevalence of parenchymal changes in the Libby, Montana vermiculite workers compared with the Ohio fertilizer plant workers (Lockey et al. 1984) may be explained by a higher average cumulative exposure index for the Montana workers.

Another study examined possible relationships between cumulative fiber exposure and chest radiographic findings for 173 workers employed in the Libby, Montana, mine and mill in July 1983, 80 of 110 former male employees who resided within 200 miles of Libby, and 47 local men without known exposure to dust (McDonald et al. 1986a). Age-standardized percentages of subjects with parenchymal opacities (small irregular opacities with ILO category 1/0) and pleural thickening of chest wall increased with increasing cumulative fiber exposure categories. For example, age-standardized percentages for small opacities were 10.6%, 18.4%, 15.4%, 31.3%, and 27.9% for subjects with mean cumulative exposures of 4.1, 17.5, 53.9, 144.4, and 495.8 fiber-year/mL, respectively. Logistic regression analysis indicated that the prevalence of small opacities (with profusion ILO category 1/0) was significantly affected by age, smoking, and cumulative exposure; prevalence for pleural thickening was significantly affected by age and cumulative exposure. The logistic regression analysis predicted that for current smokers at age 65,

---

[3]The ILO classification system (ILO 1989) for profusion of opacities in chest radiographs establishes four categories of profusion of increasing severity, each with three subcategories noted in parentheses: 0 (0/-, 0/0, 0/1); 1 (1/0, 1/1, 1/2); 2 (2/1, 2/2, 2/3); 3 (3/2, 3/3, 3/4).

the risk for developing small parenchymal opacities ILO category 1/0 would increase by about 5–10% with each cumulative exposure increment of 100 fiber-year/mL. McDonald et al. (1986a) also concluded that at 0.1 fiber/mL, no detectable excess of radiological change should be detectable after a working life of 40 years. However, in a later discussion of their Libby, Montana, regression analysis, McDonald et al. (1988) noted that the increased risk of small radiographic opacities (ILO category 1/0) was between 0.05 and 0.1% per fiber-year/mL.

There are two cohort mortality studies of tremolite-asbestos-exposed workers employed for at least 1 year at the Libby, Montana, vermiculite mine and mill. Causes of death were evaluated among 161 deaths that occurred by 1981 in 575 men who were hired before 1970 (Amandus and Wheeler 1987) and among 165 deaths that occurred by 1983 in 406 men who were hired before 1963 (McDonald et al. 1986b). Both studies assigned cumulative fiber exposure indices (fiber/year-cc = fiber-year/mL) to each subject based on individual work histories and estimated fiber concentrations in air at various job locations (fiber/mL). Workplace air concentrations were estimated from microscopic examination of membrane filter samples collected after 1968 and from dust concentrations from midget impinger samples collected before 1968 in the dry mill area (Amandus et al. 1987a; McDonald et al. 1986b). Fiber concentrations in periods before 1968 were adjusted to reflect higher fiber concentrations expected to have existed in these earlier periods at several job locations due to changes in production methods.

Elevated standardized mortality ratios (SMRs) for nonmalignant respiratory disease, using mortality rates for U.S. males as reference, were calculated for both cohorts. Amandus and Wheeler (1987) reported an SMR of 2.43 (95% confidence interval [CI] = 1.48, 3.75; 20 observed deaths versus 8.2 expected), and McDonald et al. (1986b) reported an SMR of 2.55 (95% CI was not reported; 20 observed deaths, expected deaths not reported). For workers with cumulative exposure indices >399 fiber-year/mL, Amandus and Wheeler (1987) reported a statistically significantly elevated SMR of 4.00 (7 observed versus 1.8 expected). Deaths from nonmalignant respiratory disease expected to be directly related to tremolite fiber exposure (pulmonary fibrosis or pneumoconiosis) represented 50% (10/20; Amandus and Wheeler 1987) and 40% (8/20; McDonald et al. 1986b) of deaths from nonmalignant respiratory disease. Neither study was able to demonstrate consistent, statistically significant relationships between increasing exposure index and increasing risk for death from nonmalignant respiratory disease, but the statistical power was limited in both studies because of the small numbers of workers evaluated. Other limitations of the studies include the limited follow-up periods (only 28% and 40% of the cohorts had died when the studies were conducted) and the lack of information about individual smoking histories. Nevertheless,

the results from these studies add considerable weight to the evidence that exposure to airborne asbestos, including tremolite asbestos, can lead to the development of nonmalignant respiratory disease and death.

Two studies of other groups of miners and millers at other vermiculite mines in South Africa and South Carolina did not find evidence for increased prevalence of diseases associated with asbestos exposure (Hessel and Sluis-Cremer 1989; McDonald et al. 1988). The vermiculite in these studies was reported to contain much lower levels of tremolite asbestos or other amphibole asbestos fibers than the Libby, Montana, vermiculite (Atkinson et al. 1982; Moatamed et al. 1986; McDonald et al. 1988). It is plausible that the lack of increased prevalences of diseases associated with asbestos exposure in these workers is primarily due to the very low levels of asbestiform amphibole minerals in these vermiculite deposits (Atkinson et al. 1982; Moatamed et al. 1986; Ross et al. 1993). In addition, such factors as lower levels of airborne fiber concentrations at the worksites, small numbers of subjects in the studies, and limitations in study design and exposure data may have contributed to this lack of evidence.

In a cross-sectional study by Hessel and Sluis-Cremer (1989), no increased prevalence of parenchymal or pleural abnormalities on chest radiographs, no excess of self-reported respiratory symptoms, and no lung function performance deficits were found in a group of 172 South African vermiculite workers (average duration of employment was 15.3 years) compared with a group of workers involved in mining and refining copper. Samples of unexpanded and expanded vermiculite from this mine showed 0.4% and 0.0% amphibole content (Moatamed et al. 1986). The amphibole was nonasbestiform with "rare, short fibrous structures" that were predominantly anthophyllite. From this analysis, Moatamed et al. (1986) concluded that the South Africa vermiculite samples were "essentially fiber free."

McDonald et al. (1988) evaluated causes of 51 deaths that occurred by the end of 1985 in 194 men who were employed for at least 6 months before the end of 1970 in the mining and milling of vermiculite from Enoree, South Carolina. Only 3 deaths were attributed to nonmalignant respiratory disease compared with 2.45 expected (not statistically significant); no deaths were attributed to pneumoconiosis. Chest radiographs of 83 current employees with expected dust exposure revealed no elevated percentage of subjects with parenchymal or pleural abnormalities compared with a group of 25 workers in another division of the company without exposure to dust. The vermiculite from South Carolina contains, at most, only trace amounts of tremolite asbestos (see *Occurrence of Tremolite Asbestos* section). Atkinson et al. (1982) reported that in samples of vermiculite from Patterson and Enoree, South Carolina, less than 1% of the weight was accounted for by asbestiform particles. Estimates of workplace air concentrations of particles with length 5 μm and aspect ratio > 3:1 were low, ranging from 0.4 fiber/mL in 1970

samples to 0.0 fiber/mL in 1985 in "wet zone" work areas and from 0.84 fiber/mL in 1970 to 0.02 fiber/mL in 1985 in "dry zone" areas (McDonald et al. 1988). Transmission electron microscopy and energy dispersive x-ray analysis of settled dust samples from dry zone locations showed four types of elongated particles: tremolite-actinolite (37.9%), vermiculite fragments (28.0%), talc/anthophyllite (15.9%), and iron-rich fibers (4.6%); 14% of the particles were not identified. McDonald et al. (1988) noted that the lack of observed respiratory effects in these vermiculite workers may have been due to a combination of the small number of subjects in the study (i.e., decreased detection power) and low airborne fiber concentrations. The mean cumulative fiber exposure of the Libby, Montana mortality cohort studied by McDonald et al. (1986b) was 144.6 fiber-year/mL, whereas the mean of the South Carolina cohort was estimated at 0.75 fiber-year/mL.

High prevalences of pleural calcification have been noted in inhabitants of northwestern Greece villages who had no known occupational exposure to asbestos fibers. In a 1980 study of 408 subjects who represented 15% of the population of three villages (Metsovo, Anilio, and Milea) over the age of 10, chest radiographs showed very few small opacities indicative of pulmonary fibrosis, but an overall prevalence of pleural calcification in 34.7% of men and 21.5% of women examined (Bazas 1987; Bazas et al. 1985). Constantopoulos et al. (1985, 1987a) reported that radiographic screening detected pleural calcifications in up to 323/688 (46.9%) inhabitants of the same villages and another village (Votonossi) in this area (called Metsovo). The frequency of pleural calcification increased with age; about 70% of inhabitants of age >70 years had pleural calcification (Constantopoulos et al. 1985, 1987a). Constantopoulos et al. (1991) also found pleural calcifications in 24 of 101 (23.7%) examined inhabitants of another Greek village (Distrato) outside the Metsovo region.

Constantopoulos et al. (1985, 1987a, 1991) attributed the pleural calcifications to the domestic production and use of a tremolite-asbestos-containing whitewash ("luto") made from a local soil. Analysis of samples of the whitewash material by light microscopy, transmission electron microscopy, and x-ray dispersion analysis indicated that it contained predominantly asbestiform tremolite (Langer et al. 1987). The finding of tremolite fibers in transbronchial lung biopsy specimens from individuals diagnosed with pleural calcification supported the attribution of the effect to the use of tremolite-asbestos-containing whitewash; the amphibole fibers in the tissue were described as "tremolitic and asbestiform" (Constantopoulos et al. 1985). Furthermore, pleural calcifications were not observed in nearby villagers who did not use "luto" for whitewashing; these villagers used limestone (calcium oxide) (Constantopoulos et al. 1987a). Sakellariou et al. (1996) reported that domestic use of "luto" whitewash in the Metsovo area decreased from about 92% in 1950 to 71% in 1960, to 38% in 1970, and to 18% in

1980. Mineralogic analysis of Distrato whitewash also revealed chrysotile and tremolite asbestos fibers, but details of this analysis were not reported (Constantopoulos et al. 1991).

High incidences of pleural calcifications have also been reported for inhabitants of several rural regions of Turkey where tremolite-asbestos-containing whitewash has been used to cover interior walls (Baris et al. 1988a; Coplu et al. 1996; Dumortier et al. 1998; Metintas et al. 1999; Yazicioglu et al. 1980). For example, chest radiographs of 167 inhabitants (20 years or more of age) of the village of Caparkayi showed that 63 (37.7%) had radiological abnormalities. Interlobar fissure thickening (thickening in the regions between lobes of the lung), diffuse interstitial fibrosis, calcified pleural plaques, and pleural thickening were observed in 16.8%, 15.6%, 14.4%, and 7.8% of the 167 inhabitants, respectively (Baris et al. 1988a). The whitewash material used in this village was shown to be rich in tremolite asbestos fibers, both fine and coarse (Baris et al. 1988a). In a survey of 124 inhabitants of the village of Kureysler, 14% showed calcified pleural plaques and 4% showed noncalcified pleural plaques (Coplu et al. 1996). Tremolite asbestos fibers were abundant in the whitewash material and in soil from the roads of Kureysler. Indoor air fiber concentrations in samples from a Kureysler house were 0.14 and 0.94 fiber/mL, before and after the floor was swept, respectively (Coplu et al. 1996). Tremolite fibers represented the predominant fiber type in bronchoalveolar lavage fluid samples from 64 Turkish subjects with expected environmental exposure to asbestos fibers; concentrations of fibers in the samples were similar to concentrations in samples from subjects with known occupational exposure to asbestos (Dumortier et al. 1998).

Northeastern Corsica is another region where environmental exposure to tremolite asbestos fibers has been associated with radiographic pleural abnormalities (Boutin et al. 1989; Rey et al. 1993, 1994). A retrospective survey of 1,721 chest radiographs of subjects from northern Corsica found prevalences of pleural plaques in 3.7% and 1.1% of subjects from northeastern and northwestern Corsica, respectively (Boutin et al. 1989). Northeastern Corsica, unlike the northwest, contains surface deposits of chrysotile and tremolite asbestos. Rey et al. (1993, 1994) reported that the incidence of bilateral pleural plaques was 41% in nonoccupationally exposed inhabitants of a village in northeastern Corsica where tremolite fiber concentrations in air samples ranged from 6 to 72 ng/m^3. In contrast, the incidence was 7.5% in inhabitants of a village with airborne tremolite concentrations <1 ng/m^3. Rey et al. (1993) suggested that the presence of pleural plaques is an indicator of exposure to fibers, but is not a precancerous lesion. It was noted that concomitant pleural plaques were found in only 43% of 14 Corsican cases of mesothelioma attributed to environmental exposure to tremolite asbestos fibers.

Results from a study of rats exposed repeatedly to high concentrations of tremolite asbestos confirm the capability of airborne tremolite to cause progressive pulmonary fibrosis (Davis et al. 1985a). Groups of 48 SPF male Wistar rats (AF/HAN strain) were exposed to a nominal concentration of 10 mg/m^3 tremolite asbestos, 7 hours/day, 5 days/week for 12 months starting at 10 weeks of age. The test material from Korea was determined to be about 95% tremolite asbestos (termed " 95% pure fibrous tremolite" by the authors) as confirmed by scanning electron microscopy and x-ray diffraction analysis with only minor amounts of iron and minor contamination with other silicate materials. Phase contrast microscopy of air samples determined the average fiber concentration (with lengths 5 μm) at about 1,600 fiber/mL. At 12 and 18 months after the start of exposure, 3 and 4 rats, respectively, were sacrificed and lungs were examined histologically for nonmalignant and malignant lesions (other tissues were also examined for tumors). Other rats were allowed to live until spontaneous death. At 12 months, average percentages of areas with nonmalignant lesions were 23% for peribronchiolar fibrosis, 35.2% for irregular alveolar wall thickening, and 0% for interstitial fibrosis. At 18 months, percentages of areas affected by these lesions were 13.4%, 27.7%, and 3%, respectively. None of the 12 rats dying between 27 and 29 months showed peribronchiolar fibrosis or irregular alveolar wall thickening, but 14.5% of lung area showed interstitial fibrosis. The fibrogenic activity of tremolite was also demonstrated in mice given single intratracheal instillations of suspensions of 5 mg Indian tremolite asbestos in saline (250 mg/kg body weight) (Sahu et al. 1975). Examination of lung tissue from mice sacrificed at 1, 2, 7, 15, 30, 60, 90, 120, and 150 days after instillation showed signs of a progressive fibrogenic reaction consisting of moderate proliferation of alveolar macrophages starting at 30 days, phagocytosis at 60 days, and moderate reticulinosis by 90 days. The fibrosis was classified as "grade I," compared with a more severe "grade II" fibrosis from similar exposure to amosite fiber suspensions. The results show that exposure of rats and mice to tremolite asbestos leads to a progressive development of pulmonary interstitial fibrosis after exposure has ceased. They are consistent with results from human studies indicating a long latency of development of pulmonary fibrosis from exposure to high concentrations of asbestos fibers. Animal studies designed to characterize exposure-response relationships for pulmonary fibrosis and varying concentrations of airborne tremolite asbestos were not located; neither were studies examining nonmalignant pleural changes in animals and exposure to airborne tremolite asbestos.

Lung Cancer. Elevated incidences of lung cancer and respiratory cancers have been observed in Libby, Montana, vermiculite workers exposed to tremolite asbestos. Results from studies of animals exposed to tremolite asbestos by inhalation and intratracheal instillation confirm that tremolite asbestos can induce lung cancer.

Mortality studies of Libby, Montana, vermiculite workers exposed to tremolite asbestos found excess mortalities from lung cancer (SMR=2.23; 95% CI=1.36, 3.45; 20 observed versus 9.0 expected; Amandus and Wheeler 1987) and respiratory cancer (SMR=2.45; 95% CI not reported; 23 observed deaths; expected deaths not reported; McDonald et al. 1986b). The respiratory cancer category included malignant neoplasms of the larynx, trachea, bronchus, lung, pleura, and mediastinum. Both studies found statistically significant relationships between increased risk for lung or respiratory cancer and increasing cumulative exposure. A precise tobacco smoking adjustment of the data could not be made, and some portion of the excess lung cancer occurrence may be reasonably attributed to smoking (Amandus and Wheeler 1987). Tobacco smoking, a potential confounding factor, was not addressed in the study by McDonald et al. (1986b). Comparative analysis of exposure-response relationships with other studies of asbestos-exposed workers indicated that the slope of the exposure-response regression was steeper in the Libby workers than in other workers exposed predominantly to chrysotile or to chrysotile, amosite, and crocidolite, but was less steep than the slope for workers exposed in asbestos textile plants (Amandus and Wheeler 1987).

In a mortality study of South Carolina vermiculite workers (McDonald et al. 1988), no increased risk for lung cancer was found. McDonald et al. (1988) attributed the apparent absence of cancer effect in these vermiculite miners and millers to the small number of subjects in the study and the low levels of airborne fibers at the South Carolina workplace relative to the Libby, Montana, mine and mill. As discussed earlier, this source of vermiculite does not appear to contain significant quantities of amphibole asbestos (Atkinson et al. 1982).

Lung tumors were found in 18/39 SPF male Wistar rats (AF/HAN strain) exposed to 10 mg/m^3 Korean tremolite asbestos for 12 months and allowed to live until spontaneous death occurred (Davis et al. 1985a). Rats with tumors included 2 with benign and 16 with malignant tumors. No lung tumors were found in a concomitant control group of 36 nonexposed rats (Davis et al. 1985a). Primary benign or malignant lung tumors were found in 1/38 (adenoma) and 3/37 (1 adenoma, 1 adenocarcinoma, and 1 squamous cell carcinoma) female Wistar rats given 10 or 20 twice weekly intratracheal instillations of suspensions of 0.5 mg "fibrous" tremolite in saline ($7x10^7$ or $30x10^7$ total fibers with length >5 μm, diameter <2 μm, and length:width ratio >5:1) (Pott et al. 1994). The test material in this study was not further characterized with respect to asbestiform or nonasbestiform habit. After treatment, the rats were allowed to live until spontaneous death. No lung tumors were found in 79 control rats instilled with saline. Pott et al. (1994) speculated that the lack of a marked lung carcinogenic response in their study was due to insufficient numbers of tremolite fibers instilled.

Mesothelioma. Elevated incidences of mesotheliomas have been observed in Libby, Montana, vermiculite workers exposed to tremolite asbestos and in inhabitants of rural villages in Greece, Corsica, and Turkey where tremolite-asbestos-rich surface deposits exist or where tremolite-asbestos-containing whitewashes were domestically produced and used to paint interior walls. Results from studies of animals exposed to tremolite asbestos by intrapleural implantation, intraperitoneal injection, and inhalation confirm that tremolite asbestos can induce mesothelioma.

In the cohort mortality studies of Libby, Montana, vermiculite workers exposed to tremolite asbestos, mesotheliomas were noted in 4 of the 165 deaths (proportionate mortality ratio [PMR] = 2.4%) studied by McDonald et al. (1986b) and 2 of the 161 deaths (PMR = 1.2%) studied by Amandus and Wheeler (1987). No mesotheliomas were identified among the 51 deaths in the cohort mortality study of vermiculite workers in a South Carolina mine and mill where airborne fiber concentrations were estimated to be much lower than in the Libby, Montana, workplaces (McDonald et al. 1988). Cohort mortality studies of other groups of vermiculite miners and millers were not located.

Cases of mesotheliomas have been reported among inhabitants of villages in the Metsovo region of Greece where whitewash containing tremolite asbestos was domestically produced and used to paint interior walls (Constantopoulos et al. 1987b, 1991; Langer et al. 1987; Sakellariou et al. 1996). Six pleural mesotheliomas were reported among 600 deaths (about 1%) that occurred in four of these villages between 1981 and 1985 (Constantopoulos et al. 1987b; Langer et al. 1987). Constantopoulos et al. (1987b) noted that the incidence of mesothelioma deaths in the Metsovo region between 1981 and 1985 was about 300 times greater than expected in a non-asbestos-exposed population. Sakellariou et al. (1996) later reported that eight cases were recorded in the Metsovo region between 1980 and 1984 and that six cases were recorded for the 1985–1994 period. Sakellariou et al. (1996) proposed that the incidence of pleural mesothelioma may be decreasing as the use of the tremolite–asbestos whitewash is diminishing.

Other regions in which cases of mesothelioma have been attributed to environmental exposure to tremolite asbestos (not occupational exposure) include northeastern Corsica, a region with abundant surface deposits rich in tremolite fibers (Magee et al. 1986; Rey et al. 1993), the island of Cyprus (McConnochie et al. 1987), regions of New Caledonia (Luce et al. 1994, 2001), and regions of rural Turkey where tremolite-asbestos-containing whitewashes have been used domestically (Baris et al. 1988a, 1988b; Erzen et al. 1991; Metintas et al. 1999; Schneider et al. 1998; Yazicioglu et al. 1980).

Increased incidences of pleural tumors resembling human mesotheliomas have been observed in rats (Stanton et al. 1981; Wagner et al. 1982) and hamsters (Smith et al. 1979) exposed to tremolite asbestos by intrapleural implantation, in rats exposed to tremolite asbestos or actinolite asbestos samples by intraperitoneal injection (Davis et al. 1991; Pott et al. 1989; Roller et al. 1996, 1997), and in rats exposed to airborne tremolite asbestos (Davis et al. 1985a). Increases in most of these studies were statistically significant.

For example, pleural fibrosarcomas resembling human mesotheliomas developed in 22/28 (78.6%) and 21/28 (75%) female Osborne-Mendel rats within 2 years of intrapleurally implanting 40 mg of 2 tremolite asbestos samples in gelatin, compared with 17/598 (2.8%) control rats implanted with gelatin (Stanton et al. 1981)[4]. Percentages of fibers in the 2 tremolite asbestos samples with lengths >4 μm were 34% and 31% and diameters <2.5 μm were 100% and 94%. In another study, mesotheliomas were found in 36/36, 35/36, 32/33, and 24/36 rats given single 10-mg intraperitoneal doses of four samples of tremolite asbestos and allowed to live until spontaneous death (Davis et al. 1991). Respective median survival time for these groups of AF/HAN rats were 301, 365, 428, and 755 days, indicating some variance in tumor-development period. Numbers of fibers ($x10^5$) with length 8 μm and diameter <0.25 μm in 1 mg of these samples were 121, 8, 48, and 1, respectively. Mesotheliomas developed in only 4/33 and 2/36 rats given similar injections of two samples of tremolite that did not have as distinct an asbestiform morphology (no fibers with length 8 μm and diameter <0.25 μm were detected, although some fibers were detected with length 8 μm and diameter >0.25 μm) (Davis et al. 1991). Mesotheliomas also were found in 2/39 SPF male Wistar (AF/HAN strain) rats exposed by inhalation to 10 mg/m^3 Korean tremolite asbestos for 12 months, but none were found in 36 control rats (Davis et al. 1985a).

Overall Health Effects Weight of Evidence Studies of workers exposed to airborne dusts of Libby, Montana, vermiculite containing tremolite asbestos provide strong evidence that exposure to high levels of airborne tremolite asbestos can lead to increased risk of structural changes in the lung and pleura including pulmonary fibrosis, pleural calcification, and pleural wall thickening (Amandus et al. 1987b; Lockey et al. 1984; McDonald et al. 1986a) and of death from nonmalignant respiratory disease (Amandus and Wheeler 1987; McDonald et al. 1986b). Additional observations adding to the evidence

---

[4] In the Stanton et al. (1981) experiments, seven samples of refined talc from different sources were tested. No malignancies were found in 6 of the talc-exposed groups of rats, including one group exposed to talc containing significant concentrations of particles with structures having lengths > 8 μm and diameters 0.25 μm. The incidence of rats with pleural sarcomas in the other talc-exposed group (1/26) was not significantly elevated compared with the incidence in a combined control group that included untreated rats and rats implanted with noncarcinogenic material.

that long-term exposure to airborne tremolite fibers can lead to the development of nonmalignant changes in the lung and pleura include:

> high prevalences of pleural calcification among residents of villages in Greece (Bazas 1987; Bazas et al. 1985; Constantopoulos et al. 1985, 1987a, 1991), Turkey (Baris et al. 1988a; Coplu et al. 1996; Dumortier et al. 1998; Metintas et al. 1999; Yazicioglu et al. 1980), and Corsica (Boutin et al. 1989; Rey et al. 1993, 1994) where whitewashes containing tremolite asbestos have been used domestically or where there are abundant surface deposits rich in tremolite asbestos, and progressive pulmonary fibrogenic reactions in the lungs of rats and mice after exposure to tremolite asbestos by inhalation or intratracheal instillation (Davis et al. 1985a; Sahu et al. 1975).

Evidence that repeated exposure to airborne tremolite asbestos can lead to increased risk for the development of lung cancer includes observations of statistically significantly increased rates of mortality from lung cancer in groups of Libby Montana vermiculite workers compared with rates for the general population (Amandus and Wheeler 1987; McDonald et al. 1986b), statistically significant relationships between cumulative fiber exposure measures and prevalence of lung or respiratory cancer among Libby vermiculite workers (Amandus and Wheeler 1987; McDonald et al. 1986b), and increased incidences of lung tumors in rats exposed to tremolite asbestos by inhalation (Davis et al. 1985a) or intratracheal instillation (Pott et al. 1994). The weight of the human evidence for tremolite asbestos-induced lung cancer is limited by the inability to adjust for likely confounding factors from smoking in the Libby vermiculite workers.

There is a causal relationship between long-term exposure to airborne tremolite asbestos and mesothelioma, which is a rare fatal cancer accounting for 2.87 deaths per million within the U.S. white male general population in 1996 (NIOSH 1999). The evidence includes elevated prevalences of mesothelioma deaths (of about 1/100 to 2/100) among groups of Libby, Montana, vermiculite workers (Amandus and Wheeler 1987; McDonald et al. 1986b), among residents of Greek (Constantopoulos et al. 1987b, 1991; Langer et al. 1987; Sakellariou et al. 1996), Turkish (Baris et al. 1988a, 1988b; Erzen et al. 1991; Metintas et al. 1999; Schneider et al. 1998; Yazicioglu et al. 1980), and New Caledonia (Luce et al. 1994, 2001) villages that used tremolite-asbestos whitewashes on interior walls, and in regions of northeastern Corsica and Cyprus that have abundant surface deposits of tremolite asbestos (Magee et al. 1986; McConnochie et al. 1987; Rey et al. 1993). Strong supporting evidence comes from animal studies showing increased incidences of pleural tumors resembling human mesotheliomas in rats (Stanton et al. 1981; Wagner et al. 1982) and hamsters (Smith et al. 1979) exposed to tremolite asbestos by intrapleural

implantation, in rats exposed to tremolite asbestos or actinolite asbestos samples by intraperitoneal injection (Davis et al. 1991; Pott et al. 1989; Roller et al. 1996, 1997), and in rats exposed to airborne tremolite asbestos (Davis et al. 1985a).

Clinical Aspects of Diseases Associated with Exposure to Asbestos

Exposure to tremolite asbestos or other forms of asbestos can increase risks for developing pleural plaques, pleural thickening (i.e. pleural fibrosis), pleural effusions, interstitial lung fibrosis, lung cancer, and mesothelioma.

Asbestos-related pleural abnormalities have been commonly associated with asbestos-related lung parenchyma lesions, but the American Thoracic Society (1986) noted that they should be diagnosed separately because "there are differences between pleural and parenchymal fibrosis in epidemiology, clinical features, and prognosis." Asbestos-related pleural plaques have been described as "fibrohyaline nodular lesions, most often on the parietal pleura, but also on the diaphragmatic pleura and less frequently on the pericardium" (Mossman and Gee 1989).

Unlike people with pleural plaques alone, who do not have impaired pulmonary functions or symptoms such as chest pain, persons with asbestos-related pleural thickening commonly experience symptoms and have impaired pulmonary function (American Thoracic Society 1986). Studies of groups of modern asbestos workers, who likely were exposed to lower airborne concentrations of asbestos fibers than workers in the first half of the twentieth century, found that the prevalence of pleural abnormalities (most often plaques) is often as high as 10 times higher than the prevalence of parenchymal abnormalities (Becklake 1994; Mossman and Gee 1989; Orlowski et al. 1994). Pleural effusions are early manifestations of inhalation exposure to high concentrations of asbestos; the fluid contains varying amounts of red blood cells, macrophages, lymphocytes, and mesothelial cells (American Thoracic Society 1986; Mossman and Gee 1989). Pleural effusions may be an early indication of mesothelioma and warrant further evaluation. Early identification of mesothelioma and intervention may increase chances of survival (ATSDR 2000).

The American Thoracic Society (1986) defines asbestosis as interstitial fibrosis of the lung parenchyma from exposure to asbestos. Studies of occupationally exposed patients who develop asbestosis have shown that latency periods of at least 15 years are common between the time of initial exposure to asbestos fibers and the onset of respiratory symptoms (American Thoracic Society 1986; Kamp and

Weitzman 1997; Mossman and Gee 1989). These symptoms include shortness of breath during physical exertion (i.e., exertional dyspnea), pleuritic chest pain, phlegm production, wheezing, and end-inspiratory crackles. Lung functions that can be decreased are lung volumes, pulmonary compliance, and diffusing capacity for carbon monoxide (DLCO) (Becklake 1994; Kamp and Weitzman 1997).

Clinical diagnosis of asbestosis is accomplished by a reliable exposure history; a latency period of at least 15–20 years since first exposure; chest radiographic evidence of parenchymal abnormalities (small, irregular opacifications of a profusion of 1/1 or greater); a restrictive pattern of lung impairment with a reduced forced vital capacity; reduced diffusing capacity; and bilateral late or pan inspiratory crackles (American Thoracic Society 1986). Chest radiography is the most important clinical tool for the diagnosis of asbestosis. Supplemental use of high resolution computerized tomography improves the sensitivity and accuracy of detecting parenchymal and pleural changes that can account for symptoms of respiratory distress and lung function deficits in patients (Aberle et al. 1988a, 1988b; Becklake 1994; Begin et al. 1992; Harkin et al. 1996; Klaas 1993). When clinically indicated, detection of asbestos bodies (fibers surrounded by a coat of iron and protein) in surgically removed lung parenchymal tissue with diffuse interstitial fibrosis confirms the diagnosis of asbestosis (American Thoracic Society 1986).

People who repeatedly inhale dusts with tremolite asbestos also are expected to have increased risk for lung cancer and malignant mesothelioma. Several studies of asbestos workers have found that smoking increases the risk of lung cancer in a greater than additive manner, but does not appear to increase the risk for mesothelioma (Berry et al. 1985; Hammond et al. 1979; McDonald et al. 1980; Selikoff et al. 1980).

Eighty to ninety percent of patients diagnosed with mesothelioma report a history of occupational or environmental exposure to some form of asbestos (Attanoos and Gibbs 1997; Bianchi et al. 1997; Colt 1997; Roggli et al. 1997). Malignant mesothelioma is an aggressive and fatal cancer that is most often located in the pleura (90%) and sometimes in the peritoneum (6%–10%) (Attanoos and Gibbs 1997; Kelley 1998). In a review of 1,690 cases of mesothelioma associated with occupational exposure to asbestos, the authors reported that the median period of latency between initial exposure and detection was 32 years; 99% and 96% of the cases had latency periods of more than 15 and 20 years, respectively (Lanphear and Buncher 1992).

Treatment options are few for patients diagnosed with asbestos-related nonmalignant lung or pleural disease. Preventing further exposure and ceasing any tobacco smoking activities are the most important steps individuals can take to minimize development of health problems. Once developed, these diseases

may remain stable or progress in severity in the absence of further exposure (Becklake 1994). The diseases rarely regress. Treatment options for patients diagnosed with asbestos-related cancer of the lung or pleura are restricted to resection and/or chemotherapy. One study suggests that subjects who stop smoking after already having been exposed to asbestos show some improvement in lung health (Waage et al. 1996), but long-term data for the effectiveness of cessation of smoking in large cohorts of asbestos-exposed individuals are not available.

Conclusions

- Tremolite is an amphibole mineral that most commonly exists in the earth's crust in forms that are nonasbestiform. Tremolite asbestos has only rarely been found in amounts sufficient for commercial use, but has been reported to occur at various sites throughout the world.

- Vermiculite deposits in the region of Libby, Montana, contain fibrous amphibole that is popularly called tremolite asbestos. Although scientists have called this mineral by various names, there is agreement that exposure to the mineral increased the risk of nonmalignant respiratory and pleural disorders, lung cancer, and mesothelioma in Libby mine and mill workers. The mine has been closed since 1990, and access to the sites is restricted.

- Exposure to all types of asbestos can increase the risk of developing lung cancer, malignant mesothelioma, and nonmalignant respiratory and pleural effects, including pulmonary interstitial fibrosis (asbestosis), pleural plaques, pleural calcification, and pleural thickening. Asbestos-exposed smokers have greater than additive risks for lung cancer and asbestosis than do asbestos-exposed nonsmokers.

- Important determinations of asbestos toxicity include exposure concentration, duration, fiber dimensions, and fiber durability. There is animal and human evidence that long fibers are retained in the lungs for longer periods than short fibers and that amphibole fibers, such as tremolite asbestos, are retained longer than chrysotile fibers. Short and long fibers may contribute to the pathogenesis of inflammation, fibrosis, and cancer in humans, but their relative importance is uncertain.

- Latency periods for the development of asbestos-related nonmalignant respiratory effects are usually 15–40 years from the time of initial exposure to asbestos.

- The latency periods are generally 20 years or more for lung cancer and 30 years or more for mesothelioma due to asbestos exposure.

- Occupational exposure to asbestos may occur in workers involved in mining, milling, and handling of certain sources of chrysotile and vermiculite ores; in exfoliating vermiculite that contains tremolite asbestos; and in mining, milling, and handling of other ores and rocks that may contain tremolite asbestos. Residents who live close to mining, milling, or manufacturing sites that involve tremolite asbestos-containing-material may be potentially exposed to higher levels of airborne tremolite asbestos than levels in general ambient air.

- Asbestos may be released to indoor or outdoor air as a result of the disturbance of asbestos-containing building materials such as insulation, fire-proofing material, dry wall, and ceiling and floor tile. Amphibole asbestos has been found in some sources of vermiculite that has been used as home and building insulation. Workers or homeowners involved in demolition work or asbestos removal, or in building or home maintenance, repair, and remodeling, potentially can be exposed to higher levels of airborne asbestos than levels in general ambient air. In general, exposure may occur only when the asbestos-containing material is disturbed in some way to release asbestos fibers into the air. When asbestos-containing materials are solidly embedded or contained, exposure will be negligible.

- Recently, small amounts of amphibole asbestos have been found in some samples of vermiculite-containing consumer garden products and in some talc-containing crayons. Consumers can reduce possible exposure by limiting the production of dusts when using the garden products. The risk that children might be exposed to asbestos fibers through inhalation or ingestion of crayons containing asbestos and transitional fibers is extremely low. The U.S. manufacturers of these crayons, however, have agreed to eliminate talc from their products in the near future.

- The combined use of light microscopy, electron microscopy (transmission and scanning), and x-ray dispersive methods in analyzing air and/or bulk material samples offers the most accurate approach to estimating airborne asbestos concentrations.

- Clinical diagnostic methods for determining exposure and effects of asbestos include chest radiography, pulmonary function tests, and high resolution computerized tomography.

Microscopic detection of asbestos bodies in autopsied or biopsied lung tissue can be used to confirm exposure when tissue is available.

- Pleural effusions are early manifestations of inhalation exposure to high concentrations of asbestos. Pleural effusions may be an early indication of mesothelioma and warrant further evaluation. Early identification of mesothelioma and intervention may increase chances of survival.

- Additional research may help to develop therapeutic methods to interfere with the development of nonmalignant lung and pleural disorders, and to cause the disorders to regress once they are established. Such research may include studies on the mechanism of asbestos-related disease to provide further understanding of how persistent production of reactive oxygen or nitrogen species and persistent inflammatory cellular responses precisely interact.

Recommendations

Prevention of exposure and cessation of any tobacco smoking activities are the most important steps that individuals can take to prevent or minimize the development of asbestos-related health problems.

People who were exposed to asbestos and who smoke are expected to be unusually susceptible to asbestos-related lung cancer and asbestosis and are encouraged to cease smoking. Studies of asbestos workers indicate that asbestos-exposed smokers have greater than additive risks for lung cancer and asbestosis than asbestos-exposed nonsmokers. Although the mechanism of this interaction is poorly understood, one possible mechanism that has received some support from research is that smoking can decrease the clearance of asbestos fibers from the lung by impairing mucociliary action and macrophage activity (see ATSDR 2001a for review).

Individuals residing or working in buildings with insulation or other building materials that may potentially contain asbestiform minerals (for example, vermiculite from the Libby Montana mine) are encouraged to ensure that the insulation material is solidly contained and not able to be disturbed and become airborne. If the material is to be removed, special procedures must be followed that minimize the generation of dust and specify appropriate locations for disposal. Individuals can obtain information about asbestos removal and disposal procedures from the 10 regional offices of the EPA.

Further evaluation of the progression of disease associated with exposure to Libby, Montana vermiculite contaminated with asbestos is warranted. EPA, ATSDR, and other agencies currently are investigating exposure levels that Libby, Montana, residents (including children) who were not employed in the vermiculite mines and mills may have and are experiencing. In addition, ATSDR is currently conducting medical testing of individuals potentially exposed to fibrous amphibole associated with vermiculite in Libby, Montana.

References (* indicates cited in text)

Aalto M, Heppleston AG. 1984. Fibrogenesis by mineral fibres: an in-vitro study of the roles of the macrophage and fibre length. Br J Exp Pathol 65:91-99.

*Aberle DR, Gamsu G, Ray CS, et al. 1988a. Asbestos-related pleural and parenchymal fibrosis: Detection with high-resolution CT. Radiology 166:729-734.

*Aberle DR, Gamsu G, Ray CS. 1988b. High-resolution CT of benign asbestos-related diseases: Clinical and radiographic correlation. AJR Am J Roentgenol 151:883-891.

ACGIH. 1992. Asbestos. In: Documentation of threshold limit values. American Conference of Governmental Industrial Hygienists. Cincinnati, OH, 89-94.

*ACGIH. 1996. Particulates (insoluble) Not Otherwise Classified. In: Documentation of the threshold limit values and biological exposure indices. Supplement. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

*ACGIH. 1998. Asbestos, all forms. In: Documentation of threshold limit values. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

*Addison J, Davies LST. 1990. Analysis of amphibole asbestos in chrysotile and other minerals. Ann Occup Hyg 34(2):159-175.

*Albin M, Pooley FD, Stromberg U, et al. 1994. Retention patterns of asbestos fibres in lung tissue among asbestos cement workers. Occup Environ Med 51:205-211.

*Amandus HE, Wheeler R. 1987. The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part II. Mortality. Am J Ind Med 11:15-26.

*Amandus HE, Wheeler R, Jankovic J, et al. 1987a. The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part I. Exposure estimates. Am J Ind Med 11:1-14.

*Amandus HE, Althouse R, Morgan WKC, et al. 1987b. The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part III. Radiographic findings. Am J Ind Med 11:27-37.

*American Thoracic Society. 1986. The diagnosis of nonmalignant diseases related to asbestos. Am Rev Respir Dis 134: 363-368.

*American Thoracic Society. 1990. Health effects of tremolite. Prepared by a subcommittee of the American Thoracic Society Scientific Assembly on Environmental and Occupational Health. Am Rev Respir Dis 142(6):1453-1458.

*Amethyst Galleries. 1999. The mineral tremolite. http://mineral.galleries.com/minerals/silicate/tremolit/tremolit.htm

Andrion A, Bosia S, Paoletti L, et al. 1994. Malignant peritoneal mesothelioma in a 17-year-old boy with evidence of previous exposure to chrysotile and tremolite asbestos. Hum Pathol 25:617-622.

Athanasiou K, Constantopoulos SH, Rivedal E, et al. 1992. Metsovo-tremolite asbestos fibres: *in vitro* effects on mutation, chromosome aberration, cell transformation and intercellular communication. Mutagenesis 7(5):343-347.

*Atkinson GR, Rose D, Thomas K, Jones D, Chatfield EJ, Going JE. 1982. Collection, analysis and characterization of vermiculite samples for fiber content and asbestos contamination. MRI report for EPA, project No. 4901-A32 under EPA contract 68-01-5915. F. Kutz, EPA Project officer.

*ATSDR. 2000. ATSDR/NCI workshop on asbestos-related therapies: summary report. May 8, 2000, Washington, DC.

*ATSDR. 2001a. Toxicological profile for asbestos. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Atlanta, GA.

*ATSDR 2001b. Preliminary findings of medical testing of individuals potentially exposed to asbestiform minerals associated with vermiculite in Libby, Montana: an interim report for community health planning. February 22, 2001. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Atlanta, GA.

*Attanoos RL, Gibbs AR. 1997. Pathology of malignant mesothelioma. Histopathology 30:403-417.

*Baris YI, Bilir N, Artvinli M, et al. 1988a. An epidemiological study in an Anatolian village environmentally exposed to tremolite asbestos. Br J Ind Med 45:838-840.

*Baris YI, Artvinli M, Sahin AA, et al. 1988b. Non-occupational asbestos related chest diseases in a small Anatolian village. Br J Ind Med 45:841-842.

*Bazas T. 1987. Pleural effects of tremolite in north-west Greece. Lancet 1(8548):1490-1491.

Bazas T, Bazas B, Kitas D, et al. 1981. Pleural calcification in north-west Greece. [Letter]. Lancet II:254.

*Bazas T, Oakes D, Gilson JC, et al. 1985. Pleural calcification in northwest Greece. Environ Res 38:239-247.

*Becklake MR. 1994. Symptoms and pulmonary functions as measures of morbidity. Ann Occup Hyg 38(4):569-580.

*Begin R, Gauthier J-J, Desmeules M, et al. 1992. Work-related mesothelioma in Quebec, 1967-1990. Am J Ind Med 22:531-542.

*Berman DW, Crump KS, Chatfield EJ, et al. 1995. The sizes, shapes, and mineralogy of asbestos structures that induce lung tumors or mesothelioma in AF/HAN rats following inhalation. (Errata attached). Risk Anal 15:181-195.

*Berry G, Newhouse ML, Antonis P. 1985. Combined effect of asbestos and smoking on mortality from lung cancer and mesothelioma in factory workers. Br J Ind Med 42:12-18.

*Bianchi C, Brolo A, Ramani L, et al. 1997. Pleural plaques as risk indicators for malignant pleural mesothelioma: a necropsy-based study. Am J Ind Med 32:445-449.

*Bignon J, Jaurand MC. 1983. Biological *in vitro* and *in vivo* responses of chrysotile versus amphiboles. Environ Health Perspect 51:73-80.

*BOHS. 1968. Hygiene standards for chrysotile asbestos dust. Ann Occup Hyg 11:47-69.

*Boutin G, Viallat JR, Steinbauer J, et al. 1989. Bilateral pleural plaques in Corsica: a marker of non-occupational asbestos exposure. IARC Sci Publ 90:406-410.

Brown DP, Dement JM, Wagoner JK. 1979. Mortality patters among miners and millers occupationally exposed to asbestiform talc. In: Lemen R, Dement JM, eds. Dust and disease: proceedings of the conference on occupational exposures to fibrous and particulate dust and their extension into the environment, 1977, Washington, DC. Park Forest South, IL: Pathotox Publishers, Inc., 317-324.

Brown GM, Cowie H, Davis JMG, et al. 1986. *In vitro* assays for detecting carcinogenic mineral fibres: a comparison of two assays and the role of fibre size. Carcinogenesis 7(12):1971-1974.

*Camus M, Siemiatycki J, Meek B. 1998. Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. N Engl J Med 338(22):1565-1571.

*Case BW. 1991. Health effects of tremolite: now and in the future. Ann N Y Acad Sci 643:491-504.

*Case BW. 1994. Biological indicators of chrysotile exposure. Ann Occup Hyg 38:503-518.

Case BW, Dufresne A. 1997. Asbestos, asbestosis, and lung cancer: observations in Quebec chrysotile workers. Environ Health Perspect Suppl 5:1113-1119.

*Case BW, Dufresne A, McDonald AD, et al. 2000. Asbestos fiber type and length in lungs of chrysotile textile and production workers: fibers longer than 18 μm. Inhal Toxicol 12:411-418.

Case BW, Sebastien P. 1987. Environmental and occupational exposures to chrysotile asbestos: a comparative microanalytic study. Arch Environ Health 42(4):185-191.

*Churchill RK, Higgins CT, Hill RL. 2001. A pilot project to map areas likely to contain natural occurrences of asbestos – El Dorado County, California. Poster presentation. 2001 Asbestos Health Effects Conference. Sponsored by U.S. Environmental Protection Agency. May 24-25, 2001. San Francisco, CA.

*Churg A. 1988. Chrysotile, tremolite, and malignant mesothelioma in man. Chest 93:621-628.

*Churg A. 1994. Deposition and clearance of chrysotile asbestos. Ann Occup Hyg 38(4):625-633.

Churg A, DePaoli L. 1988. Clearance of chrysotile asbestos from human lung. Exp Lung Res 14:567-574.

Churg A, Wiggs B. 1986. Fiber size and number in workers exposed to processed chrysotile asbestos, chrysotile miners, and the general population. Am J Ind Med 9:143-152.

*Churg A, Wright JL. 1989. Fibre content of lung in amphibole- and chrysotile-induced mesothelioma: implications for environmental exposure. IARC Sci Publ 90:314-318.

*Churg A, Wright JL. 1994. Persistence of natural mineral fibers in human lungs: an overview. Environ Health Perspect Suppl 102(5):229-233.

*Churg A, Wright J, Wiggs B, et al. 1990. Mineralogic parameters related to amosite asbestos-induced fibrosis in humans. Am Rev Respir Dis 142:1331-1336.

*Churg A, Wright JL, Vedal S. 1993. Fiber burden and patterns of asbestos-related disease in chrysotile miners and millers. Am Rev Respir Dis 148:25-31.

Chuwers P, Barnhart S, Blanc P, et al. 1997. The protective effect of beta-carotene and retinol on ventilatory function in an asbestos-exposed cohort. Am J Respir Crit Care Med 155:1066-1071.

*Coin PG, Roggli VL, Brody AR. 1992. Deposition, clearance, and translocation of chrysotile asbestos from peripheral and central regions of the rat lung. Environ Res 58:97-116.

*Colt HG. 1997. Mesothelioma: epidemiology, presentation, and diagnosis. Semin Respir Med 18:353-361.

*Constantopoulos SH, Goudevenos JA, Saratzis N, et al. 1985. Metsovo lung: pleural calcification and restrictive lung function in northwestern Greece. Environmental exposure to mineral fiber as etiology. Environ Res 38:319-331.

*Constantopoulos SH, Saratzis NA, Kontogiannis D, et al. 1987a. Tremolite whitewashing and pleural calcifications. Chest 92:709-712.

*Constantopoulos SH, Malamou-Mitsi VD, Goudevenos JA, et al. 1987b. High incidence of malignant pleural mesothelioma in neighboring villages of northwestern Greece. Respiration 51:266-271.

*Constantopoulos SH, Theodoracopoulos P, Dascalopoulos G, et al. 1991. Metsovo lung outside Metsovo: endemic pleural calcifications in the ophiolite belts of Greece. Chest 99:1158-1161.

*Constantopoulos SH, Dalavanga YA, Sakellariou K, et al. 1992. Lymphocytic alveolitis and pleural calcifications in nonoccupational asbestos exposure. Am Rev Respir Dis 146:1565-1570.

*CPSC. 2000. CPSC staff report on asbestos fibers in children's crayons. U.S. Consumer Product Safety Commission. Washington DC. http://www.cpsc.gov/LIBRARY/FOIA/Foia00/os/crayons.pdf

*Coplu L, Dumortier P, Demir AU, et al. 1996. An epidemiological study in an Anatolian village in Turkey environmentally exposed to tremolite asbestos. J Environ Pathol Toxicol Oncol 15(2-4):177-182.

*Crane DT. 2000. Background information regarding the analysis of industrial talcs. June 12, 2000 Report. U.S. Department of Labor, Occupational Safety and Health Administration, Salt Lake Technical Center, Salt Lake City, UT.

Davis JMG. 1983. Carcinogenic effect of mineral fibers in inhalation studies. VDI-Ber 475:241-246.

*Davis JMG. 1989. Mineral fibre carcinogenesis: experimental data relating to the importance of fibre type, size, deposition, dissolution and migration. IARC Sci Publ 90:33-45.

Davis JMG, Beckett ST, Bolton RE, et al. 1980. The effects of intermittent high asbestos exposure (peak dose levels) on the lungs of rats. Br J Exp Pathol 61:272-280.

*Davis JMG, Addison J, Bolton RE, et al. 1985a. Inhalation studies on the effects of tremolite and brucite dust in rats. Carcinogenesis 6(5):667-674.

Davis JM, Bolton RE, Cowie H, et al. 1985b. Comparisons of the biological effects of mineral fibre samples using in vitro and in vivo assay systems. NATO ASI Ser G 3:405-411.

*Davis JMG, Addison J, McIntosh C, et al. 1991. Variations in the carcinogenicity of tremolite dust samples of differing morphology. Ann N Y Acad Sci 643:473-490.

De Klerk NH, Musk AW, Ambrosini GL, et al. 1998. Vitamin A and cancer prevention II: comparison of the effects of retinol and beta-carotene. Int J Cancer 75:362-367.

Dement JM, Brown DP. 1994. Lung cancer mortality among asbestos textile workers: a review and update. Ann Occup Hyg 38:525-532.

Dement JM, Brown DP. 1998. Cohort mortality and case-control studies of white male chrysotile asbestos textile workers. J Clean Technol Environ Toxicol Occup Med 7(4):413-419.

Dement JM, Brown DP, Okun A. 1994. Follow-up study of chrysotile asbestos textile workers: cohort mortality and case-control analyses. Am J Ind Med 26:431-447.

*De Vuyst P, Dumortier P, Jacobovitz D, et al. 1994. Environmental asbestosis complicated by lung cancer. Chest 105(5):1593-1595.

*Dodson RF, O'Sullivan M, Corn CJ, et al. 1997. Analysis of asbestos fiber burden in lung tissue from mesothelioma patients. Ultrastruct Pathol 21:321-336.

*Dodson RF, Williams MG, Huang J, et al. 1999. Tissue burden of asbestos in nonoccupationally exposed individuals from east Texas. Am J Ind Med 35:281-286.

*DOL. 1980. Asbestiform and/or fibrous minerals in mines, mills, and quarries. Washington, DC: U.S. Department of Labor, Mine Safety and Health Administration. IR 1111.

Dufresne A, Harrigan M, Masse S, et al. 1995. Fibers in lung tissues of mesothelioma cases among miners and millers of the township of Asbestos, Quebec. Am J Ind Med 27:581-592.

Dufresne A, Begin R, Masse S, et al. 1996. Retention of asbestos fibres in lungs of workers with asbestosis, asbestosis and lung cancer, and mesothelioma in Asbestos township. Occup Environ Med 53:801-807.

*Dumortier P, Coplu L, de Maertelaer V, et al. 1998. Assessment of environmental asbestos exposure in Turkey by bronchoalveolar lavage. Am J Respir Crit Care Med 158:1815-1824.

Elmes P. 1994. Mesotheliomas and chrysotile. Ann Occup Hyg 38(4):547-553.

*EPA. 1986. Airborne asbestos health assessment update. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environment Assessment. EPA/600/8-84/003F.

*EPA. 2000. Sampling and analysis of consumer garden products that contain vermiculite. U.S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances. EPA 744-R-00-010. http://www.epa.gov/opptintr/asbestos/verm.htm

*Erzen C, Eryilmaz M, Kalyoncu F, et al. 1991. CT findings in malignant pleural mesothelioma related to nonoccupational exposure to asbestos and fibrous zeolite (erionite). J Comput Assist Tomogr 15(2):256-260.

Finkelstein MM, Dufresne A. 1999. Inferences on the kinetics of asbestos deposition and clearance among chrysotile miners and millers. Am J Ind Med 35:401-412.

*Frank AL, Dodson RF, Williams MG. 1998. Carcinogenic implications of the lack of tremolite in UICC reference chrysotile. Am J Ind Med 34:314-317.

Gamble JF, Fellner W, Dimeo MJ. 1979. An epidemiologic study of a group of talc workers. Am Rev Respir Dis 119:741-753.

*Hammond EC, Selikoff IJ, Seidman H. 1979. Asbestos exposure, cigarette smoking and death rates. Ann N Y Acad Sci 330:473-490.

*Harkin TJ, McGuinness G, Goldring R, et al. 1996. Differentiation of the ILO boundary chest roentgenograph (0/1 to 1/0) in asbestosis by high-resolution computed tomography scan, alveolitis, and respiratory impairment. J Occup Environ Med 38:46-52.

*HEI. 1991. Health Effects Institute. Asbestos in public and commercial buildings: a literature review and synthesis of current knowledge. Report of the asbestos literature review panel. Cambridge, MA: Health Effects Institute.

*Henderson DW, de Klerk NH, Hammar SP, et al. 1997. Asbestos and lung cancer: is it attributable to asbestosis or to asbestos fiber burden? In: Corrin B, ed. Pathology of lung tumors. New York, NY: Churchill Livingstone, 83-118.

*Hessel PA, Sluis-Cremer GK. 1989. X-ray findings, lung function, and respiratory symptoms in black South African vermiculite workers. Am J Ind Med 15:21-29.

*Hillerdal G, Henderson GW. 1997. Asbestos, asbestosis, pleural plaques and lung cancer. Scand J Work Environ Health 23:93-103.

*Hodgson JT, Darnton A. 2000. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg 44(8):565-601.

*Hughes JM. 1994. Human evidence: lung cancer mortality risk from chrysotile exposure. Ann Occup Hyg 38(4):555-560.

*Hughes JM, Weill H. 1991. Asbestosis as a precursor of asbestos related lung cancer: results of a prospective mortality study. Br J Ind Med 48:229-233.

*IARC. 1987a. Asbestos and certain asbestos compounds. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Chemicals, industrial processes and industries associated with cancer in humans. IARC monographs, Vols 1 to 42. IARC monographs, supplement 7. Lyon, France: World Health Organization, International Agency for Research on Cancer, 29-33, 56-58.

IARC. 1987b. Talc. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Silica and some silicates. IARC monographs, volume 42. Lyon, France: World Health Organization, International Agency for Research on Cancer, 185-224.

ILO. 1989. International Labour Office. Guidelines for the use of the ILO international classification of radiographs of pneumoconiosis, revised edition. Geneva, Switzerland: ILO Occupational Safety and Health Series. No 22.

*Jackson JA. 1997. Glossary of Geology. Fourth Edition. American Geological Institute, Alexandria, VA.

*Jolicoeur CR, Alary JF, Sokov A. 1992. Asbestos. In: Kroschwitz JI, Howe-Grant M, ed. Kirk-Othmer encyclopedia of chemical technology. New York: John Wiley & Sons, 659-688.

*Jones RN , Hughes JM, Weill H. 1996. Asbestos exposure, asbestosis, and asbestos-attributable lung cancer. Thorax 51: S9-S15.

*Kamp DW, Weitzman SA. 1997. Asbestosis: clinical spectrum and pathogenic mechanisms. Proc Soc Exp Biol Med 214:12-26.

*Kamp DW, Weitzman SA. 1999. The molecular basis of asbestos induced lung injury. Thorax 54:638-652.

*Kamp DW, Graceffa P, Pryor WA, et al. 1992. The role of free radicals in asbestos-induced diseases. Free Radic Biol Med 12:293-315.

Kamp DW, Dunne M, Dykewicz MS, et al. 1993. Asbestos-induced injury to cultured human pulmonary epithelial-like cells: role of neutrophil elastase. J Leukoc Biol 54:73-80.

*Kelley J. 1998. Occupational lung disease caused by asbestos, silica, and other silicates. In: Baum GL, Crapo JD, Celli BR, et al., eds. Textbook pulmonary diseases. Philadelphia, PA: Lippincott-Raven, 659-682.

*Klaas VE. 1993. A diagnostic approach to asbestosis, utilizing clinical criteria, high resolution computed tomography, and gallium scanning. Am J Ind Med 23:801-809.

Kleinfeld M, Messite J, Kooyman O, et al. 1967a. Mortality among talc miners and millers in New York State. Arch Environ Health 14:663-667.

Kleinfeld M, Messite J, Kooyman O. 1967b. Mortality experience in a group of asbestos workers. Arch Environ Health 15:177-180.

Kleinfeld M, Messite J, Langer AM. 1973. A study of workers exposed to asbestiform minerals in commercial talc manufacture. Environ Res 6:132-143.

Kleinfeld M, Messite J, Zaki MH. 1974. Mortality experiences among talc workers: a follow-up study. J Occup Med 16:345-349.

*Landrigan PJ. 1998. Asbestos-still a carcinogen. N Engl J Med 338(22):1618-1619.

*Langer AM, Nolan RP. 1998. Asbestos in the lungs of persons exposed in the USA. Monaldi Arch Chest Dis 53(2):168-180.

*Langer AM, Nolan RP, Constantopoulos SH, et al. 1987. Association of Metsovo lung and pleural mesothelioma with exposure to tremolite-containing whitewash. Lancet 1(8539):965-967.

*Lanphear BP, Buncher CR. 1992. Latent period for malignant mesothelioma of occupational origin. J Occup Med 34(7):718-721.

*Lash TL, Crouch EAC, Green LC. 1997. A meta-analysis of the relation between cumulative exposure to asbestos and relative risk of lung cancer. Occup Environ Med 54:254-263.

*Leake BE. 1978. Nomenclature of amphiboles. Am Mineral 63: 1023-1052.

*Leake BE, Wooley AR, Arps CES, et al. 1997. Nomenclature of amphiboles: report of the subcommittee on amphiboles of the International Mineralogical Association, Commission on New Minerals and Mineral Names. Am Mineral 82: 1019-1037.

*Lee RJ, Van Orden DR, Corn M, et al. 1992. Exposure to airborne asbestos in buildings. Regul Toxicol Pharmacol 16:93-107.

*Lippmann M. 1994. Deposition and retention of inhaled fibres: effects on incidence of lung cancer and mesothelioma. Occup Environ Med 51:793-798.

*Lockey JE, Brooks SM, Jarabek AM, et al. 1984. Pulmonary changes after exposure to vermiculite contaminated with fibrous tremolite. Am Rev Respir Dis 129:952-958.

*Luce D, Brochard P, Quenel P, et al. 1994. Malignant pleural mesothelioma associated with exposure to tremolite. Lancet 344:1777.

*Luce D, Billon-Galland MA, Bugel I, et al. 2001. Environmental exposure to tremolite and respiratory cancer in New Caledonia (South Pacific). Poster presentation, 2001 Asbestos Health Effects Conference. Sponsored by U.S. Environmental Protection Agency. May 24-25, 2001. San Francisco, CA.

*Luster MI, Simeonova PP. 1998. Asbestos induces inflammatory cytokines in the lung through redox sensitive transcription factors. Toxicol Lett 102-103:271-275.

*Magee F, Wright JL, Chan N, et al. 1986. Malignant mesothelioma caused by childhood exposure to long-fiber low aspect ratio tremolite. Am J Ind Med 9:529-533.

*Mansinghka BK, Ranawat PS. 1996. Mineral economics and occupational health hazards of the asbestos resources of Rajathan. J Geol Soc India 47: 375-382.

McConnell EE, Rutter HA, Ulland BM, et al. 1983. Chronic effects of dietary exposure to amosite asbestos and tremolite in F344 rats. Environ Health Perspect 53:27-44.

*McConnochie K, Simonato L, Mavrides P, et al. 1987. Mesothelioma in Cyprus: the role of tremolite. Thorax 42:342-347.

McDonald AD, Case BW, Churg A, et al. 1997. Mesothelioma in Quebec chrysotile miners and millers: epidemiology and aetiology. Ann Occup Hyg 41(6):707-719.

*McDonald JC. 1998. Mineral fibre persistence and carcinogenicity. Ind Health 36:372-375.

*McDonald JC, McDonald AD. 1997. Chrysotile, tremolite and carcinogenicity. Ann Occup Hyg 41(6):699-705.

*McDonald JC, Liddell FDK, Gibbs GW, et al. 1980. Dust exposure and mortality in chrysotile mining, 1910-75. Br J Ind Med 37:11-24.

*McDonald JC, Sebastien P, Armstrong B. 1986a. Radiological survey of past and present vermiculite miners exposed to tremolite. Br J Ind Med 43:445-449.

*McDonald JC, McDonald AD, Armstrong B, et al. 1986b. Cohort study of mortality of vermiculite miners exposed to tremolite. Br J Ind Med 43:436-444.

*McDonald JC, McDonald AD, Sebastien P, et al. 1988. Health of vermiculite miners exposed to trace amounts of fibrous tremolite. Br J Ind Med 45:630-634.

*McDonald JC, Armstrong B, Case B, et al. 1989. Mesothelioma and asbestos fiber type. Evidence from lung tissue analysis. Cancer 63:1544-1547.

*McDonald JC, McDonald AD, Hughes JM. 1999. Chrysotile, tremolite and fibrogenicity. Ann Occup Hyg 43(7):439-442.

*Meeker GP, Brownfield IK, Clark RN, et al. 2001. The chemical composition and physical properties of amphibole from Libby, Montana: a progress report. Poster presentation, 2001 Asbestos Health Effects Conference. Sponsored by U.S. Environmental Protection Agency. May 24-25, 2001. San Francisco, CA.

*Metintas M, Ozdemir N, Hillerdal G, et al. 1999. Environmental asbestos exposure and malignant pleural mesothelioma. Respir Med 93:349-355.

*Moatamed F, Lockey JE, Parry WT. 1986. Fiber contamination of vermiculites: a potential occupational and environmental health hazard. Environ Res 41:207-218.

Mossman BT. 1990. *In vitro* studies on the biologic effects of fibers: correlation with *in vivo* bioassays. Environ Health Perspect 88:319-322.

*Mossman BT, Churg A. 1998. Mechanisms in the pathogenesis of asbestosis and silicosis. Am J Respir Crit Care Med 157:1666-1680.

*Mossman BT, Gee JBL. 1989. Asbestos-related diseases. N Engl J Med 320(26):1721-1730.

*Mossman B, Light W, Wei E. 1983. Asbestos: mechanisms of toxicity and carcinogenicity in the respiratory tract. Annu Rev Pharmacol Toxicol 23:595-615.

*Mossman BT, Bignon J, Corn M, et al. 1990. Asbestos: scientific developments and implications for public policy. Science 247:294-301.

*Mossman BT, Kamp DW, Weitzman SA. 1996. Mechanisms of carcinogenesis and clinical features of asbestos-associated cancers. Cancer Invest 14(5):466-480.

NIOSH. 1980. Occupational exposure to talc containing asbestos, morbidity, mortality, and environmental studies of miners and millers. Cincinnati, OH: U.S. National Institute for Occupational Safety and Health. NTIS PB80-193352.

NIOSH. 1986. Occupational respiratory diseases. Washington, DC: 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. 86-102.

*NIOSH. 1989. Fibers-method 9002. In: Manual of analytical methods, 3rd edition. Supplement. Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

*NIOSH. 1994a. Asbestos and other fibers by PCM. In: Manual of analytical methods, 4th edition. Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

*NIOSH. 1994b. Asbestos by TEM. In: Manual of analytical methods, 4th edition. Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

*NIOSH. 1999. Work-related lung disease surveillance report 1999. Washington, DC: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Respiratory Disease Studies. DHHS (NIOSH) Publication No. 96-134.

*NRC. 1984. National Research Council. Asbestiform fibers: nonoccupational health risks. Washington, DC: National Academy Press.

NTP. 1990. National Toxicology Program. Technical report on the toxicology and carcinogenesis studies of tremolite (CAS no. 14567-73-8) in Fischer 344 rats (feed study). Research Triangle Park, NC: U. S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH Publication No. 90-2531. NTP TR 277.

*NTP. 1993. National Toxicology Program. Toxicology and carcinogenesis studies of talc (CAS no. 14807-96-6) in Fischer 344/N rats and B6C3F1 mice. (Inhalation studies). Research Triangle Park, NC: U. S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH Publication No. 93-3152. NTP TR 421.

*NTP. 2001. National Toxicology Program. Asbestos: CAS No. 1332-21-4. In: Report on carcinogenicity, ninth edition. Revised January 2001. Research Triangle Park, NC: U.S. Department of Health and Human Services.

*Oberdorster G. 1994. Macrophage-associated responses to chrysotile. Ann Occup Hyg 38(4):601-615.

Okayasu R, Wu L, Hei TK. 1999. Biological effects of naturally occurring and man-made fibres: in vitro cytotoxicity and mutagenesis in mammalian cells. Br J Cancer 79(9/10):1319-1324.

Omenn GS, Goodman GE, Thornquist MD, et al. 1996a. Risk factors for lung cancer and for intervention effects in CARET, the beta-carotene and retinol efficacy trial. J Natl Cancer Inst 88(21):1550-1559.

Omenn GS, Goodman GE, Thornquist MD, et al. 1996b. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 334:1150-1155.

*Orlowski E, Pairon JC, Ameille J, et al. 1994. Pleural plaques, asbestos exposure, and asbestos bodies in bronchoalveolar lavage fluid. Am J Ind Med 26:349-358.

Osgood C, Sterling D. 1991. Chrysotile and amosite asbestos induce germ-line aneuploidy in drosophila. Mutat Res 261:9-13.

*OSHA. 1986. U.S. Department of Labor, Occupational Safety and Health Administration. Federal Register 51:22612-22790.

*OSHA. 1992. U.S. Department of Labor, Occupational Safety and Health Administration. Federal Register 57:7877-7878, 24310-24331, 49657-49661.

*OSHA. 1994. Occupational exposure to asbestos. U.S. Department of Labor, Occupational Safety and Health Administration. Federal Register 59(153):40964-41162.

*Pang TWS, Schonfeld-Starr RA, Patel K. 1989. An improved membrane filter technique for evaluation of asbestos fibers. Am Ind Hyg Assoc J 50(3):174-180.

*Paoletti L, Caiazza S, Donelli G, et al. 1984. Evaluation by electron microscopy techniques of asbestos contamination in industrial, cosmetic, and pharmaceutical talcs. Regul Toxicol Pharmacol 4:222-235.

Peto J, Seidman H, Selikoff IJ. 1982. Mesothelioma mortality in asbestos workers: implications for models of carcinogenesis and risk assessment. Br J Cancer 45:124-135.

Pooley FD. 1981. Mineralogy of asbestos: the physical and chemical properties of the dusts they form. Semin Oncol 8(3):243-249.

Pott F, Ziem U, Reiffer F-J, et al. 1987. Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats. Exp Pathol 32:129-152.

*Pott F, Roller M, Ziem U, et al. 1989. Carcinogenicity studies on natural and man-made fibres with the intraperitoneal test in rats. IARC Sci Publ 90:173-179.

*Pott F, Dungworth DL, Heinrich U, et al. 1994. Lung tumours in rats after intratracheal instillation of dusts. Ann Occup Hyg 38(Suppl. 1):357-363.

*Renner R. 2000. Asbestos in the air. Sci Am Feb:34.

*Rey F, Boutin C, Steinbauer J, et al. 1993. Environmental pleural plaques in an asbestos exposed population of northeast Corsica. Eur Respir J 6:978-982.

*Rey F, Boutin C, Viallat JR, et al. 1994. Environmental asbestotic pleural plaques in northeast Corsica: correlations with airborne and pleural mineralogic analysis. Environ Health Perspect 102(Suppl 5):251-252.

*Rödelsperger K, Woitowitz H-J, Brückel B, et al. 1999. Dose-response relationship between amphibole fiber lung burden and mesothelioma. Cancer Detect Prev 23(3):183-193.

*Rogers AJ, Leigh J, Berry G, et al. 1991. Relationship between lung asbestos fiber type and concentration and relative risk of mesothelioma. Cancer 67:1912-1920.

Roggli VL, Pratt PC, Brody AR. 1993. Asbestos fiber type in malignant mesothelioma: an analytical scanning electron microscopic study of 94 cases. Am J Ind Med 23:605-614.

Roggli VL, Pratt PC, Brody AR. 1994. Fiber potency vs. importance. Am J Ind Med 25:611-612.

*Roggli VL, Oury TD, Moffatt EJ. 1997. Malignant mesothelioma in women. In: Anatomic pathology. Chicago, Ill: American Society of Clinical Pathologists, 2:147-163.

Rohl AN, Langer AM, Selikoff IJ, et al. 1976. Consumer talcums and powders: mineral and chemical characterization. J Toxicol Environ Health 2:225-284.

Rohl AN, Langer AM, Selikoff IJ. 1977. Environmental asbestos pollution related to use of quarried serpentine rock. Science 196:1319-1322.

*Roller M, Pott F, Kamino K, et al. 1996. Results of current intraperitoneal carcinogenicity studies with mineral and vitreous fibres. Exp Toxicol Pathol 48:3-12.

*Roller M, Pott F, Kamino K, et al. 1997. Dose-response relationship of fibrous dusts in intraperitoneal studies. Environ Health Perspect 105 (Suppl 5):1253-1256.

*Rom WN, Travis WD, Brody AR. 1991. Cellular and molecular basis of the asbestos-related diseases. Am Rev Respir Dis 143:408-422.

Ross D, McDonald JC. 1995. Occupational and geographical factors in the epidemiology of malignant mesothelioma. Monaldi Arch Chest Dis 50(6):459-462.

*Ross M. 1981. The geologic occurrences and health hazards of amphibole and serpentine asbestos. In: Veblen DR, ed. Reviews in mineralogy. Chelsea, MI: Bookcrafters, Inc., 279-323.

Ross M, Kuntze RA, Clifton RA. 1984. A definition for asbestos. ASTM Spec Tech Publ 834:139-147.

*Ross M, Nolan RP, Langer AM, and Cooper WC. 1993. Health effects of mineral dusts other than asbestos. In: Guthrie GD, Mossman BT, eds. MSA Reviews in Mineralogy Vol 28: 361-407.

*Sahu AP, Dogra RKS, Shanker R, et al. 1975. Fibrogenic response in murine lungs to asbestos. Exp Pathol 11:21-24.

*Sakellariou K, Malamou-Mitsi V, Haritou A, et al. 1996. Malignant pleural mesothelioma from nonoccupational asbestos exposure in Metsovo (north-west Greece): slow end of an epidemic? Eur Respir J 9:1206-1210

*Schneider J, Rodelsperger K, Bruckel B, et al. 1998. Environmental exposure to tremolite asbestos: pleural mesothelioma in two Turkish workers in Germany. Rev Environ Health 13(4):213-220.

Seaborg GT. 1991. Actinides and transactinides. In: Kroschwitz J, Howe-Grant M, ed. Kirk-Othmer encyclopedia of chemical technology. New York, NY: John Wiley and Sons, Inc., 456-488.

*Sebastien P, Janson X, Gaudichet A. et al. 1980. Asbestos retention in human respiratory tissues: comparative measurements in lung parenchyma and in parietal pleura. IARC Sci Publ 30: 237-246.

Sebastien P, McDonald JC, McDonald AD, et al. 1989. Respiratory cancer in chrysotile textile and mining industries: exposure inferences from lung analysis. Br J Ind Med 46:180-187.

*Selikoff IJ, Seidman H, Hammond C. 1980. Mortality effects of cigarette smoking among site asbestos factory workers. J Natl Cancer Inst 65(3):507-513.

Selevan SG, Dement JM, Wagoner JK, Froines JR. 1979. Mortality patterns among miners and millers of non-asbestiform talc: preliminary report. In: Lemen R, Dement JM, eds. Dust and disease: proceedings of the conference on occupational exposures to fibrous and particulate dust and their extension into the environment, 1977, Washington, DC. Park Forest South, IL: Pathotox Publishers, Inc., 379-388.

*Skinner HCW, Ross M, Frondel C. 1988. Asbestos and other fibrous materials: mineralogy, crystal chemistry, and health effects. New York, NY: Oxford University Press.

Sluis-Cremer GK. 1988. Linking chrysotile asbestos with mesothelioma. [Letter]. Am J Ind Med 14:631-632.

Sluis-Cremer GK, Liddell FDK, Logan WPD, et al. 1992. The mortality of amphibole miners in South Africa, 1946-80. Br J Ind Med 49:566-575.

*Smith WE, Hubert DD, Sobel HJ, et al. 1979. Biologic tests of tremolite in hamsters. In: Lemen R, Dement JM Eds. Proc. Conf. Occup. Exp. Fibrous Part. Dust. Ther. Ext. Environ. Park Forest South IL: 335-339.

Smith WE, Hubert DD, Sobel HJ. 1980. Dimensions of fibres in relation to biological activity. In: Biological effects of mineral fibres. Lyon, France: International Agency for Research on Cancer, 357-360.

Srebro SH, Roggli VL. 1994. Asbestos-related disease associated with exposure to asbestiform tremolite. Am J Ind Med 26:809-819.

*Stanton MF, Layard M, Tegeris A, et al. 1981. Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. J Natl Cancer Inst 67(5):965-975.

*Stayner LT, Dankovic DA, Lemen RA. 1996. Occupational exposure to chrysotile asbestos and cancer risk: a review of the amphibole hypothesis. Am J Public Health 86(2):179-186.

*Stayner L, Smith R, Bailer J, et al. 1997. Exposure-response analysis of risk of respiratory disease associated with occupational exposure to chrysotile asbestos. Occup Environ Med 54:646-652.

Stille WT, Tabershaw IR. 1982. The mortality experience of Upstate New York talc workers. J Occup Med 24(6):480-484.

Streib WC. 1978. Asbestos. In: Grayson M, Eckroth D, eds. Kirk-Othmer encyclopedia of chemical technology. New York, NY: John Wiley & Sons, Inc., 269-278.

Suzuki K, Hei TK. 1996. Induction of heme oxygenase in mammalian cells by mineral fibers: distinctive effect of reactive oxygen species. Carcinogenesis 17(4):661-667.

*Tanaka S, Choe N, Hemenway DR, et al. 1998. Asbestos inhalation induces reactive nitrogen species and nitrotyrosine formation in the lungs and pleura of the rat. J Clin Invest 102:445-454.

USGS. 1998a. Talc and pyrophyllite. In: Minerals yearbook. U.S. Geological Survey. http://minerals.usgs.gov/minerals/pubs/commodity/talc/650498.pdf

*USGS. 1998b. Vermiculite. In: Minerals handbook. U.S. Geological Survey. http://minerals.usgs.gov/minerals/pubs/commodity/vermiculite/index.htm

USGS. 1998c. Directory of companies mining talc and pyrophyllite in the United States in 1997. In: Minerals industry surveys. U.S. Geological Survey. http://minerals.usgs.gov/minerals/pubs/commodity/talc/650297.pdf

*USGS. 1999. Talc and pyrophyllite. In: Minerals commodity summaries. U.S. Geological Survey. http://minerals.usgs.gov/minerals/pubs/commodity/talc/650399.pdf

Vacek PM, McDonald JC. 1991. Risk assessment using exposure intensity: an application to vermiculite mining. Br J Ind Med 48:543-547.

*Verkouteren JR, Wylie AG. 2000. The tremolite-actinolite-ferro-actinolite series: systematic relationships among cell parameters, composition, optical properties, and habit, and evidence of discontinuities. Am Mineral 85: 1239-1254.

Vianna NJ, Pola AK. 1978. Nonoccupational exposure to asbestosis and malignant mesothelioma in females. Lancet 1:1061.

*Veblen DR, Wylie AG. 1993. Mineralogy of amphiboles and 1:1 layer silicates. In: Guthrie GD, Mossman BT, eds. MSA Reviews in Mineralogy Vol 28: 61-137.

*Vu V. 1993. Regulatory approaches to reduce human health risks associated with exposures to mineral fibers. In: Guthrie GD, Mossman BT, eds. MSA Reviews in Mineralogy Vol 28: 545-554.

*Waage HP, Vatten LJ, Opedal E, and Hilt B. 1996. Lung function and respiratory symptoms related to changes in smoking habits in asbestos-exposed subjects. J Occup Environ Med 38: 178-183.

*Wagner JC, Berry G, Skidmore JW, et al. 1974. The effects of the inhalation of asbestos in rats. Br J Cancer 29:252-269.

*Wagner JC, Chamberlain M, Brown RC, et al. 1982. Biological effects of tremolite. Br J Cancer 45:352-360.

*WHO. 1998. Chrysotile asbestos: Environmental health criteria 203. Geneva, Switzerland: World Health Organization.

*Wilkinson P, Hansell DM, Janssens J, et al. 1995. Is lung cancer associated with asbestos exposure when there are no small opacities on the chest radiograph? Lancet 345:1074-1078.

*Wylie AG, Bailey KF, Kelse JW, et al. 1993. The importance of width in asbestos fiber carcinogenicity and its implications for public policy. Am Ind Hyg Assoc J 54(5):239-252.

*Wylie AG, Skinner HCW, Marsh J, et al. 1997. Mineralogical features associated with cytotoxic and proliferative effects of fibrous talc and asbestos on rodent tracheal epithelial and pleural mesothelial cells. Toxicol Appl Pharmacol 147:143-150.

*Wylie AG and Verkouteren R. 2000. Amphibole asbestos from Libby, Montana: aspects of nomenclature. Am Mineral 85: 1540-1542.

*Yazicioglu S, Ilcayto R, Balci K, et al. 1980. Pleural calcification, pleural mesotheliomas, and bronchial cancers caused by tremolite dust. Thorax 35:564-569.

*Zazenski R, Ashton WH, Briggs, D, et al. 1995. Talc: occurrence, characterization, and consumer applications. Regul Toxicol Pharmacol 21:218-229.

*Zoltai, T. 1979. Asbestiform and acicular mineral fragments. Ann N Y Acad Sci 330: 621-643.

*Zoltai, T. 1981. Amphibole asbestos mineralogy. In: Veblen DR, ed Amphiboles and other hydrous particles. MSA Reviews in Mineralogy. Vol 9A: 235-278.

APPENDIX F

INDEX

asbestos-related disease 26, 27, 43, 49, 63
diagnosis . . . . . v, vi, 1, 21, 27, 40, 45, 49
exposure units 5, 18
family members . . . . . v, 19, 21
fiber-year/mL . . . . . iv, 5, 18, 28-31
garden . . . . . iv, 13, 14, 20, 42, 51
gastrointestinal cancer 21, 22
household . . . . . v, 21
interlobar fissure thickening 32
interstitial . . . . . iv, 2, 4-6, 20, 21, 25, 27, 32-34, 39-41
Libby, Montana . . . . . ii-v, vii, 1, 3, 7, 8, 10, 12, 13, 19, 27-31, 34-38, 41, 44, 46, 57, 66
lung cancer . . . . . ii, iv, v, vii, 1, 20-27, 34, 35, 38-43, 47, 48, 50-53, 55, 59, 65
mesothelioma . . . . . ii, iv-vi, 1, 5, 20-27, 33, 35, 36, 38-43, 45-49, 51-53, 55-57, 60-63, 65
milling . . . . . iv, 4, 10, 11, 18, 19, 31, 42
mining . . . . . iv, 3, 4, 10, 11, 18, 19, 30, 31, 42, 56, 62, 64
parenchyma 4, 6, 39, 62
parenchymal abnormalities 28, 39, 40
parenchymal opacities 28, 29
pleural abnormalities 6, 28, 30, 31, 33, 39
pleural calcifications 32, 49
pleural cavity 6, 25
pleural effusion 6, 28
pleural plaques . . . . . iv, 6, 20, 32, 33, 39, 41, 47, 52, 59-61
pleural thickening . . . . . iv, 6, 20, 26, 29, 32, 39, 41
residents . . . . . iv, vii, 19, 27, 37, 38, 42, 44
tremolite asbestos 1-vi, 1, 2, 4, 6, 11, 12, 14-16, 18-23, 27, 28, 30-42, 45, 46, 49, 62
vermiculite . . . . . ii-v, vii, 1, 3, 6-10, 12-14, 18-20, 27-31, 34-38, 41-46, 51, 52, 55-57, 64
whitewash 32, 36, 55
workers . . . . . ii, iv, v, vii, 1, 2, 5, 17-19, 21-31, 34, 35, 37-43, 45, 47, 48, 50-52, 54, 60, 62, 64