# TOXICOLOGICAL PROFILE FOR SYNTHETIC VITREOUS FIBERS

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

September 2004

# DISCLAIMER

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

# UPDATE STATEMENT

A Toxicological Profile for Synthetic Vitreous Fibers, Draft for Public Comment was released in September 2002. This edition supersedes any previously released draft or final profile.

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE,
Mailstop F-32
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:

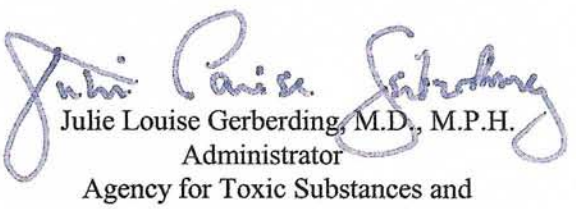
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(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.



Julie Louise Gerberding, 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 prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 7, 2003 (68 FR 63098) . For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999(64 FR 56792) and October 25, 2001 (66 FR 54014). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

# QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

---

***Primary Chapters/Sections of Interest***

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

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

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

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

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

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

**Other Sections of Interest:**

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

---

***ATSDR Information Center***

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

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

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

*and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

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

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

---

***Other Agencies and Organizations***

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

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

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

---

***Referrals***

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

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

# CONTRIBUTORS

## CHEMICAL MANAGER(S)/AUTHOR(S):

Malcolm Williams, D.V.M., Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

Peter R. McClure, Ph.D., D.A.B.T.
Andrew McDougal, Ph.D.
Mario J. Citra, Ph.D.
Syracuse Research Corporation, North Syracuse, NY

## THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

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

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

# PEER REVIEW

A peer review panel was assembled for synthetic vitreous fibers. The panel consisted of the following members:

1. Jeffrey I. Everitt, D.V.M., Senior Scientist, CIIT Centers for Health Research, Research Triangle Park, North Carolina;

2. Morton Lippmann, Ph.D., Professor of Environmental Medicine, New York University School of Medicine, Tuxedo, New York;

3. John A. Pickrell, Ph.D., D.V.M., Associate Professor of Environmental Toxicology, Kansas State University, Diagnostic Medical Pathobiology Department, Manhattan, Kansas; and

4. Ernest McConnell, DVM, MS (path), DABT, DACVP, President, Toxpath Inc., Raleigh, North Carolina.

These experts collectively have knowledge of synthetic vitreous fibers' 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

APPENDICES

# LIST OF FIGURES

# LIST OF TABLES

# 1. PUBLIC HEALTH STATEMENT

This public health statement tells you about synthetic vitreous fibers (SVFs) and the effects of exposure to them.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Synthetic vitreous fibers have not been detected in the 1,647 current or former NPL sites. Although the total number of NPL sites evaluated for these substances is not known, the possibility exists that synthetic vitreous fibers may be found in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to these substances may harm you.

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 synthetic vitreous fibers, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with them. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

## 1.1 WHAT ARE SYNTHETIC VITREOUS FIBERS?

Synthetic vitreous fibers are a group of fibrous inorganic materials that contain aluminum or calcium silicates and other trace oxides and metals, and are made from rock, slag, clay, or glass. These fibers differ from natural mineral fibers such as asbestos because they do not have a crystalline molecular structure. The randomly oriented molecular structure of synthetic vitreous fibers is called an amorphous structure. There are two broad categories of synthetic vitreous

fibers: filaments and wools. The filaments consist of continuous glass filaments, while the wools are subdivided into glass wool, rock wool, slag wool, refractory ceramic fibers, and other types of newer fibers. The primary uses of synthetic vitreous fibers are for heat and sound insulating purposes, to reinforce other materials, and as filtration materials. Glass wools are some of the most widely used insulating materials in homes and buildings. The production and use of synthetic vitreous fibers has increased in recent years because these products are often used as a replacement for asbestos.

A fiber is simply a long, slender particle. Technically, to be counted as a fiber, the particle must be at least 5 micrometers long (1 micrometer equals 1/1,000,000 of a meter and has the symbol μm), and have an aspect ratio of at least 3 to 1 or sometimes 5 to 1 (the aspect ratio is the ratio of a fiber's length to its diameter). The diameter of a fiber is an important property because very thin fibers are more easily suspended in air than thick fibers, and they can be breathed in and deposited deep in the lungs. Only very thin fibers with diameters less than 3 μm are able to be breathed into the lower respiratory tract of humans. Thicker fibers are deposited on the mucous-lined surface of the upper respiratory tract, which includes the nose and mouth. The World Health Organization (WHO) counts respirable fibers as particles with lengths greater than 5 μm, diameters less than 3 μm, and aspect ratios ≥3:1. Depending upon the way that they are produced, fibers can have relatively large or small diameters. Generally speaking, glass wool, rock wool, slag wool, and refractory ceramic fibers have the smallest diameters, while continuous filament glass fibers have the largest diameters.

See Chapters 4 and 5 for more information on the properties and uses of synthetic vitreous fibers.

## 1.2 WHAT HAPPENS TO SYNTHETIC VITREOUS FIBERS WHEN THEY ENTER THE ENVIRONMENT?

Synthetic vitreous fibers do not evaporate into air or dissolve in water. They are generally not broken down to other compounds in the environment and will remain virtually unchanged over long periods. Eventually, synthetic vitreous fibers will be broken down if the water or soil is very acidic or very alkaline. Fibers can enter the air, water, and soil from the manufacture, use,

and disposal of synthetic vitreous fiber-containing materials. Fibers with small diameters become airborne more easily than thick fibers, and can be transported by wind for longer distances. Synthetic vitreous fibers are not likely to move through soil.

See Chapter 6 for more information on the behavior of synthetic vitreous fibers in the environment.

## 1.3 HOW MIGHT I BE EXPOSED TO SYNTHETIC VITREOUS FIBERS?

If materials containing synthetic vitreous fibers, such as insulation or ceiling boards in your home or where you work, are disturbed, synthetic vitreous fibers can become airborne. When these fibers become airborne, you can be exposed to low levels of synthetic vitreous fibers primarily by breathing air. Your skin and eyes can also be exposed to synthetic vitreous fibers if you install your own home insulation or come into contact with insulation in your home without using protective equipment such as gloves, protective glasses, or masks.

The vast majority of exposure to synthetic vitreous fibers occurs to workers who produce or use synthetic vitreous fiber-containing products. Employees at manufacturing facilities where synthetic vitreous fibers products are produced, as well as workers who regularly install or come into contact with insulating material, are most frequently exposed to synthetic vitreous fibers. Workers involved in demolition work, as well as in building maintenance and repair, are potentially exposed to higher levels of synthetic vitreous fibers once these materials are disturbed.

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

## 1.4 HOW CAN SYNTHETIC VITREOUS FIBERS ENTER AND LEAVE MY BODY?

If you breathe synthetic vitreous fibers, some will be deposited in the nasal and oral passages, and on the surfaces that line your lungs. Most fibers deposited in the nasal and upper lung airways are removed by being carried away in a layer of mucous to the throat, where they are swallowed into the stomach. This usually takes place within a few hours. Fibers deposited in the deepest parts of the lungs where gas exchange occurs are removed more slowly by special cells called macrophages. Macrophages can engulf the fibers and move them to the mucous layer and the larynx where they can be swallowed. Swallowed fibers and macrophages are excreted in the feces within a few days.

Synthetic vitreous fibers deposited in the gas exchange area of the lungs also slowly dissolve in lung fluid. Fibers that are partially dissolved in lung fluid are more easily broken into shorter fibers. Shorter fibers are more easily engulfed by macrophages and removed from the lung than long fibers. Synthetic vitreous fibers dissolve more readily in the lung than asbestos fibers. Refractory ceramic fibers dissolve more slowly than most types of insulation (e.g., glass wools, stone wools, and slag wools).

If you swallow synthetic vitreous fibers (by eating, drinking, or by swallowing fibers that have moved from nasal or lung airways to your larynx), nearly all of the fibers pass through your intestines within a few days and are excreted in the feces.

If you get synthetic vitreous fibers on your skin or in your eyes, very few of these fibers, if any, pass through into your body.

See Chapter 3 for more information on how synthetic vitreous fibers enter and leaves the body.

## 1.5 HOW CAN SYNTHETIC VITREOUS FIBERS 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 informed 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.

Synthetic vitreous fibers can cause irritation of the eyes and skin known as "fiberglass itch." They can also irritate the upper respiratory tract (the nose, throat) and parts of the lung, causing sore throat, nasal congestion, and cough. These effects usually go away with time. Because most people are not exposed to high levels of synthetic vitreous fibers, serious health effects are not expected to happen in most people.

Most of the information regarding the possible effects of repeated exposure to synthetic vitreous fibers in people comes from large studies of workers who make synthetic vitreous fibers. Very few effects were detected. A few workers who made refractory ceramic fibers had pleural plaques on the lining of their chests. These plaques did not seem to harm the workers. Other workers who smoked could not breathe quite as well as smokers who did not work with refractory ceramic fibers. Nonsmoking refractory ceramic fiber workers could breathe as well as other nonsmokers. This suggests that repeatedly breathing in refractory ceramic fibers from workplace air worsens the effects of smoking. Pleural plaques and decreased breathing ability have not been found in workers who made glass wool and stone wool. Other studies have found that the numbers of deaths from lung diseases, including lung cancer or mesothelioma, in groups of workers involved in the manufacture of glass wool, stone wool, or refractory ceramic fibers are not consistently different from what is found in the general U.S. population. Mesothelioma is

a cancer of the membrane lining the lung. Increased risk for mesothelioma has been found in asbestos workers, but increased risks for this cancer have not been found in workers involved in the manufacture of synthetic vitreous fibers.

Results from animal experiments show that when synthetic vitreous fibers or other inhaled dust particles are deposited in the deepest part of the lung in high numbers, the lung responds with a process called pulmonary inflammation. In this process, macrophage numbers in the lung increase so that they can engulf and move the fibers out of the lung. When high numbers of fibers are deposited, the macrophages can become clumped together. If pulmonary inflammation continues, the cells lining the lung may thicken from a process called bronchiolization. Bronchiolization may reduce the amount of oxygen that the body gets from the air during breathing. If exposure stops, deposited synthetic vitreous fibers slowly dissolve in the lung fluid or are moved out of the lung by the macrophages, and pulmonary inflammation disappears with time.

Results from animal studies also show that repeatedly breathing high levels of some types of synthetic vitreous fibers may cause a slow buildup of scar-like tissue in the lungs and in the membrane surrounding the lungs. This scar-like tissue does not expand and contract like normal lung tissue, and breathing can become difficult. This condition is called pulmonary fibrosis. The types of synthetic vitreous fibers that cause this condition in animals stay in the lung for longer periods of time than the types that do not. They are called durable or biopersistent synthetic vitreous fibers. Results from animal studies also show that repeatedly breathing high levels of durable synthetic vitreous fibers may also cause cancer of the lung and mesothelioma. The most common types of glass wools, stone wools, or slag wools used for insulation are less durable than refractory ceramic fibers. In rat studies, they did not cause the severe lung effects caused by the more durable refractory ceramic fibers.

Scientists studying pulmonary fibrosis, lung cancer, and mesothelioma in animals from durable synthetic vitreous fibers have shown that the development of these conditions depends on four factors: dose, duration, dimension, and durability. Dose is the amount of fibers deposited in the lung, and duration is the time period when exposure occurs. High doses and long durations of

exposure are required for these conditions to develop. Dimension refers to the length and diameter of the fibers. Fibers with diameters greater than about 3 μm are not inhaled into the deepest regions of the lungs. Fibers with lengths greater than about 15–20 μm are not engulfed by macrophages, and are more likely to lead to lung injury than shorter fibers that are more readily removed by macrophages. Durability refers to how readily a fiber dissolves in lung fluid. Different types of synthetic vitreous fibers have different durabilities due to differences in chemical makeup. Most synthetic vitreous fibers used as insulation in homes and buildings, such as fiberglass wools and stone wools, are more readily dissolved in lung fluid than are refractory ceramic fibers, which are used in insulation materials for furnaces. Long, durable fibers deposited in the gas-exchange region of the lung can lead to long-term inflammation, pulmonary fibrosis, lung cancer, or mesothelioma.

Levels of synthetic vitreous fibers in outdoor air, indoor air, and in most workplaces are usually well below levels that caused reversible pulmonary inflammation in animals or levels of durable synthetic vitreous fibers that caused pulmonary fibrosis, lung cancer, or mesothelioma in animals. For example, levels of a refractory ceramic fiber that caused pulmonary fibrosis, lung cancer, and mesothelioma in rats are about one million times higher than levels of synthetic vitreous fibers detected in outdoor air close to synthetic vitreous fiber manufacturing factories, or indoor air from buildings with fiberglass or stone wool insulation. The levels experienced by the diseased rats are about 50 times higher than levels of synthetic vitreous fibers in the most dusty workplaces where insulation containing synthetic vitreous fibers was removed or installed.

In 2002, the International Agency for Research on Cancer (IARC) considered all of the evidence regarding the possible carcinogenicity of synthetic vitreous fibers. Much of the evidence was collected in the 1990s and was not available for earlier assessments made by the U.S. Department of Health and Human Services (DHHS). IARC determined that refractory ceramic fibers are possibly carcinogenic to humans because of their high biopersistence. IARC also determined that insulation glass wool, stone wool, and slag wool, and continuous filament glass were not classifiable as to carcinogenicity to humans because of inadequate evidence of carcinogenicity in humans and the relatively low biopersistence of these materials. EPA has not

assessed the potential carcinogenicity of glass wool, stone wool, slag wool, or continuous filament glass, but has classified refractory ceramic fibers as a probable human carcinogen.

See Chapters 2 and 3 for more information on how synthetic vitreous fibers may affect your health.

## 1.6 HOW CAN SYNTHETIC VITREOUS FIBERS AFFECT CHILDREN?

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

Because synthetic vitreous fibers are not absorbed into the body (when inhaled or ingested), it is unlikely that they would cause birth defects or be transferred in breast milk to nursing infants.

Like adults, children who are exposed to synthetic vitreous fibers may experience irritation of the eyes, skin, and upper respiratory tract. Children breathe differently and have different lung structures than do adults. It is not likely that these differences will cause a greater amount of synthetic vitreous fibers to stay in the lungs of children than in the lungs of adults.

It is possible that exposure of young children to highly durable fibers could lead to pulmonary effects after very long latency periods. However, there is no evidence to support this possibility, and the durability of many types of synthetic vitreous fibers in the lung is low. This concern also has been raised for children exposed to asbestos fibers, which are more durable than synthetic vitreous fibers, but, as with synthetic vitreous fibers, there is inadequate evidence to support the idea that exposed young children may be at greater risk to develop pulmonary effects from durable fibers than are adults.

## 1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO SYNTHETIC VITREOUS FIBERS?

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

Very low levels of synthetic vitreous fibers can be found in virtually all homes, buildings, and outside air, but there is little concern regarding these low levels. The most important way that families can lower their exposures to synthetic vitreous fibers is to be aware of the sources of synthetic vitreous fibers in their homes and avoid exposure to these sources. The most common source of synthetic vitreous fibers in a home is from insulating material that may be in your attic or walls. Damaged or deteriorating ceiling boards are another potential source. As long as the materials are not physically disturbed or breaking down, the levels of synthetic vitreous fibers in the air should be very low. Relatively high levels of airborne synthetic vitreous fibers have been detected during the installation of insulating materials in attics, but these levels decline rapidly in 1 or 2 days as airborne dust settles. If you are installing your own insulation, wear protective clothing and masks, and follow the recommendations provided by the manufacturer for installing this material.

You can bring synthetic vitreous fibers home in the dust on your hands or clothes if you work in facilities that produce or use synthetic vitreous fibers, or install or remove materials with synthetic vitreous fibers. Your occupational health and safety (OHS) officer can and should tell you whether chemicals you work with are dangerous and likely to be carried home on your clothes, body, or tools. Your OHS officer can also tell you 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 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 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 SYNTHETIC VITREOUS FIBERS?

No tests are specific for determining whether or not you have been exposed to synthetic vitreous fibers. Because synthetic vitreous fibers leave the body quickly, most nonspecific tests would not be very useful. A chest x-ray is a common method to determine if you have certain conditions, such as pleural plaques, lung or pleural fibrosis, lung tumors, or mesotheliomas, but x-rays cannot show the presence of fibers in the lung.

## 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; they are then 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 synthetic vitreous fibers include the following:

In 1999, a Health and Safety Partnership Program was established as a voluntary workplace safety program for workers involved in the manufacture, fabrication, installation, and removal of glass wool, rock wool, and slag wool products. The program was established as a result of negotiations between the OSHA, the North American Insulation Manufacturers Association, the National Insulation Association, and the Insulation Contractors Association of America. The program established a voluntary 8-hour time-weighted average (TWA) permissible exposure limit (PEL) of 1 respirable fiber per cc of air. Under this agreement, respirable fibers are counted as particles with length greater than 5 μm, diameter less than 3 μm, and aspect ratio greater than or equal to 3:1. The agreement specifies that when the PEL is exceeded in a workplace (such as when insulation is blown into attics or removed), workers will wear NIOSH certified dust respirators.

## 1.10 WHERE CAN I GET MORE INFORMATION?

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

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

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

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

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

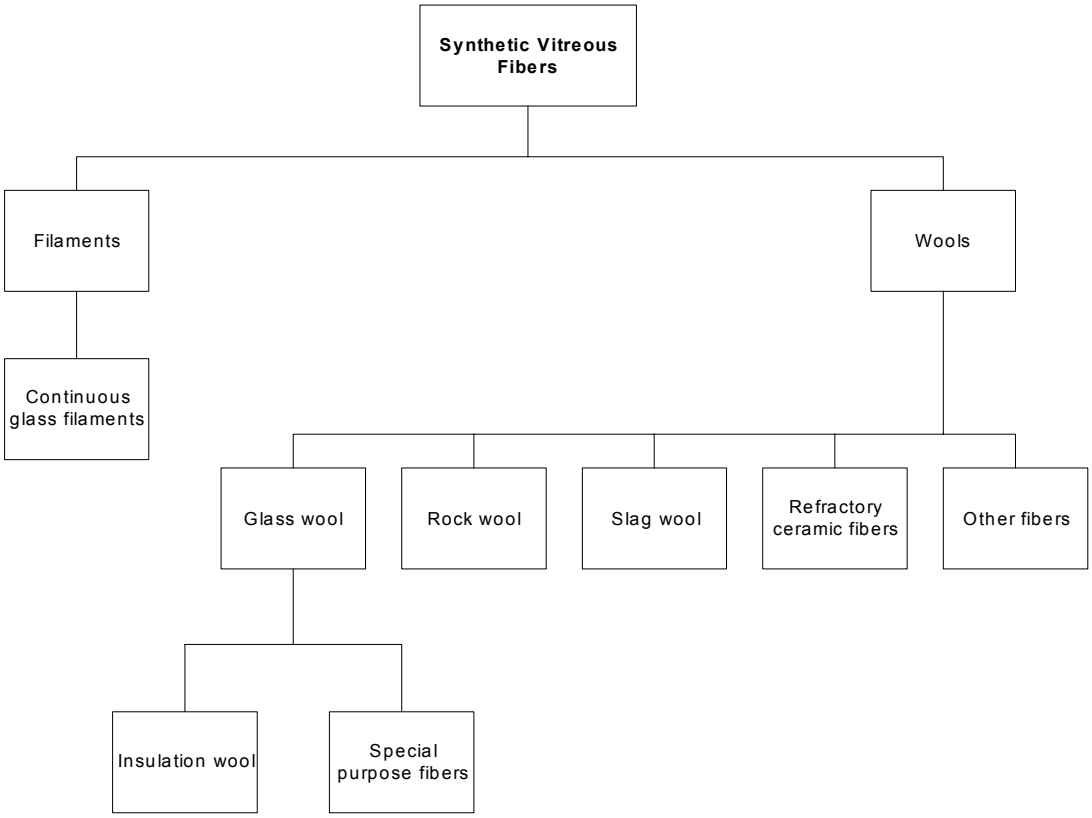
# 2. RELEVANCE TO PUBLIC HEALTH

## 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO SYNTHETIC VITREOUS FIBERS IN THE UNITED STATES

Synthetic vitreous fibers are inorganic fibrous materials, manufactured principally from glass, rock, minerals, slag, and processed inorganic oxides. Synthetic vitreous fibers are manufactured by several processes, all of which involve cooling of a stream of high-temperature, molten inorganic oxides. Commercially important synthetic vitreous fibers are primarily silica-based, but contain various amounts of other oxides (e.g., aluminum, boron, calcium, or iron oxides). Synthetic vitreous fibers have amorphous molecular structures, while naturally occurring mineral fibers, such as asbestos, possess crystal structures. In the past, synthetic vitreous fibers were classified into three categories: fibrous glass; rock wool and slag wool (sometimes collectively referred to as mineral wool); and refractory ceramic fibers. The fibrous glass category included continuous filament glass fibers (sometimes called textile fibers) and glass wools. Recently, the World Health Organization (WHO) IARC classified synthetic vitreous fibers into two broad categories: filaments and wools. A schematic of this classification scheme is shown in Figure 2-1. The filaments category refers to glass fibers that are produced by extrusion (continuous glass filaments). IARC noted that more than 98% of currently produced continuous glass filaments are for electrical applications. The wools category includes five subgroups: glass wool, rock wool, slag wool, refractory ceramic fibers, and other fibers. Included in the glass wool category are the subgroups, insulation wools and special purpose fibers. The special purpose fiber group includes glass fibers produced by flame attenuation for special applications such as high-efficiency air filtration and include special fine-diameter glass fibers. The other fibers group includes fibers such as alkaline earth silicate wools and high-alumina, low-silica wools that have been recently developed to be more biosoluble than older high-temperature synthetic vitreous fibers such as refractory ceramic fibers or rock wools.

The production and use of synthetic vitreous fibers can cause their release to the environment. Glass wool, rock wool, and slag wool are primarily used in insulating materials for homes, buildings, and appliances. Continuous filament fibers have been used to reinforce plastics, cement, papers, and roofing materials or woven into industrial fabrics, and currently are used mostly for electrical purposes. Refractory ceramic fibers are primarily used in insulating materials that require very high temperature

## Figure 2-1. IARC (2002) Categories of Synthetic Vitreous Fibers



resistance (e.g., furnace insulation). Approximately 80% of the synthetic vitreous fibers produced and used in the United States are glass wool, rock wool, and slag wool. Refractory ceramic fibers only account for about 2% of the total amount of synthetic vitreous fibers produced.

Synthetic vitreous fibers are persistent in the environment because they are not removed by mechanisms that usually degrade organic compounds (e.g., biodegradation, photolysis). Small diameter synthetic vitreous fibers with large surface areas can undergo dissolution in aqueous solutions, particularly at very high or very low pH levels, but this is more important in biological systems than in the environment (see Section 3.4 for more details regarding dissolution in physiologic fluids). The transport and partitioning of synthetic vitreous fibers in the environment are largely governed by their size. Large fibers are removed from air and water by gravitational settling at a rate primarily dependent on their diameter, but small diameter fibers may remain suspended for longer periods of time before settling down to the ground.

Inhalation exposure to airborne synthetic vitreous fibers is of public health concern because, like other particulate matter, fibers that get suspended in air can be inhaled and deposited in the lung. Measurements to determine the concentration of synthetic vitreous fibers in air samples are usually reported as the number of fiber(s) per cubic centimeter of air (fiber/cc). Different studies have used different rules for counting fibers in air samples, but in general, a fiber is a particle that has a length ≥5 μm and a length:diameter ratio (aspect ratio) of ≥3:1 or ≥5:1. The WHO counts fibers as particles with lengths >5 μm, widths <3 μm, and aspect ratios ≥3:1. The National Institute for Occupational Safety and Health (NIOSH) counts fibers as particles with lengths >5 μm and aspect ratios ≥3:1. The levels of synthetic vitreous fibers in air are measured by phase contrast microscopy (PCM), transmission electron microscopy (TEM), or scanning electron microscopy (SEM) (see Chapter 7 for more details). A human respirable fiber (a fiber that can be inhaled and reach the lower air-exchange portion of the respiratory tract) is usually defined as a fiber having a diameter <3 μm.

When materials containing synthetic vitreous fibers are physically disturbed, fibers can become suspended in indoor or outdoor air. In general, fibers with small diameters are more easily suspended and remain suspended in air longer than larger-diameter fibers. Among synthetic vitreous fiber types, continuous filament glass fibers usually have the largest average diameters, while refractory ceramic fibers, glass wool, rock wool, and slag wool generally have smaller average diameters (see Chapter 4 for more details). Levels of synthetic vitreous fibers detected in outdoor or indoor air samples are very low, usually on the order of about ≤0.0001 NIOSH fiber/cc. In workplaces that manufacture synthetic vitreous

fibers, reported air concentrations have mostly been reported to be <0.1–1 NIOSH fiber/cc. Higher levels have been observed during the installation of insulation in a home or building (respirable airborne levels >1 fiber/cc have been observed); however, these levels quickly fall back to preinstallation levels within 1 or 2 days. The geometric mean concentration of respirable synthetic vitreous fibers ranged from 0.01 to 3.51 fibers/cc at five construction sites where either refractory ceramic fibers, rock wool, or glass wool insulating materials were being installed or removed. The greatest levels were observed during the removal of refractory ceramic fiber insulating material from the inside walls of industrial furnaces, and the lowest levels were observed during the installation of fiberglass panels around ventilation ducts at an industrial construction site.

## 2.2 SUMMARY OF HEALTH EFFECTS

Reversible acute irritations of the skin, eyes, and upper respiratory tract are well-known health hazards associated with direct dermal and inhalation exposure to refractory ceramic fibers, fibrous glass, rock wool, or slag wool in construction and manufacturing workplaces. Wearing protective clothing and respiratory equipment has been recommended to prevent these health hazards (and possible chronic health hazards) when time-weighted average (TWA) airborne concentrations of fibers exceed recommended occupational exposure limits of 1 NIOSH fiber (length >5 μm; aspect ratio ≥3:1)/cc for continuous filament glass fibers, glass wool, rock wool, slag wool, and special purpose glass fibers or 0.2 NIOSH fibers/cc for refractory ceramic fibers.

Although several respiratory health effects have been associated with occupational exposure to asbestos (pulmonary or pleural fibrosis [i.e., tissue scarring], lung cancer, and pleural or peritoneal mesothelioma), none of these diseases has been associated with occupational exposure during the manufacture of synthetic vitreous fibers. Results from animal studies indicate that high-level inhalation exposure to any synthetic vitreous fiber may cause reversible pulmonary inflammation, but only the most biopersistent of synthetic vitreous fibers have been demonstrated to produce irreversible pleural or pulmonary fibrosis, lung cancer, or mesothelioma. Health effects at other target organs are not expected from exposure to airborne synthetic vitreous fibers.

Mechanistic and pharmacokinetic studies with asbestos and synthetic vitreous fibers indicate that greater potential for toxicity of inhaled inorganic fibers is associated with higher exposure concentrations, longer exposure durations, longer fiber lengths, greater fiber durability, and thinner fiber diameters. As

discussed in Sections 3.4 and 3.5, fiber dimensions influence several of these key determinants of toxicity including:

- The amount of material deposited in the alveolar region of the lung (fibers with diameters >3 μm do not reach this region; they are deposited in the upper respiratory tract and lung conductive airways, cleared by mucociliary action to the pharynx, swallowed, and eliminated via the feces);
- The rate at which macrophages engulf and clear fibers deposited in the lower lung (human macrophages cannot fully engulf fibers with lengths longer than about 15–20 μm); and
- The extent of movement of deposited fibers from the alveoli to the lung interstitium and the pleural cavity (fibers with diameters >0.3–0.4 μm may move less freely into the interstitium and pleural cavity).

Fibers that can dissolve in physiologic fluids (i.e., that are less durable) develop weak points that can facilitate (1) transverse breakage by physical forces into shorter fibers and (2) faster clearance by macrophages, compared with fibers that do not dissolve, like amphibole asbestos fibers.

Synthetic vitreous fibers differ from asbestos in two ways that may provide at least partial explanations for their lower toxicity. Because most synthetic vitreous fibers are not crystalline like asbestos, they do not split longitudinally to form thinner fibers. They also generally have markedly less biopersistence in biological tissues than asbestos fibers because they can undergo dissolution and transverse breakage (see Sections 3.4 and 3.5).

***Irritation Effects.*** Occupational exposure to fibrous glass materials, including glass wool insulation and fiberglass fabrics, has been associated with acute skin irritation ("fiberglass itch"), eye irritation, and symptoms of upper respiratory tract irritation such as sore throat, nasal congestion, laryngeal pain, and cough. The skin irritation has been associated with glass wool fibers having diameters >5 μm and becomes less pronounced with continued exposure. Symptoms of irritation of the upper respiratory tract have been mostly associated with unusually dusty workplace conditions (concentrations >1 fiber/cc) involving removal of fibrous glass materials in closed spaces without respiratory protection. The symptoms have been reported to disappear shortly following cessation of exposure. Similar symptoms of dermal and upper respiratory irritation may also occur in workers involved in the manufacture, application, or removal of insulation materials containing refractory ceramic fibers, rock wool, or slag wool.

***Cancer and Nonmalignant Respiratory Disease.*** Studies of workers predominantly involved in the manufacture of fibrous glass, rock wools, or slag wools have focused on the prevalence of respiratory symptoms through the administration of questionnaires, pulmonary function testing, and chest x-ray examinations. In general, these studies reported no consistent evidence for increased prevalence of adverse respiratory symptoms, abnormal pulmonary functions, or chest x-ray abnormalities; however, one study reported altered pulmonary function (decreased forced expiratory volume in 1 second) in a group of Danish insulation workers compared with a group of bus drivers. Longitudinal health evaluations of workers involved in the manufacture of refractory ceramic fibers have not found consistent evidence of exposure-related changes in chest x-rays or pulmonary functions, with the exception that pleural plaques were found in about 3% of examined U.S. refractory ceramic fiber manufacturing workers and that pleural plaque prevalence showed statistically significant trends with increasing exposure categories.

Epidemiologic studies (cohort mortality and case-control studies) of causes of mortality among groups of workers involved in the manufacture of fibrous glass, rock wool, or slag wool provide no consistent evidence for increased risks of mortality from nonmalignant respiratory disease, lung cancer, or pleural mesothelioma. A number of reviews of these cohort mortality and case-control studies concur that the studies provide inadequate evidence for the carcinogenicity of synthetic vitreous fibers in humans. In an initial report of the only available cohort mortality study of refractory ceramic fiber manufacturing workers, the only statistically significant excess mortality was for deaths associated with cancer of the urinary system. No mesotheliomas and no excess deaths associated with respiratory cancers or nonmalignant respiratory disease were found.

For all synthetic vitreous fibers tested, pulmonary inflammation has been observed in animals (predominately rodents) following intermediate- or chronic-duration inhalation exposure at concentrations more than an order of magnitude higher than 1 NIOSH fiber (length >5μm; aspect ratio ≥3:1)/cc. This concentration is the current occupational exposure limit for insulation wools recommended by the American Conference of Governmental Industrial Hygienists; for refractory ceramic fibers the limit is 0.2 NIOSH fibers/cc.

The most extensively studied refractory ceramic fiber, RCF1, caused minimal-to-mild pulmonary inflammation in rats and hamsters at concentrations as low as 26 WHO fibers (length >5 μm; diameter <3 μm; aspect ratio ≥3:1)/cc (36 total fibers with aspect ratios ≥3:1 per cc) at 3 months. The severity of inflammation increased with duration and exposure concentration, but the severity of inflammatory

lesions did not exceed a moderate rating of "3" in most rats (on a 0–5 grade scale where 0 was "normal" and 5 was "severe") even with exposure for 24 months to a concentration of 187 WHO fibers/cc. The inflammation showed signs of regression after cessation of exposure.

Other refractory ceramic fibers, RCF2, RCF3, and RCF4, caused minimal-to-mild pulmonary inflammation in rats at single exposure levels in the concentration range of 153–220 WHO fiber/cc. The insulation glass wool MMVF10 caused pulmonary inflammation at concentrations as low as 29 WHO fibers/cc in hamsters and rats. Other multiple-exposure tests in male rats have demonstrated the induction of minimal pulmonary inflammation from concentrations as low as 41 WHO fibers/cc of the glass wool, MMVF11, 34 WHO fibers/cc of the rock wool, MMVF21, and 30 WHO fibers/cc of the slag wool, MMVF22. Several of these studies also showed that signs of inflammation subsided to various degrees after cessation of exposure.

Pulmonary inflammation has also been observed in single-concentration experiments in male rats following intermediate- or chronic-duration inhalation exposure to the newly developed high-temperature rock wool, MMVF34, at 291 WHO fibers/cc, the high-silica synthetic vitreous fiber, X607, at 180 WHO fibers/cc, the special-purpose 104E-glass fiber, at 1,022 WHO fibers/cc, and GB100R glass wool at 2.2 $mg/m^3$ (fiber counts in air samples were not measured). Pulmonary inflammation also occurred in hamsters repeatedly exposed to the special-purpose durable glass fiber, MMVF33, at 310 WHO fibers/cc. An intermediate-duration study in male baboons reported that 1,122 NIOSH fibers/cc of C102/C104 blend fibrous glass induced pulmonary inflammation. The only study to report a no-observed-adverse-effect-level (NOAEL) for pulmonary inflammation (from chronic-duration exposure) exposed female Wistar rats to 252 WHO fibers/cc of Code 104/475 glass fiber for 12 months.

Following intermediate- or chronic-duration inhalation exposure, pulmonary or pleural fibrosis has been observed: in rats exposed to several refractory ceramic fibers, RCF1, RCF2, RCF3, and RCF4, in the concentration range of 153–220 WHO fibers/cc; in hamsters exposed to the special-purpose durable glass fiber, MMVF33, at 310 WHO fibers/cc; in rats exposed to the insulation rock wool, MMVF21, at 150 WHO fibers/cc; in rats exposed to the special-purpose 104E-glass fiber at 1,022 WHO fibers/cc; and in baboons exposed to C102/104 blend fibrous glass at 1,122 fibers/cc. Exposure-response relationships for pulmonary or pleural fibrosis are best described, among these "fibrotic" synthetic vitreous fibers, for the refractory ceramic fiber, RCF1. In rats exposed to RCF1 for up to 2 years, signs of irreversible pulmonary or pleural fibrosis were induced at concentrations >75 WHO fibers/cc, but not at 26 WHO

fibers/cc. In general, synthetic vitreous fibers that cause fibrosis are more biopersistent than those that do not.

Synthetic vitreous fibers that have not induced pulmonary or pleural fibrosis in animals following intermediate- or chronic-duration inhalation exposure include the insulation glass wools, MMVF10 and MMVF11, at concentrations in the 232–339 WHO fibers/cc range, the slag wool, MMVF22, at 213 WHO fibers/cc, the high-temperature rock wool, MMVF34, at 291 WHO fibers/cc, and the high-silica synthetic vitreous fiber, X607, at 180 WHO fibers/cc. All of these studies involved rats.

Chronic inhalation exposure of animals to several biopersistent synthetic vitreous fibers has been shown to induce lung tumors or mesothelioma, whereas several less biopersistent synthetic fibers have not induced tumorigenic responses in animals exposed by inhalation for chronic durations. In these experiments, statistically significant increases in lung tumor incidence (adenomas or carcinomas) have been accepted as evidence of a tumorigenic response, whereas any detection of a mesothelioma has been generally accepted as evidence for this relatively rare type of tumor.

Tumorigenic responses in the lung or pleura were observed in hamsters and rats exposed to the refractory ceramic fiber, RCF1, at concentrations as low as 75 WHO fibers/cc, in rats exposed to RCF2, RCF3, or RCF4 at concentrations between 153 and 220 WHO fibers/cc, in hamsters exposed to the durable glass fiber, MMVF33, at 310 WHO fibers/cc, and in rats exposed to the special purpose 104E-glass fiber at 1,022 WHO fibers/cc. The carcinogenic response to 104E-glass fiber in rats was observed after only 1 year of exposure, in contrast to another special purpose glass fiber, 100/475, which did not induce cancer in rats exposed to 1,119 WHO fibers/cc for 1 year.

No other synthetic vitreous fiber types have produced evidence of carcinogenicity in chronic inhalation animal testing. Neither increased lung tumor incidence or the presence of mesotheliomas were found in rats exposed for 2 years to: the insulation glass wools, MMVF10 or MMVF11 at 232 or 246 WHO fibers/cc; the insulation rock wool, MMVF21, at 243 WHO fibers/cc of; the slag wool, MMVF22, at 213 WHO fibers/cc; the newly developed high-temperature rock wool, MMVF34, at 291 WHO fibers/cc; or the high-silica synthetic vitreous fiber, X607, at 180 WHO fibers/cc. Additionally, evidence for carcinogenic responses was not found in male hamsters exposed to MMVF10a at 339 WHO fibers. Although no tumors were found in male baboons exposed to 1,122 NIOSH fibers/cc of C102/C104 blend fibrous glass for 30 months, the study was limited by small study size (biopsies of only two animals).

Increased incidences of fibrosis or tumors (e.g., lung tumors, mesotheliomas, sarcomas, or abdominal cavity tumors) have been observed in studies of rodents exposed to glass wool, rock wool, slag wool, or refractory ceramic fibers by intratracheal instillation, by intrapleural implantation or injection, and by intraperitoneal injection. These lesions were not observed in a few studies involving intraperitoneal injection of continuous filament glass fibers. Most of these studies involve a single administration followed by observation periods up to 2 years. The relevance of these studies to human inhalation exposure is limited because of the high doses used, the bypassing of the natural defense systems of the nasal and upper respiratory system, and the overloading or lack (for intraperitoneal studies) of clearance mechanisms mediated by pulmonary macrophages.

The U.S. Department of Health and Human Services, National Toxicology Program classified glass wool (respirable size) as *reasonably anticipated to be a human carcinogen*, based on sufficient evidence of carcinogenicity in experimental animals. This assessment was originally prepared in 1993–1994 for the *7th Report on Carcinogens*, but has not been updated since then in the *8th, 9th, or 10th Reports on Carcinogens*. Continuous filament glass, rock wool, slag wool, or refractory ceramic fibers were not listed or assessed for carcinogenicity in the *7th, 8th, 9th, or 10th Report on Carcinogens*.

In 2001, IARC convened a scientific working group of 19 experts from 11 countries to review a new monograph on "man-made vitreous fibers" that replaced the previous IARC monograph on these materials. The new monograph and the working group concluded that epidemiologic studies published since the previous IARC assessment provide no evidence of increased risks of lung cancer or of mesothelioma from occupational exposure during the manufacture of man-made vitreous fibers and inadequate evidence overall of any excess cancer risk. IARC concluded that there was (1) sufficient evidence in experimental animals for the carcinogenicity of certain special purpose glass fibers and of refractory ceramic fibers; (2) limited evidence in experimental animals for the carcinogenicity of insulation glass wool, rock (stone) wool, and slag wool; and (3) inadequate evidence in experimental animals for the carcinogenicity of continuous glass filament and certain newly developed, less biopersistent fibers such as X-607 and MMVF34. Insulation glass wool, rock (stone) wool, slag wool, and continuous filament glass were classified in Group 3, *not classifiable as to carcinogenicity to humans* because of the inadequate evidence of carcinogenicity in humans and the relatively low biopersistence of these materials. In contrast, refractory ceramic fibers and certain special-purpose glass fibers (104E-glass

and 475 glass fibers) not used as insulating materials were classified in Group 2B*, possibly carcinogenic to humans,* because of their relatively high biopersistence.

The U.S. EPA Integrated Risk Information System (IRIS) has not classified the potential carcinogenicity of glass wool, continuous filament glass, rock wool, or slag wool, but assigned refractory ceramic fibers to Group B2, *probable human carcinogen*, based on no data on carcinogenicity in humans and sufficient evidence of carcinogenicity in animal studies. Currently, EPA is developing a cancer assessment for refractory ceramic fibers based on the multiple-exposure chronic inhalation animal bioassays. The assessment is considering the development of quantitative inhalation unit risk estimates for refractory ceramic fibers based on the animal tumorigenic responses, but, as of June 2004, the assessment has not been released.

## 2.3 MINIMAL RISK LEVELS

***Inhalation MRLs***

- A minimal risk level (MRL) of 0.03 WHO fibers/cc has been derived for chronic-duration inhalation exposure to refractory ceramic fibers

The 2-year, multiple-exposure level inhalation bioassay of the refractory ceramic fiber, RCF1, in male Fischer 344 rats provides the best available data describing exposure-response relationships for nonneoplastic lesions in the lung and pleura from chronic inhalation exposure to refractory ceramic fibers (Mast et al. 1995a, 1995b). The study identifies pulmonary inflammation as the critical nonneoplastic end point of concern and identifies other more serious effects at the higher exposure levels (pulmonary and pleural fibrosis and cancer of the lung and pleura). Other studies of rats exposed to RCF1 by inhalation provide strong support for pulmonary inflammation as the critical end point (Bellman et al. 2001; Everitt et al. 1997; Gelzleichter et al. 1999; McConnell et al. 1995), as well as other animal inhalation studies of other refractory ceramic fibers (Mast et al. 1995a) and other synthetic vitreous fibers such as insulation glass wools, MMVF10 and MMVF11 (Hesterberg et al. 1993c; McConnell et al. 1999), slag wool MMVF22 (McConnell et al. 1994), and rock wool MMVF21 (McConnell et al. 1994). Chronic-duration MRLs for the other synthetic vitreous fibers with adequate rat exposure-response data (e.g., MMVF10, MMVF11, MMVF21, and MMVF22) were not derived because of the lack of fully developed lung deposition and clearance models for these materials to aid in cross-species extrapolation from rats to humans.

The MRL was derived using a benchmark dose modeling approach and a cross-species dosimetric scaling factor derived from lung deposition and clearance models for RCF1 fibers in rats and humans, which were developed by C.P. Yu (University of Buffalo) and colleagues (Maxim et al. 2003b; Yu et al. 1995a, 1995b, 1996, 1997, 1998a, 1998b). There are distinct differences between laboratory animal species and humans in respiratory tract size and geometry, ventilation rates and pattern, and macrophage sizes that influence the retention (the net result of deposition and clearance) of fibers in the lung. The lung retention models for RCF1 in rats and humans incorporate many of these interspecies differences, and significantly decrease uncertainty in extrapolating doses from rats to humans.

The approach (described more completely in Appendix A) involved the following steps.

(1) Continuous-variable models in the EPA Benchmark Dose Software were fit to exposure-response data for lung weight and scores for macrophage aggregation, bronchiolization, and collagen deposition at the bronchoalveolar junction in male Fischer 344 male rats exposed to RCF1 for 2 years.

(2) The best-fitting model for each end point was used to calculate a benchmark concentration and a lower 95% confidence limit (BMCs and BMCLs in units of total fibers/cc) associated with a 10% increase in lung weight, compared with controls, or a mean minimal score of 1.0 (on a 0–5 scale) for the lesion.

(3) The point of departure for the MRL was selected as the BMCL associated with the most sensitive end point, the BMCL for macrophage aggregation (9 total fibers/cc).

(4) The selected rat BMCL was converted to a human equivalent concentration ($BMCL_{HEC}$=1 WHO fibers/cc) using a cross-species scaling factor, 0.07, derived from the lung deposition and clearance models developed for RCF1 in rats and humans.

(5) The $BMCL_{HEC}$ for macrophage aggregation was divided by an uncertainty factor of 30 (3 for interspecies extrapolation with dosimetric adjustment and 10 for human variability).

The rat BMCL for pulmonary macrophage aggregation was selected as the point of departure for the MRL from the set of rat BMCLs for different pulmonary end points shown in Table 2-1. The ATSDR MRL Workgroup considered an alternative MRL derivation with bronchoalveolar collagen deposition as the critical effect, but preferred selection of macrophage aggregation as the critical effect because this effect occurred at lower concentrations than the other effects, as evidenced by the values of the rat BMCs and BMCLs in Table 2-1. When collagen deposition was selected as the critical effect for the MRL, an alternative MRL of 0.02 WHO fibers/cc was derived, which is similar in value to the MRL based on

## Table 2-1. BMCs and BMCLs for 10% Lung Weight Increase and Pulmonary Lesion Scores of 1 in Rats Exposed to RCF1 for 24 Months

| Endpoint | BMC (total fiber/cc) | BMCL (total fiber/cc) |
|---|---|---|
| Lung weight | 133 | 79 |
| Pulmonary macrophage aggregation | 12 | 9 |
| Bronchiolization | 37 | 30 |
| Collagen deposition at the bronchoalveolar junction | 37 | 32 |

Source: Mast et al. 1995a, 1995b; see text and Appendix A for more details on the benchmark dose analysis.

macrophage aggregation (0.03 WHO fibers/cc). (The alternative MRL used a rat benchmark concentration of 32 total fibers/cc, a cross-species scaling factor of 0.07, and a total uncertainty factor of 90: 3 for cross-species extrapolation, 10 for human variability, and 3 for the selection of a potentially serious adverse effect as the critical effect; see Appendix A.)

The rat BMCs and BMCLs shown in Table 2-1 were calculated from the best-fitting models for the exposure-response data for the most sensitive nonneoplastic pulmonary effects observed in Fischer 344 rats and shown in Table 2-2. The data in Table 2-2 show that each of these effects increased in severity with increasing exposure level. The severity of each of these effects also was positively related with concentrations of fibers in the lungs of the rats following 24 months of exposure (see Table 2-2).

Although the 2-year RCF1 bioassays (Mast et al. 1995a, 1995b) provide the best available exposure-response data for refractory ceramic fibers, the presence of nonfibrous particles in the RCF1 test atmosphere is widely acknowledged to have added to the lung responses in rats to an undetermined degree (Bellmann et al. 2001; Mast et al. 2000; Maxim et al. 2003b). Under conditions in which lung clearance mechanisms become overloaded, many types of nonfibrous or fibrous materials can produce pulmonary fibrosis or tumors in rats (Oberdörster 1994). The ratio of total fibers:nonfibrous particles for the RCF1 material used in the 2-year rat bioassay has been reported to be about 3:1 by Bellmann et al. (2001), about 1–2:1 from data reported by Mast et al. (1995a, 1995b), and 9:1 by Maxim et al. (1997). In contrast, workplace air samples showed a ratio of about 0.5:1 (Maxim et al. 1997). The likelihood that the nonfibrous particles in the RCF1 material contributed, to an undetermined degree, to the lung responses in rat indicates that the MRL may underestimate the daily human exposure that is likely to be without appreciable risk of adverse noncancer health effects. As such, the MRL is expected to be protective of public health.

Some evidence that the presence of the nonfibrous particles can enhance the effects on the lung was provided by comparing responses in rats exposed by inhalation for 3 weeks to concentrations of about 125 fibers (with lengths >20 μm)/cc of either RCF1 or a sample of refractory ceramic fiber, called RCF1a, in which only 2% of the mass was accounted for by nonfibrous particles (Bellmann et al. 2001). Expressed as WHO fibers/cc, the mean concentrations were 481 fibers/cc for RCF1a and 679 fibers/cc for RCF1. Pulmonary clearance ability was markedly depressed by RCF1, but not by RCF1a, and indices of pulmonary inflammation were more persistently increased by RCF1 than by RCF1a (Bellmann et al. 2001).

## Table 2-2. Non-neoplastic Lung Responses in F344 Rats Exposed for 24 Months to RCF1

| Exposure level (total fibers/cc) | Fiber concentrations in lungs at 24 months (mean total fibers per mg lung x$10^4$) | Lung weight (Percent of control) | Mean score±standard deviation (0–5 Scale) | | |
|---|---|---|---|---|---|
| | | | Macrophage aggregation | Bronchio-lization | Collagen deposition at the broncho-alveolar junction |
| 0 (n=12) | NR | 100.0±14.0 | 0±0 | 0±0 | 0±0 |
| 36 (n=6) | 5.55±1.71 | 116.8±12.3 | 2.0±0 | 1.2±0.4 | 0.7±0.82 |
| 91 (n=6) | 18.80±3.59 | 110.9±8.1 | 2.5±0.6 | 1.8±0.4 | 2±0 |
| 162 (n=6) | 27.80±6.06 | 131.8±15.3 | 3.0±0 | 2.7±0.5 | 2.8±0.4 |
| 234 (n=6) | 37.00±8.01 | 164.7±44.2 | 3.2±0.4 | 2.7±0.5 | 2.2±0.4 |

Source: Mast et al. 1995a, 1995b; Bernstein et al. 2001b; see Appendix A

0–5 Scale: 0=normal; 1=minimal; 2=mild; 3=moderate; 4=marked; 5=severe; NR= not reported

The chronic MRL is expected to be appropriately applied to intermediate-duration exposure scenarios, based on evidence from interim sacrifice data from the Mast et al. (1995a, 1995b) bioassay that exposure-response relationships for pulmonary inflammation and chronic exposure are similar to those for intermediate-duration exposure. Scores for pulmonary inflammation progressed to only a limited degree with progression from intermediate to chronic duration. For example, mean scores for macrophage aggregation in rats exposed to 3, 9, 16, and 30 mg/m$^3$ at 3 months were 1.7, 2, 2, and 2, respectively. The respective scores were 2, 2.3, 3, and 3 at 24 months and 2, 2.5, 3, and 3.2 at 24 months.

Exposure-response relationships for pulmonary inflammation from acute inhalation exposure to synthetic vitreous fibers are inadequately characterized for deriving an acute inhalation MRL for any type of synthetic vitreous fiber.

Any use of the MRL for refractory ceramic fibers in assessing likely health hazards from the insulation wools should acknowledge the evidence that many of the insulation wools are markedly less durable and less potent than refractory ceramic fibers (Bernstein et al. 2001a, 2001b; Eastes and Hadley 1996; Eastes et al. 2000; Hesterberg et al. 1998a). There are data from multiple-exposure-level 2-year rat inhalation bioassays on the glass wools, MMVF10 and MMVF11 (Hesterberg et al. 1993c; McConnell et al. 1999), the slag wool, MMVF22 (McConnell et al. 1994), and the rock wool, MMVF21 (McConnell et al. 1994) that adequately describe exposure-response relationships for nonneoplastic pulmonary effects (i.e., pulmonary inflammation) from intermediate- and chronic-duration exposure to these materials. However, lung deposition and clearance models for these synthetic vitreous fibers (such as the ones developed by C.P. Yu and colleagues for RCF1) are not yet fully developed to carry out physiologically based dosimetric calculations of human equivalent concentrations.

There are no adequate data (from multiple-exposure level studies) for deriving inhalation MRLs for the other types of synthetic vitreous fibers (special applications glass fibers or continuous filament glass fibers that are woven).

***Oral MRLs***

No MRLs were derived for oral exposure to any synthetic vitreous fibers for any duration of exposure. No studies were located regarding noncancer health effects in humans or animals orally exposed to synthetic vitreous fibers. Oral exposure to synthetic vitreous fibers does not present a high priority public

health concern, given the low probability of exposure by this route. Supporting the lack of concern, results from an extensive series of lifetime studies of asbestos fibers in the diet of rats and hamsters found no consistent evidence for increased nonneoplastic lesions in exposed compared with control animals (see Agency for Toxic Substance and Disease Registry 2001).

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

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

## 3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

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

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

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

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

### 3.2.1 Inhalation Exposure

#### 3.2.1.1 Death

No studies were located in which acute- or intermediate-duration inhalation exposure to synthetic vitreous fibers caused mortality in humans. As discussed in Sections 3.2.1.2 and 3.2.1.7, cohort mortality studies of workers involved in the manufacture of fiberglass, rock wool, slag wool, and refractory ceramic fibers have not found consistently increased risk of mortality associated with nonmalignant or malignant respiratory disease.

None of the animal studies described below observed increased risk of death after inhalation exposure to synthetic vitreous fibers.

#### 3.2.1.2 Systemic Effects

No studies were located regarding hematological, musculoskeletal, endocrine, dermal, ocular, or body weight effects in humans or animals after inhalation exposure to synthetic vitreous fibers. The principal target organ of inhaled synthetic vitreous fibers is the respiratory system.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects from inhalation exposure to synthetic vitreous fibers are summarized in Table 3-1 and plotted in Figure 3-1.

Although there are epidemiological studies of workers involved in the manufacture of synthetic vitreous fibers such as refractory ceramic fibers, the results do not characterize exposure-response relationships for potential health effects in humans. In contrast, animal inhalation studies identify several types of respiratory effects from various types of synthetic vitreous fibers and provide information on exposure-response relationships. Thus, data in Table 3-1 and Figure 3-1 are restricted to reliable NOAEL and LOAEL values from animal inhalation toxicity studies. Units of exposure in animal studies include gravimetric measurements ($mg/m^3$), which include the weight of nonfibrous particles present in air samples, and fiber count measurements (# fibers/cc), which rely on microscopically aided counting of fiber numbers in air samples. The most frequently reported unit of exposure among the available animal toxicity studies is based on the WHO fiber counting rules (i.e., a fiber is counted as a particle with length

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| | **ACUTE EXPOSURE** | | | | | | |
| | **Systemic** | | | | | | |
| 1 | Rat (Fischer- 344) | 5 d 6 hr/d (nose only) | Resp | | 1700[b] M (pulmonary and pleural inflammation; increased lung and diaphragm mesothelial cell proliferation) | | Everitt et al. 1994 RCF1 |
| 2 | Rat (Fischer- 344) | 5 d 6 hr/d | Resp | | 2645 M (pulmonary and pleural inflammation) | | Gelzleichter et al. 1996a, 1996c RCF1 |
| 3 | Hamster (Golden Syrian) | 5 d 6 hr/d (nose only) | Resp | | 1700[b] M (pulmonary and pleural inflammation; increased lung mesothelial cell proliferation) | | Everitt et al. 1994 RCF1 |
| | **INTERMEDIATE EXPOSURE** | | | | | | |
| | **Systemic** | | | | | | |
| 4 | Rat (Wistar) | 3 wk 6 hr/day 5 d/wk (nose only) | Resp | | | 679 F (very slight interstitial fibrosis, pulmonary inflammation, reduced alveolar clearance) | Bellman et al. 2001 RCF1 |
| 5 | Rat (Wistar) | 3 wk 6 hr/day 5 d/wk (nose only) | Resp | | | 481 F (very slight interstitial fibrosis, pulmonary inflammation) | Bellman et al. 2001 RCF1a |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **6** | Rat (Wistar) | 1 yr 7 hr/d 5 d/wk | Resp | | 1119 M (pulmonary inflammation) | | Cullen et al. 2000 100/475 special purpose glass fiber |
| **7** | Rat (Wistar) | 1 yr 7 hr/d 5 d/wk | Resp | | | 1022 M (advanced pulmonary fibrosis; pulmonary inflammation) | Cullen et al. 2000 104 E-glass special purpose glass fiber |
| **8** | Rat (Fischer- 344) | 4 wk 4 hr/d 5 d/wk (nose only) | Resp | | 300 M (pulmonary and pleural inflammation; incr. lung and diaphragm mesothelial cell proliferation) | | Everitt et al. 1997 RCF1 |
| **9** | Rat (Fischer- 344) | 12 wk 4 hr/d 5 d/wk (nose only) | Resp | | 300 M (pulmonary and pleural inflammation; incr. lung and diaphragm mesothelial cell proliferation) | | Everitt et al. 1997 RCF1 |
| **10** | Rat (Fischer- 344) | 12 wk 4 hr/d 5d/wk | Resp | | 296 M (pulmonary and pleural inflammation) | | Gelzleichter et al. 1999 RCF1 |

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **11** | Rat (Fischer- 344) | 3 mo 6 hr/d 5 d/wk (nose only) | Resp | | 29 M (minimal pulmonary inflammation) | | Hesterberg et al. 1993 MMVF10 glass wool |
| | | | Bd Wt | 232 M | | | |
| **12** | Rat (Fischer- 344) | 6 mo 6 hr/d 5 d/wk (nose only) | Resp | | 29 M (minimal-to-mild pulmonary inflammation) | | Hesterberg et al. 1993 MMVF10 glass wool |
| | | | Bd Wt | 232 M | | | |
| **13** | Rat (Fischer- 344) | 12 mo 6 hr/d 5 d/wk (nose only) | Resp | | 29 M (minimal-to-mild pulmonary inflammation) | | Hesterberg et al. 1993 MMVF10 glass wool |
| | | | Bd Wt | 232 M | | | |
| **14** | Rat (Fischer- 344) | 3 mo 6 hr/d 5 d/wk (nose only) | Resp | | 41 M (minimal pulmonary inflammation) | | Hesterberg et al. 1993 MMVF11 glass wool |
| | | | Bd Wt | 246 M | | | |

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **15** | Rat (Fischer- 344) | 6 mo 6 hr/d 5 d/wk (nose only) | Resp | | 41 M (minimal-to-mild pulmonary inflammation) | | Hesterberg et al. 1993 MMVF11 glass wool |
| | | | Bd Wt | 256 M | | | |
| **16** | Rat (Fischer- 344) | 12 mo 6 hr/d 5 d/wk (nose only) | Resp | | 41 M (minimal-to-mild pulmonary inflammation) | | Hesterberg et al. 1993 MMVF11 glass wool |
| | | | Bd Wt | 246 M | | | |
| **17** | Rat (Fischer- 344) | 3 mo 6 hr/d 5 d/wk (nose only) | Resp | | 180 M (pulmonary inflammation) | | Hesterberg et al. 1998b X607 |
| | | | Hepatic | 180 M | | | |
| | | | Renal | 180 M | | | |
| | | | Bd Wt | 180 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **18** | Rat (Fischer- 344) | 6 mo 6 hr/d 5 d/wk (nose only) | Resp | | 180 M (pulmonary inflammation) | | Hesterberg et al. 1998b X607 |
| | | | Hepatic | 180 M | | | |
| | | | Renal | 180 M | | | |
| | | | Bd Wt | 180 M | | | |
| **19** | Rat (Fischer- 344) | 1 yr 6 hr/d 5 d/wk (nose only) | Resp | | 180 M (pulmonary inflammation) | | Hesterberg et al. 1998b X607 |
| | | | Hepatic | 180 M | | | |
| | | | Renal | 180 M | | | |
| | | | Bd Wt | 180 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **20** | Rat (Fischer- 344) | 3 mo 6 hr/d 5 d/wk (nose only) | Resp | | 291 M (minimal pulmonary inflammation) | | Kamstrup et al. 2001 MMVF34 rock wool |
| | | | Bd Wt | 291 M | | | |
| **21** | Rat (Fischer- 344) | 6 mo 6 hr/d 5 d/wk (nose only) | Resp | | 291 M (minimal-to-slight pulmonary inflammation; bronchoalveolar collagen deposition without fibrosis) | | Kamstrup et al. 2001 MMVF34 rock wool |
| | | | Bd Wt | 291 M | | | |
| **22** | Rat (Fischer- 344) | 12 mo 6 hr/d 5 d/wk (nose only) | Resp | | 291 M (minimal-to-slight pulmonary inflammation) | | Kamstrup et al. 2001 MMVF34 rock wool |
| | | | Bd Wt | 291 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **23** | Rat (Fischer- 344) | 3 mo 6 hr/d 5 d/wk (nose only) | Resp | | 220 M (minimal-to-mild pulmonary inflammation) | | Mast et al. 1995a RCF2 |
| | | | Cardio | 220 M | | | |
| | | | Hepatic | 220 M | | | |
| | | | Renal | 220 M | | | |
| | | | Bd Wt | 220 M | | | |
| **24** | Rat (Fischer- 344) | 6 mo 6 hr/d 5 d/wk (nose only) | Resp | | 220 M (minimal-to-mild pulmonary inflammation) | | Mast et al. 1995a RCF2 |
| | | | Cardio | 220 M | | | |
| | | | Hepatic | 220 M | | | |
| | | | Renal | 220 M | | | |
| | | | Bd Wt | 220 M | | | |

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **25** | Rat (Fischer- 344) | 9 mo 6 hr/d 5 d/wk (nose only) | Resp | | | 220 M (minimal-to-mild interstitial fibrosis, minimal pleural fibrosis, pulmonary inflammation) | Mast et al. 1995a RCF2 |
| | | | Cardio | 220 M | | | |
| | | | Hepatic | 220 M | | | |
| | | | Renal | 220 M | | | |
| | | | Bd Wt | 220 M | | | |
| **26** | Rat (Fischer- 344) | 12 mo 6 hr/d 5 d/wk (nose only) | Resp | | | 220 M (mild interstitial fibrosis, pulmonary inflammation) | Mast et al. 1995a RCF2 |
| | | | Cardio | 220 M | | | |
| | | | Hepatic | 220 M | | | |
| | | | Renal | 220 M | | | |
| | | | Bd Wt | 220 M | | | |

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **27** | Rat (Fischer- 344) | 3 mo 6 hr/d 5 d/wk (nose only) | Resp | | 182 M (minimal-to-mild pulmonary inflammation) | | Mast et al. 1995a RCF3 |
| | | | Cardio | 182 M | | | |
| | | | Hepatic | 182 M | | | |
| | | | Renal | 182 M | | | |
| | | | Bd Wt | 182 M | | | |
| **28** | Rat (Fischer- 344) | 6 mo 6 hr/d 5 d/wk (nose only) | Resp | | | 182 M (minimal-to-mild interstitial fibrosis, pulmonary inflammation) | Mast et al. 1995a RCF3 |
| | | | Cardio | 182 M | | | |
| | | | Hepatic | 182 M | | | |
| | | | Renal | 182 M | | | |
| | | | Bd Wt | 182 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **29** | Rat (Fischer- 344) | 9 mo 6 hr/d 5 d/wk (nose only) | Resp | | | 182 M (mild interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation) | Mast et al. 1995a RCF3 |
| | | | Cardio | 182 M | | | |
| | | | Hepatic | 182 M | | | |
| | | | Renal | 182 M | | | |
| | | | Bd Wt | 182 M | | | |
| **30** | Rat (Fischer- 344) | 12 mo 6 hr/d 5 d/wk (nose only) | Resp | | | 182 M (mild-to-moderate interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation) | Mast et al. 1995a RCF3 |
| | | | Cardio | 182 M | | | |
| | | | Hepatic | 182 M | | | |
| | | | Renal | 182 M | | | |
| | | | Bd Wt | 182 M | | | |

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **31** | Rat (Fischer- 344) | 3 mo 6 hr/d 5 d/wk (nose only) | Resp | | 153 M (minimal-to-mild pulmonary inflammation) | | Mast et al. 1995a RCF4 |
| | | | Cardio | 153 M | | | |
| | | | Hepatic | 153 M | | | |
| | | | Renal | 153 M | | | |
| | | | Bd Wt | 153 M | | | |
| **32** | Rat (Fischer- 344) | 6 mo 6 hr/d 5 d/wk (nose only) | Resp | | 153 M (minimal-to-mild pulmonary inflammation) | | Mast et al. 1995a RCF4 |
| | | | Cardio | 153 M | | | |
| | | | Hepatic | 153 M | | | |
| | | | Renal | 153 M | | | |
| | | | Bd Wt | 153 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **33** | Rat (Fischer- 344) | 9 mo 6 hr/d 5 d/wk (nose only) | Resp | | 153 M (minimal-to-mild pulmonary inflammation) | | Mast et al. 1995a RCF4 |
| | | | Cardio | 153 M | | | |
| | | | Hepatic | 153 M | | | |
| | | | Renal | 153 M | | | |
| | | | Bd Wt | 153 M | | | |
| **34** | Rat (Fischer- 344) | 12 mo 6 hr/d 5 d/wk (nose only) | Resp | | | 153 M (minimal-to-mild interstitial fibrosis, pulmonary inflammation) | Mast et al. 1995a RCF4 |
| | | | Cardio | 153 M | | | |
| | | | Hepatic | 153 M | | | |
| | | | Renal | 153 M | | | |
| | | | Bd Wt | 153 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **35** | Rat (Fischer- 344) | 3 mo 6 hr/d 5 d/wk (nose only) | Resp | | 26 M (minimal-to-mild pulmonary inflammation) | | Mast et al. 1995a, 1995b RCF1 |
| | | | Cardio | 187 M | | | |
| | | | Hepatic | 187 M | | | |
| | | | Renal | 187 M | | | |
| | | | Bd Wt | 187 M | | | |
| **36** | Rat (Fischer- 344) | 6 mo 6 hr/d 5 d/wk (nose only) | Resp | | 26 M (minimal-to-mild pulmonary inflammation) | 187 M (minimal-to-mild interstitial fibrosis, pulmonary inflammation) | Mast et al. 1995a, 1995b RCF1 |
| | | | Cardio | 187 M | | | |
| | | | Hepatic | 187 M | | | |
| | | | Renal | 187 M | | | |
| | | | Bd Wt | 187 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **37** | Rat (Fischer- 344) | 12 mo 6 hr/d 5 d/wk (nose only) | Resp | | 36 M (minimal-to-mild pulmonary inflammation) | 91 M (minimal-to-mild interstitial fibrosis) | Mast et al. 1995a, 1995b RCF1 |
| | | | Cardio | 234 M | | | |
| | | | Hepatic | 234 M | | | |
| | | | Renal | 234 M | | | |
| | | | Bd Wt | 234 M | | | |
| **38** | Rat (Fischer- 344) | 3 mo 6 hr/d 5 d/wk (nose only) | Resp | | 34 M (pulmonary inflammation) | | McConnell et al. 1994 MMVF21 rock wool |
| | | | Cardio | 243 M | | | |
| | | | Hepatic | 243 M | | | |
| | | | Renal | 243 M | | | |
| | | | Bd Wt | 243 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **39** | Rat (Fischer- 344) | 6 mo 6 hr/d 5 d/wk (nose only) | Resp | | 34 M (pulmonary inflammation) | | McConnell et al. 1994 MMVF21 rock wool |
| | | | Cardio | 243 M | | | |
| | | | Hepatic | 243 M | | | |
| | | | Renal | 243 M | | | |
| | | | Bd Wt | 243 M | | | |
| **40** | Rat (Fischer- 344) | 12 mo 6 hr/d 5 d/wk (nose only) | Resp | | 34 M (pulmonary inflammation) | | McConnell et al. 1994 MMVF21 rock wool |
| | | | Cardio | 243 M | | | |
| | | | Hepatic | 243 M | | | |
| | | | Renal | 243 M | | | |
| | | | Bd Wt | 243 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **41** | Rat (Fischer- 344) | 3 mo 6 hr/d 5 d/wk (nose only) | Resp | | 30 M (pulmonary inflammation) | | McConnell et al. 1994 MMVF22 slag wool |
| | | | Cardio | 213 M | | | |
| | | | Hepatic | 213 M | | | |
| | | | Renal | 213 M | | | |
| | | | Bd Wt | 213 M | | | |
| **42** | Rat (Fischer- 344) | 6 mo 6 hr/d 5 d/wk (nose only) | Resp | | 30 M (pulmonary inflammation) | | McConnell et al. 1994 MMVF22 slag wool |
| | | | Cardio | 213 M | | | |
| | | | Hepatic | 213 M | | | |
| | | | Renal | 213 M | | | |
| | | | Bd Wt | 213 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **43** | Rat (Fischer- 344) | 12 mo 6 hr/d 5 d/wk (nose only) | Resp | | 30 M (pulmonary inflammation) | | McConnell et al. 1994 MMVF22 slag wool |
| | | | Cardio | 213 M | | | |
| | | | Hepatic | 213 M | | | |
| | | | Renal | 213 M | | | |
| | | | Bd Wt | 213 M | | | |
| **44** | Rat (Wistar) | 12 mo 5 hr/d 4 d/wk (nose only) | Resp | 252 | | | Muhle et al. 1987 100/475 special purpose glass fiber |
| **45** | Hamster (Golden Syrian) | 4 wk 4 hr/d 5 d/wk (nose only) | Resp | | 300 M (pulmonary and pleural inflammation; incr. lung and diaphragm mesothelial cell proliferation) | | Everitt et al. 1997 RCF1 |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **46** | Hamster (Golden Syrian) | 12 wk<br>4 hr/d<br>5 d/wk<br>(nose only) | Resp | | | 300 M (pulmonary and pleural inflammation; incr. lung and diaphragm mesothelial cell proliferation; early signs of pleural fibrosis) | Everitt et al. 1997<br>RCF1 |
| **47** | Hamster (Golden Syrian) | 12 wk<br>4 hr/d<br>5d/wk | Resp | | 296 M (pulmonary and pleural inflammation) | | Gelzleichter et al. 1999<br>RCF1 |
| **48** | Hamster (Golden Syrian) | 7 wk<br>6 hr/d<br>5 d/wk<br>(nose only) | Resp | | 316 M (pulmonary inflammation) | | Hesterberg et al. 1999<br>MMVF10 glass wool |
| **49** | Hamster (Golden Syrian) | 13 wk<br>6 hr/d<br>5 d/wk<br>(nose only) | Resp | | 36 M (pulmonary inflammation) | | Hesterberg et al. 1999<br>MMVF10 glass wool |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **50** | Hamster (Golden Syrian) | 3 mo 5 d/wk 6 hr/d (nose only) | Resp | | 215 M (mild-to-moderate pulmonary inflammation) | | McConnell et al. 1995 RCF1 |
| | | | Cardio | 215 M | | | |
| | | | Hepatic | 215 M | | | |
| | | | Renal | 215 M | | | |
| | | | Bd Wt | 215 M | | | |
| **51** | Hamster (Golden Syrian) | 3 mo 6 hr/d 5 d/wk (nose only) | Resp | | 339 M (minimal-to-moderate pulmonary inflammation) | | McConnell et al. 1999 MMVF10a glass wool |
| | | | Bd Wt | 339 M | | | |
| **52** | Hamster (Golden Syrian) | 6 mo 6 hr/d 5 d/wk (nose only) | Resp | | 339 M (minimal-to-mild pulmonary inflammation) | | McConnell et al. 1999 MMVF10a glass wool |
| | | | Bd Wt | 339 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **53** | Hamster (Golden Syrian) | 12 mo 6 hr/d 5 d/wk (nose only) | Resp | | 339 M (minimal-to-mild pulmonary inflammation) | | McConnell et al. 1999 MMVF10a glass wool |
| | | | Bd Wt | 339 M | | | |
| **54** | Hamster (Golden Syrian) | 3 mo 6 hr/d 5 d/wk (nose only) | Resp | | 310 M (minimal-to-mild pulmonary inflammation) | | McConnell et al. 1999 MMVF33 special purpose glass |
| | | | Bd Wt | 310 M | | | |
| **55** | Hamster (Golden Syrian) | 6 mo 6 hr/d 5 d/wk (nose only) | Resp | | | 310 M (minimal to mild pulmonary and pleural fibrosis, pulmonary inflammation) | McConnell et al. 1999 MMVF33 special purpose glass |
| | | | Bd Wt | 310 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **56** | Hamster (Golden Syrian) | 6 mo<br>6 hr/d<br>5 d/wk<br>(nose only) | Resp | | | 310 M (mild pulmonary and pleural fibrosis, pulmonary inflammation) | McConnell et al. 1999<br>MMVF33 special purpose glass |
| | | | Bd Wt | 310 M | | | |
| **57** | Baboon | 8 mo<br>7 hr/d<br>5 d/wk<br>(nose only) | Resp | | 1122[b] M (pulmonary inflammation, scant ferruginous bodies) | | Goldstein et al. 1983<br>C102-C104 blend glass wool |
| | **Cancer** | | | | | | |
| **58** | Rat (Wistar) | 1 yr<br>7 hr/d<br>5 d/wk | | | | 1022 M (CEL: pleural mesotheliomas, lung adenomas and carcinomas) | Cullen et al. 2000<br>104 E-glass special purpose glass fiber |
| **59** | Hamster (Golden Syrian) | 40 wk<br>5 d/wk<br>6 h/d<br>(nose only) | | | | 215 M (CEL: pleural mesotheliomas) | McConnell et al. 1995<br>RCF1 |

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| | **CHRONIC EXPOSURE** | | | | | | |
| | **Systemic** | | | | | | |
| **60** | Rat (Fischer- 344) | 18 mo 6 hr/d 5 d/wk (nose only) | Resp | | 29 M (minimal-to-mild pulmonary inflammation) | | Hesterberg et al. 1993 MMVF10 glass wool |
| | | | Bd Wt | 232 M | | | |
| **61** | Rat (Fischer- 344) | 2 yr 6 hr/d 5 d/wk (nose only) | Resp | | 29 M (minimal-to-mild pulmonary inflammation) | | Hesterberg et al. 1993 MMVF10 glass wool |
| | | | Bd Wt | 232 M | | | |
| **62** | Rat (Fischer- 344) | 18 mo 6 hr/d 5 d/wk (nose only) | Resp | | 41 M (minimal-to-mild pulmonary inflammation) | | Hesterberg et al. 1993 MMVF11 glass wool |
| | | | Bd Wt | 246 M | | | |
| **63** | Rat (Fischer- 344) | 2 yr 6 hr/d 5 d/wk (nose only) | Resp | | 41 M (minimal-to-mild pulmonary inflammation) | | Hesterberg et al. 1993 MMVF11 glass wool |
| | | | Bd Wt | 246 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **64** | Rat (Fischer- 344) | 18 mo 6 hr/d 5 d/wk (nose only) | Resp | | 180 M (pulmonary inflammation) | | Hesterberg et al. 1998b X607 |
| | | | Hepatic | 180 M | | | |
| | | | Renal | 180 M | | | |
| | | | Bd Wt | 180 M | | | |
| **65** | Rat (Fischer- 344) | 2 yr 6 hr/d 5 d/wk (nose only) | Resp | | 180 M (pulmonary inflammation) | | Hesterberg et al. 1998b X607 |
| | | | Hepatic | 180 M | | | |
| | | | Renal | 180 M | | | |
| | | | Bd Wt | 180 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **66** | Rat (Fischer- 344) | 18 mo 6 hr/d 5 d/wk (nose only) | Resp | | 291 M (minimal-to-slight pulmonary inflammation) | | Kamstrup et al. 2001 MMVF34 rock wool |
| | | | Bd Wt | 291 M | | | |
| **67** | Rat (Fischer- 344) | 24 mo 6 hr/d 5 d/wk (nose only) | Resp | | 291 M (minimal-to-moderate pulmonary inflammation) | | Kamstrup et al. 2001 MMVF34 rock wool |
| | | | Bd Wt | 291 M | | | |
| **68** | Rat (Fischer- 344) | 15 mo 6 hr/d 5 d/wk (nose only) | Resp | | | 220 M (mild interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation) | Mast et al. 1995a RCF2 |
| | | | Cardio | 220 M | | | |
| | | | Hepatic | 220 M | | | |
| | | | Renal | 220 M | | | |
| | | | Bd Wt | 220 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **69** | Rat (Fischer- 344) | 18 mo<br>6 hr/d<br>5 d/wk<br>(nose only) | Resp | | | 220 M (mild interstitial fibrosis, minimal pleural fibrosis, pulmonary inflammation) | Mast et al. 1995a<br>RCF2 |
| | | | Cardio | 220 M | | | |
| | | | Hepatic | 220 M | | | |
| | | | Renal | 220 M | | | |
| | | | Bd Wt | 220 M | | | |
| **70** | Rat (Fischer- 344) | 2 yr<br>6 hr/d<br>5 d/wk<br>(nose only) | Resp | | | 220 M (mild-to-moderate interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation) | Mast et al. 1995a<br>RCF2 |
| | | | Cardio | 220 M | | | |
| | | | Hepatic | 220 M | | | |
| | | | Renal | 220 M | | | |
| | | | Bd Wt | 220 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **71** | Rat (Fischer- 344) | 15 mo 6 hr/d 5 d/wk (nose only) | Resp | | | 182 M (mild interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation) | Mast et al. 1995a RCF3 |
| | | | Cardio | 182 M | | | |
| | | | Hepatic | 182 M | | | |
| | | | Renal | 182 M | | | |
| | | | Bd Wt | 182 M | | | |
| **72** | Rat (Fischer- 344) | 18 mo 6 hr/d 5 d/wk (nose only) | Resp | | | 182 M (mild interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation) | Mast et al. 1995a RCF3 |
| | | | Cardio | 182 M | | | |
| | | | Hepatic | 182 M | | | |
| | | | Renal | 182 M | | | |
| | | | Bd Wt | 182 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **73** | Rat (Fischer- 344) | 2 yr 6 hr/d 5 d/wk (nose only) | Resp | | | 182 M (mild-to-moderate interstitial fibrosis, minimal pleural fibrosis, pulmonary inflammation) | Mast et al. 1995a RCF3 |
| | | | Cardio | 182 M | | | |
| | | | Hepatic | 182 M | | | |
| | | | Renal | 182 M | | | |
| | | | Bd Wt | 182 M | | | |
| **74** | Rat (Fischer- 344) | 15 mo 6 hr/d 5 d/wk (nose only) | Resp | | | 153 M (minimal-to-mild interstitial fibrosis, pulmonary inflammation) | Mast et al. 1995a RCF4 |
| | | | Cardio | 153 M | | | |
| | | | Hepatic | 153 M | | | |
| | | | Renal | 153 M | | | |
| | | | Bd Wt | 153 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **75** | Rat (Fischer- 344) | 18 mo 6 hr/d 5 d/wk (nose only) | Resp | | | 153 M (minimal-to-mild interstitial fibrosis, minimal pleural fibrosis, pulmonary inflammation) | Mast et al. 1995a RCF4 |
| | | | Cardio | 153 M | | | |
| | | | Hepatic | 153 M | | | |
| | | | Renal | 153 M | | | |
| | | | Bd Wt | 153 M | | | |
| **76** | Rat (Fischer- 344) | 2 yr 6 hr/d 5 d/wk (nose only) | Resp | | | 153 M (minimal-to-mild interstitial fibrosis, pulmonary inflammation) | Mast et al. 1995a RCF4 |
| | | | Cardio | 153 M | | | |
| | | | Hepatic | 153 M | | | |
| | | | Renal | 153 M | | | |
| | | | Bd Wt | 153 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **77** | Rat (Fischer- 344) | 18 mo<br>6 hr/d<br>5 d/wk<br>(nose only) | Resp | | 26 M (minimal-to-mild pulmonary inflammation) | 75 M (minimal-to-mild interstitial fibrosis) | Mast et al. 1995a, 1995b<br>RCF1 |
| | | | Cardio | 187 M | | | |
| | | | Hepatic | 187 M | | | |
| | | | Renal | 187 M | | | |
| | | | Bd Wt | 187 M | | | |
| **78** | Rat (Fischer- 344) | 2 yr<br>6 hr/d<br>5 d/wk<br>(nose only) | Resp | | 26[c] M (minimal-to-mild pulmonary inflammation) | 75 M (minimal-to-mild interstitial fibrosis, pulmonary inflammation) | Mast et al. 1995a, 1995b<br>RCF1 |
| | | | Cardio | 187 M | | | |
| | | | Hepatic | 187 M | | | |
| | | | Renal | 187 M | | | |
| | | | Bd Wt | 187 M | | | |

[a] 

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **79** | Rat (Fischer- 344) | 18 mo 6 hr/d 5 d/wk (nose only) | Resp | | 34 M (pulmonary inflammation) | 150 M (mild pulmonary fibrosis, pulmonary inflammation) | McConnell et al. 1994 MMVF21 rock wool |
| | | | Cardio | 243 M | | | |
| | | | Hepatic | 243 M | | | |
| | | | Renal | 243 M | | | |
| | | | Bd Wt | 243 M | | | |
| **80** | Rat (Fischer- 344) | 2 yr 6 hr/d 5 d/wk (nose only) | Resp | | 34 M (pulmonary inflammation) | 150 M (mild pulmonary fibrosis, pulmonary inflammation) | McConnell et al. 1994 MMVF21 rock wool |
| | | | Cardio | 243 M | | | |
| | | | Hepatic | 243 M | | | |
| | | | Renal | 243 M | | | |
| | | | Bd Wt | 243 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **81** | Rat (Fischer- 344) | 18 mo 6 hr/d 5 d/wk (nose only) | Resp | | 30 M (pulmonary inflammation) | | McConnell et al. 1994 MMVF22 slag wool |
| | | | Cardio | 213 M | | | |
| | | | Hepatic | 213 M | | | |
| | | | Renal | 213 M | | | |
| | | | Bd Wt | 213 M | | | |
| **82** | Rat (Fischer- 344) | 24 mo 6 hr/d 5 d/wk (nose only) | Resp | | 30 M (pulmonary inflammation) | | McConnell et al. 1994 MMVF22 slag wool |
| | | | Cardio | 213 M | | | |
| | | | Hepatic | 213 M | | | |
| | | | Renal | 213 M | | | |
| | | | Bd Wt | 213 M | | | |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **83** | Hamster (Golden Syrian) | 18 mo 5 d/wk 6 hr/d (nose only) | Resp | | | 215 M (mild-to-moderate interstitial fibrosis, moderate-to-marked pleural fibrosis, pulmonary inflammation, mesothelial hyperplaisa) | McConnell et al. 1995 RCF1 |
| | | | Cardio | 215 M | | | |
| | | | Hepatic | 215 M | | | |
| | | | Renal | 215 M | | | |
| | | | Bd Wt | 215 M | | | |
| **84** | Hamster (Golden Syrian) | 18 mo 6 hr/d 5 d/wk (nose only) | Resp | | 339 M (minimal-to-mild pulmonary inflammation) | | McConnell et al. 1999 MMVF10a glass wool |
| | | | Bd Wt | 339 M | | | |

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **85** | Hamster (Golden Syrian) | 18 mo 6 hr/d 5 d/wk (nose only) | Resp | | | 310 M (mild pleural and interstitial fibrosis; mesothelial hyperplasia) | McConnell et al. 1999 MMVF33 special purpose glass |
| | | | Bd Wt | 310 M | | | |
| **86** | Baboon | 18 mo 7 hr/d 5 d/wk (nose only) | Resp | | | 1122[b] M (focal peribronchiolar fibrosis; numerous pulmonary ferruginous bodies) | Goldstein et al. 1983 C102-C104 blend glass wool |
| **87** | Baboon | 30 mo 7 hr/d 5 d/wk (nose only) | Resp | | | 1122[b] M (focal peribronchiolar fibrosis; numerous pulmonary ferruginous bodies) | Goldstein et al. 1983 C102-C104 blend glass wool |
| | **Cancer** | | | | | | |
| **88** | Rat (Fischer- 344) | 2 yr 6 hr/d 5 d/wk (nose only) | | | | 182 M (CEL: pulmonary adenomas and carcinomas, pleural mesotheliomas) | Mast et al. 1995a RCF3 |
| **89** | Rat (Fischer- 344) | 2 yr 6 hr/d 5 d/wk (nose only) | | | | 153 M (CEL: pleural mesothelioma) | Mast et al. 1995a RCF4 |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **90** | Rat (Fischer- 344) | 2 yr<br>6 hr/d<br>5 d/wk<br>(nose only) | | | | 220 M (CEL: pulmonary carcinomas, pleural mesotheliomas) | Mast et al. 1995a<br>RCF2 |
| **91** | Rat (Fischer- 344) | 2 yr<br>6 hr/d<br>5 d/wk<br>(nose only) | | | | 187 M (CEL: pulmonary adenomas and carcinomas) | Mast et al. 1995a, 1995b<br>RCF1 |
| **92** | Rat (Fischer- 344) | 2 yr<br>6 hr/d<br>5 d/wk<br>(nose only) | | | | 75 M (CEL: pleural mesothelioma) | Mast et al. 1995a, 1995b<br>RCF1 |
| **93** | Hamster (Golden Syrian) | 18 mo<br>5 d/wk<br>6 hr/d<br>(nose only) | | | | 215 M (CEL: pleural mesotheliomas) | McConnell et al. 1995<br>RCF1 |
| **94** | Hamster (Golden Syrian) | 78 wk<br>6 hr/d<br>5 d/wk<br>(nose only) | | | | 310 M (CEL: pleural mesothelioma) | McConnell et al. 1999<br>MMVF33 special purpose glass |

**Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (WHO fibers/cc) | LOAEL Less Serious (WHO fibers/cc) | LOAEL Serious (WHO fibers/cc) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **95** | Hamster (Golden Syrian) | 24 mo 6 hr/d 5 d/wk (nose only) | | | | 200 (CEL: pleural mesothelioma) | Smith et al. 1987 RCF |

a The number corresponds to entries in Figure 3-1.
Doses are reported as WHO fibers/cc; (WHO fibers = particles with length >5µm, diameter <3 µm, and a length:width ratio =3:1)

b Dose reported as NIOSH fibers/cc; (NIOSH fibers = particles with length >5µm and a length:width ratio =3:1)

c Used to derive a chronic inhalation minimal risk level (MRL) of 0.03 WHO fibers/cc for refractory ceramic fibers, as described in detail in Appendix A. The MRL was derived using a benchmark dose modeling approach and a cross-species dosimetric scaling factor derived from lung deposition and clearance models for RCF1 fibers in rats and humans. Continuous-variable models in the EPA Benchmark Dose Software were fit to data for macrophage aggregation, bronchiolization, collagen deposition at the bronchoalveolar junction, and lung weight in F344 male rats exposed to RCF1 for 2 years. The best-fitting model for each endpoint was used to calculate benchmark concentrations and their lower 95% confidence limits (BMCs and BMCLs in units of total fibers/cc) associated with 10% increase in lung weight, compared with controls, or a mean minimal score of 1.0 (on a 0-5 scale) for the lesions. The point of departure for the MRL was selected as the BMCL associated with the most sensitive endpoint, the BMCL for macrophage aggregation - 9 total fibers/cc. The selected rat BMCL was converted to a human equivalent concentration (BMCLHEC =1 WHO fibers/cc) using a cross-species scaling factor of 0.07. The BMCLHEC for macrophage aggregation was divided by an uncertainty factor of 30 (3 for interspecies extrapolation with dosimetric adjustment and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; G = gavage; Gastro = gastrointestinal; gd = gestational day; Gn pig = guinea pig; hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); MMVF = man-made vitreous fiber; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; occup = occupational; NS = not specified; RCF = refractory ceramic fiber; Resp = respiratory; (W) = drinking water; wk = week(s); yr = year(s)

## Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation

Acute (≤14 days)

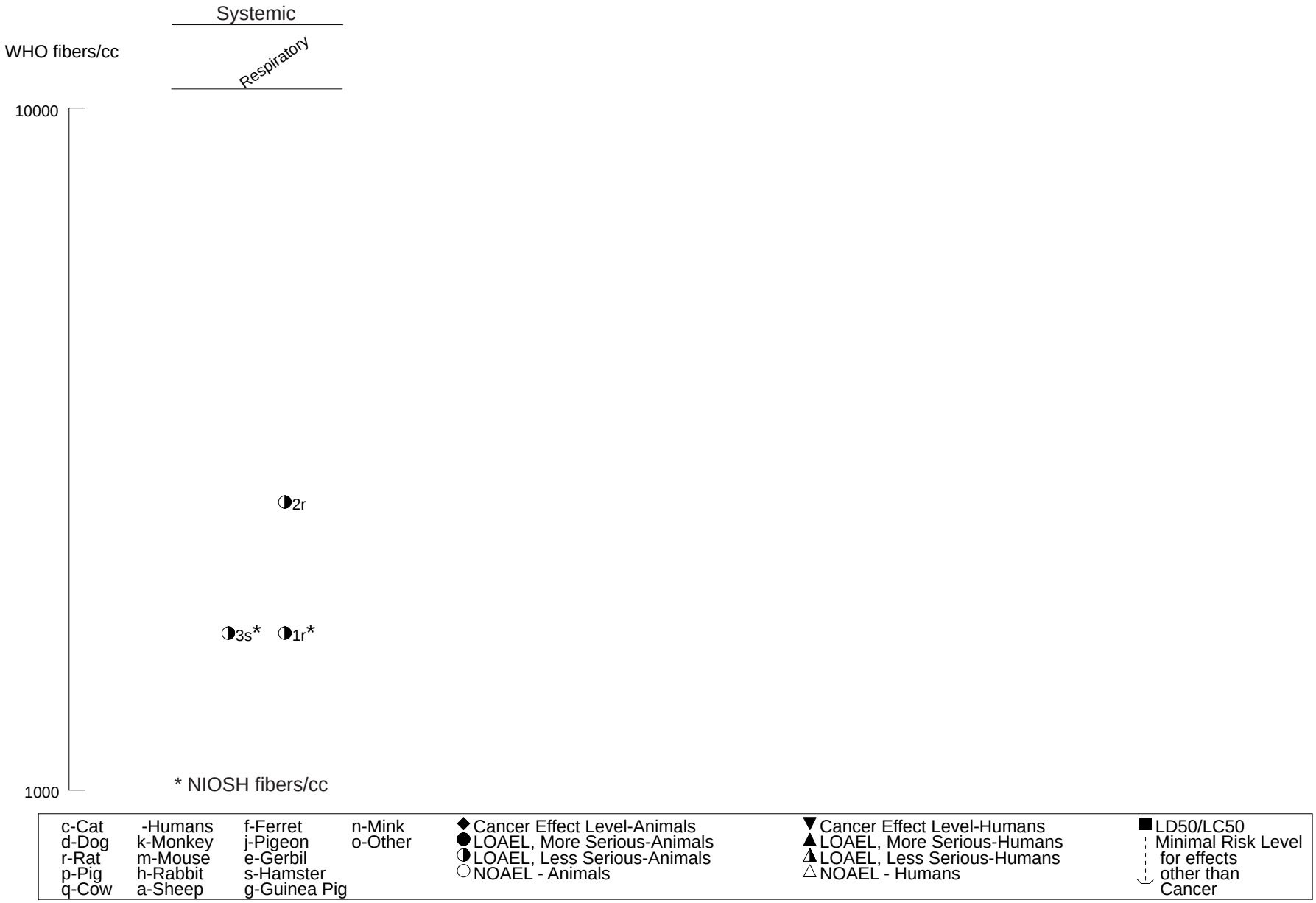


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Intermediate (15-364 days)

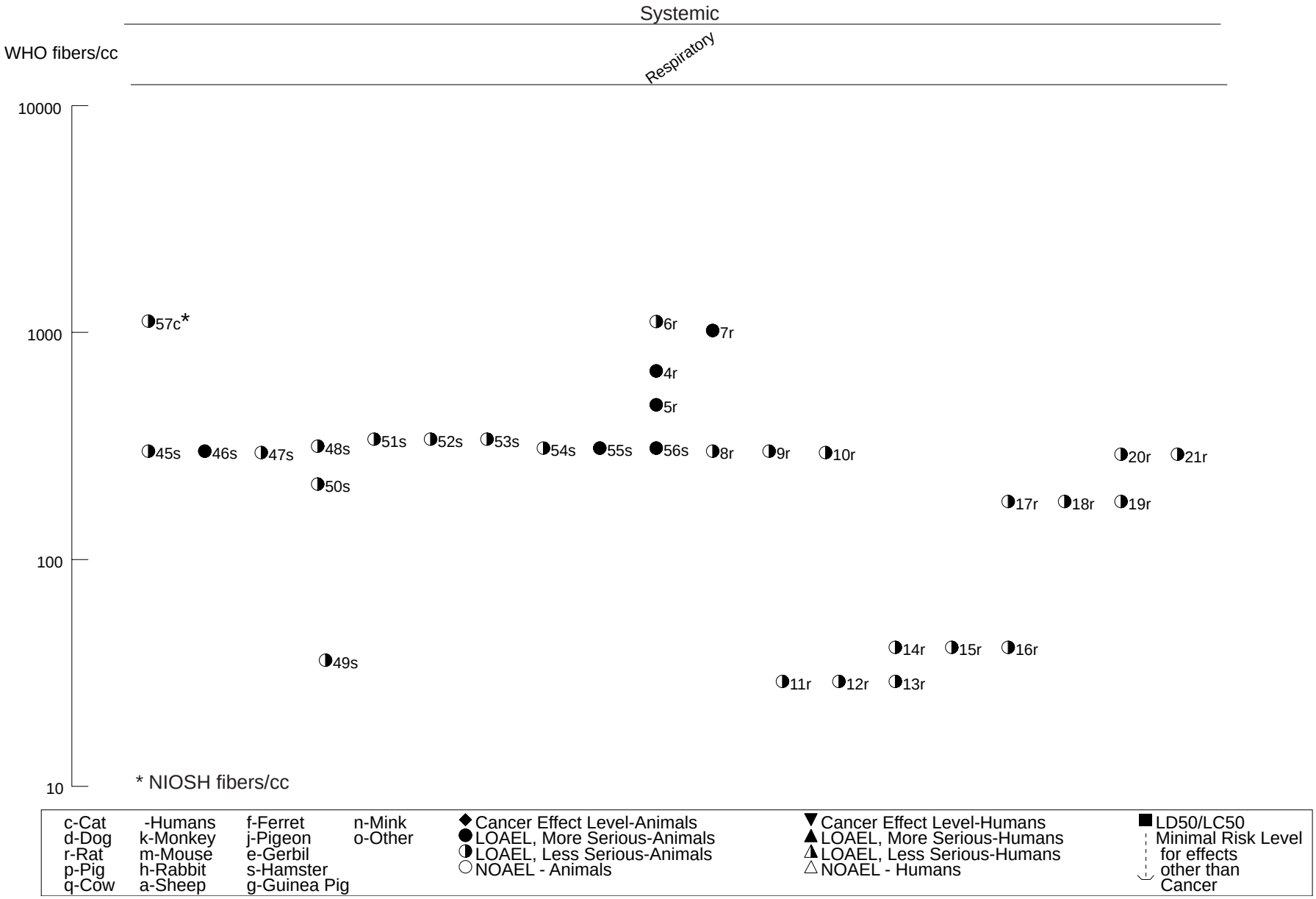


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Intermediate (15-364 days)

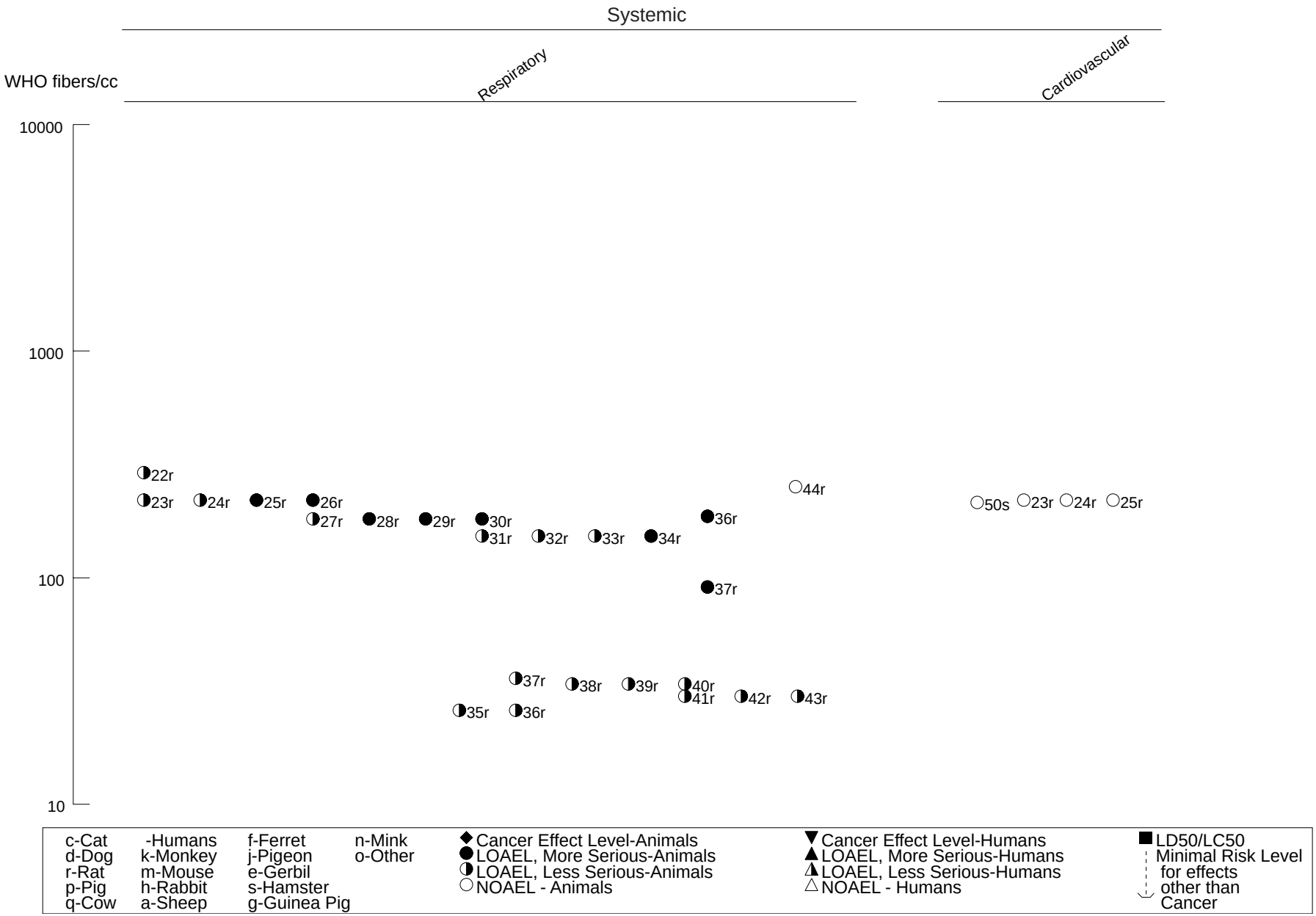


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Intermediate (15-364 days)

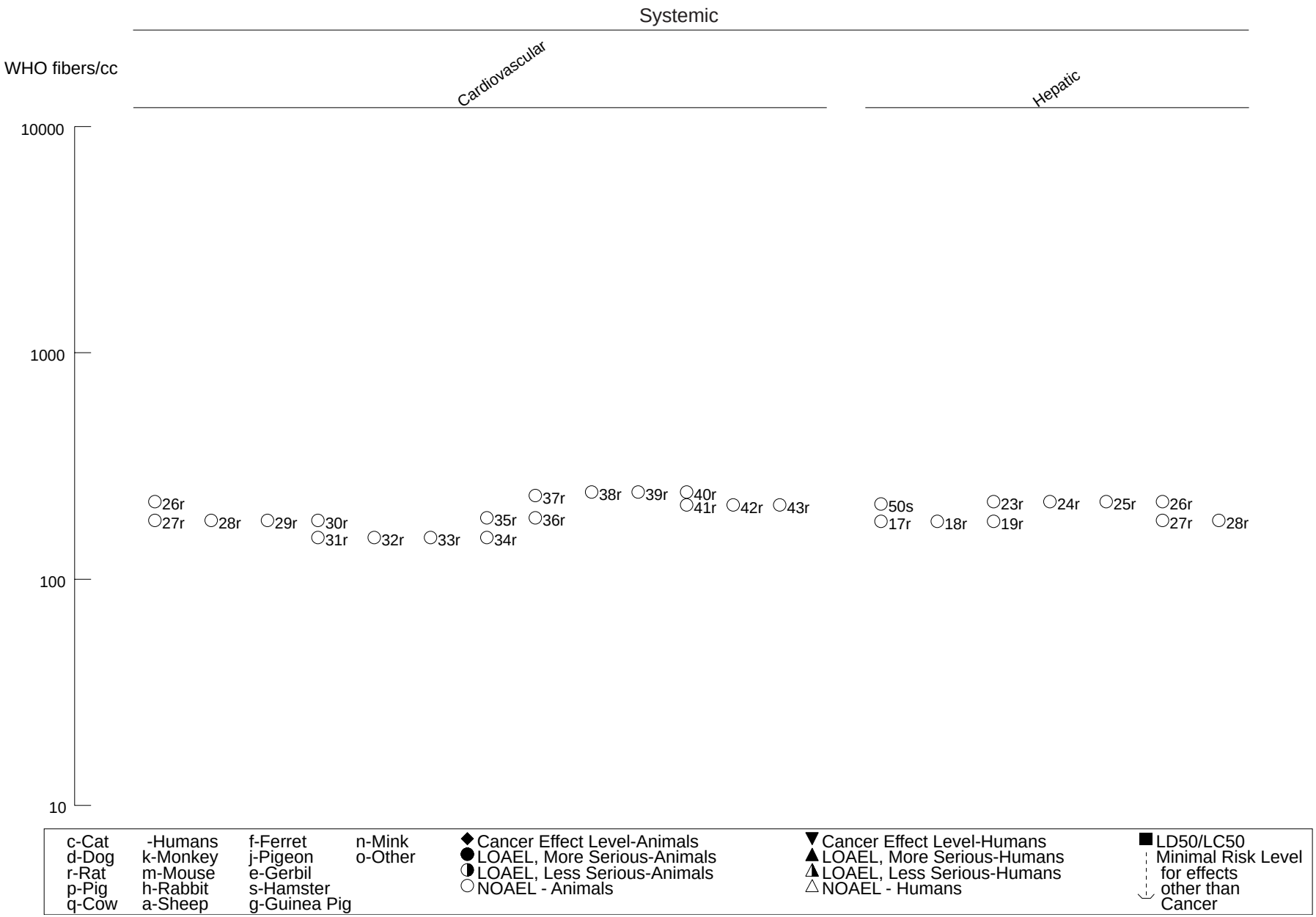


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Intermediate (15-364 days)

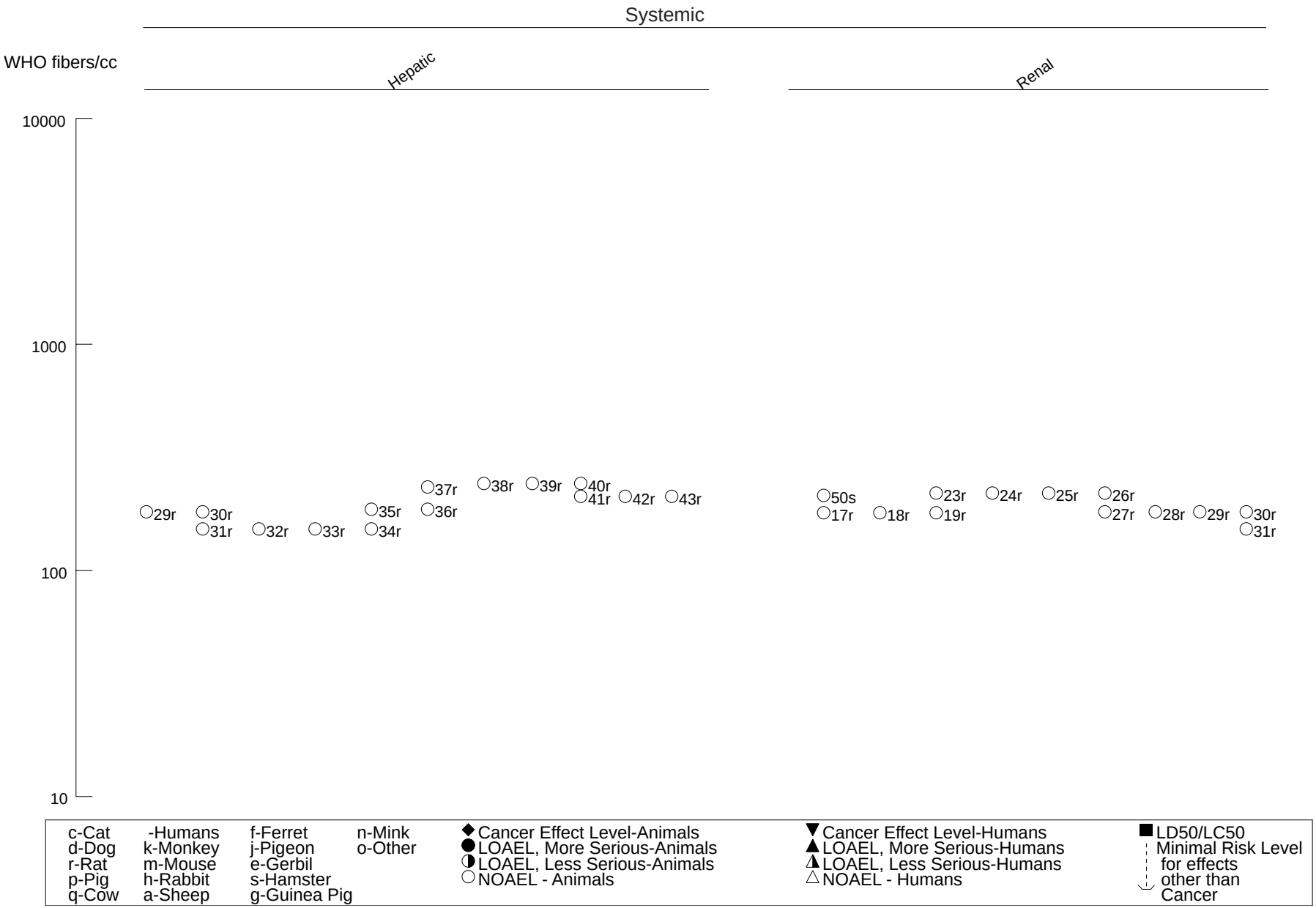
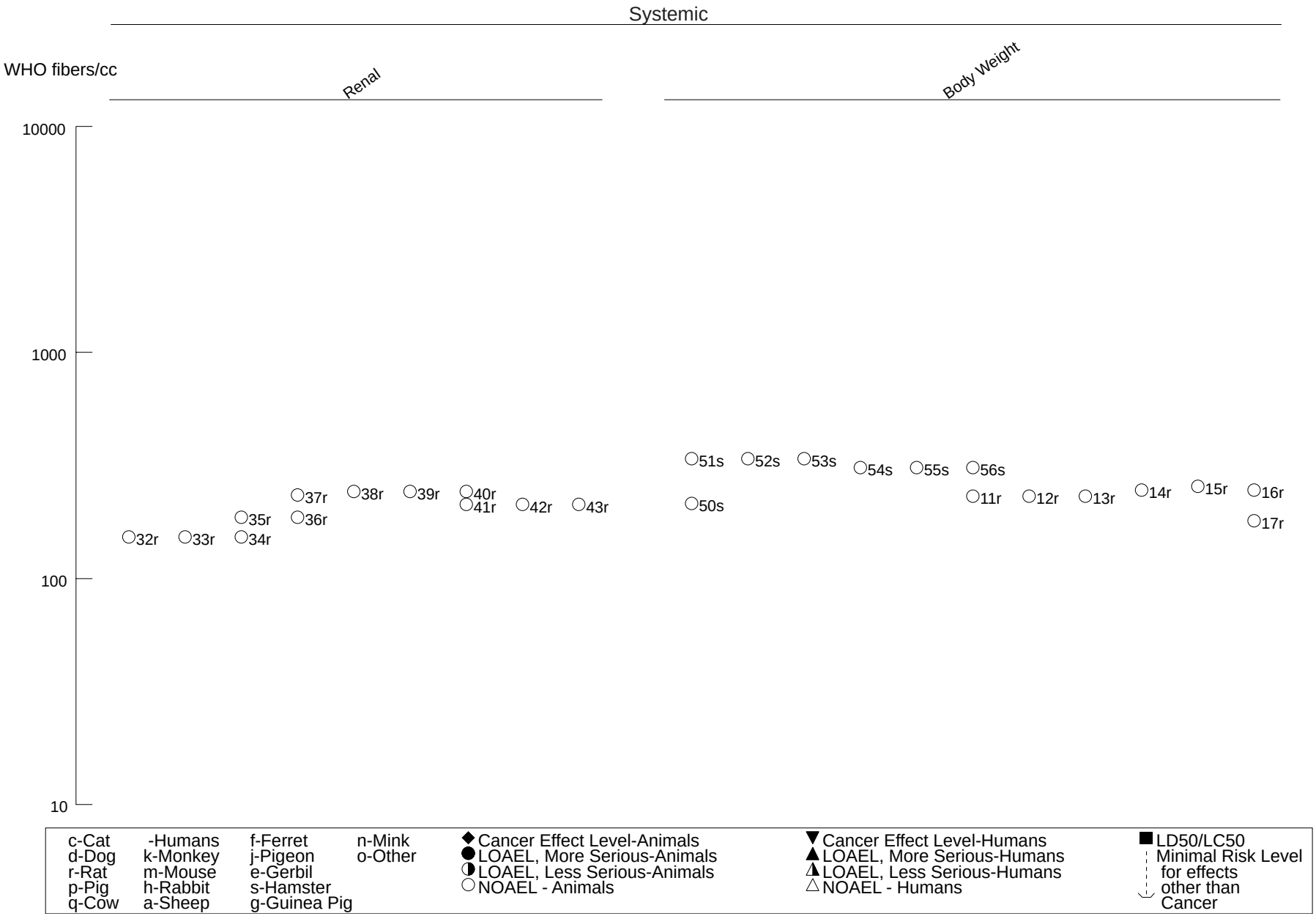


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Intermediate (15-364 days)



## Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Intermediate (15-364 days)

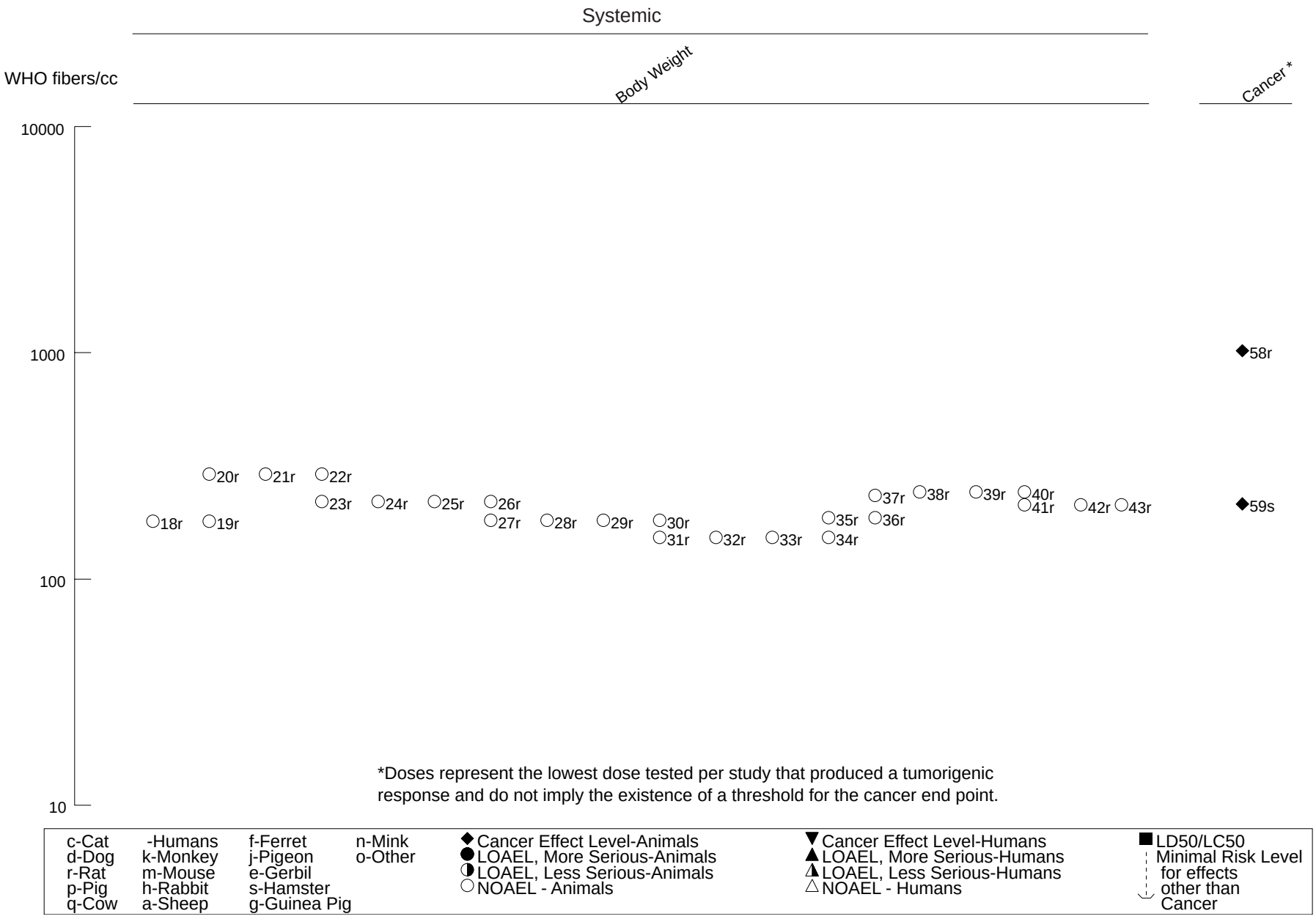


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Chronic (≥365 days)

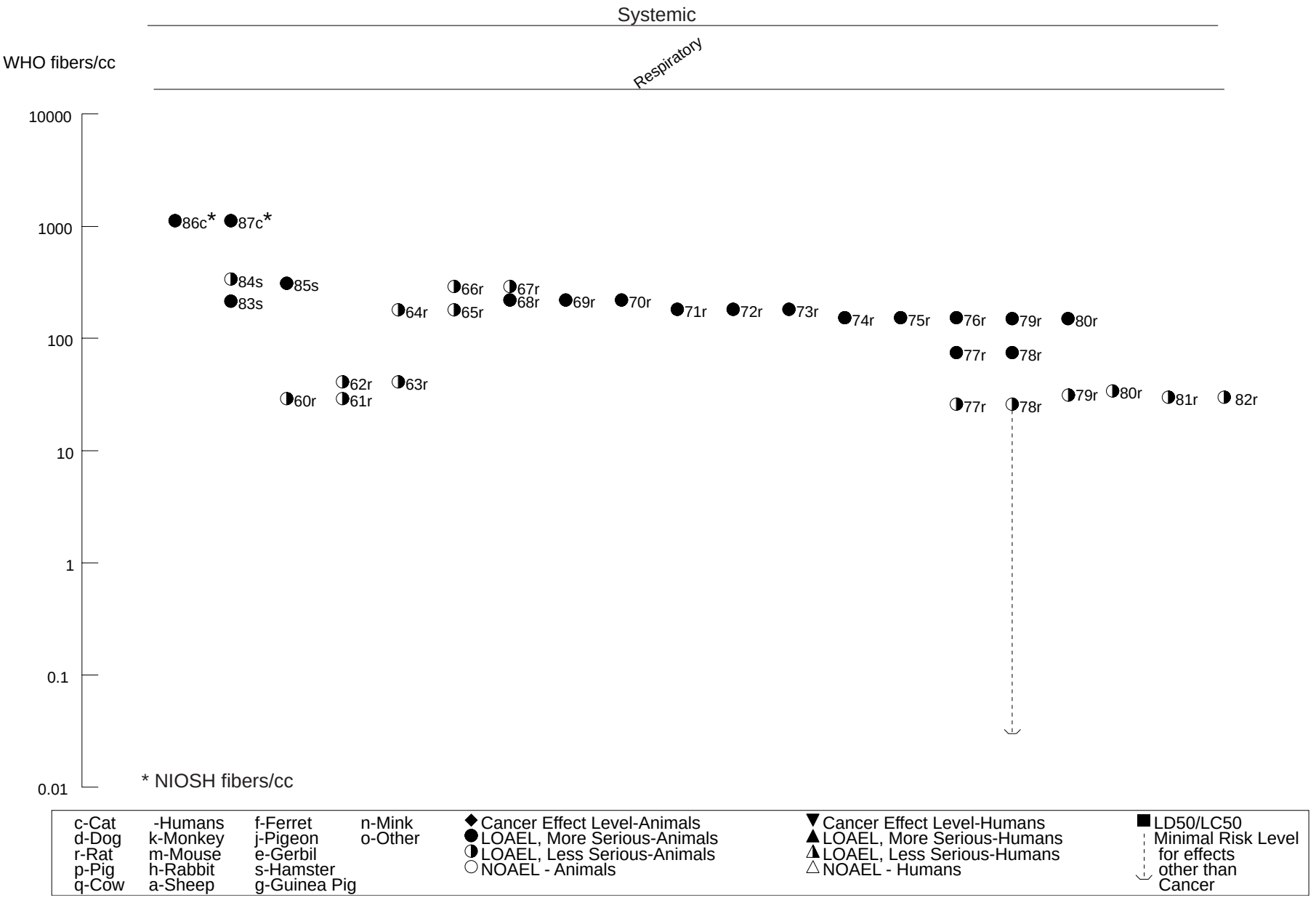


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

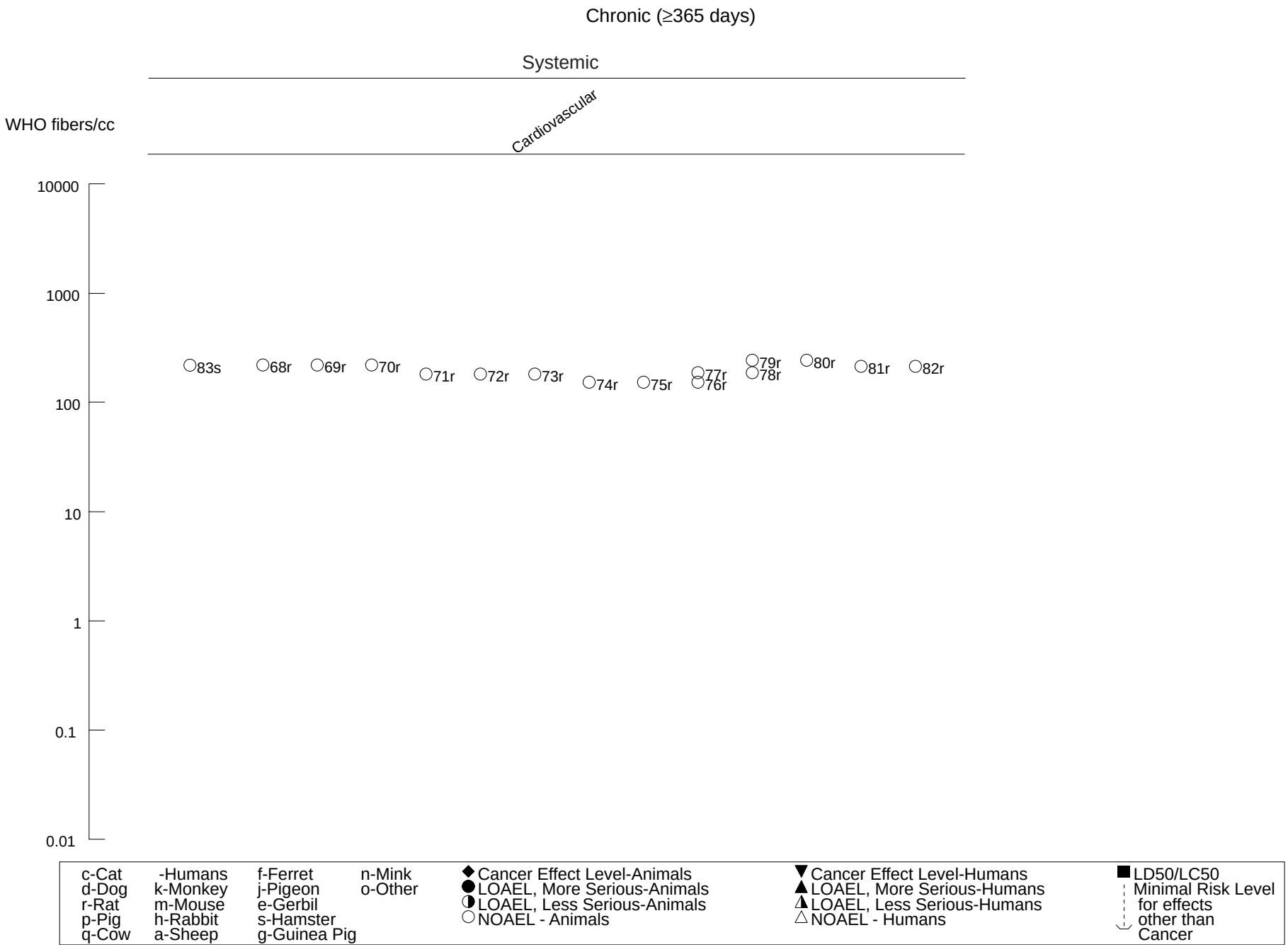


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Chronic (≥365 days)

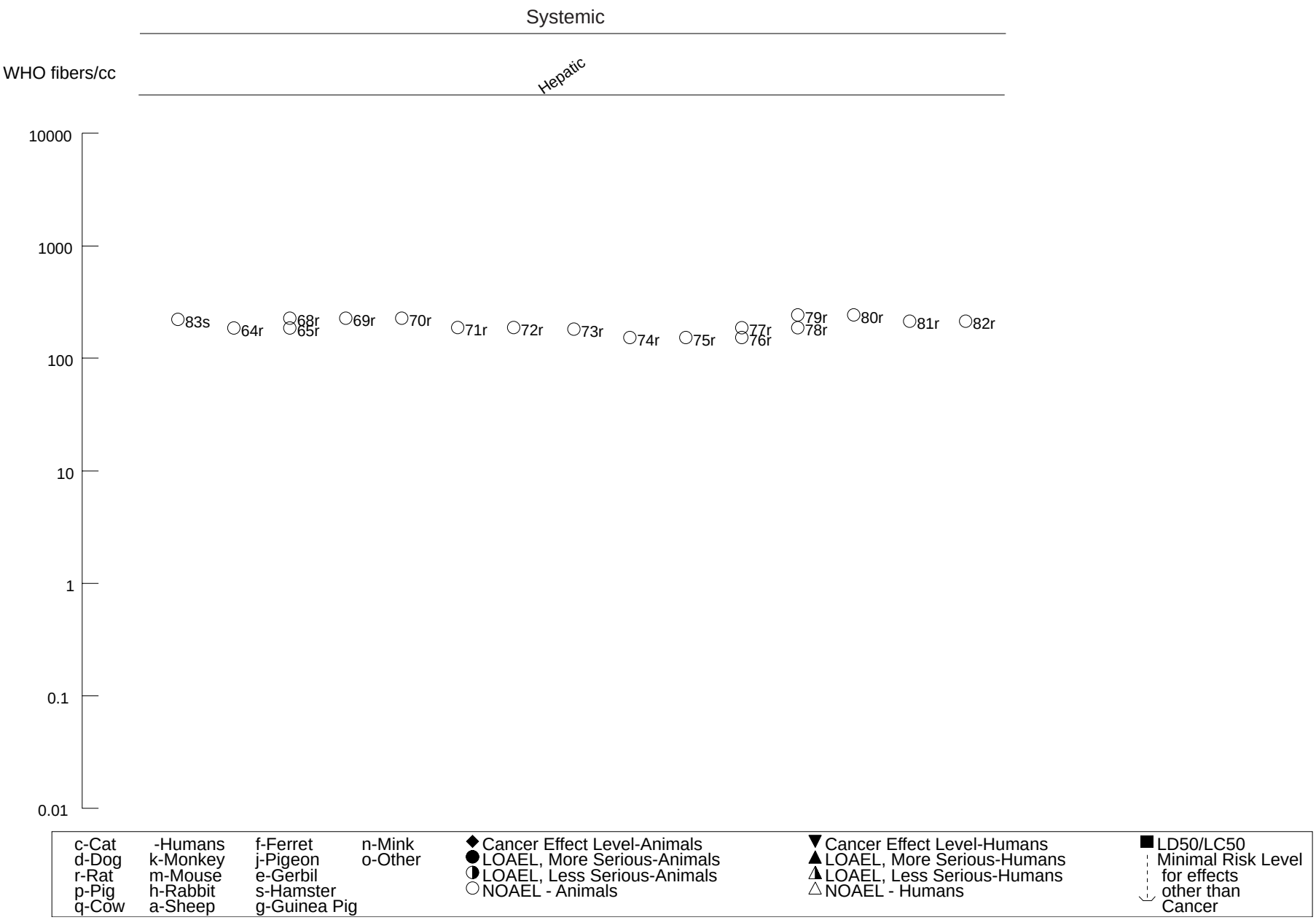
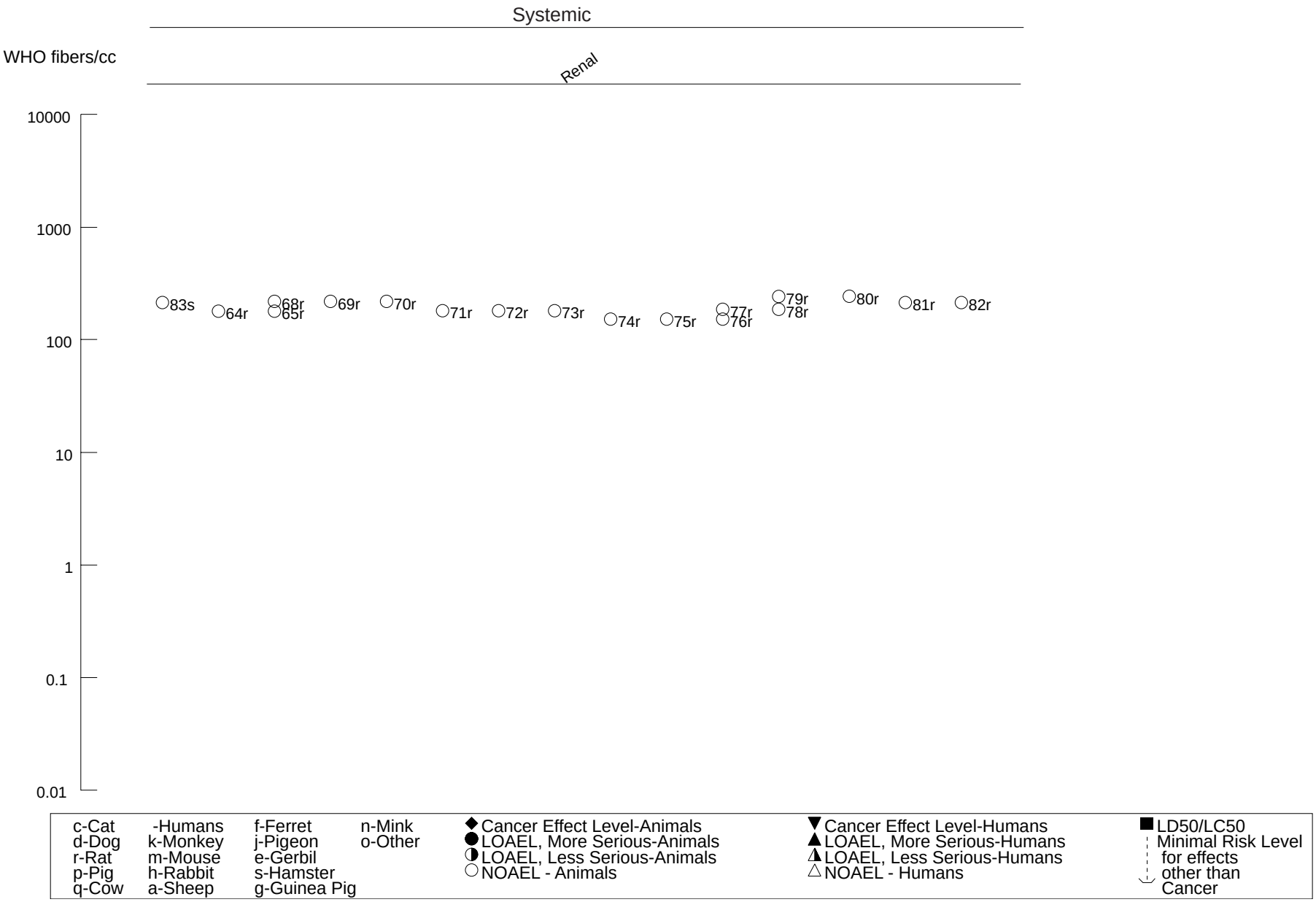


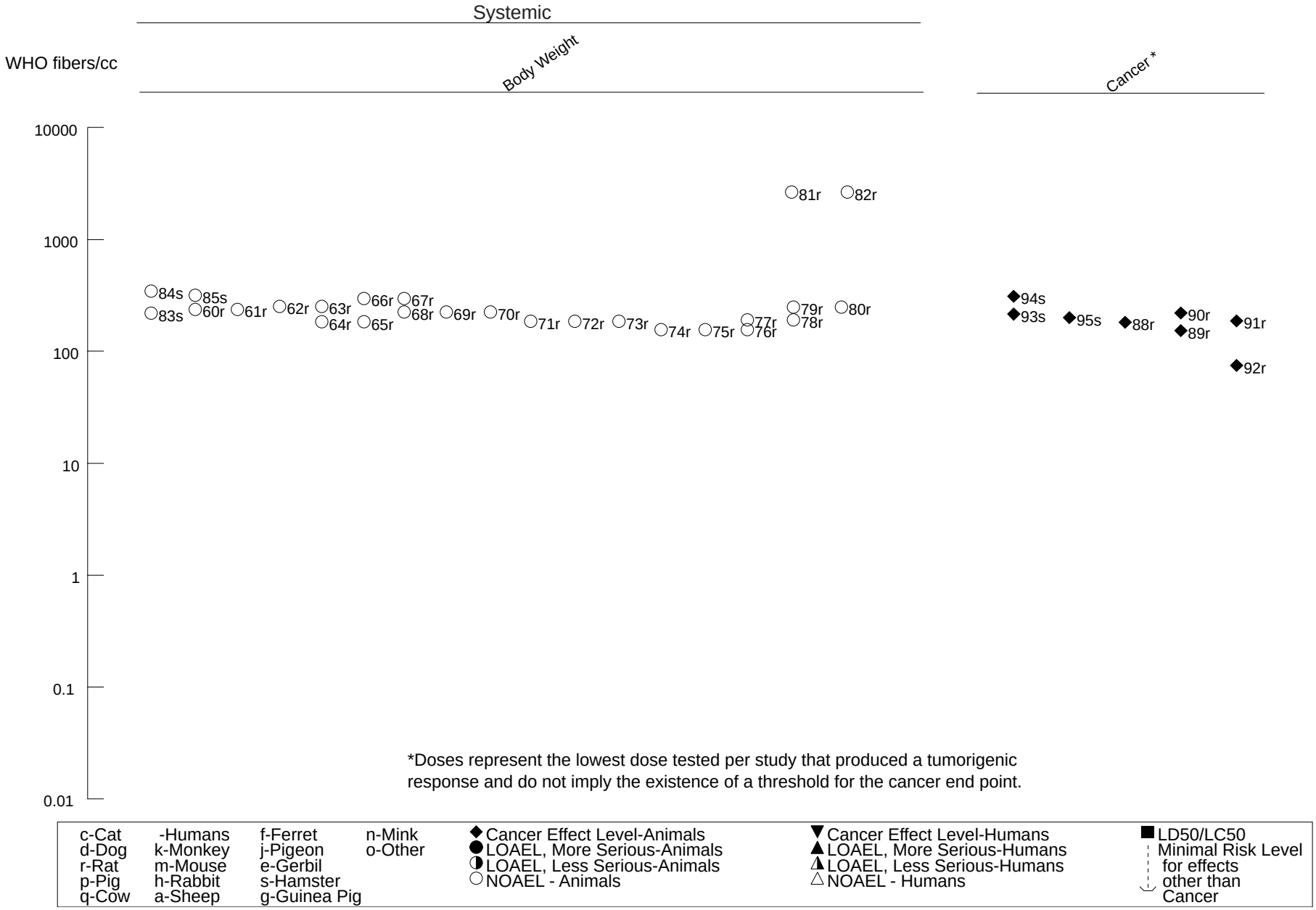
Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Chronic (≥365 days)



## Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Chronic (≥365 days)



>5 μm, diameter <3 μm, and aspect ratio ≥3:1). To facilitate comparison of effects across studies, this exposure unit is cited in Table 3-1 and Figure 3-1, except for a few studies (Everitt et al. 1994; Goldstein et al. 1983) in which fiber counting measurements were reported only in units using the NIOSH fiber counting rules (i.e., length >5 μm; aspect ratio ≥3:1).

## Respiratory Effects.

### Human Studies.

***Refractory Ceramic Fibers***. Research into the health effects of refractory ceramic fibers has been limited by the relatively short time since manufacture began (50 years), small numbers of exposed workers, and confounding exposures (e.g., smoking and asbestos).

Information regarding the effects of acute inhalation exposure to refractory ceramic fibers in humans is limited to a case-report that provided suggestive evidence of respiratory symptoms (cough, eye and throat irritation, wheezing, shortness of breath, and bronchospasm) that required medical treatment following 1 hour of exposure to high levels ("like a snow storm") of refractory ceramic fibers without respiratory protection (Forrester 1997).

No human inhalation studies of intermediate duration (2 weeks–1 year) were located for refractory ceramic fibers.

A low prevalence of pleural plaques (about 3%) has been the most biologically significant effect found in retrospective and longitudinal evaluations of the health of workers involved in the manufacture of refractory ceramic fibers in the United States (LeMasters et al. 1994; Lentz et al. 2003; Lockey et al. 1996, 2002) and Europe (Cowie et al. 2001). However, consistent statistically significant associations with exposure to refractory ceramic fibers were only found in the U.S. cohort (Lentz et al. 2003; Lockey et al. 1996, 2002). Although diffuse pleural thickening and circumscribed pleural plaques have been associated with impairment of respiratory functions, localized pleural plaques are not thought to be a significant health hazard and have not been mechanistically linked to increased risks of lung fibrosis, lung cancer, or mesothelioma (Agency for Toxic Substances and Disease Registry 2001). Symptoms of dry cough, runny nose, wheezing, and breathlessness also have been reported in European manufacturing workers exposed to refractory ceramic fibers and other dusts (Burge et al. 1995; Trethowan et al. 1995).

Additionally, some studies have observed decreased pulmonary function, usually in exposed workers with histories of smoking (Cowie et al. 2001; LeMasters et al. 1998; Lockey et al. 1998; Trethowan et al. 1995). No fibrosis or other serious health effects have been demonstrated. Although participation rates are high, these studies have been limited by small cohort sizes and relatively short exposure durations. In the only cohort mortality study of refractory ceramic fiber manufacturing workers, there were no statistically significant excesses of death associated with any nonmalignant disease, including nonmalignant respiratory disease (LeMasters et al. 2003).

A U.S. study of 627 current and 220 former refractory ceramic fiber production workers identified pleural changes in 23 men (LeMasters et al. 1994). The pleural changes were classified as plaques for 21 of the cases and thickening for the other 2 cases. Even after adjusting for potential asbestos exposure, a significant association remained between time since first employment and pleural plaques.

A retrospective cohort study of radiographically detected chest changes in 652 workers from five U.S. refractory ceramic fiber plants initially detected 20 cases of pleural plaques (Lockey et al. 1996). In a later report of the survey of radiographic chest changes in U.S. refractory ceramic fiber workers (625 current workers at five plants and 383 former workers at two of the five plants), pleural changes were detected in 27 workers (2.7%) (Lockey et al. 2002). Twenty-two of the cases showed pleural plaques (86% of which were bilateral). In logistic regression analyses that adjusted for asbestos exposure and age, three exposure metrics (duration, time since first employment, and cumulative exposure) showed statistically significant trends for increasing odds ratios with increasing exposure. For example, respective odds ratios (ORs) for pleural changes were OR=2.2 (95% confidence interval (CI) 0.5–11.8), OR=5.6 (95% CI 1.5–28.1), and OR=6.0 (95% CI 1.4–31.0) for the following categories of increasing cumulative exposure (measured in units of fibers-month/$cm^3$): >15–45, >45–135, and >135. In a similar logistic regression analysis of data collected from the same cohort, odds ratios for pleural plaques showed statistically significant trends with increasing exposure categories for three different cumulative exposure metrics: cumulative exposure; cumulative pulmonary dose of all fibers; and cumulative pulmonary dose of fibers with diameters <0.4 μm and length <10 μm (Lentz et al. 2003). Pulmonary doses for each worker were estimated using air monitoring data from the plants, job histories, and a lung deposition model.

A prospective study of 361 current male U.S. refractory ceramic fiber production workers found a statistically significant (but not biologically significant) decrease in forced vital capacity (FVC) among

workers employed for >7 years at initial testing in 1987 compared to unexposed workers (OR not reported) (Lockey et al. 1998). However, these effects did not remain statistically significant in longitudinal analyses conducted until 1994.

In an initial report of a cohort mortality study of male workers employed at two U.S. refractory ceramic fiber manufacturing plants between 1952 and 2000, no statistically significant excesses were found for deaths by any cause or deaths associated with nonmalignant diseases (LeMasters et al. 2003). A total of 87 deaths were recorded among the 942 men included in the study (9% of the cohort). Eight deaths associated with nonmalignant respiratory disease were recorded, compared with an expected 7.49 deaths based on U.S. mortality rates (standardized mortality ratios [SMR]=107; 95% CI 46–211).

A cross-sectional study of workers from seven European refractory ceramic fiber manufacturing plants showed an association between nasal, skin, and eye symptoms and worker exposure (Burge et al. 1995; Rossiter et al. 1994; Trethowan et al. 1995). A total of 628 employees participated in the study (91% were men). Workplace air monitoring data were available for inspirable dust mass and respirable fibers. In a multiple logistic regression analysis of exposure to inspirable dust and respirable fibers, significantly increased odds ratios for dry cough, dyspnea (grade 2), stuffy nose, eye irritation, and skin irritation were noted for the highest exposure group compared with the lowest exposure group (Burge et al. 1995). No relationships were noted for wheeze or chronic bronchitis with increasing exposure (Burge et al. 1995). When the effects of exposure to inspirable dust mass or respirable fibers were examined as independent variables, the odds ratio was significantly increased only for skin irritation for respirable fibers and for wheeze, dyspnea, and eye irritation for inspirable mass (Burge et al. 1995). A multiple linear regression analysis (which adjusted for confounders such as age) showed that lung function variables in current smokers (forced expiratory volume in 1 second [$FEV_1$] and forced midexpiratory flow, [$FEF_{25-75}$]) decreased with increasing cumulative exposure to respirable fibers (Trethowan et al. 1995). Chest x-rays did not show any effects related to exposure to respirable fibers (Trethowan et al. 1995).

In a subsequent cross-sectional morbidity study of 774 ceramic fiber production workers from six European refractory ceramic fiber manufacturing plants, the prevalence of radiographic pleural changes was more strongly related to age and any previous occupational exposure to asbestos than to exposure metrics for refractory ceramic fibers (Cowie et al. 2001). Pleural plaques or pleural changes were noted in 9 or 32 workers, respectively, among the 355 workers without some occupational exposure to asbestos (about 3 or 9%, respectively). In logistic regression analyses that adjusted for age, elevated odds ratios

for pleural plaques or pleural changes were calculated for refractory ceramic workers without asbestos exposure and with >10 years since first exposure to refractory ceramic fibers: OR=2.03 (95% CI 0.78–5.25) for pleural plaques and OR=2.22 (95% CI 1.17–4.24) for pleural changes. Exposure-related changes in pulmonary function variables were restricted to the finding that $FEV_1$ and FVC in workers who smoked showed decreasing values with increasing measures of exposure.

***Glass Wool, Rock and Slag Wool, and Continuous Filament Glass Fibers.*** In people, acute exposures to fibrous glass materials including continuous glass filament (e.g., fiberglass fabrics), glass wool insulation, and rock and slag wool have been associated with symptoms of upper respiratory tract irritation such as nasal itching and congestion, nosebleed, sore throat, cough, and laryngeal and pharyngeal pain (Horvath 1995; Milby and Wolf 1969; Nasr et al. 1971; Newball and Brahim 1976; Petersen and Sabroe 1991; Thriene et al. 1996). These symptoms have been reported to disappear shortly following cessation of exposure. Upper respiratory tract irritation has been associated mostly with unusually dusty workplace conditions (concentrations >1 fiber/cc) involving removal of fibrous glass materials in closed spaces without respiratory protection (ACGIH 2001; EPA 1980), and similar symptoms of upper respiratory irritation may also occur in workers involved in the manufacture, application, or removal of insulation materials made from rock wool or slag wool (ACGIH 2001).

Reliable data regarding the effects of intermediate (2 weeks–1 year) inhalation exposure of people to continuous glass fibers, glass wool, and rock and slag wool are limited because cross-sectional studies have been limited to workers with longer exposures and cohort studies have frequently been confounded by strong healthy worker effects (Boffetta et al. 1997, 1998, 1999; Lea et al. 1999; Marsh et al. 2001a; Sali et al. 1999; Shannon et al. 1987, 1990).

The possible effects of chronic exposure to continuous glass fibers, glass wool, and rock and slag wool have been investigated in cross-sectional health evaluation studies, cohort mortality studies, and case-control studies. Respiratory symptoms similar to those seen in acute studies (decreased pulmonary function, coughing, bronchitis) have been reported (Albin et al. 1998; Clausen et al. 1993; Engholm and von Schmalensee 1982; Kilburn et al. 1992). Attempts to determine whether or not exposure to continuous glass filament, glass wool, and rock and slag wool induced pleural plaques have been inconclusive or negative (Hughes et al. 1993; Kilburn and Warshaw 1991; Kilburn et al. 1992; Sanden and Jarvholm 1986; Scansetti et al. 1993; Weill et al. 1983). Cohort mortality studies have found no

association between exposure and increased risk for mortality from nonmalignant respiratory disease (Hunting and Welch 1993; Marsh et al. 2001a; Sali et al. 1999; Shannon et al. 1987, 1990).

Cross-sectional studies of populations working with fibrous glass have focused on the prevalence of respiratory symptoms through the administration of questionnaires, pulmonary function testing, and chest x-ray examinations (Clausen et al. 1993; Ernst et al. 1987; Gross 1976; Hansen et al. 1999; Hill et al. 1973; Hughes et al. 1993; Kilburn et al. 1992; Moulin et al. 1988; Nasr et al. 1971; Sanden and Jarvholm, 1986; Weill et al. 1983; Wright 1968). In general, these studies reported no consistent evidence for increased prevalences of adverse respiratory symptoms, abnormal pulmonary functions, or chest x-ray abnormalities (e.g., pneumonia, bronchitis, emphysema, pleural effusion and thickening, solid lesions, and abnormal heart and aorta). However, increased incidences of coughing (Albin et al. 1998) and bronchitis (Engholm and von Schmalensee 1982) among Swedish construction workers exposed to glass and rock wool as well as decreased pulmonary function (forced expiratory volume in 1 second) among Danish construction workers exposed to glass and rock wool (Clausen et al. 1993) and U.S. appliance assembly workers exposed to glass wool (Kilburn et al. 1992) have been observed. These studies did not have data regarding symptoms following cessation of exposure, so the persistence of these symptoms is unknown. In addition, information of exposure levels experienced by these workers was unavailable.

Because occupational exposure to inhaled asbestos has been associated with changes in the pleural membrane (such as plaques, thickening, and fibrosis) (Agency for Toxic Substances and Disease Registry 2001), several cross-sectional studies analyzed chest x-rays of workers exposed to synthetic vitreous fibers but did not find consistent evidence for an association between pleural changes and exposure to fibrous glass, rockwool, or slag wool. No increased incidence of pleural plaques or radiographic densities were seen in a study of 1,401 continuous glass filament and glass wool production workers (Wright 1968) or in a study of 788 male and 145 female rock wool production workers (Jarvholm et al. 1995). An initial cross-sectional study performed in 1979–1980 of U.S. fiberglass and mineral wool workers detected a low prevalence of small lung opacities of low profusion that correlated significantly with duration of employment at two of the seven plants studied (Weill et al. 1983). However, in a follow-up study that used prevalences of opacities in a local population as a control, no excesses of opacities were identified in the exposed workers that were related to fiber exposure (Hughes et al. 1993). Two other studies observed opacities in groups of workers, but did not report data for reference populations, so the results are inconclusive (Kilburn and Warshaw 1992; Kilburn et al. 1992). Lung radiographic abnormalities were seen in 8 of 38 glass wool production workers exposed to fiberglass but not to asbestos and in 23 of

137 workers exposed to both asbestos and fiberglass (Kilburn and Warshaw 1992). A separate study of appliance assembly workers exposed to glass wool observed radiographic abnormalities in 43 of 284 workers (Kilburn et al. 1992). Although 36 of these cases were attributed to fiberglass exposure, the adjustments made for self-reported asbestos exposure and smoking data were unclear (Bender 1993). Other studies observed pleural plaques and cough with phlegm only among fibrous glass workers with reported or suspected co-exposure to asbestos (Sanden and Jarvholm 1986; Scansetti et al. 1993).

Data for mortality from nonmalignant respiratory diseases were analyzed for three major groups of workers involved in the manufacture of workers exposed to filament glass fibers, glass wool, rock wool, or slag wool in the United States (Bayliss et al. 1976; Chiazze et al. 1997, 2002; Enterline and Henderson 1975; Enterline et al. 1983; Marsh et al. 1990, 2001a; Robinson et al. 1982; Wong et al. 1991; Watkins et al. 1997), Europe (Claude and Frentzel-Beyme 1984, 1986; Gustavsson et al. 1992; Lea et al. 1999; Sali et al. 1999; Simonato et al. 1986a; Teppo and Kojonen 1986), and Canada (Shannon et al. 1984, 1987, 1990). These cohort studies (and their associated case-control studies) have the strengths of large sample sizes, long follow-up periods, low losses in follow-up, and use of existing employment records to assess exposure, but have the limitations of imprecise estimations of actual exposure levels and the inability to adjust for confounding from tobacco smoke and concomitant exposure to other hazardous agents in the workplace. (These cohort studies are also discussed in Section 3.2.1.7, Cancer.)

The available cohort studies observed no increased risk of mortality from nonmalignant respiratory diseases in U.S., European, or Canadian workers. Significantly decreased risks of mortality from nonmalignant respiratory disease compared with national rates reported in the U.S. fiberglass cohort (Marsh et al. 2001a) and in the Canadian studies on glass wool (Shannon et al. 1984, 1987) and glass filament (Shannon et al. 1990) workers are consistent with a possible healthy worker effect, but the European cohort study did not find decreased risks (Sali et al. 1999). Categories of nonmalignant respiratory disease considered by these major studies were divided by organ (larynx, bronchus, trachea, and lung) and health effect (including asthma, bronchitis, emphysema, influenza, and pneumonia). Similarly, a cohort of 333 U.S. sheet metal workers investigating obstructive lung disease did not consider exposure to fiberglass as a risk factor (Hunting and Welch 1993).

**Animal Studies.**

Although many animal studies administering various synthetic vitreous fibers by injection or implantation into the intrapleural or intraperitoneal cavities have reported the development of administration site nonneoplastic and neoplastic lesions (see Section 2.2.4, Other Routes of Exposure), these results are of limited usefulness for predicting health hazards in humans exposed by inhalation. Studies that exposed animals by inhalation to well-measured levels of respirable fibers are considered more appropriate for assessing potential risk to human health.

Studies in rats (Bellmann et al. 2001; Brown et al. 2000; Cullen et al. 2000; Everitt et al. 1997; Gelzleichter et al. 1996a, 1996b, 1996c, 1999; Haratake et al. 1995; Hesterberg et al. 1993c, 1998b, 1999; Johnson and Wagner 1980; Kamstrup et al. 1998, 2001; Le Bouffant et al. 1987; Lee et al. 1981b; Mast et al. 1995a, 1995b; McConnell et al. 1994, 1999; Muhle et al. 1987; Smith et al. 1987; Yokosakai et al. 1991), hamsters (Everitt et al. 1997; Gelzleichter et al. 1996a, 1996b, 1996c, 1999; Hesterberg et al. 1999; Lee et al. 1981b; McConnell et al. 1995; Smith et al. 1987), guinea pigs (Lee et al. 1981b), and baboons (Goldstein et al. 1983) have observed consistent, dose-related responses to the inhalation of synthetic vitreous fibers; and only one study reported a NOAEL for respiratory effects (Muhle et al. 1987; see Figure 3-1). In the lungs, an immediate inflammatory response has been observed in rats and mice at the lowest exposure-levels tested, approximately 30–40 WHO fibers/cc of glass wool (Hesterberg et al. 1993c, 1999), rock wool (McConnell et al. 1994), slag wool (McConnell et al. 1994), and refractory ceramic fibers (Mast et al. 1995a, 1995b). End points used to measure lung inflammation include infiltration of macrophages (which accumulate fibrous and nonfibrous inhaled particles), microgranuloma formation (nonneoplastic focal accumulations of macrophages), increases in other immune cells, and increases in biochemical markers (lactate dehydrogenase, gamma-glutamyl transferase, N-acetylglucose-aminidase, glutathione, fibronectin, and total protein). Although the intensity of inflammatory changes increased with increasing exposure, these effects have subsided rapidly after cessation of exposure and are therefore not considered serious in the absence of other lesions. The reversible pulmonary inflammatory effects observed following repeated inhalation exposure to synthetic vitreous fibers are typical of the lung's response to other relatively water-insoluble particles, both non-fibrous and fibrous particles (Churg et al. 2000; Driscoll 1996; Hesterberg and Hart 2001; Kane 1996; Mossman and Churg 1998). In animal studies where exposure atmospheres included nonfibrous particles (e.g., the studies of the refractory ceramic fiber preparation, RCF1, reported by Mast et al. [1995a, 1995b]), the nonfibrous

particles are expected to have contributed to the observed inflammatory responses to some undetermined degree (Maxim et al. 2003b).

With repeated exposure scenarios to higher concentrations, more serious effects have been seen. Epithelial hyperplasia and alveolar bronchiolization, an epithelial cell transition from flat to cuboidal morphology, have been seen following chronic exposure to concentrations as low as about 180–240 WHO fibers/cc for several types of synthetic vitreous fibers including insulation glass wools (MMVF10, MMVF11; Hesterberg et al. 1993c), refractory ceramic fibers (RCF1, RCF2, RCF 3, RCF4; Mast et al. 1995a, 1995b), and rock and slag wools (MMVF21, MMVF22; McConnell et al. 1994). For some fibers (e.g., refractory ceramic fibers, MMVF21, MMVF33, C102/C104 blend fibrous glass), signs of minimal-to-moderate fibrosis following repeat exposure have been observed (Bellman et al. 2001; Goldstein et al. 1983; Mast et al. 1995a, 1995b; McConnell et al. 1994, 1995, 1999). Severe fibrosis was reported by only one study, with 104E-glass, a specialty continuous glass filament (Cullen et al. 2000). Because no regression has been observed following cessation of exposure, fibrosis is considered a serious respiratory lesion.

***Refractory Ceramic Fibers.*** The nonneoplastic respiratory effects of inhalation exposure to refractory ceramic fibers have been studied in conjunction with carcinogenicity studies (see Section 3.2.1.7, Cancer). In addition to intermediate and chronic studies in both rats and hamsters demonstrating reversible inflammation and irreversible fibrosis (Bellmann et al. 2001; Brown et al. 2000; Everitt et al. 1994, 1997; Gelzleichter et al. 1996a, 1996b, 1996c, 1999; Hesterberg et al. 1998b; Mast et al. 1995a, 1995b; McConnell et al. 1995; Smith et al. 1987; Yokosakai et al. 1991), acute- and intermediate-duration studies have found increased pleural mesothelial cell proliferation following acute and intermediate exposure in both hamsters and rats (Everitt et al. 1994, 1997; Gelzleichter et al. 1999).

Although early rodent inhalation studies provided only limited information regarding the refractory ceramic fiber tested (Smith et al. 1987; Yokosakai et al. 1991), subsequent studies have identified specific types of refractory ceramic fibers: RCF1 is a kaolin-based refractory ceramic fiber (55–75% fiber), RCF1a is a fiber-enriched preparation of RCF1 containing 98% fiber, RCF2 is an aluminum zirconia-based fiber, RCF3 is a high-purity kaolin, and RCF4 is an “after-service” kaolin-based fiber previously exposed to high temperatures. Most studies have focused on RCF1, which is comparable to RCF3 (Mast et al. 1995a) and more toxic than RCF2 or RCF4 (Mast et al. 1995a).

Acute studies are only available for RCF1, and have observed pulmonary and pleural inflammation (Everitt et al. 1994; Gelzleichter et al. 1996a, 1996b, 1996c). In both Fischer 344 rats and male Syrian Golden hamsters exposed nose-only to 1,700 NIOSH fibers/cc of RCF1 (6,900 total particles/cc) for 5 days, end points demonstrating inflammation included increased relative numbers of pulmonary neutrophils (without changing total numbers of lavaged cells in the bronchoalveolar lavage fluid) and increased lung mesothelial cell proliferation; pleural neutrophil frequency was increased only in hamsters (Everitt et al. 1994). Similarly, male Fischer 344 rats exposed to 2,645 WHO fibers/cc of RCF1 (55% fiber; 89 mg/m$^3$) exhibited pulmonary and pleural inflammation following 5 days of exposure or at 4 weeks postexposure (Gelzleichter et al. 1996a, 1996b). The pulmonary inflammation consisted of a dramatic and transient increase in bronchoalveolar levels of neutrophils, a delayed increase in pleural monocyte and eosinophil numbers, and a sustained (for 4 weeks) increase in bronchoalveolar markers for inflammation (lactate dehydrogenase, N-acetyl glucosaminidase, alkaline phosphatase, total protein, albumin, soluble fibronectin, and leukocyte fibronectin secretion). Pleural inflammation was more limited, and was measured with biochemical markers (increased N-acetyl glucosaminidase and leukocyte fibronectin secretion only immediately after exposure and increased total protein, albumin, and soluble fibronectin only at 4 weeks postexposure).

Intermediate-duration nose-only inhalation experiments with refractory ceramic fibers in male Fischer 344 rats (Mast et al. 1995a, 1995b), female Wistar rats (Bellmann et al. 2001; Brown et al. 2000), and male Syrian Golden hamsters (Everitt et al. 1997; Gelzleichter et al. 1999; McConnell et al. 1995) have verified the observations of pulmonary and pleural inflammation, and have also shown signs of progressive fibrosis.

In male Fischer 344 rats, concentrations of RCF1 as low as 26 WHO fibers/cc (3 mg/m$^3$) for 3 months have caused pulmonary inflammation (statistically significant increases in relative lung weight, macrophage infiltration, and microgranuloma [nonneoplastic focal accumulation of macrophages] formation) (Mast et al. 1995a, 1995b). Exposure for the same duration to at least 75 WHO fibers/cc (9 mg/m$^3$) caused another sign of inflammation, alveolar bronchiolization. Alveolar bronchiolization is a pathologic response in which cells lining the alveoli become cuboidal (i.e., resembling cells lining the bronchioles). No fibrosis was seen in rats exposed to 26 WHO fibers/cc of RCF1; 75 WHO fibers/cc caused minimal-to-mild interstitial fibrosis by 12 months, and 187 WHO fibers/cc of RCF1 caused minimal-to-mild pleural fibrosis by 9 months (Mast et al. 1995a, 1995b). Following cessation of exposure, macrophage infiltration and bronchiolization rapidly regressed, but fibrosis neither progressed

nor regressed. Other studies in male Fischer 344 rats with RCF1 have also reported pulmonary inflammation (statistically significant increases in pleural neutrophil, eosinophil and lymphocyte numbers, and biochemical markers of inflammation [pleural lactate dehydrogenase, N-acetylglucos-aminidase, total protein, and fibronectin]) as well as pleural mesothelial cell proliferation following at least 4 weeks of exposure to 300 WHO fibers/cc (45.6 mg/m$^3$) (Everitt et al. 1997; Gelzleichter et al. 1999).

Exposure of male Fischer 344 rats to single exposure levels of RCF2, RCF3, or RCF4 (220, 182, or 153 WHO fibers/cc, respectively, equivalent to 30 mg/m$^3$ for each) for at least 3 months caused pulmonary inflammation (macrophage infiltration and microgranuloma formation, bronchiolization of proximal alveoli) (Mast et al. 1995a). Minimal-to-mild focal pleural fibrosis was induced by RCF2 and RCF3 in as little as 6 months and by RCF4 within 9 months (Mast et al. 1995a).

Pulmonary inflammation and slight interstitial fibrosis were also seen in female Wistar rats exposed to 679 WHO fibers/cc of RCF1 (51.2 mg/m$^3$) or 481 WHO fibers/cc of RCF1a (25.8 mg/m$^3$) for 3 weeks (Bellmann et al. 2001; Brown et al. 2000). RCF1a was a preparation of the same material cerused to prepare RCF1, but was prepared so that aerosols made from it contained less nonfibrous particles than RCF1 aerosols. Approximately 25% of the mass of RCF1 was accounted for by nonfibrous particles compared to about 2% in RCF1a. Inflammation consisted of statistically significantly increased relative and absolute lung weight, biochemical markers of bronchoalveolar inflammation (lactic dehydrogenase, gamma-glutamyl transferase, total protein, and glutathione), and bronchoalveolar infiltration by both macrophages and lymphocytes. Histopathological analyses observed slight interstitial fibrosis, bronchio-alveolar hyperplasia, and alveolar histiocytosis. Bronchioalveolar inflammation and hyperplasia subsided within 3 months postexposure, but neither interstitial fibrosis nor alveolar histiocytosis decreased within the 1-year postexposure observation period. Exposure to RCF1 caused a severe retardation of alveolar clearance, but RCF1a did not, suggesting that the effect may have been a nonspecific response to total lung burden.

Intermediate-duration studies with RCF1 in male Syrian Golden hamsters also demonstrated pulmonary inflammation and both interstitial and pleural fibrosis (Everitt et al. 1997; Gelzleichter et al. 1999; McConnell et al. 1995). In hamsters, concentrations as low as 215 WHO fibers/cc (30 mg/m$^3$) of RCF1 induced a dramatic bronchioalveolar infiltration by macrophages accompanied by the appearance of microgranulomas, and progressive pulmonary and pleural fibrosis (including alveolar bronchiolization,

punctate pleural foci, and collagen deposition) from 3 months onward (McConnell et al. 1995). In the recovery animals (treatment stopped at 3, 6, 9, or 12 months) examined at 18 months, no progression or regression of fibrosis was observed versus comparably-exposed interim sacrifices, although macrophage levels quickly reverted to normal. Male Syrian hamsters exposed to approximately 300 WHO fibers/cc of RCF1 (46 mg/$m^3$) for as short a duration as 4 weeks also exhibited statistically significant increases in pleural neutrophil, eosinophil, and lymphocyte numbers; biochemical markers of inflammation (pleural lactate dehydrogenase, N-acetylglucosaminidase, total protein, and fibronectin); pleural mesothelial cell proliferation; and visceral pleural collagen levels (Everitt et al. 1997; Gelzleichter et al. 1999).

Chronic studies have observed similar respiratory effects in rats (Hesterberg et al. 1998b; Mast et al. 1995a, 1995b) and hamsters (McConnell et al. 1995; Smith et al. 1987). Male Fischer 344 rats exposed to at least 26 WHO fibers/cc of RCF1 (3 mg/$m^3$) for 18 or 24 months showed increased lung weight, macrophage infiltration with microgranuloma formation, alveolar bronchiolization, and pleural and interstitial fibrosis (Mast et al. 1995b). Exposure of male Fischer 344 rats to RCF2, RCF3, or RCF4 (220, 182, or 153 WHO fibers/cc, respectively, equivalent to 30 mg/$m^3$ for each) for 18 or 24 months caused pulmonary inflammation (macrophage infiltration and microgranuloma formation, bronchiolization of proximal alveoli) and minimal-to-moderate interstitial fibrosis and focal pleural fibrosis (Mast et al. 1995a). Exposure to RCF1, RCF2, or RCF3 (but not RCF4) also caused bronchiolar-alveolar hyperplasia

No nonmalignant respiratory effects were reported for male Syrian hamsters or female Osborne-Mendel rats exposed to 200 fibers/cc (12 mg/$m^3$) of an unspecified refractory ceramic fiber (diameter 1.8 μm) for 2 years, but these results are inconclusive due to data reporting limitations (Smith et al. 1987; this NOAEL is not in Table 3-1 or Figure 3-1). Male Syrian Golden hamsters exposed for 15 or 18 months to 215 WHO fibers/cc (30 mg/$m^3$) of RCF1 exhibited dramatic pulmonary inflammation (bronchioalveolar infiltration of macrophages, accompanied by the appearance of microgranulomas, alveolar bronchiolization), as well as mild-to-moderate interstitial and pleural fibrosis (McConnell et al. 1995).

***Glass Wool (Insulation Glass Wools and Special Purpose Glass Fibers).*** No acute-duration glass wool inhalation studies in animals were identified.

All but one (Tempstran 475, Code 104 fiber, a special purpose glass fiber) of the glass wools induced pulmonary inflammation in animals following intermediate- or chronic-duration inhalation exposure (Muhle et al. 1987). However, the only glass wools to induce fibrosis were C102/C104 blend fibrous

glass (with chronic- but not intermediate-duration exposure) (Goldstein et al. 1983), and two special purpose glass fibers (with intermediate- and chronic-duration exposures): MMVF33 (McConnell et al. 1999) and 104E-glass (Cullen et al. 2000).

The glass wools best characterized in animal inhalation studies are MMVF10, MMVF11, and MMVF33 (Hesterberg et al. 1993c, 1999; McConnell et al. 1999). MMVF10 and MMVF11 are standard building insulation glass wools, whereas MMVF33 is a more durable special purpose glass fiber. Short-duration multiple-exposure-level studies with MMVF10 in male Syrian Golden hamsters observed minimal pulmonary inflammation (macrophage infiltration and microgranuloma formation) at levels as low as 36 WHO fibers/cc after 13 weeks and 316 WHO fibers/cc after 7 weeks (3.2 and 30.5 mg/$m^3$, respectively) (Hesterberg et al. 1999). At 13 weeks, additional signs of inflammation were seen at the next-lowest concentration (increased numbers of pleural and pulmonary neutrophils and lymphocytes at concentrations as low as 206 WHO fibers/cc [16.5 mg/$m^3$]) (Hesterberg et al. 1999). These results are consistent with observations of pulmonary inflammation (macrophage infiltration and microgranuloma formation) in male Wistar rats exposed to the same approximate gravimetric concentration (2.2 mg/$m^3$; fiber/cc counts not reported) of GB100R glass wool (Haratake et al. 1995) and in male Fischer rats exposed to 29 and 41 WHO fibers/cc (3.1 and 4.8 mg/$m^3$) of either MMVF10 or MMVF11, respectively (Hesterberg et al. 1993c). No differences between MMVF10 and MMVF11 were observed in the latter experiment; no fibrosis was induced at the highest concentrations tested, 232 and 246 WHO fibers/cc (27.8 and 28.3 mg/$m^3$), and no progression of effects was seen in animals sacrificed at 18 or 24 months compared to those sacrificed at 12 months.

The other rodent experiment, which included both intermediate and chronic timepoints, tested MMVF10a (a low fluorine preparation of MMVF10) and MMVF33 (a durable special applications glass fiber) for 18 months in male Syrian Golden hamsters at concentrations of 339 or 310 WHO fibers/cc, respectively (29.6 or 37 mg/$m^3$) (McConnell et al. 1999). Pulmonary inflammation was seen as early as 13 weeks (macrophage infiltration and microgranuloma formation). MMVF10a did not induce fibrosis, but MMVF33 induced mild-to-moderate interstitial and pleural fibrosis as well as other markers of inflammation (increased absolute lung weight; neutrophil, eosinophil, and lymphocyte infiltration; elevated lactate dehydrogenase, beta-glucuronidase, and total protein levels; alveolar bronchiolization), beginning at 13 weeks. Both glass fibers induced mesothelial (but not bronchoalveolar) hyperplasia at 18 months (not measured at previous timepoints).

In male Wistar rats exposed whole-body at 1,022 WHO fibers/cc to 104E-glass or 1,019 WHO fibers/cc of 100/475 glass (two special-purpose glass fibers) for 1 year, both fiber types caused "considerable" pulmonary inflammation (macrophage infiltration associated with alveolar wall thickening), but only 104E-glass produced considerable fibrosis (Cullen et al. 2000). Rats exposed for 1 year to 104E-glass and allowed to recover for an additional year exhibited bronchoalveolar hyperplasia and fibrosis more advanced than in animals sacrificed immediately after exposure. In nine rats exposed to 104E-glass that survived during the "recovery" period, advanced alveolar fibrosis and bronchoalveolar hyperplasia covered an average 8% of lung parenchyma area. In contrast, this lesion covered only 0.2 and 0.08% of lung parenchyma in 100/475-exposed rats and control rats, respectively.

The other intermediate (Goldstein et al. 1983; Johnson and Wagner 1980; Lee et al. 1981b; Muhle et al. 1987) and chronic (Goldstein et al. 1983; Le Bouffant et al. 1987; Smith et al. 1987) studies of other glass wools reported minimal respiratory effects (pulmonary inflammation), but no serious nonneoplastic health effects (such as fibrosis).

The only experiment with glass wool performed in a nonrodent species used baboons (*Papio ursinus*) and was applicable to both intermediate and chronic exposure (Goldstein et al. 1983). A group of 10 male baboons were exposed to 1,122 fibers (with lengths >5 μm)/cc of a C102–C104 blend of fibrous glass (7.54 mg/m$^3$; 5.80 mg/m$^3$ respirable) for 35 months with periodic lung biopsies. Pulmonary inflammation was seen at 8 months (pulmonary infiltration by histiocytes, fibroblasts, and giant cells, respiratory bronchiole wall thickening, and occurrences of ferruginous bodies). By 18 months, focal peribronchiolar fibrosis was detected. These results are inconclusive because data were not provided regarding lung fiber burdens and the frequency with which lesions were observed in the exposed and control groups.

No significant respiratory effects were observed in female Wistar rats exposed nose-only to 252 WHO fibers/cc of Tempstran 475 (Code 104) glass fiber for 1 year (Muhle et al. 1987). This study represents the only animal inhalation NOAEL reported for a synthetic vitreous fiber.

Two intermediate studies with unspecified types of glass wool reported cell lysis, suggesting that clearance mechanisms may have been overloaded (Johnson and Wagner 1980; Lee et al. 1981b). Exposure of Fischer rats to 10 mg/m$^3$ of a glass wool for 50 weeks caused focal fibrosis and pulmonary inflammation (localized bronchiolar and alveolar degeneration and hyperplasia, and lysis of debris-filled macrophages) (Johnson and Wagner 1980). Rats and guinea pigs exposed to 70 fibers/cc of a ball-milled

(7% fiber) glass wool for 3 months exhibited pulmonary inflammation (hyperplasia and lysis of dust-filled lung cells [presumably macrophages], and a very slight increase in the incidence of ferruginous bodies [iron deposits]) that subsided within 6 months (Lee et al. 1981b). Apparently, no inflammation occurred in similarly exposed hamsters, but conclusions could not be drawn from the study due to limited reporting.

A 2-year assay of four types of glass wool in female Osborne-Mendel rats and male Syrian Golden hamsters did not report any signs of nonmalignant respiratory effects (Smith et al. 1987). The results of this study are inconclusive, because reporting of study details was very limited. As such, NOAELs and LOAELs from this study are not included in Table 3-1 or Figure 3-1. The concentrations were 300 or 3,000 fibers/cc of a 0.45 μm diameter glass (0.3 or 3.0 mg/m$^3$), 100 fibers/cc of a 3.1 μm diameter glass (10 mg/m$^3$), 10 or 100 fibers/cc of a 5.4 μm diameter glass (1.2 or 12 mg/m$^3$), and 25 fibers/cc of 6.1 μm diameter glass (9 mg/m$^3$).

In Wistar rats exposed for 2 years to a glass wool (concentration not specified), the reported signs were "simple alveolar macrophage reactions" and fibrosis (Le Bouffant et al. 1987). These effects were reported for all of the fibers tested (asbestos, glass wool, and rock wool).

***Rock Wool.*** No acute-duration rock wool inhalation studies in animals were identified.

Two parallel studies, with intermediate and chronic timepoints, provide the most reliable information for the respiratory effects of MMVF21 and MMVF34/HT rock wool (Kamstrup et al. 1998, 2001; McConnell et al. 1994). MMVF21 is a traditional basalt-based, rock (stone) wool. MMVF34/HT is a more recently developed rock wool characterized as having a relatively high content of aluminum and low content of silica, compared with MMVF21. Supporting information is provided by an intermediate (Johnson and Wagner 1980) and a chronic (Le Bouffant et al. 1987) study. Pulmonary inflammation was seen for all of the rock wools tested; fibrosis was seen for MMVF21 (and unspecified types of rock wool), but not for MMVF34.

In male Fischer 344 rats exposed nose-only to MMVF21 at concentrations of 34, 150, or 243 WHO fibers/cc (3.1, 16.1, or 30.4 mg/m$^3$) for up to 24 months with interim sacrifices, minimal pulmonary inflammation (increase in pulmonary macrophages) was seen at levels as low as 34 WHO fibers/cc (3.1 mg/m$^3$) by 3 months, and severity of the inflammatory response increased with increasing exposure

level (Kamstrup et al. 2001; McConnell et al. 1994). For example, rats in the highest exposure group showed mild bronchiolization, in addition to increased pulmonary macrophages, by 3 months of exposure. Signs of minimal fibrosis (collagen deposition at the bronchoalveolar junction) were found in 2/6 rats exposed to 264 WHO fibers/cc at 12 months of exposure. By 18 months of exposure, all rats exposed to 150 or 264 WHO fibers/cc showed signs of minimal or mild fibrosis (rats with mild fibrosis showed some interlobular linking), but the fibrosis was not more pronounced at these exposure levels after 24 months.

In male Fischer 344 rats exposed nose-only to 291 WHO fibers/cc (30.1 mg/m$^3$) of MMVF34/HT, for up to 2 years, inflammation (increased absolute and relative lung weight, macrophage infiltration and microgranuloma formation, alveolar bronchiolization) was seen as early as 3 months (Kamstrup et al. 1998, 2001). Minimal bronchoalveolar collagen deposition (a sign of fibrosis) was seen in a few rats at 6 and 18 months, but was not observed in rats exposed for 12 or 24 months. As such, no clear and consistent signs of pulmonary fibrosis were found in rats exposed to 291 WHO fibers/cc of MMVF34/HT for up to 24 months. The results indicate that the newly developed rock wool, MMVF34/HT, is a less potent respiratory toxicant than the traditional rock wool, MMVF21.

Exposure of Fischer rats to 10 mg/m$^3$ of an unspecified rock wool for 50 weeks reportedly caused focal fibrosis, localized bronchiolar and alveolar degeneration and hyperplasia, and lysis of debris-filled macrophages (Johnson and Wagner 1980).

In Wistar rats exposed for 2 years to a rock wool (concentration not specified), the reported signs were "simple alveolar macrophage reactions" and fibrosis (Le Bouffant et al. 1987). These effects were reported for several fibers tested (asbestos, glass wool, and rock wool) in this study.

***Slag Wool***. No acute-duration slag wool inhalation studies in animals were identified. Pulmonary inflammation, but no fibrosis, has been reported for slag wool.

Male Fischer 344 rats exposed nose-only for 2 years to levels as low as 33 fibers/cc of MMVF22, a blast-furnace slag wool (30 WHO fibers/cc; 3.1 mg/m$^3$) exhibited minimal pulmonary inflammation by 3 months (macrophage infiltration, microgranuloma development, and bronchiolization) (McConnell et al. 1994). The severity of these effects increased with increasing concentration and with longer exposure duration. No fibrosis or effects in the pleura were seen at levels up to 213 WHO fibers/cc (29.9 mg/m$^3$).

Another study reported no fibrosis or bronchoalveolar metaplasia in female Osborne-Mendel rats or male Syrian Golden hamsters exposed for 2 years to 200 fibers/cc of a 2.7 μm diameter slag wool (10 mg/m$^3$) (Smith et al. 1987). This apparent NOAEL was not included in Table 3-1 or Figure 3-1 due to limiting reporting of experimental details and results for this study.

***Continuous Filament Glass.*** No inhalation studies in animals with continuous glass filaments were identified. Because this type of synthetic vitreous fiber most frequently has large diameters that render the fibers nonrespirable (ACGIH 2001; Lee et al. 1995), studies have focused on other routes of exposure (see Section 3.2.4).

***Other Fibers.*** Exposure of male Fischer 344 rats to high-silica synthetic vitreous fiber, X607, at a concentration of 180 WHO fibers/cc (equivalent to 30 mg/m$^3$), caused pulmonary inflammation (macrophage aggregation by 13 weeks, alveolar bronchiolization by 39 weeks, and macrophage microgranulation as early as 52 weeks), but no evidence of bronchioalveolar or pleural fibrosis even after 2 years of exposure (Hesterberg et al. 1998b). X607 is a high-silica synthetic vitreous fiber with glass-like characteristics, which is produced using processes similar to those used for rock wool, slag wool, and refractory ceramic fibers. It has temperature resistance properties that are intermediate between those of insulation glass wools and refractory ceramic fibers (Hesterberg et al. 1998b).

The highest reliable NOAEL values and all reliable LOAEL values for respiratory effects (and other systemic effects) in animals exposed by inhalation to synthetic vitreous fibers are summarized in Table 3-1 and plotted in Figure 3-1.

**Cardiovascular Effects.** Analysis of cause-of-death information for 2,758 male workers (from a cohort of 11,373 men) included in the European cohort study found a statistically significant increase in mortality from ischemic heart disease among continuous filament workers (51 of 172 total deaths, standardized mortality ratio (SMR) of 1.22 with a 95% CI=1.06–1.88), but not among workers exposed to glass or rock and slag wool (mean SMRs of 1.05, and 0.97, respectively) (Sali et al. 1999). Among rock and slag wool workers, the trend for increased risk of mortality from ischemic heart disease correlated significantly with age. No elevations of risk for mortality from diseases of the circulatory system or cerebrovascular disease were observed (SMR ranged from 0.99 to 1.22 and from 0.95 to 1.21, respectively). The results from this study do not clearly establish an association between increased risk of

death from ischemic heart disease and occupational exposure during the manufacture of continuous filament glass, due to the lack of measures of confounding influences on ischemic heart disease such as heat, other chemical exposures in the workplace such as carbon monoxide, and physical strain.

The risk of death from cardiovascular diseases related to occupational exposure to continuous glass fibers, glass wool, and rock and slag wool were not increased significantly in either the U.S. cohort study (Marsh et al. 2001a) or the Canadian studies (Shannon et al. 1987, 1990).

Some intermediate- and chronic-duration animal studies conducted routine heart histopathology, but did not find any adverse effects (see Table 3-1).

**Gastrointestinal Effects.** The majority of synthetic vitreous 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 as a result of inhalation exposure.

Despite this exposure, inhalation exposure to continuous glass filament, glass wool, and rock and slag wool were not associated with increased risk of mortality from diseases of the digestive tract in the death records of 9,060 workers (from a cohort of 32,110) in the U.S. study (Marsh et al. 2001a), 2,758 male workers (from a cohort of 11,373 men) in the IARC study (Sali et al. 1999), 157 insulating glass wool workers (from a cohort of 2,557) in Sarnia, Canada (Shannon et al. 1984, 1987), 96 continuous glass filament workers (from a cohort of 1,465) in Guelph, Canada (Shannon et al. 1990), or 554 prefabricated houses builders (from a cohort of 1,068) in Sweden with glass and rock wool exposure (Gustavsson et al. 1992).

Some intermediate- and chronic-duration animal studies did not find any adverse histopathologic changes in the gastrointestinal tracts (see Table 3-1).

**Hepatic Effects.** The European cohort study reported that mortality from cirrhosis of the liver was significantly increased among continuous filament workers (12 of 172 total deaths, SMR=2.12, 95% CI=1.10–3.71), but not among workers exposed to glass or rock and slag wool (mean SMRs of 0.99 and 1.10, respectively) (Sali et al. 1999). The cause for this slight increase is unclear, but may be related to confounding factors related to lifestyle. Cause-of-death information for 2,758 workers (from a cohort of

11,373 men) was analyzed. In contrast, the number of mortalities caused by liver cirrhosis was significantly decreased among the total U.S. cohort compared to national (but not local county) rates (SMRs of 0.68 and 0.88, respectively) (Marsh et al. 2001a). A smaller study analyzing 554 deaths from a cohort of 1,068 prefabricated house builders found no correlation between liver cirrhosis and exposure to glass and rock wool (Gustavsson et al. 1992).

Some intermediate- and chronic-duration animal studies conducted routine liver histopathology but did not report any adverse effects (see Table 3-1).

**Renal Effects.** No relationship between occupational exposure to rock and slag wool, glass wool, or continuous filament and mortality from nonmalignant renal disease has been detected in occupational cohort studies in the United States (Marsh et al. 2001a), European (Sali et al. 1999), or Swedish (Gustavsson et al. 1992) cohorts. Data for mortality from nonmalignant renal disease were not reported for the Canadian cohorts (Shannon et al. 1987, 1990).

Some intermediate- and chronic-duration animal studies conducted routine kidney histopathology, but did not find any adverse effects (see Table 3-1).

No reliable studies were located regarding the following effects in humans or animals after inhalation exposure to synthetic vitreous fibers:

#### 3.2.1.3 Immunological and Lymphoreticular Effects

#### 3.2.1.4 Neurological Effects

#### 3.2.1.5 Reproductive Effects

#### 3.2.1.6 Developmental Effects

#### 3.2.1.7 Cancer

The principal target organs of concern for cancer are the lungs (bronchoalveolar adenoma and carcinoma) and the pleura (mesothelioma). Single layers of mesothelial cells compose the pleura, the delicate serous membrane that covers the lungs (visceral pleura) and chest wall and diaphragm (parietal pleura), as well

as the peritoneum, the membrane lining the abdominal walls and viscera. Mesotheliomas are rare malignant tumors of mesothelial cells; their incidence in the general human population is low, and pleural mesotheliomas have not been observed in control animals.

Available epidemiological results provide inadequate evidence of the carcinogenicity of synthetic vitreous fibers in humans (see below). Animal studies have detected elevated incidences of lung tumors and the formation of mesotheliomas following exposure to refractory ceramic fibers and two other fiber types (e.g., special-purpose glass microfiber 104E-glass and MMVF33, a durable special purpose glass fiber), but not for other synthetic vitreous fibers, such as traditional building insulation glass wools, that are less biopersistent (see below and Section 3.5).

Intermediate-duration (1-year) exposure of male Wistar rats to special purpose 104E-glass fibers was associated with a statistically significant increase in the combined (but not individual) incidence of lung adenomas and carcinomas (Cullen et al. 2000). Chronic exposure of male Fischer 344 rats to refractory ceramic fibers, RCF1 or RCF3, was associated with statistically significant elevations in lung adenoma and carcinoma incidence, and exposure to RCF2 was associated with increased lung carcinoma (but not adenoma) incidence (Mast et al. 1995a). In contrast, RCF1 did not induce lung tumors in male Syrian Golden hamsters (McConnell et al. 1995). The discrepancy between the two studies may be related to species specificity or differences in exposure duration (24 months for rats, 18 months for hamsters). No increased lung tumor incidence was reported in intermediate-duration studies with 100/475 special-purpose glass microfiber (Cullen et al. 2000), Code 104/475 special purpose glass fiber (Muhle et al. 1987), or GB100R glass wool (Haratake et al. 1995) in rodents or in chronic-duration studies with MMVF10, MMVF11 (Hesterberg et al. 1993c), MMVF21, MMVF22 (McConnell et al. 1994), MMVF33 (McConnell et al. 1999), MMVF34 (Kamstrup et al. 2001), or X607 fiber (Hesterberg et al. 1998b) in rodents or with C102/C104 blend fibrous glass in baboons (Goldstein et al. 1983).

Only one study has observed a statistically significant increase in pleural mesotheliomas, in male Syrian Golden hamsters exposed to 215 WHO fibers/cc of RCF1 for 18 months (42/102 versus 0/106 for controls) (McConnell et al. 1995); mesotheliomas were first seen at 40 weeks. Other studies have detected one or two mesotheliomas per treatment group among rats exposed to 1,022 WHO fibers/cc of 104E-glass for 1 year (Cullen et al. 2000), rats exposed for 2 years to 75 or 220 (but not 120) WHO fibers/cc of RCF1, as well as RCF2, RCF3, or RCF4 (220, 182, or 153 WHO fibers/cc, respectively)

(Mast et al. 1995a, 1995b), and hamsters exposed to 310 WHO fibers/cc of MMVF33, a durable special purpose glass fiber, for 18 months (McConnell et al. 1999).

**Human Studies.**

***Refractory Ceramic Fibers.*** In a recent initial report of a cohort mortality study of male workers employed at two U.S. refractory ceramic fiber manufacturing plants between 1952 and 2000 (LeMasters et al. 2003), the only statistically significant excess mortality was deaths associated with cancer of the urinary system. As of December 31, 2000, a total of 87 deaths were recorded among the 942 men (average age=51 years) included in the study (about 9% of the cohort). Observed number of deaths and SMRs for selected cancer-related deaths were as follows (with 95% CI noted in parentheses): all cancers, 29 deaths, SMR=94.2 (63–135); malignancies of the respiratory system, 9 deaths, SMR=78.8 (36–150); and malignancies of the urinary system, 5 deaths, SMR=344.8 (112–806). No mesotheliomas were identified among the cohort to date, based on careful review of death certificates, medical records, and lung tissue analysis. LeMasters et al. (2003) noted that the finding for excess urinary cancer deaths may be a chance finding given the wide confidence interval for the SMR, the large number of statistical tests that were conducted (n=46), and the lack of a plausible mechanistic explanation of how fibers may increase the risk for urinary cancer mortality. Continued monitoring of the mortality experience of this cohort is planned.

***Glass Wool, Rock and Slag Wool, and Continuous Filament Glass Fibers.*** Major cohort mortality and nested case-control studies of groups of workers engaged in the production of filament glass fibers, glass wool, rock wool and slag wool are ongoing in the United States (Bayliss et al. 1976; Buchanich et al. 2001; Chiazze et al. 1992, 1993, 1995, 1997, 2002; Enterline and Henderson 1975; Marsh et al. 1990, 2001a, 2001b, 2001c; Morgan 1981; Quinn et al. 2001; Robinson et al. 1982; Smith et al. 2001; Stone et al. 2001; Watkins et al. 1997; Wong et al. 1991; Youk et al. 2001) and Europe (Andersen and Langmark 1986; Bertazzi et al. 1986; Boffetta et al. 1997, 1999; Claude and Frentzel-Beyme 1984, 1986; Khaerheim et al. 2002; Lea et al. 1999; Olsen and Jensen 1984; Olsen et al. 1986; Plato et al. 1995c; Sali et al. 1999; Saracci et al. 1984; Simonato et al. 1986a, 1987; Teppo and Kojonen 1986; Westerholm and Bolander 1986). Smaller studies have been conducted in Canada (Shannon et al. 1984, 1987, 1990), Sweden (Gustavsson et al. 1992; Plato et al. 1997), and the United States (Bayliss et al. 1976; Enterline and Henderson 1975; Morgan 1981; Robinson et al. 1982). These studies provide inadequate evidence of carcinogenicity in humans with occupational exposure. Although some small, statistically significant

elevations in respiratory system cancer risk were detected, the lack of sufficient data regarding potential confounding factors prevents a conclusive determination that the increased risks were due to these synthetic vitreous fibers (see below).

Early studies of U.S. fibrous glass production workers did not associate exposure to fibrous glass or rock and slag wool with increased risk of respiratory or other cancers (Bayliss et al. 1976; Enterline and Henderson 1975; Morgan 1981; Robinson et al. 1982), but lacked statistical power due to their small size (cohorts of <1,500 men and cause-of-death information obtained for <400 workers). A larger study analyzed mortality statistics for workers from 17 U.S. plants manufacturing either fiberglass (glass wool or continuous filament glass) or rock wool and slag wool from the 1940s to the 1980s; it was conducted by the University of Pittsburgh under the sponsorship of the Thermal Insulation Manufacturers Association (TIMA), analyzing mortality statistics from the 1940s to the 1980s (Chiazze et al. 1992, 1993, 1995, 1997, 2002; Enterline 1990; Enterline et al. 1983, 1987; Marsh et al. 1990; Watkins et al. 1997; Wong et al. 1991); the results found either none or small and occasionally statistically significant elevations in the risk for respiratory system cancer among glass wool and rock and slag wool workers, but observed no correlation between length of exposure and increased risk. To overcome limitations in these initial studies, a comprehensive surveillance of the U.S. cohort was performed by the University of Pittsburgh under the sponsorship of the North American Insulation Manufacturer's Association (NAIMA) (Buchanich et al. 2001; Marsh et al. 2001a, 2001b, 2001c; Quinn et al. 2001; Smith et al. 2001; Stone et al. 2001; Youk et al. 2001). Mortality data collected until 1992 for 9,060 workers from a cohort of 32,110 workers in the 10 largest and longest-operating factories were analyzed (Marsh et al. 2001a). The mean exposure to respirable fibers was estimated at 0.073 fibers/cc. A small, but statistically significant, increase in the SMR for respiratory system cancer was limited to workers employed <5 years (SMR=1.12, 95% CI=1.01–1.24), suggesting an exposure-independent "healthy worker" effect. No patterns or statistically significant trends associated increasing risk for respiratory system cancer mortality with increasing measures of exposure (years of employment or estimated cumulative exposure). A nested-case control analysis (632 cases, 572 controls) did not observe any relationship between respiratory system cancer risk and exposure indices (Marsh et al. 2001a; Youk et al. 2001).

The IARC began a large international cohort study of European workers involved in the manufacture of synthetic vitreous fibers in 1976. The study includes 13 factories that produced glass wool, continuous glass filament, or rock and slag wool in Denmark, Finland, Norway, Sweden, the United Kingdom, Germany, and Italy. Early reports frequently focused on data from single countries (Andersen and

Langmark 1986; Bertazzi et al. 1986; Claude and Frentzel-Beyme 1984, 1986; Olsen and Jensen 1984; Olsen et al. 1986; Plato et al. 1995c; Teppo and Kojonen 1986; Westerholm and Bolander 1986) going back as far as the 1930s. The ongoing European study has incorporated these data and has published follow-up reports for data collected through the 1980s (Boffetta et al. 1992; Gardner et al. 1986, 1988; Saracci et al. 1984; Simonato et al. 1986a, 1987) and early 1990s (Lea et al. 1999; Sali et al. 1999), with the most recent reports considering data up to 1995 (Boffetta et al. 1997, 1999). Most recently, cause-of-death information for 4,521 workers (191 continuous filament workers from two factories, 1,679 glass wool workers from five factories, and 1,281 rock and slag wool workers from seven factories) was analyzed from a cohort of 22,002 individuals (Boffetta et al. 1997). No increased risk of cancer incidence was clearly related to exposure, and none were related to duration of employment or time since first employment. Among glass wool workers, a statistically significant overall increase (SMR=1.27, 95% CI=1.07–1.50) in mortality from cancers of the trachea, bronchus, and lung did not persist either when local mortality rates were used or when workers with <1 year of employment were excluded (a national healthy worker effect). The increase of mortality from lung cancer among continuous filament workers (SMR=1.11, 95% CI=0.61–1.86) was not significant overall and was attributed to one factory in Italy. Potential exposure to asbestos was associated with a significant increase (SMR=1.69, 95% CI=1.22–2.29) in the risk of lung cancer among all workers. A statistically significant increase (SMR=1.34, 95% CI=1.08–1.63) in the SMR for risk of death from cancers of the trachea, bronchus, and lung for all rock and slag wool workers was attributed to one factory in Germany where exposure to asbestos was reported. After exclusion of that factory, no significant elevation in risk remained (SMR=1.16, 95% CI=0.87–1.51) for rock and slag wool workers. The authors concluded that “these results are not sufficient” to conclude that exposure to synthetic vitreous fibers increased the risk of lung or other cancer types.

Because cancer incidence may be a more sensitive tool than mortality incidence for the detection of adverse health effects, a cancer incidence study of the European cohort was conducted (Bofetta et al. 1999). Data were obtained from the national cancer registrations of Denmark, Finland, Norway, and Sweden for 3,685 rock and slag wool workers and 2,611 glass wool workers who had been employed for at least 1 year in one of nine factories in between 1933 and 1995. Although the elevation for cancers of the oral cavity and pharynx was statistically significant (27 cases, standard incidence ratio [SIR]=1.84, 95% CI=1.22–2.68) for slag wool workers, the combined incidence of cancers of the oral cavity, pharynx, and larynx combined was not significant (31 cases, SIR=1.46, 95% CI=0.99–2.07). Among glass wool workers, these incidences were not significantly elevated (11 cases, SIR=1.31, 95% CI=0.65–2.34 and 16 cases, SIR=1.41, 95% CI=0.80–2.28, respectively) but the trend between increasing time since first

employment working with glass wool and increased incidences of oral, pharyngeal, and laryngeal cancers was statistically significant. The authors concluded that these data were inadequate evidence of carcinogenicity because potential effects from confounding factors such as smoking had not been included.

In a nested case-control study of 133 lung cancer cases and 513 matched controls among men who worked in seven rock and slag wool manufacturing plants in Denmark, Norway, Sweden, or Germany, no statistically significant associations with exposure were found (Kjaerheim et al. 2002). Occupational exposure was assessed on the basis of interview data and exposure information from the manufacturing plants; cases and controls were placed in quartile categories of exposure. Smoking-adjusted odds ratios for workers with at least 15 years since first exposure showed no evidence of increasing odds ratio with increasing category of cumulative exposure; odds ratios for the second, third, and fourth quartiles of cumulative exposure (with 95%CI noted in parentheses) were 1.3 (0.7–2.3), 1.0 (0.5–1.9), and 0.7 (0.3–1.3), respectively. Similar results were obtained with other exposure metrics and after controlling for other potential confounders.

Two mortality studies were conducted in Canada, using mortality data collected from the national Vital Statistics and Disease Registry. An initial (Shannon et al. 1984) and follow-up (Shannon et al. 1987) study obtained information for 157 male workers employed between 1955 and 1977 for at least 90 days at an insulating glass wool manufacturing plant in Sarnia, Ontario, Canada. In 1978, the mean concentration of glass wool fibers with diameters <3.5 μm in the plant was 0.1 fiber/cc, but the authors believed that earlier concentrations had been higher. A statistically significant increase (SMR=1.99, 95% CI=1.28–3.11) for mortality from lung cancer was detected among exposed employees based on an observed 19 deaths versus 9.5 expected. However, four of these deaths occurred in men with <1 year of exposure, and cancer risk was not elevated in people with at least 5 years of exposure. Because increasing length of exposure did not correlate with increasing risk or decreased latency, the authors considered the results inconclusive. The other mortality study identified 96 deaths from a cohort of workers who had been employed for at least 1 year between 1951 and 1986 at a glass filament plant in Guelph, Ontario, Canada (Shannon et al. 1990). The mean number of fibers in dust samples collected at that plant between 1979 and 1987 reportedly ranged from 0.02 to 0.5 fibers/cc with values as high as 0.91 fibers/cc, but the proportion of glass fibers was not determined. No significant difference in lung cancer mortality was seen. For both Canadian studies, no other differences in cancer mortality incidence were significant (all

cancers combined, cancer of the digestive system and peritoneum, cancer of the genito-urinary organs, lymphatic and hepatopoietic malignancies), and data were not adjusted for smoking habits.

European case-control studies of lung cancer, multiple myeloma, mesothelioma, and cancers of the larynx and hypopharynx conducted separately from the European cohort mortality study have been inconclusive due to relatively few cases exposed to synthetic vitreous fibers without confounding exposures (Brueski-Hohlfeld et al. 2000; Lee et al. 2003; Marchand et al. 2000; Pohlabeln et al. 2000; Rodelsperger et al. 2001). Exposure was estimated by employment information collected from questionnaires, and the potential for co-exposure to asbestos was a confounding factor. An analysis of pooled lung cancer incidence data collected in Germany (1988–1993 and 1990–1996) identified only 51 cases and 28 matched controls (identified from a national mandatory registry of residents) who had been exposed to glass wool or mineral wool (as insulators in the construction industry) without asbestos co-exposure (Brueski-Hohlfeld et al. 2000; Pohlabeln et al. 2000); after adjustment for smoking, this difference was not statistically significant (OR=1.56, 95% CI=0.92–2.65). No statistically significant association between occupational exposure to mineral wool and multiple myeloma was found in a case-control study of 446 cases of multiple myeloma among Swedish construction workers (Lee et al. 2003). A German case-control study for mesothelioma was inconclusive because only two cases of diffuse malignant mesothelioma and two controls (matched from a national mandatory registry of residents) who had been exposed to synthetic mineral fibers, but not asbestos, were identified from a total of 125 cases and 125 controls (Rodelsperger et al. 2001). A French case-control study for squamous cell carcinoma of the larynx or hypopharynx did not associate exposure to exposures to mineral wool (OR=1.33, 95% CI=0.91–1.95 and OR=1.55, 95% CI=0.99–2.41), glass filaments (OR=0.44, 95% CI=0.15–1.31 and OR=0.91, 95% CI=0.30–2.76), or ceramic fibers (OR=1.28, 95% CI=0.51–3.22 and OR=0.78, 95% CI=0.26–2.38) to increased risks of these cancers in 528 cases and 205 controls (hospital patients with nonmalignant respiratory disease) (Marchand et al. 2000).

Small studies of exposure in other occupations have also been inconclusive. A cohort study of 1,342 unexposed workers and 1,068 workers exposed to glass and rock wool in the production of prefabricated houses in 11 Swedish plants did not detect any statistically significant elevation in risk of mortality from any type of cancer (Gustavsson et al. 1992). The study assigned three categories of exposure: the mean for 478 men was 0.11 fibers/cc (range 0.05–0.17 fibers/cc), for 375 men was 0.09 fibers/cc (range 0.05–0.13 fibers/cc), and for 215 men was 0.06 fibers/cc (range 0.02–0.08 fibers/cc). Another cohort study of 2,807 workers (including 478 insulators, the occupation with highest exposure)

in the Swedish prefabricated house industry observed no increased risk of lung cancer (for the general cohort, SMR=0.56, 95% CI=0.45–1.44; for insulators, SMR=0.85, 95% CI=0.01–3.01) associated with exposure to synthetic vitreous fibers (not specified, presumably glass wool) (Plato et al. 1997). The mean exposure to synthetic vitreous fibers (not specified, presumably glass wool) was 0.14 fibers/cc; insulators, as high as 0.18 fibers/cc (Plato et al. 1997).

In summary, studies of workers involved in the manufacture of continuous glass filament, glass wool, and rock and slag wool provide inadequate evidence for carcinogenicity in humans. A number of reviews of the fibrous glass cohort mortality and case-control studies concur with this conclusion (ACGIH 2001; Hesterberg and Hart 2001; IARC 1988, 2002; Lee et al. 1995; NIOSH 1977; NRC Subcommittee on Manufactured Vitreous Fibers 2000; Wilson et al. 1999). No evidence has associated inhalation exposure to these materials with nonrespiratory cancers.

**Animal Studies.**

***Refractory Ceramic Fibers.*** Studies conducted in rats and hamsters have associated inhalation exposure to refractory ceramic fibers with mesothelioma formation and increased incidences of lung adenomas and carcinomas (Davis et al. 1984; Hesterberg et al. 1998b; Mast et al. 1995a, 1995b; McConnell et al. 1995; Smith et al. 1987).

Two studies relevant to intermediate-duration exposure were identified. Exposure of Wistar rats to 95 WHO fibers/cc of a ceramic aluminum silicate glass for 12 months followed by a 20-month observation period was associated with a statistically significant increase in the combined incidence of respiratory tumors (one adenoma, three carcinomas, and four malignant histiocytomas in a group of 48 rats) compared to controls (no observed tumors in 40 rats) (Davis et al. 1984). Additionally, one peritoneal mesothelioma was identified; the relevance of this tumor outside the pleural cavity is unclear, but it might represent a metastasis of an occult lesion. A chronic study that exposed male Syrian Golden hamsters exposed to 215 WHO fibers/cc (30 mg/$m^3$) of RCF1 for up to 18 months detected mesotheliomas in animals that reportedly died from other (noncancer) causes: 2 at 40 weeks, 1 at 45 weeks, and 1 at 47 weeks (McConnell et al. 1995). Additionally, a mesothelioma (1/3) was observed in the interim-sacrifice group euthanized at 12 months (McConnell et al. 1995). At study termination, no lung adenomas or carcinomas were seen in control or exposed animals (0/106, 0/102). However, the

incidences of mesothelial cell hypertrophy (0/106 versus 33/102) and pleural mesothelioma (0/106 versus 42/102) were significantly increased.

Other chronic studies have also found evidence of carcinogenicity. No lung tumors were seen in male Fischer 344 rats exposed nose-only to RCF1 at concentrations as high as 120 WHO fibers/cc (17 mg/m$^3$) for 2 years, although a single mesothelioma was seen at 75 WHO fibers/cc (Mast et al. 1995b). A companion 2-year study exposed male Fischer 344 rats nose-only to single concentrations of RCF1, RCF2, RCF3, or RCF4 (187, 220, 182, or 153 WHO fibers/cc; 30 mg/m$^3$ for each) (Mast et al. 1995a). The first three concentrations induced statistically significant increases in the incidences of bronchiolar-alveolar hyperplasia (control 5/130; 17/123, 15/121, 15/121, and 8/118 for RCF1, RCF2, RCF3, and RCF4, respectively) and pulmonary carcinoma (control 0/130; 8/123, 5/121, 9/121, and 2/118 for RCF1, RCF2, RCF3, and RCF4, respectively). Only RCF1 and RCF3 significantly induced pulmonary adenomas (control 2/130; 8/123, 5/121, 9/121, and 2/118 for RCF1, RCF2, RCF3, and RCF4, respectively). Although the incidences were not statistically significant, mesotheliomas were detected for RCF1, RCF2, and RCF3 (but not RCF4) (control 0/130; 2/120, 3/123, 2/121, 0/118 for RCF1, RCF2, RCF3, and RCF4, respectively). Data from the 2-year bioassays with male Fischer 344 rats exposed to RCF1 (Mast et al. 1995a, 1995b) provide the best available data describing exposure-response relationships for cancer and chronic exposure to refractory ceramic fibers; however, the presence of non-fibrous particles in the RCF1 test atmosphere is widely acknowledged to have added to the noncancer and cancer responses to an undetermined degree (Bellmann et al. 2001; Mast et al. 2000; Maxim et al. 2003b). Under conditions in which lung clearance mechanisms become overloaded, many types of nonfibrous or fibrous materials can produce pulmonary fibrosis or tumors in rats (Oberdörster 1994).

A mesothelioma was also found in male Syrian Golden hamsters exposed to 200 fibers/cc (12 mg/m$^3$) of an unspecified type of refractory ceramic fiber for 2 years (Smith et al. 1987). No lung tumors were observed in these hamsters, or in similarly-treated female Osborne-Mendel rats. The study was inconclusive because the positive control (crocidolite asbestos) failed to induce lung tumors and reporting of experimental details was limited.

In summary, different samples of refractory ceramic fibers induced lung tumors in rats and meso-theliomas in both hamsters and rats. These results have demonstrated the carcinogenicity of refractory ceramic fibers in animals following inhalation exposure, and indicate that fiber type and exposure levels are important factors influencing carcinogenicity. It should be noted that the degree to which nonfibrous

particles in RCF1 may have contributed to the carcinogenic responses in RCF1-exposed rats (Mast et al. 1995a, 1995b) is undetermined.

***Glass Wool (Insulation Glass Wools and Special Purpose Glass Fibers).*** Mesothelioma formation has been found in one chronic rat study with MMVF33, a durable special purpose glass fiber (Hesterberg et al. 1999) and another rat study involving 1-year exposures to special purpose 104E-glass fiber (Cullen et al. 2000). No mesotheliomas were found in rats exposed to the insulation glass wools, MMVF10 or MMVF11 (Hesterberg et al. 1993), or in hamsters exposed to MMVF10a (McConnell et al. 1999). Exposure to special purpose 104E-glass fiber also induced increased incidences of lung tumors in rats (Cullen et al. 2000). In contrast, inhalation studies with MMVF33 and the insulation glass wools, MMVF10, MMVF11, and C102/C104 fibrous glass blend, did not find exposure-related increases in lung tumor incidence (Goldstein et al. 1983; Haratake et al. 1995; Johnson and Wagner 1980; Kamstrup et al. 1998, 2001; McConnell et al. 1994, 1999; Muhle et al. 1987; Smith et al. 1987).

Intermediate-duration experiments did not provide evidence of carcinogenicity. No increased lung tumor incidence was found in female Wistar rats exposed nose-only to 252 fibers/cc (3 mg/m$^3$) of Code 104/475 special purpose glass fiber for 1 year (Muhle et al. 1987) or in small experiments (<16 animals/exposure group) with male Wistar rats exposed to 2.2 mg/m$^3$ of a glass wool (fiber counts not reported) for 1 year (Haratake et al. 1995), or rats, hamsters, and guinea pigs exposed to 70 fibers/cc of a ball-milled fiberglass (7% fiber) for 3 months (Lee et al. 1981b), with post-exposure periods up to 1 year.

In male Wistar rats exposed whole-body to 1,022 WHO fibers/cc of special purpose 104E-glass fiber for 1 year followed by a 1-year recovery period, the combined lung tumor incidence was statistically significantly different from controls (3/43 versus 1/38 adenomas and 7/42 versus 1/38 carcinomas, respectively) (Cullen et al. 2000); additionally, one mesothelioma was induced (1/43 versus 0/38 for controls). Exposure of rats to 1,119 WHO fibers/cc of special purpose glass fiber code 100/475 using the same protocol did not induce any mesotheliomas or statistically significantly increased incidences of lung tumors (Cullen et al. 2000).

One pleural mesothelioma (1/83 versus 0/83 for controls) and no lung tumors were observed in male Syrian Golden hamsters exposed to 310 WHO fibers/cc (37 mg/m$^3$) of MMVF33, a durable special applications glass fiber for 18 months (Hesterberg et al. 1999). No lung tumors or mesotheliomas were observed in male Syrian Golden hamsters exposed to 339 WHO fibers/cc (29.6 mg/m$^3$) of MMVF10a

glass wool (a low fluorine preparation of MMVF10) for 18 months (McConnell et al. 1999). No lung tumors and no increased incidences of bronchoalveolar metaplasia were seen in male Syrian Golden hamsters or female Osborne-Mendel rats exposed for 2 years to 300 or 3,000 fibers/cc of a 0.45 μm diameter glass wool (0.3 or 3.0 mg/$m^3$), 100 fibers/cc of a 3.1 μm diameter glass wool (10 mg/$m^3$), 10 or 100 fibers/cc of 5.4 μm diameter glass wool (1.2 or 12 mg/$m^3$), 25 fibers/cc of 6.1 μm diameter glass wool (9 mg/$m^3$), or 200 fibers/cc of a 2.7 μm diameter slag wool (10 mg/$m^3$) (Smith et al. 1987). Similarly, tumor incidence was not elevated in male Fischer 344 rats exposed nose-only to three concentrations of MMVF10 or MMVF11 glass wool for 2 years (Hesterberg et al. 1993c). MMVF10 was tested at 29, 145, and 232 WHO fibers/cc (3.1, 17.1, and 27.8 mg/$m^3$) and MMVF11 was tested at 41, 153, and 246 WHO fibers/cc (4.8, 15.8, and 28.3 mg/$m^3$).

No tumors were seen in biopsies collected at 8, 18, and 30 months (2/animals per time point) from a group of 10 male baboons (*Papio ursinus*) exposed to 1,122 NIOSH fibers (lengths >5 μm)/cc of a blend of C102 and C104 fibrous glass wools (7.54 mg/$m^3$; 5.80 mg/$m^3$ respirable) for 35 months (Goldstein et al. 1983). The study was inconclusive because of the small numbers used and the small amount of tissue available for analysis.

***Slag Wool***. The limited animal inhalation studies identified for slag wool did not provide any evidence of carcinogenicity.

No lung tumors and no increased incidences of bronchoalveolar metaplasia were seen in male Syrian Golden hamsters or female Osborne-Mendel rats exposed for 2 years to 200 fibers/cc of a 2.7 μm diameter slag wool (10 mg/$m^3$) (Smith et al. 1987).

In male Fischer 344 rats exposed nose-only for 24 months to 30, 131, or 213 WHO fibers/cc (3.1, 16.1, or 29.9 mg/$m^3$) of MMVF22, a blast-furnace slag wool, no significant increases were seen in the individual or combined incidences of pulmonary adenoma or pulmonary carcinoma (McConnell et al. 1994).

***Rock Wool.*** The limited animal studies identified for rock wool did not provide any evidence of carcinogenicity.

No tumors were reported in Fischer rats exposed to 10 mg/$m^3$ of rock wool (fiber count not reported) for 50 weeks and allowed to recover for 4 months prior to sacrifice (Johnson and Wagner 1980).

In male Fischer 344 rats exposed nose-only for 24 months to 34, 150, or 243 WHO fiber/cc (3.1, 16.1, or 30.4 mg/$m^3$) of MMVF21, a traditional basalt-based rock (stone) wool, no significant increases were seen in the individual or combined incidences of pulmonary adenoma or pulmonary carcinoma (McConnell et al. 1994). Similarly, in male Fischer 344 rats exposed nose-only to 291 WHO fibers/cc (30.1 mg/$m^3$) of MMVF34/HT, a newly developed high-temperature rock wool, for 2 years (6 hours/day, 5 days/week), lung tumor incidence was not significantly increased (Kamstrup et al. 1998, 2001).

***Continuous Filament Glass.*** No inhalation cancer studies in animals with continuous glass filaments were identified. Because these fibers are not normally respirable (ACGIH 2001; Lee et al. 1995), studies have been limited to injection and implantation (see Section 3.2.4, Other Routes of Exposure).

***Other Fibers.*** No mesotheliomas or increased incidences of lung adenomas (1/121 versus 2/130 for controls or lung carcinomas (1/121 versus 0/130 for controls) were seen in male Fischer 344 rats exposed to 180 WHO fibers/cc (30 mg/$m^3$) of X-607 (Hesterberg et al. 1998b).

### 3.2.2 Oral Exposure

#### 3.2.2.1 Death

No studies were located regarding death in humans or animals after oral exposure to synthetic vitreous fibers.

#### 3.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculo-skeletal, hepatic, renal, endocrine, dermal, ocular, body weight, or metabolic effects in humans or animals after oral exposure to synthetic vitreous fibers.

No studies were located regarding the following effects in humans or animals after oral exposure to synthetic vitreous fibers:

#### 3.2.2.3 Immunological and Lymphoreticular Effects

#### 3.2.2.4 Neurological Effects

#### 3.2.2.5 Reproductive Effects

#### 3.2.2.6 Developmental Effects

#### 3.2.2.7 Cancer

### 3.2.3 Dermal Exposure

#### 3.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to synthetic vitreous fibers.

#### 3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, or body weight effects in humans or animals after dermal exposure to synthetic vitreous fibers.

**Dermal Effects.** Strong itching and contact dermatitis (with erythema, maculae, papules, and other eczematous symptoms) have been associated with occupational exposure to synthetic vitreous materials, including glass wool insulation and fiberglass fabrics (Bendsoe et al. 1987; Bjornberg 1985; Bjornberg et al. 1979a, 1979b, 1979c; Fisher 1982; Fisher and Warkentin 1969; Heisel and Hunt 1968; Koh and Khoo, 1995; Longely and Jones 1966; Minamoto et al. 2002; Possick et al. 1970; Stam-Westerveld et al. 1994; Tarvainen et al. 1993), rock wool (Bjornberg and Lowhagen 1977; Eun et al. 1991; Fisher 1982; Kiec-Swierczynska and Szymczk 1995; Peterson and Sabroe 1991; Thriene et al. 1996), and refractory ceramic fibers (Kiec-Swierczynska and Wojtczak 2000). The skin irritation has been associated with fibers

having diameters >5 μm and becomes less pronounced with continued exposure, a "hardening" of the skin (ACGIH 2001; Heisel and Hunt 1968; Stam-Westerveld et al. 1994).

No studies were located regarding the dermal effects of synthetic vitreous fibers in animals after dermal exposure.

**Ocular Effects.** Occupational exposure to fibrous glass materials, including glass wool insulation and fiberglass fabrics, has been associated with acute eye irritation (Longley and Jones 1966; Petersen and Sabroe 1991; Stokholm et al. 1982).

No studies were located regarding the ocular effects of synthetic vitreous fibers in animals after dermal exposure.

No studies were located regarding the following effects in humans or animals after dermal exposure to synthetic vitreous fibers:

#### 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

### 3.2.4 Other Routes of Exposure

No studies were located regarding adverse health effects in humans after exposure by other routes to synthetic vitreous fibers.

Intratracheal instillation, interpleural implantation, and intraperitoneal injection studies with synthetic vitreous fibers have been performed. Most have been acute-duration studies (single administration followed by observation periods up to 2 years). The relevance of these studies to human inhalation exposure is unclear because of the high doses and rapid dose rates used, the bypassing of the natural

defense systems of the nasal and upper respiratory system, and the overloading or lack (for intraperitoneal studies) of pulmonary clearance mechanisms

***Continuous Filament Glass Fibers***. Neither intrapleural implantation (Stanton et al. 1972, 1977) nor intraperitoneal injection of continuous glass filaments into rats was carcinogenic (Pott et al. 1987).

***Glass Wool.*** Studies in which glass wool was instilled into the trachea of animals were equivocal; some (but not all) demonstrated pulmonary fibrosis (Feron et al. 1985; Mohr et al. 1984; Pickrell et al. 1983; Renne et al. 1985; Smith et al. 1987; Wright and Kuschner 1977). Only two of these studies reported tumor induction in rats and hamsters (Mohr et al. 1984; Smith et al. 1987).

***Rock Wool.*** Intratracheal instillation of rock wool did not cause tumor formation in female Syrian Golden hamsters (Adachi et al. 1991).

***Slag Wool.*** No studies were located regarding the adverse health effects of slag wool in animals following other routes of exposure.

***Refractory Ceramic Fibers.*** Intratracheal instillation of a refractory ceramic fiber caused lung cancer in male Syrian Golden hamsters, but not in female Osborne-Mendel rats (Smith et al. 1987). Intraperitoneal injection of ceramic aluminum silicate fibers in rats and hamsters induced cancer (Davis et al. 1984; Smith et al. 1987). Refractory alumina and zirconia fibers injected intraperitoneally did not induce fibrosis in rats (Pigott and Tshmael 1981).

## 3.3 GENOTOXICITY

No evidence for genotoxic activity of several synthetic vitreous fibers was found in bacterial mutation assays (Chamberlain and Tarmy 1977) or sister chromatid exchange assays in cultured human cells (Casey 1983). However, several cytogenetic effects have been observed in other *in vitro* assays. Notably absent are data on genotoxic end points following *in vivo* exposure of animal or humans to synthetic vitreous fibers. Results from short-term *in vitro* genotoxicity assays are of limited applicability to *in vivo* exposure scenarios because of evidence that long-term residence of synthetic vitreous fibers in the principal toxicity target, the lung, can lead to changes (dissolution, breakage into shorter fibers) that can decrease biological activities of longer fibers (IARC 2002; also see Section 3.4).

Synthetic vitreous fibers induced: chromosomal aberrations in cultured Chinese hamster cells (Brown et al. 1979a, 1979b); morphological transformations in Syrian hamster embryo cells (Hesterberg and Barrett 1984; Hesterberg et al. 1985; Oshimura et al. 1984) and BALB/c-3T3 cells (Gao et al. 1995; Whong et al. 1999); micronuclei and multinuclei in Chinese hamster ovary cells (Hart et al. 1992), Chinese hamster lung fibroblasts (Ong et al. 1997; Zhong et al. 1997), Syrian hamster epithelial lung cells (Peraud and Riebe-Imre 1994), Syrian hamster embryo fibroblasts (Dopp and Schiffmann 1998), and human amniotic fluid cells (Dopp and Schiffmann 1998; Dopp et al. 1997); polyploidy in Chinese hamster lung cells (Koshi et al. 1991; Sincock et al. 1982); and deoxyribose nucleic acid (DNA) strand breaks and DNA-DNA interstrand crosslinks in human lung epithelial A549 cells (Wang et al. 1999b). In addition, several synthetic vitreous fiber types have been demonstrated to damage isolated DNA (Donaldson et al. 1995c) and to hydroxylate 2-deoxyguanosine to 8-hydroxydeoxyguanosine, presumably via hydroxyl radicals (Leanderson et al. 1988, 1989).

There is evidence that fiber dimensions can influence *in vitro* cytogenetic activities (Hesterberg and Barrett 1984; Hesterberg et al. 1985; Ong et al. 1997) and that synthetic vitreous fibers are often less active than asbestos fibers (e.g., Donaldson et al. 1995c; Leanderson et al. 1988, 1989; Peraud and Rieve-Imre 1994; Wang et al. 1999b). For example, thin glass fibers (diameters 0.1–0.2 μm, lengths >10 μm) were very active in transforming Syrian hamster embryo cells, whereas thick glass fibers (diameter about 0.8 μm) were much less potent (Hesterberg and Barrett 1984). Milling of the thin glass fibers to reduce the length to <1 μm diminished the transforming activity.

Gene amplification of several proto-oncogenes, *H-ras*, *K-ras*, *c-myc*, and *c-fos*, has been reported in several transformed BALB/C-3T3 cell lines that were induced by a glass fiber (AAA-10 microfiber) (Whong et al. 1999). Point mutations, detected by sequencing analysis of DNA from several of the transformed cell lines, were also found in the proto-oncogene *K-ras*, and in the *p53* tumor suppressor gene (Whong et al. 1999). Induction of *c-fos* and *c-jun* proto-oncogenes by crocidolite asbestos was demonstrated in cultured hamster tracheal epithelial cells and rat pleural mesothelial cells, but induction activities of a glass wool (MMVF10) and a refractory ceramic fiber (RCF1) were much less in this test system (Janssen et al. 1994a).

## 3.4 TOXICOKINETICS

### 3.4.1 Absorption

Absorption of synthetic vitreous fibers across the epithelial layers of the respiratory tract, the gastro-intestinal tract, and the skin is expected to be low to negligible due to the relatively large physical dimensions of these elongated particles (see Chapter 4). However, deposition of inhaled fibers on the surface of the epithelial layers of the respiratory tract is an initial process that has been well studied and, along with the process of lung clearance, plays an important role in determining toxicity (especially the deposition and clearance of fibers in the alveolar region of the respiratory tract). An overview of the deposition of inhaled synthetic vitreous fibers in the respiratory tract is presented in the next section (Section 3.4.1.1). The deposition of inhaled fibers has been reviewed in more detail in other published sources (Dai and Yu 1998; Jones 1993; Lippmann 1990; Morgan 1995; Oberdörster 1994, 2000; Stober 1972; Stober and McClellan 1997; Timbrell 1965; Yu et al. 1995a).

#### 3.4.1.1 Inhalation Exposure

Very limited amounts of inhaled synthetic vitreous fibers are expected to be absorbed in humans or animals. Consistent with the expectation of limited, if any, absorption are findings from a study in which rats were given single intratracheally-instilled doses (1 mg/rat, equivalent to $3.5x10^6$ fibers/rat) of a saline suspension of radiolabeled ($^{24}Na$) glass fibers (Morgan et al. 1993). The fibers were produced as a continuous filament with an approximate uniform diameter of 2 μm. The fibers in the instilled material had a log-normal distribution of lengths, with a median of 16 μm and geometric standard deviation of 1.8. Radioactivity measured in urine collected for 24 hours after dose administration accounted for <1% of administered radioactivity, and no radioactivity was detected in 24- to 48-hour urine samples. Radioactivity in feces collected for 48 hours and in the gastrointestinal tracts and lungs accounted for >96% of administered radioactivity in 4/8 rats sacrificed 48 hours after dose administration. The average total recovery of administered radioactivity in feces, gastrointestinal tract, and lungs of all eight rats was 93%. The average individual percentages of administered radioactivity in the feces, gastrointestinal tract, and lungs were 30, 2, and 61%. (In these experiments, radioactivity detected in the gastrointestinal tract and feces represents fibers deposited in the respiratory tract, removed by mucous flow to the gastro-intestinal tract, and eliminated with the feces—see Sections 3.4.2 and 3.4.4). Morgan et al. (1993) reported that, during dose administration, occasional losses of small volumes of the fiber suspension occurred (i.e., small volumes remained in the administration apparatus), and that these losses may account

for the small differences between the calculated administered doses of radioactivity and the total radioactivity recovered in the feces, gastrointestinal tract, and lungs.

There is evidence to suggest that a small amount of inhaled synthetic vitreous fibers may enter the body via the lymph nodes. For example, in hamsters exposed for 78 weeks to MMVF10a or MMVF33, elevated concentrations of fibers (# fibers/mg dry tissue) were measured in mediastinal tissue containing lymph nodes, the diaphragm, and the thoracic wall (Hesterberg et al. 1999).

The fraction of inhaled synthetic vitreous fibers deposited on the epithelial surface of the respiratory tract and the region where deposition occurs are determined by fiber dimensions, fiber density, ventilation parameters, and the structure and airway size of the respiratory tract (Dai and Yu 1998; Lippmann 1990; Morgan 1995; Yu et al. 1995a). In general, relatively thick inhaled fibers are deposited in the upper airways (i.e., the nasopharyngeal region and tracheobronchial regions), and only relatively thin fibers are carried to distal regions of the respiratory tract (i.e., the terminal bronchiole and alveolar regions). In the large conducting airway regions of the lung and in the nonciliated bronchoalveolar regions, fiber deposition is particularly enhanced at branching points (Brody and Roe 1983; Lippmann 1990; Myojo 1987).

In published studies of animals exposed by inhalation to different types of fibers, estimates of the fraction of inhaled fibers deposited in the lung have ranged from about 1–23% (Okabe et al. 1997). Given the complexity of factors influencing apparent lung deposition (e.g., fiber dimensions, exposure duration and concentration, ventilation parameters, and airways size and geometry) and the differences in experimental conditions and techniques used in these studies, the wide range is not surprising. However, studies that restricted periods of exposure to glass wool fibers to 30 minutes (Morgan 1995) or 10 minutes (Okabe et al. 1997) to minimize clearance by mucociliary action (see Section 3.4.2) reported values in the upper end of the range (15–23%).

Major mechanisms involved in the deposition of nonelectrostatically charged fibers in the respiratory tract include impaction (under high velocity airflows experienced in the larger airways of the respiratory tract), gravitational sedimentation (under low velocity airflows), interception, and diffusion. Impaction and sedimentation are influenced by the aerodynamic diameter of the particle, whereas interception is influenced by the length of the fiber. One formula for aerodynamic diameter (DA) of fibers is:

$$DA = 1.3\, p^{1/2} d^{5/6} L^{1/6}$$

where p=particle density; d=actual diameter; and L=length (Hesterberg and Hart 2001; Stober 1972). For glass fibers of uniform particle density, aerodynamic diameters are described by the following formula:

$$DA = 66d\left[\frac{\beta}{2+4\beta}\right]^{2.2}$$

where β=length:diameter ratio (Gross 1981). Calculated values of aerodynamic diameters of fibers of a uniform density range from about 2.5–4 times that of the actual diameter (Gross 1981; Timbrell 1965). More complicated mathematical expressions for aerodynamic diameters of fibers have been derived to account for changing orientation of fibers with respect to direction of airflow (Dai and Yu 1998). Fibers or particles with aerodynamic diameters >3–5 μm are expected to be predominantly deposited in the upper airways and have less probability of traveling to the lower lung than particles or fibers with smaller aerodynamic diameters (Morgan et al. 1980; Oberdörster 1994). Based on a review of the literature on particle deposition in the human lung, ACGIH (2001) published an algorithm predicting the collection efficiency of particles of varying aerodynamic diameters. The algorithm predicts that inhalation exposure to particles of uniform aerodynamic diameters of 1, 5, 6, or 10 μm would lead to the following mass percentages being deposited in the alveolar or gas-exchange region: 97, 30, 17, or 1%.

More specific mathematical models to predict the deposition of inhaled fibers in rodents and humans have been developed and are discussed in more detail by Yu et al. (1995a) and Dai and Yu (1998), and in Section 3.4.5, Physiologically Based Pharmacokinetic/Pharmacodynamic Models. The fraction of inhaled fibers that is deposited in the alveolar region is of particular toxicologic interest because fibers deposited in this region are more slowly removed than fibers deposited in the nasopharyngeal or tracheobronchial regions. Models that predict alveolar deposition fraction for refractory ceramic fibers in rats, hamsters, and humans have been used to examine the influence of differences in ventilation parameters, airway size, and fiber characteristics on this important parameter (Dai and Yu 1998). The human model predicts that increasing workload reduces alveolar deposition fraction and switching from nose-breathing to mouth-breathing increases alveolar deposition fraction. The models predict that alveolar deposition of fibers with aerodynamic fibers >3.5 μm and length:diameter ratios >10 is insignificant in rats and hamsters, whereas in humans, considerable alveolar deposition occurs with fibers having aerodynamic diameters as large as 5–6 μm. For example, for exposure to fibers with 30 μm length, 1.5 μm diameter, and 3.26 μm aerodynamic diameter at an air concentration of 1 fiber/cc, calculated alveolar deposition fractions

(expressed as percentage of inhaled fibers) were 0.04% for rats, 0.27% for hamsters, and 6.82% for humans (Dai and Yu 1998).

#### 3.4.1.2 Oral Exposure

No studies were located examining the possible absorption of ingested synthetic vitreous fibers in humans or animals.

#### 3.4.1.3 Dermal Exposure

No studies were located examining the possible absorption of synthetic vitreous fibers across the skin of humans or animals.

### 3.4.2 Distribution

#### 3.4.2.1 Inhalation Exposure

Fibers deposited on the epithelial surfaces of the nasal passages and the tracheobronchial tree, which are lined with ciliated cells and coated with a mucous layer, are quickly removed by the flow of mucous to the pharynx and swallowed into the gastrointestinal tract. This mechanical distribution is generally thought to be completed within about 24–48 hours (Jones 1993; Lippmann 1990; Morgan and Holmes 1980; Oberdörster 1994). A small fraction of fibers deposited in the trachea can be retained within the epithelium, as demonstrated in rats intratracheally instilled with suspensions of glass fibers (Morgan 1995; Morgan et al. 1994a).

The removal and clearance of fibers deposited on epithelial surfaces of the lower lung, which are lined with nonciliated cells without a mucous layer, is comparatively slow. Clearance from this region is accomplished by several mechanisms: engulfment by macrophages (phagocytosis) and movement to the mucociliary escalator (sometimes referred to as mechanical macrophage-mediated clearance); dissolution (either in near neutral [pH 7.4–7.5] extracellular pulmonary fluid or in presumably acidic [pH 4.5–5] phagolysosomes of macrophages); and translocation of fibers to the interstitium, the lymphatic circulation, and the pleural cavity. These mechanisms influence the biopersistence of inhaled fibers, which, along with deposited dose and fiber dimensions, play key roles in determining pulmonary

pathogenesis. Some data illustrating these distribution mechanisms are discussed in this section. For more comprehensive reviews, the reader is referred to recent papers by Bernstein et al. (2001a, 2001b), Hesterberg and Hart (2000, 2001), and Oberdörster (2000) and other earlier papers (Bellmann et al. 1994a, 1994b; Bernstein et al. 1995; Muhle and Bellmann 1995, 1997; Musselman et al. 1994; Oberdörster 1994).

Macrophages are motile cells found in the lung interstitium, on the surface of epithelial cells lining the alveoli, and on the surface of ciliated epithelial cells (Carpenter and Wilson 1999; Valberg and Blanchard 1991). They are capable of engulfing foreign materials in the conducting airways, the alveoli, and the interstitium and moving onto the mucociliary escalator. Macrophages facilitate a major clearance mechanism for the lower respiratory tract. Macrophage engulfment, however, is limited to fibers with lengths less than the diameter of the macrophage. Alveolar macrophage diameters range from about 10–13 μm in rats and 14–21 μm in humans (Hesterberg and Hart 2001; Oberdörster 2000). Fibers longer than about 20 μm are not expected to be cleared by macrophages unless they undergo transverse breakage (Eastes et al. 2000; Hesterberg and Hart 2001; Hesterberg et al. 1998a; Oberdörster 2000).

Results from early studies of lung clearance of intratracheally-instilled glass wool fibers of varying lengths in rats provided evidence of the inability of macrophages to engulf and clear long fibers, the dissolution and transverse breakage of synthetic vitreous fibers in the lung, and the limited degree to which fibers may be translocated to the lymph nodes (Morgan et al. 1982). In these studies, rats were given single intratracheal instillations of sized glass wool fibers with median diameters of about 1.5 μm and median lengths of 5, 10, 30, or 60 μm.

***Long Fibers are Poorly Cleared by Macrophages.*** For the 5- and 10-μm length fibers, the number of fibers remaining in lungs declined smoothly with time after administration (Morgan et al. 1982). At 1 year, 90 and 80% of the injected 5- and 10-μm length fibers, respectively, had been cleared. In contrast, the number of fibers in lungs of rats exposed to 30- or 60-μm length fibers did not decline over a 9-month period after administration, indicating no discernible clearance. The fibers recovered at 9 and 18 months from the lungs of rats exposed to 60-μm length fibers showed evidence of transverse breakage of the fibers. The respective median lengths of recovered fibers at these times were 40 and 25 μm. The number of fibers in lungs at 9 months was 20–30% greater than the number in lungs of similarly exposed rats at 2 days after administration. (Fibers were not counted at 18 months because the 9-month results indicated

that transverse breakage would influence recovered fiber number more than any possible clearance mechanism).

***Glass Fibers Dissolve at pH 7.4–7.5.*** Fibers recovered at 18 months also showed decreased diameters indicating dissolution within the lung (Morgan et al. 1982). Median diameters of recovered fibers at 18 months in the groups exposed to 5-, 10-, 30-, and 60-µm length fibers were decreased by 12, 28, >50, and >50%, respectively, of the original 1.5-µm diameters, indicating faster dissolution of longer fibers than shorter fibers. This result is consistent with the faster *in vitro* dissolution of glass fibers at pH 7.4–7.5 (the pH of extracellular fluid in the lung) than at acidic pHs (4.5–5) found within the phagolysosomes of macrophages (Oberdörster 2000). However, not all types of synthetic vitreous fibers show faster *in vitro* dissolution at pH 7.4–7.5 than at acidic pHs. For example, MMVF34, a stone wool, has been shown to be very biosoluble in the rat lung, poorly soluble *in vitro* at pH 7.4–7.5, and soluble *in vitro* at pH 4.5 (Hesterberg and Hart 2001).

***Limited Translocation of Fibers to the Lymphatic Circulation may Occur.*** One year after administration, the fibers detected in hilar lymph nodes of rats exposed to 5-µm long glass fibers accounted for only 4% of the total lung fiber number (Morgan et al. 1982). The hilar lymph nodes contained smaller proportions of recovered fibers in rats exposed to the 10- and 30-µm length fibers. At the same time period, no fibers were detected in the hilar lymph nodes of rats exposed to 60-µm length fibers. The results indicate that only limited numbers of glass fibers were translocated to the lymph nodes under these experimental conditions.

Other studies with rats, hamsters, or guinea pigs indicate that considerable translocation of inhaled fibers to lymph nodes and the pleural cavity can occur under conditions that overload the mucociliary clearance mechanism (Lee et al. 1981a). In these studies, animals were exposed by inhalation to high concentrations (2,900, 13,500, or 41,800 fibers/cc) of potassium octatitanate fibers (average length of 6.7 µm and diameter of 0.2 µm) for 3 months. Numerous dust-laden macrophages were observed in tracheobronchial and mediastinal lymph nodes and in mediastinal adipose tissue adjacent to the lymph nodes when the animals were sacrificed 15 months after exposure ceased. Dust-laden macrophages also accumulated in the pleural cavity. Exposed animals showed fibrosis in the respiratory bronchiolar region and hyperplasia of the pleural mesothelium that increased in severity with exposure concentration (Lee et al. 1981a).

Evidence of rapid translocation of small numbers of short and thin fibers to pleural tissue has been observed in rats and hamsters after inhalation exposure to a refractory ceramic fiber, RCF1 (Everitt et al. 1997; Gelzleichter et al. 1996a, 1996c, 1999). In an acute exposure study, rats were exposed (nose-only) to concentrations of 2,645 WHO respirable fibers/cc (length:diameter ≥3:1, length >5 μm, diameter <3 μm) 6 hours/day for 5 days (Gelzleichter et al. 1996a, 1996c). The aerosol concentration of total fibers (length:diameter ratio ≥3:1) was 6,206 fibers/cc. Rats were sacrificed immediately after and 32 days after exposure. Fiber concentrations and dimensions in lung and pleural tissue samples were measured using scanning electron microscopy. At both sampling dates, lung fiber concentrations were about 1,000-fold greater than pleural fiber concentrations, indicating that relatively small numbers of fibers were translocated from the lung to the pleura. Average pleural fiber concentrations declined from 25,000 fibers/pleura at day 5 to 15,700 fibers/pleura at day 32, indicating some clearance of pleural fibers after exposure ceased. All fibers found in pleural tissues had lengths <5 μm and diameters <0.35 μm. Fibers detected in the pleural samples had geometric mean lengths of 1.4 and 1.5 μm, and geometric mean diameters of 0.87 and 0.10 μm, at days 5 and 32, respectively. In contrast, geometric mean lengths and diameters of fibers detected in lung tissue were notably larger than pleural fibers and were similar to the values for the exposure aerosol (geometric mean length, 4.54 μm [range: 0.7–111 μm] and geometric mean diameter, 0.56 μm). In subsequent studies in which rats or hamsters were exposed to about 300 WHO fibers/cc of RCF1, 4 hours/day, 5 days/week for up to 12 weeks, fibers detected in pleural tissue (sampled at 4 or 12 weeks or 12 weeks after exposure ceased) also displayed shorter mean lengths and thinner mean diameters than the fibers in the exposure aerosol (Everitt et al. 1997; Gelzleichter et al. 1999). In lung tissues in both species at all time points, fibers longer than 5 μm accounted for approximately 67% of detected fibers, whereas in pleural tissue, fibers longer than 5 μm accounted for 12% in hamsters and 4% in rats (Gelzleichter et al. 1999).

The biopersistence of fibers in lungs has been examined in several studies of rodents following acute (5-day) inhalation exposures to a number of glass wools, continuous filament glass, rock and slag wools, and a refractory ceramic fiber, as well as amosite or crocidolite asbestos (Bernstein et al. 1996; Eastes and Hadley 1995; Hesterberg et al. 1996, 1998a, 1998b). Lung tissues were sampled at several times after exposure from 1 hour up to 1 year, and concentrations and dimensions of fibers in the tissues were measured using scanning electron microscopy. These studies focused on the clearance of fibers with lengths >20 μm, which is thought to be mediated mainly by dissolution and subsequent transverse breakage, rather than direct mechanical macrophage-mediated clearance. One- and two-compartment first-order exponential models were fit to lung concentration data for fibers with lengths >20 μm. For

most fiber types, the two-compartment model provided a better fit than the one-compartment model. From the two models, two measures of lung clearance were used to compare the biopersistence of fiber types—a weighted clearance half-time that incorporated the half-times from the slow and fast compartment of the two-compartment model ($WT_{1/2}$: Bernstein et al. 1996) or the days required for clearance of 90% of the fibers with lengths >20 μm that were present in the lung 1 day after cessation of exposure. For fiber types for which a two-compartment model did not provide an improved fit over a one-compartment model, clearance half-time ($T_{1/2}$) was compared with $WT_{1/2}$ for the other fibers.

Using either measure of lung biopersistence ($WT_{1/2}$ or T-90 for fibers with lengths >20), synthetic vitreous fibers showed a considerable range of values, but all were markedly less biopersistent than amosite and crocidolite asbestos (Table 3-2). Amosite and crocidolite asbestos showed high $WT_{1/2}$ values (418 and 817 days, respectively), several durable synthetic vitreous fibers showed moderately high $WT_{1/2}$ values between 37 and 91 days, and several glass wools, a slag wool, and newly developed rock wools showed $WT_{1/2}$ values below 13 days (Table 3-2).

The dissolution of a variety of synthetic vitreous fibers has been extensively studied *in vitro* in simulated physiological fluids (Bernstein et al. 1996; Christensen et al. 1994; Eastes and Hadley 1995; Knudsen et al. 1996; Mattson 1994; Potter and Mattson 1991; Scholze and Conradt 1987). These studies are often conducted at pH 7.4 to simulate acellular dissolution and pH 4.5 to simulate dissolution in the acidic phagolysosomes of macrophages. The following equation is fit to *in vitro* data for changing fiber diameter (D) with time (t) to provide estimates of $K_{dis}$, the dissolution rate coefficient, for different fiber types:

$$D(t) = D_0 - 2K_{dis}t / \rho$$

where ρ is the density of the fiber, and $K_{dis}$ is usually in units of ng/cm$^2$-hour. A larger coefficient indicates faster dissolution. Amphibole asbestos fibers, such as crocidolite or amosite, essentially do not dissolve at pH 7.4 and have $K_{dis}$ values <1 (Table 3-2). In contrast, synthetic vitreous fibers dissolve, but show variance among fiber types in rates of dissolution. $K_{dis}$ values for synthetic vitreous fibers in Table 3-2 range from 3 to >500 ng/cm$^2$-hour. *In vitro* dissolution rates are correlated with rates of lung clearance, but several exceptions indicate that dissolution at pH 7.4 is not the only determinant of lung biopersistence (Table 3-2). For example, MMVF34 (HT rock wool) has a moderately low *in vitro* pH 7.4 $K_{dis}$ (59 ng/cm$^2$-hour), but displays very fast lung clearance ($WT_{1/2}$=6 days). In contrast, MMVF10 (insulation glass wool) has a high pH 7.4 $K_{dis}$ (300 ng/cm$^2$-hour), but displays slow lung clearance

## Table 3-2. Lung Clearance of Fibers with Lengths >20 µm in F344 Male Rats Following Nose-only Inhalation Exposure (6 Hours/Day for 5 Days) to 19 Different Synthetic Vitreous Fibers or Two Types of Asbestos

| Fiber name | Type | Weighted half-time ($WT_{1/2}$, days) | 90% clearance (T-90, days) | *In vitro* $K_{dis}$, pH 7.4[a] |
|---|---|---|---|---|
| Amosite | Asbestos | 418 | 2,095 | <1 |
| Crocidolite | Asbestos | 817[b] | 2,270 | <1 |
| MMVF32 | Special application continuous filament glass | 79 | 371 | 9 |
| MMVF21 | Rock (stone) wool | 67 (91)[c] | 264 (206)[c] | 21 |
| RCF1a | Refractory ceramic fiber | 55 | 227 | 3 |
| MMVF33 | Durable special applications glass | 49 | 240 | 12 |
| L | Traditional rock wool | 45 | 186 | 20 |
| MMVF10 | Insulation glass wool | 37[b] | 123 | 300 |
| H | New rock wool | 13 | 49 | 270 |
| MMVF11 | Insulation glass wool | 9 (13)[c] | 38 (40)[c] | 100 |
| MMVF22 | Slag wool | 9 | 37 | 400 |
| J | Experimental | 10 | 18 | 170 |
| F | New rock wool | 9[b] | 28 | 160 |
| MMVF34 | New rock wool (HT fiber, soluble in acid) | 6 | 19 | 59 |
| O | Rock wool | 6[b] | 20 | >500 |
| P | Glass wool | 6[b] | 19 | >500 |
| M | Glass wool | 5[b] | 18 | >500 |
| G | New rock wool | 5[b] | 18 | 210 |
| A | New glass wool | 4 | 9 | 250 |
| C | New glass wool | 4 | 14 | >500 |
| B | B-01/09 (glass wool) | 2 | 8 | >500 |

[a]$K_{dis}$ is the empirically derived coefficient (in ng/cm$^2$-hour) for *in vitro* dissolution in a flowing physiological saline solution at pH 7.4. A larger coefficient indicates faster dissolution.
[b]Values are half-times ($T_{1/2}$) from a one-compartment model; the two-compartment model did not provide an improved fit.
[c]Values in parentheses are from a second experiment.

Source: Hesterberg et al. 1998a

($WT_{1/2}$=37 days) compared with other synthetic vitreous fibers. Short-term *in vivo* lung clearance tests and *in vitro* dissolution tests have been proposed as preliminary screening tools to predict lung biopersistence and subsequent toxicity of untested fibers (Davis et al. 1996; Eastes et al. 2000; Zoitos et al. 1997).

Results from short-term *in vivo* lung clearance tests reflect the accumulation and biopersistence of fibers in the lungs of animals exposed for chronic durations. For example, lung elimination half-times for fibers with lengths >20 μm after 5 days of inhalation exposure of rats to comparable concentrations of rock wools MMVF21 or MMVF 34 (HT rock wool) were 92 days and 5 days, respectively, reflecting moderate and low biopersistence of the two rock wools (Kamstrup et al. 1998). This difference in biopersistence was reflected in lung concentrations in rats exposed (nose-only, 6 hours/day, 5 days/week) to comparable concentrations of the two rock wools for up to 18 months. Rats exposed to MMVF34 showed lung concentrations for fibers with lengths >20 μm of 8, 11, 10, and 11 fibers per mg dry lung $x10^3$ at respective sampling times of 3, 6, 12, and 18 months. These findings are consistent with early attainment of a balance between continued exposure and fast dissolution (i.e., low biopersistence) of this fiber. In contrast, concentrations in rats exposed to the moderately biopersistent fiber, MMVF21, were higher and showed evidence of accumulation with time at the same sampling times: 18, 23, 55, and 62 fibers per mg lung $x10^3$.

#### 3.4.2.2 Oral Exposure

No studies were located examining distribution of ingested synthetic vitreous fibers in humans or animals.

#### 3.4.2.3 Dermal Exposure

No studies were located examining distribution of dermally applied synthetic vitreous fibers in humans or animals.

#### 3.4.2.4 Other Routes of Exposure

The clearance kinetics of a variety of synthetic vitreous fibers from the respiratory tract following intratracheal instillations of suspensions of fibers has been studied in several animal species including

rats, hamsters, and sheep (Bellmann et al. 1994a, 1994b, 1995; Dufresne et al. 1999; Eastes et al. 1995; Morgan et al. 1982, 1994a; Morris et al. 1995; Searl et al. 1999). Intratracheal instillation offers the advantage of being less expensive than inhalation experiments, and results from these studies are supportive of results from clearance studies following inhalation. For example, the intratracheal instillation study by Morgan et al. (1982) discussed in the previous section provided evidence of the inability of macrophages to engulf and clear long fibers, the dissolution and transverse breakage of synthetic vitreous fibers in the lung, and the limited degree to which fibers may be translocated to the lymph nodes. However, this mode of administration has a few disadvantages, relative to inhalation exposure, including the increased potential to form clumps of fibers and the induction of inflammatory responses to high bolus doses (Oberdörster 2000). Because clumping and inflammation may influence fiber dissolution and clearance, the results from clearance studies following intratracheal instillations are not discussed further in this section.

### 3.4.3 Metabolism

#### 3.4.3.1 Inhalation Exposure

Synthetic vitreous fibers are not metabolized via typical enzyme-mediated processes, but undergo dissolution at varying rates depending on fiber composition, manufacturing processes under which the fibers were formed, and physical and chemical conditions in which the fiber may exist (Hesterberg and Hart 2001; Zoitos et al. 1997). In general, the dissolution of vitreous fibers in physiological fluids is thought to occur via reactions in which a water molecule (or some part thereof) replaces a cation in the matrix of the fiber (Eastes et al. 2000). In the simplest model for dissolution, all components in the matrix are assumed to dissolve at approximately the same rate. This model is used in the traditional determinations of $K_{dis}$, the *in vitro* dissolution rate coefficient, for various fibers. However, for many synthetic vitreous fibers, certain components dissolve more rapidly than others. Vitreous fibers with high alumina and silica contents favor a uniform rate of dissolution of all components, whereas fibers with a lower proportion of alumina and silica (<63 mole%) show nonuniform dissolution rates in which oxides of calcium, magnesium, and potassium dissolve quickly, leaving a weakened silica matrix (Hesterberg and Hart 2001). At points where the matrix is weakened, applied physical stress can lead to transverse breakage of the fiber. More complicated models to predict fiber dissolution without assuming uniform dissolution rates for all components are under development (Eastes et al. 2000; Hesterberg and Hart 2001).

Synthetic vitreous fibers have amorphous molecular structures that do not have planes of cleavage such as those in the crystal structure of chrysotile asbestos. The longitudinal cleavage of asbestos fibers can form thinner fibers that may more readily move into the interstitium or the pleura cavity (Agency for Toxic Substances and Disease Registry 2001). This property is not expected with synthetic vitreous fibers and may contribute to the difference in potency between asbestos and synthetic vitreous fibers. In addition, asbestos fibers, especially amphibole fibers, undergo very little, if any, dissolution in *in vitro* pH 7.4 tests (see Table 3-2). The relatively high persistence of long amphibole asbestos fibers in lungs is demonstrated by long clearance half-times of amphibole asbestos in rats (as shown in Table 3-2). Chrysotile asbestos, the least persistent asbestos type, is also expected to be more persistent in lungs than most synthetic vitreous fibers. For example, in rats following 10-day inhalation exposure to similar concentrations of chrysotile or a special purpose Code 100/475 glass fiber, the lung clearance half-time for long (>15 μm) chrysotile fibers was 46.2 weeks, whereas the half-time for long Code 100/475 glass fibers was 6.6 weeks (Searl 1997).

#### 3.4.3.2 Oral Exposure

No studies were located regarding compositional or structural changes in synthetic vitreous fibers in the gastrointestinal tract.

#### 3.4.3.3 Dermal Exposure

No studies were located regarding compositional or structural changes in synthetic vitreous fiber after dermal exposure.

### 3.4.4 Elimination and Excretion

#### 3.4.4.1 Inhalation Exposure

As discussed in Section 3.4.2.1, the principal pathways by which synthetic vitreous fibers are removed from the respiratory tract involve (1) mechanical mucociliary translocation to the pharynx, swallowing into the gastrointestinal tract, and elimination in the feces, (2) dissolution, and (3) transverse breakage of long fibers into shorter fibers. Mechanical translocation is mediated directly with fibers deposited on the surface of the ciliated epithelium of the respiratory tract and via macrophages when fibers are deposited in

the nonciliated epithelial region in the lower respiratory tract. After fibers or fiber-laden macrophages are on the mucociliary escalator, mechanical translocation is thought to be complete within about 24–48 hours (Jones 1993; Lippmann 1990; Morgan and Holmes 1980; Oberdörster 1994). Clearance of synthetic vitreous fibers from the lower airways is slower but shows variance with fiber types and dimensions. For example, clearance half-times for fibers longer than 20 μm in the lungs of rats have been reported to range from 2 to 79 days for 19 different synthetic vitreous fibers (Hesterberg et al. 1998a; see Table 3-2). For asbestos fibers in rats, more rapid clearance of shorter (<5 μm) fibers than of longer (>10 or 20 μm) fibers has been observed. This is explained as a result of the relative difficulty with which longer fibers are engulfed by macrophages. In contrast, many synthetic vitreous fibers show a more rapid clearance rate for long fibers compared with short fibers. This difference is consistent with the inability of macrophages to engulf long fibers, the relatively rapid dissolution of many synthetic vitreous fibers in the near-neutral pH solution of the intracellular spaces in the lung, and the subsequent transverse breakage of long vitreous fibers into shorter fibers. For example, lung clearance half-times in rats for long (>20 μm) fibers were 44, 6, and 986 days for MMVF10, MMVF11, and crodidolite asbestos, respectively; for short (<5 μm) fibers, the respective half-times were 111, 46, and 44 days (Hesterberg et al. 1996).

#### 3.4.4.2 Oral Exposure

No studies were located regarding excretion of synthetic vitreous fibers after oral exposure. Most, if not all, synthetic vitreous fibers that are ingested are expected to be excreted in the feces. Fecal elimination of a single oral dose of asbestos fibers has been demonstrated to be essentially complete within 48 hours (Gross and Stanton 1974).

#### 3.4.4.3 Dermal Exposure

No studies were located regarding excretion of synthetic vitreous fibers following dermal exposure, but it is generally considered that dermal exposure does not result in absorption of these fibers.

#### 3.4.4.4 Other Routes of Exposure

As with inhaled fibers, intratracheally-instilled synthetic vitreous fibers are cleared by mucociliary translocation, dissolution, and transverse breakage (Bellmann et al. 1994a, 1994b, 1995; Dufresne et al. 1999; Eastes et al. 1995; Morgan et al. 1982, 1994a; Morris et al. 1995; Searl et al. 1999). Fibers swallowed into the gastrointestinal are efficiently excreted in the feces.

### 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) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

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

PBPK models for insoluble or slowly soluble inhaled materials, such as synthetic vitreous fibers, focus on the retention of the inhaled materials in the alveolar region of the lung (Stober and McClellan 1997). The models recognize that alveolar retention (the net result of the deposition and clearance processes in the alveolar region) is also dependent on deposition and clearance of particles in the upstream regions of the respiratory tract. The models divide the respiratory system into a number of connected compartments (most often into the nasopharyngeal, tracheobronchial, and alveolar regions) with each compartment having a distinct set of deposition and clearance parameters. As reviewed below, alveolar retention models for refractory ceramic fibers have been developed for rats, hamsters, and humans; the rat model has recently been extended to other synthetic vitreous fibers such as glass, rock, and slag wools (Yu et al. 1994, 1995b, 1996, 1998a, 1998b).

Models for alveolar retention of refractory ceramic fibers in rats and hamsters have been developed based on: (1) theoretical and empirical understanding of deposition processes (e.g., sedimentation and impaction) in various regions of the respiratory tract as they are influenced by particle dimensions, airflow characteristics, and airway geometry; (2) understanding that clearance processes include direct

mechanical mucociliary clearance, macrophage-mediated mucociliary clearance, dissolution, and transverse breakage of long fibers into shorter fibers; and (3) data for lung concentrations and size distributions of fibers in animals exposed chronically to accurately measured inhaled concentrations of refractory ceramic fiber (RCF1) aerosols (Yu et al. 1994, 1995b, 1996). The rat model for refractory ceramic fibers was also extended to a more general model to apply to other synthetic vitreous fiber including glass wools and rock wools (Yu et al. 1998a, 1998b).

The most recent of the retention models developed by Yu and colleagues include mathematical descriptions of alveolar deposition rates with the following explanatory variables: tidal volume, breathing frequency, air concentrations of fibers of specific lengths and diameters, and alveolar deposition fraction of fibers with specific diameter and length. The deposition models account for the dependence of the fraction of inhaled fibers depositing in the alveolar region not only on the deposition efficiency of the alveolar region itself (i.e., the amount deposited divided by the amount entered), but also on deposition efficiencies in the nasopharyngeal and tracheobronchial regions. The clearance models describe removal of fibers from lungs by three simultaneous processes: alveolar macrophage-mediated clearance (as a function of fiber length and alveolar macrophage volume); dissolution (decrease in fiber diameter with time at a constant rate); and transverse breakage of long fibers into shorter fibers (Yu et al. 1996, 1997, 1998a, 1998b). Macrophage-mediated clearance in the model is also a function of lung burden, the total accumulated fiber and particle volume in the lung; the rate of clearance slows at high lung burdens.

Model simulations of lung concentrations of fibers of various length classes (lengths <5, 5–10, 10–20, and >20 μm) showed good agreement with empirical lung concentrations in rats exposed (nose-only, 6 hours/day, 5 days/week) for up to 104 weeks to RCF1 concentrations of 36, 91, 162, and 234 total fibers/cc (Yu et al. 1996). Good agreement was also found between model simulations and empirical lung concentrations in rats at various postexposure periods following exposure (nose-only, 6 hours/day for 5 days) to each of four types of synthetic vitreous fibers (two glass wools—MMVF10, MMVF11; one rock wool—MMVF21; or one slag wool—MMVF22) at gravimetric concentrations of 30 mg/m$^3$ (Yu et al. 1998a). Model simulations were also compared with lung concentration data for rats exposed by inhalation for up to 104 weeks to several concentrations of the same synthetic vitreous fibers (MMVF10, MMVF11, MMVF21, or MMVF22) (Yu et al. 1998b). The model simulations were reported to “compare quite well” with the data, but a statistical analysis of fit was not conducted.

A deposition and clearance model for refractory ceramic fibers in humans was developed from the rat model based on anatomical and physiological differences between rats and humans (Yu et al. 1995a, 1997). Some of the differences used in developing the human model are described in Table 3-3. Appropriate data to examine the accuracy of the human model are not available (i.e., lung fiber concentrations from autopsied lungs of exposed subjects and accurate information regarding time-weighted average air concentrations to which the subjects were exposed and durations of exposure). The model was used, however, to predict human lung concentrations following 15–20 years of occupational exposure to various air concentrations of refractory ceramic fibers. These were compared with lung concentration data for three workers who worked in a refractory ceramic fiber manufacturing plant for 13–17 years (Yu et al. 1997). The comparison suggested that one subject may have been exposed to an average air concentration of 0.25 fibers/cc and that the other subjects may have been exposed to 0.6–0.7 fibers/cc. These concentrations are within the range of air concentrations measured for some refractory ceramic fiber manufacturing plants (Yu et al. 1997).

For refractory ceramic fiber size ranges and concentrations encountered in workplaces, the deposition models predicted that: (1) the average alveolar deposition fraction in humans is 8.4% for nose-breathing and 15.9% for mouth-breathing; (2) the average alveolar deposition fraction in rats and hamsters are 3.7 and 5.7%, respectively; (3) humans have 1–2.5 times less deposited fiber per unit lung surface area than rats and hamsters; and (4) the geometric mean size dimensions (diameter and length) of fibers deposited in the lungs of rats and hamsters are smaller than those of fibers deposited in human lungs (Yu et al. 1995a).

One impetus to develop rat, hamster, and human alveolar retention models for synthetic vitreous fibers is to use the models to facilitate animal-to-human extrapolations of dose-response relationships for adverse effects in rodents exposed by inhalation to synthetic vitreous fibers (see Section 3.5.3, Animal-to-Human Extrapolations and Appendix A). Several quantitative human cancer risk estimates have been prepared using the data from the RCF1 2-year rat bioassay and the lung deposition and clearance models developed by C.P. Yu and colleagues (Maxim et al. 2003b; Moolgavkar et al. 1999, 2000; Turim and Brown 2003; Yu and Oberdörster 2000).

## Table 3-3. Comparative Human and Rat Anatomical and Physiological Parameters Relevant to Alveolar Retention of Refractory Ceramic Fibers

| Parameter | Human | Rat |
|---|---|---|
| Body weight (kg) | 70 | 0.3 |
| Lung weight (g) | 1,000 | 1.48 |
| Airway volume ($cm^3$) | 3,200 | 6.5 |
| Airway surface area ($cm^2$) | 627,000 | 5,500 |
| Number of alveolar macrophages | $7x10^9$ | $2.6x10^7$ |
| Alveolar macrophage volume ($\mu m^3$ per lung) | 2,500 | 1,000 |
| Total alveolar macrophage volume ($mm^3$) | 17,500 | 26 |
| Tidal volume ($cm^3$) | 500 | 2.74 |
| Breathing frequency ($minute^{-1}$) | 14 | 98 |
| Minute ventilation ($cm^3$/minute) | 7,000 | 268 |
| Life span (years) | 70 | 2 |

Source: Yu et al. 1997

## 3.5 MECHANISMS OF ACTION

The mechanisms by which inhaled fibers and particles, including synthetic vitreous fibers, induce adverse effects on the lung and pleural membrane are incompletely understood, but extensive research over the past few decades with asbestos fibers, silica, and synthetic vitreous fibers of various types has led to a complex working hypothesis that includes pharmacokinetic mechanisms influencing the dose of fibers to the lung and toxicity mechanisms involving the responses of lung cells and tissues to retained fibers. Evidence has accumulated that these mechanisms are influenced to varying degrees by fiber dimensions, dose to the lung, and fiber durability; surface area and chemical composition not related to durability may also play roles in the mechanisms. This section provides a brief overview of mechanisms involved in fiber-induced effects on the lung (inflammation, cytotoxicity, genotoxicity, cell proliferation, fibrosis, and lung tumors) and the pleural membrane (pleural plaques, pleural thickening and pleural mesothelioma). More detailed and comprehensive information on this area of research can be found in reviews by Churg et al. (2000), Driscoll (1996), Hart et al. (1994), Hesterberg and Hart (2001), Hesterberg et al. (1993c), Kane (1996), and Mossman and Churg (1998).

### 3.5.1 Pharmacokinetic Mechanisms

The amount of fibers deposited in the alveolar region of the lung is a key determinant of the potential development of adverse effects in the interstitium of the lung and in the pleural membrane. The aerodynamic diameter of fibers, along with ventilation parameters and geometry and size of airways, strongly influence alveolar deposition (Dai and Yu 1998; Oberdörster 2000). Fibers with aerodynamic diameters >3–4 μm are mostly excluded from the alveolar region due to deposition in upstream regions of the respiratory tract. The fraction of inhaled fibers deposited in alveoli decreases to zero with aerodynamic diameters of about 5 μm in rats and 10 μm in humans (Dai and Yu 1998).

The mechanisms whereby fibers deposited in the alveoli move to the interstitium, the pleural membrane, or the lymphatic system are unknown, although it is believed that movement into these regions is enhanced when rates of dissolution and macrophage-mediated clearance are overwhelmed by intakes at high exposure concentrations (Gross and Stanton 1973; Oberdörster 2000). Using electron microscopy, recent experiments have detected predominately short (<5 μm) and thin (<0.35 μm) fibers in pleural tissues after acute or intermediate inhalation exposure of rats and hamsters to a refractory ceramic fiber,

RCF1 (Everitt et al. 1997; Gelzleichter et al. 1996a, 1996b, 1999). These findings suggest that rapid fiber movement into pleural tissues occurs and has size limitations. Whether the movement is principally passive through intracellular spaces or mediated by the movement of inflammatory cells is unknown. The detection of fibers in the pleural tissues in the intermediate-duration studies was accompanied by inflammation and cell proliferative changes in pleural tissue. Hamsters showed more severe pleural changes than rats, but this was not correlated with a greater total number of fibers in hamster pleural tissues (Everitt et al. 1997). However, more extensive subsequent examinations of fiber size distributions in pleural tissues from rats and hamsters following intermediate-duration exposure to RCF1 found that fibers longer than 5 μm accounted for 12 and 4% of the fiber burden in hamsters and rats, respectively (Gelzleichter et al. 1999). The pleural surface density of these "long" fibers in hamsters (150 fibers per $cm^2$) was about 2–3 times that in the rat, whereas the pleural burden of short (<5 μm) fibers in the rats was about 1.5–2 times that in the hamster. The differences between hamsters and rats in intermediate-duration pleural cell proliferative changes may be due, in part, to the differences in retained "long" fiber surface density, but contributions from other mechanisms, such as release of reactive oxygen species, cytokines, or growth factors from alveolar macrophages or other cells are also plausible (Adamson et al. 1994).

The dose of fibers that remains in the lower lung is a net result of the amount of fibers deposited and the amount of deposited fibers removed by macrophage-mediated clearance via the mucociliary escalator, and by the combined actions of dissolution and transverse breakage of long fibers into shorter fibers. Whereas fiber aerodynamic diameter is a critical factor for deposition, fiber length is a critical factor for macrophage engulfment. Fibers longer than 15–20 μm are expected to be too long for human macrophages to completely engulf and transport out of the lung. Thus, clearance of long fibers from the lower lung cannot occur until the fibers either dissolve or break into shorter fibers that can be removed by macrophages (Eastes et al. 2000; Hesterberg and Hart 2001; Hesterberg 1998a; Oberdörster 2000).

Dissolution of fibers is influenced by their chemical composition and structure. As discussed in Section 3.4, synthetic vitreous fibers of various types show a range of *in vitro* dissolution rates (that are correlated with *in vivo* lung clearance half-times in rats), but all synthetic vitreous fibers tested to date are less biopersistent than amphibole asbestos fibers, which undergo no dissolution and are very biopersistent. Vitreous fibers with relatively high alumina and silica contents favor a relatively uniform, slower rate of dissolution, but increasing content of oxides of calcium, magnesium, and potassium can

lead to nonuniform rates of dissolution, faster breakage, and faster clearance (Eastes et al. 2000; Hesterberg and Hart 2001; Morgan et al. 1994b; Potter and Mattson 1991).

When rates of fiber deposition exceed the rates of removal, fibers can accumulate in the lung leading to chronic and persistent inflammation and tissue damage. For a variety of synthetic vitreous fibers and some amphibole asbestos fibers (amosite and crocidolite) correlations have been demonstrated among fiber durability in simulated pH 7.4 physiological fluids, fiber breakage rates, fiber lung clearance half-times in rodent models, and the ability to induce prefibrotic lesions (e.g., cell proliferation or collagen deposition), fibrosis, or tumors in rodents following repeated inhalation exposure (Bernstein et al. 2001a, 2001b; Eastes and Hadley 1996; Eastes et al. 2000; Hesterberg et al. 1998a). These correlations stress the importance of fiber durability in determining fiber pathogenicity and are the basis of proposals for using *in vitro* dissolution tests and short-term rodent lung clearance tests as preliminary screening tools to assess the potential toxicity of newly developed fibers. Measurements of *in vitro* dissolution rates for a number of synthetic vitreous fibers of varying chemical content indicate that substitution of sodium, potassium, boron, calcium, and magnesium in the silicate network tends to increase dissolution rate, whereas increasing aluminum oxide content tends to decrease dissolution rate.

In support of the hypothesis that chemical composition, fiber durability, and fiber pathogenicity are linked, Wardenbach et al. (2000) demonstrated a significant correlation between the potencies of seven synthetic vitreous fibers to induce tumors in rats following intraperitoneal injection and their "carcinogenicity index", which was defined as the summation of sodium-, potassium-, boron-, calcium-, magnesium-, and barium-oxide weight percentage minus 2 times the aluminum-oxide weight percentage. However, chemical composition is not expected to be the sole determinant of fiber biopersistence, as conditions in the manufacturing process, such as flame attenuation versus air attenuation, have been demonstrated to influence the dissolution rate of synthetic vitreous fibers (see Hesterberg and Hart 2001 for review).

### 3.5.2 Mechanisms of Toxicity

The deposition of relatively insoluble particles, such as synthetic vitreous fibers, in the lower lung of animals is well known to cause a complex defensive inflammatory response characterized by increased numbers of alveolar macrophages and other inflammatory cells. Chronic and persistent inflammation from deposited fibers (expected with continued high level exposure to all synthetic vitreous fibers) has

been linked for the most biopersistent synthetic vitreous fibers and asbestos to the development of cell injury, DNA changes, cell proliferation, deposition of collagen and other extracellular components leading to fibrosis (tissue scarring), and tumor development (Greim et al. 2001; IARC Expert Panel 1996; Kane 1996; Mossman and Churg 1998). Cellular and molecular events in these fiber-induced nonneoplastic and neoplastic effects are poorly understood, but several mechanistic hypothesis have been proposed based predominately on research with asbestos. The following discussion highlights results relevant to synthetic vitreous fibers.

The penetration or engulfment of fibers into macrophages, other inflammatory cells, epithelial cells, or mesothelial cells generates reactive oxygen and nitrogen species that can damage DNA, lipids, and proteins, lead to cytotoxicity, and stimulate release of inflammatory mediators, cytokines, and growth factors that may induce epithelial and mesothelial cell proliferation (Churg et al. 2000; Driscoll 1996; IARC Expert Panel 1996). Reactive oxygen species may also be generated by reactions on the surfaces of fibers, but this activity appears to be much greater with certain asbestos fibers (e.g., amosite) than with insulation wools (e.g., MMVF10) and refractory ceramic (e.g., RCF1) fibers (Gilmour et al. 1995, 1997). Experiments with cultured cells exposed to asbestos fibers have demonstrated that anti-oxidant systems can protect against fiber-induced cytotoxicity, providing support for the importance of reactive oxygen species in the development of fiber-induced disease (Mossman and Churg 1998).

Fibers of similar size distributions, but different chemical compositions, may elicit different responses from macrophages. For example, *in vitro* incubation of MMVF10 fibers with rat alveolar or peritoneal macrophages did not produce detectably increased levels of superoxide anions, but MMVF21 fibers with a similar distribution of fiber sizes caused increased production of superoxide anions by either type of macrophage (Dörger et al. 2001). This difference was associated with the finding that significantly higher numbers of macrophages completely phagocytized MMVF21 compared with MMVF10 fibers. The chemical or cellular basis for these differences is unknown, but may be related to lesser ability of MMVF10 fibers to directly elicit cytokines and proinflammatory mediators that modulate phagocytic functions of cells (Driscoll 1996).

In addition to fiber-induced reactive oxygen-mediated mechanisms that may lead to cytotoxic and cytoproliferative or hyperplastic responses, other proposed mechanisms in which fibers may directly induce cell proliferation include: (1) a “healing” response secondary to direct fiber-induced cell injury; (2) direct induction by fibers (at noncytoxic levels) of inflammatory cells and other lung cells to release

mediators that cause tissue damage and stimulate cell proliferation; and (3) a direct cell proliferative effect of fibers on cells (Driscoll 1996). It is likely that multiple mechanisms play variable roles in the cell proliferation responses to different fiber types and exposure scenarios. Understanding of the interactions among the possible multiple mechanisms is too incomplete to provide reliable in depth explanations for observed differences in apparent potency among fiber types, although there is sufficient evidence to indicate that fiber durability plays a key role. The comparative examination of cellular and molecular responses related to cell proliferation and inflammation from fibers with similar size distributions, but varying pathogenic potency, is an area of intensive current research (e.g., Barchowsky et al. 1997; Brown et al. 1998, 1999, 2000; Donaldson et al. 1995a, 1995b; Dörger et al. 2000, 2001; Gilmour et al. 1997; Jensen and Watson 1999; Johnson and Jaramillo 1997; Leikauf et al. 1995; Luoto et al. 1997; Marks-Konczalik et al. 1998; Morimoto et al. 1999a; Tsuda et al. 1999).

Fiber-induced cell proliferative responses that can lead to tissue scarring in the lung and pleural tissues are also thought to play a role in the development of lung carcinomas or mesotheliomas by enhancing the frequency of cells transformed by spontaneous or fiber-induced genetic changes (Driscoll 1997; Greim et al. 2001; IARC Expert Panel 1996; Kane 1996). Thus, the carcinogenic responses to synthetic vitreous fibers observed in animals may develop via both genotoxic and non-genotoxic modes of action. As discussed in Section 3.3, results from *in vitro* tests indicate that, like asbestos fibers, several types of synthetic vitreous fibers can induce cytogenetic changes and alter DNA. Proposed mechanisms for fiber-induced genetic changes include DNA alterations from reactive oxygen species and physical interference of fibers with cellular cytoskeletons and chromosomes (Kane 1996).

### 3.5.3 Animal-to-Human Extrapolations

As discussed in Section 3.4.5, there are distinct differences between animal species and humans in respiratory tract size and geometry, ventilation rates and patterns, and macrophage size that influence the retention (the net result of deposition and clearance) of fibers in the lung. Yu and colleagues have developed lung retention models for refractory ceramic fibers in rats, hamsters, and humans that incorporate many of these interspecies differences, some of which are shown in Table 3-3 (Dai and Yu 1998; Yu et al. 1994, 1995a, 1995b, 1996, 1997). The models incorporate mechanisms of deposition in the nasopharyngeal, tracheobronchial, and alveolar regions, macrophage-mediated clearance (with shorter fibers preferred and impaired clearance occurring at high levels of fiber lung concentration), fiber dissolution, and fiber transverse breakage. The rat model was also extended to lung retention of other

synthetic vitreous fibers, but extension of the human model to other synthetic vitreous fibers has not been reported (Yu et al. 1998a, 1998b). The dosimetric models for refractory ceramic fibers predict fiber lung concentration as a function of time for both humans and rodents for given air concentrations of fibers with specified distributions of length and diameter. The models can be used to convert exposure levels in animal inhalation toxicity and cancer studies to human equivalent exposure levels (Appendix A describes the use of these models in deriving a chronic inhalation MRL for refractory ceramic fibers). As discussed in Section 3.4.5, several quantitative human cancer risk estimates have been prepared using the data from the RCF1 2-year rat bioassay and the lung deposition and clearance models developed by C.P. Yu and colleagues (Maxim et al. 2003b; Moolgavkar et al. 1999, 2000; Turim and Brown 2003; Yu and Oberdörster 2000).

In contrast to the relatively robust understanding of fiber pharmacokinetics in animals and humans, understanding of the relative sensitivity of rodents and humans to synthetic vitreous fibers or asbestos fibers (i.e., the relative pharmacodynamics) is poor. For asbestos, rats appear to be a suitable *qualitative* model for humans given that effects observed in groups of workers exposed to high levels of airborne asbestos (chronic inflammation, pulmonary fibrosis, lung cancer, and mesothelioma) have also been observed in rat inhalation studies (Agency for Toxic Substances and Disease Registry 2001). However, similar *qualitative* comparisons between rodent and human responses to synthetic vitreous fibers are not possible. Available epidemiological studies of workers involved in the manufacture of fibrous glass, rock wool, or slag wool, or in the manufacture of refractory ceramic fibers have not found consistently increased risks for nonmalignant respiratory disease, lung cancer, or mesothelioma, although pulmonary fibrosis, lung cancer, and mesothelioma have been demonstrated in rats and hamsters exposed by inhalation to the most potent synthetic vitreous fibers (see Section 3.2).

For asbestos, limited *quantitative* data are insufficient to conclusively determine the relative sensitivity of humans and rodents to fibers, although several hypotheses have been proposed on this issue. Rodelsperger and Woitowitz (1995) proposed that humans may be more susceptible to asbestos's capability to induce mesothelioma based on a finding that lung fiber concentrations in a group of humans who died from asbestos-induced mesothelioma were markedly higher than concentrations in a bioassay of crocidolite-exposed rats. Earlier, Rowe and Springer (1986) proposed that humans and rodents may be equally sensitive to asbestos based on a comparison of estimated human lung cancer risks based on rodent inhalation bioassays and those derived in epidemiological studies of asbestos-exposed workers. Maxim and McConnell (2001) analyzed lung fiber concentrations associated with pulmonary fibrosis in rats and

hamsters exposed to a series of asbestos (crocidolite, chrysotile) and synthetic vitreous fibers (rockwool MMVF21 and refractory ceramic fiber RCF1) and compared these with fiber concentrations in autopsied lungs from several studies of workers with asbestosis (i.e., pulmonary fibrosis from asbestos exposure). Estimated concentrations in rodents ranged from $1.7x10^6$ to $20x10^6$ fibers (>20 μm long) per g dry lung compared with $1.6x10^6$ to $30x10^6$ fibers (>20 μm long) per g dry lung in humans. Maxim and McConnell (2001) concluded, based on these and other considerations, that "there seems little reason to believe that humans and rats have greatly different sensitivities with respect to the development of pulmonary fibrosis or lung cancer."

## 3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

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

are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding the possible effects of synthetic vitreous fibers on the neuroendocrine axis in humans or animals or in *in vitro* systems.

## 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).

No information was located specifically concerning health effects in children exposed to synthetic vitreous fibers. There was no indication from the available literature that specialized respiratory defense mechanisms might be less active or underdeveloped in children relative to adults. Results from animal studies indicate that inflammation, fibrosis, and cancer of the lung or pleura are possible outcomes resulting from repeated inhalation exposure to certain synthetic vitreous fibers depending on the exposure dose, exposure duration, fiber dimensions, and fiber durability. However, no studies were located that have compared immature and mature animals with respect to pharmacokinetics of, or susceptibility to, inorganic fibers of any type (including asbestos) by any route of exposure.

No human or animal studies were located regarding the possible developmental toxicities of synthetic vitreous fibers by any route of exposure. Direct effects on the developing fetus would be unexpected given the very small, if any, absorption of synthetic vitreous fibers by the lungs, gastrointestinal tract, or skin. For asbestos fibers of various types, no consistent indication of potential for developmental toxicity

was indicated in several oral administration studies with rats, mice, and hamsters (Agency for Toxic Substances and Disease Registry 2001).

## 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 synthetic vitreous fibers 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 synthetic vitreous fibers 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 Synthetic Vitreous Fibers

Uncoated or coated fibers in bronchoalveolar lavage fluid samples or in autopsied or surgically resected lung tissue samples are the principal biomarkers of exposure to biopersistent asbestos fibers (Agency for Toxic Substances and Disease Registry 2001).[1] However, similar biomarkers to identify or quantify human exposure to synthetic vitreous fibers, which are less biopersistent than asbestos fibers, have not been developed for routine clinical use. Nevertheless, aluminum-silicate fibers with chemical compositions consistent with synthetic vitreous fibers have been detected in human lung tissues (McDonald et al. 1990; Roggli 1989; Sébastien et al. 1994) and in bronchoalveolar lavage samples (Dumortier et al. 2001).

For example, among 1,800 bronchoalveolar samples submitted to a Belgium hospital between 1992 and 1997 for fiber analysis, pseudoasbestos bodies were detected in samples from nine patients (0.5%) (Dumortier et al. 2001). In samples from these nine patients (all of whom had occupational experience with furnaces or welding), fibers of composition consistent with refractory ceramic fiber composition were detected in 42% of core fibers analyzed (Dumortier et al. 2001). Other nonasbestos fibers and asbestos fibers accounted for 28 and 30% of the core fibers analyzed in these samples, respectively.

In another study, lung fiber concentrations were determined in autopsied tissue samples from a subset of deaths occurring between 1950 and 1979 in a cohort of U.S. workers involved in the manufacture of synthetic vitreous fibers (McDonald et al. 1990). The 145 autopsied tissue samples analyzed represented about 3% of the deaths that occurred in the cohort during this period. Lung fiber concentrations were

[1] Particles or fibers that are deposited in the lung and are too large to be phagocytized by alveolar macrophages may become coated with an iron-rich protein coat. The generic term for these structures is ferruginous bodies. When the core fiber is asbestos, the resultant structure is termed an asbestos body (Agency for Toxic Substances and Disease Registry 2001). Ferruginous bodies having the appearance of asbestos bodies under light microscopy and a nonasbestos core fiber have been termed pseudoasbestos bodies (Dumortier et al. 2001).

compared with concentrations in 124 autopsied referents who had no known occupational experience with synthetic vitreous fibers, were matched for location of death (i.e., hospital), age, and year of death, and died from causes other than malignant disease. Lung fiber concentrations (lengths >5 μm and length:diameter ratio >3:1) determined by phase contrast microscopy were about 60% higher in workers than referents. Electron microscopy (coupled with energy dispersive spectrometry and selected area electron diffraction) showed no statistically significant excess of any particular type of fiber in the workers compared with the referents, although asbestos fibers were detected with greater frequency than synthetic vitreous fibers in both workers and referents. Nonasbestos fibers described as "siliceous" displayed a strong energy dispersive signal for silicon without sodium, aluminum, potassium, calcium, titanium, or iron signals and represented >90% of fibers identified as synthetic vitreous fibers. However, lung samples from only 26% of the workers contained any synthetic vitreous fibers. The low detection frequency of synthetic vitreous fibers in the worker lung samples may reflect both low exposure concentrations and low biopersistence of these fibers.

In animal inhalation experiments with synthetic vitreous fibers, concentrations of fibers in the lung have been used to assay internal doses (e.g., Hesterberg et al. 1993c, 1999; Mast et al. 1995a, 1995b; McConnell et al. 1999). Based on rat experiments involving intraperitoneal injection of three different types of synthetic vitreous fibers, urinary levels of titanium or barium were proposed as potential biomarkers of exposure to synthetic vitreous fibers that contain these elements normally present in humans and animals in small quantities (Wastiaux et al. 1994). Reports of further development of urinary titatnium or barium as biomarkers of exposure to synthetic vitreous fibers were not located.

### 3.8.2 Biomarkers Used to Characterize Effects Caused by Synthetic Vitreous Fibers

Epidemiological studies of synthetic vitreous fiber manufacturing workers have not found consistent evidence for increased risks of malignant or nonmalignant respiratory or pleural effects, but results from animal experiments indicate that repeated inhalation exposure to synthetic vitreous fibers may result in pulmonary or pleural fibrosis, lung cancer, or mesothelioma, depending on fiber dimensions, fiber durability in the lung, duration of exposure, and exposure levels.

The chest x-ray is the most common means of detecting the onset of pleural or pulmonary changes that may precede or accompany fibrosis (i.e., irreversible scarring of lung or pleural tissue that can lead to restricted breathing). The International Labour Office (ILO) established a classification system for

profusion of opacities in chest x-rays 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 1980). The American Thoracic Society (1986) recommends that chest x-rays be scored for pleural and pulmonary changes separately because of the experience with asbestos-exposed workers indicating that pleural and pulmonary fibrosis have differences in "epidemiology, clinical features, and prognosis." Computerized tomography (CT) and high-resolution computed tomography provide alternative techniques to the chest x-ray that may more sensitively detect pleural and pulmonary changes in some cases (Agency for Toxic Substances and Disease Registry 2001). Lung function tests are also useful to characterize the development of pulmonary or pleural fibrosis; forced vital capacity is diminished with increasing severity of pulmonary or pleural fibrosis.

Clinical diagnostic criteria for pulmonary fibrosis include chest x-rays with small irregular opacifications of a profusion of 1/1 or greater, impaired forced vital capacity below the lower limit of normal, and a diffusing capacity below the lower limit of normal (American Thoracic Society 1986). Pleural changes associated with chronic inflammation from inhaled fibers or particles include pleural plaques, pleural fibrosis (also referred to as thickening or calcification), and pleural effusions. Pleural plaques are localized or diffuse areas of thickening of the pleura that appear as opaque, shiny, and rounded lesions in the chest x-ray. Pleural fibrosis represents a more pronounced thickening or scarring that, when severe, can make the pleura appear as a thick peel encasing the lung in chest x-rays. Persons with pleural fibrosis can experience chest pain and impaired pulmonary functions, but persons with pleural plaques alone usually do not (American Thoracic Society 1986). Pleural effusion is the exudation of cell-containing fluid from lung tissue into the pleural cavity, which is often taken as an early manifestation of exposure to asbestos fibers (American Thoracic Society 1986). Pleural effusions have been reported in groups of people exposed occupationally to asbestos (Agency for Toxic Substances and Disease Registry 2001), but have not been reported in workers involved in the manufacture of synthetic vitreous fibers.

## 3.9 INTERACTIONS WITH OTHER CHEMICALS

Epidemiological and clinical studies of asbestos workers have indicated that workers who smoked tobacco had greater risks of developing lung cancer and pulmonary fibrosis than workers who did not smoke, and that smoking may increase these risks by more than risks predicted by an additive model (see Agency for Toxic Substance and Disease Registry 2001 for review). In contrast, the studies provided no indication that smoking increased the risk of mesothelioma. The mechanism of this interaction is not

fully understood, but there is evidence to suggest that smoking may decrease the ability of lungs to clear fibers or other particles. For example, the lungs of smoking workers with heavy asbestos occupational exposure showed higher concentrations of chrysotile and amosite fibers compared with nonsmoking workers (Churg and Stevens 1995), and the clearance rate of short chrysotile fibers was decreased by 30% in guinea pigs after coexposure to chrysotile and cigarette smoke compared with guinea pigs exposed to chrysotile alone (Churg et al. 1992).

A similar interaction between smoking and inhalation exposure to synthetic vitreous fibers in jointly affecting lung cancer or pulmonary fibrosis is plausible, but direct evidence to support the possible interaction is very limited. In a study of European refractory ceramic fiber production workers, a statistically significant association between indices of cumulative exposure to fibers and decreased pulmonary function was observed in workers who smoked, but not in nonsmokers (Cowie et al. 2001; Rossiter et al. 1994; Trethowan et al. 1995). Alveolar macrophages from rats exposed to sidestream cigarette smoke produced statistically significantly greater quantities of a cytokine involved in regulating cellular proliferation (tumor necrosis factor) in response to chrysotile fibers *in vitro* than did macrophages from rats not exposed to smoke (Morimoto et al. 1993). Refractory ceramic fibers also induced tumor necrosis factor production by macrophages *in vitro*. Macrophages from smoke exposed rats produced more tumor necrosis factor than macrophages from nonexposed rats, but the difference was not statistically significant (Morimoto et al. 1993). The only other published finding of relevance to the possible interactive effects smoking and exposure to synthetic vitreous fibers is the observation that *in vitro* oxidative damage to calf thymus DNA (assayed as the formation of 8-hydroxydeoxyguanosine residues) produced by cigarette smoke condensate and rockwool fibers together was greater than the sum of the damage by each agent alone (Leanderson and Tagesson 1989).

## 3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

Persons with impaired pulmonary clearance mechanisms (e.g., due to chronic exposure to cigarette smoke or repeated exposure to dusty air leading to high burdens of particles in the lung) or genetically determined relatively poor ability to detoxify reactive oxidative molecules produced during pulmonary disposition of fibers (e.g., reactive oxygen radicals or nitrogen oxide) may be more susceptible than others to possible nonmalignant or malignant pulmonary or pleural disorders from chronic exposure to synthetic vitreous fibers. Direct evidence in support of these hypotheses, however, is lacking for synthetic vitreous fibers, except for the observation that cumulative exposure indices were associated with decreased pulmonary function in European refractory ceramic fiber workers who smoked, but not in nonsmokers (Cowie et al. 2001; Rossiter et al. 1994; Trethowan et al. 1995).

In case-control studies of asbestos-exposed persons, associations have been observed between deletion of the gene (GSTM1) encoding one class of glutathione S-transferase (GSTμ), an enzyme that protects against oxidative tissue damage, and increased risks for mesothelioma, other cancers, or nonmalignant pulmonary disorders (Hirvonen 1997; Hirvonen et al. 1996; Kelsey et al. 1997). Increased risks for developing nonmalignant pulmonary disorders or mesothelioma were also observed among persons with histories of high-level asbestos exposure who lacked the GSTM1 gene and had a slow genotype for N-acetyltransferase 2 (NAT2), compared with risks in exposed subjects with the GSTM1 gene and the fast NAT2 genotype (Hirvonen et al. 1996). Slow acetylation by NAT2 may lead to accumulation of polyamines that stimulate cell proliferation.

## 3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to synthetic vitreous fibers. 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 synthetic vitreous fibers. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to synthetic vitreous fibers:

Standard texts of medical toxicology (e.g., Ellenhorn et al. 1997; Goldfrank et al. 1998) do not provide specific information about treatment of acute irritation effects or possible chronic effects from exposure to synthetic vitreous fibers, but recommend minimizing exposure. Since the early 1990s, manufacturers of

synthetic vitreous fibers have been making modifications to new products in order to make them more biosoluble (i.e., less biopersistent) and potentially less hazardous than older products (Hesterberg and Hart 2001; IARC 2002).

### 3.11.1 Reducing Peak Absorption Following Exposure

Absorption of synthetic vitreous fibers is expected to be negligible following inhalation, ingestion, or dermal exposure. Recommendations have been made to avoid contact with the fibers by wearing protective clothing and using ocular and respiratory protection when working with materials containing synthetic vitreous fibers and to minimize physical disturbance of the material and generation of dusts, in order to avoid the acute dermal, respiratory, or ocular irritation experienced from contact with synthetic vitreous fibers (e.g., "fiberglass itch"), and prevent the possible pulmonary or pleural disorders from chronic inhalation exposure (Ellenhorn et al. 1997; Goldfrank et al. 1998; Jeffress 1999; Mentzer 1999; OSHA 1999). Rinsing of exposed areas with water also minimizes contact.

### 3.11.2 Reducing Body Burden

As discussed in Section 3.4, the principal pathways by which inhaled and deposited synthetic vitreous fibers are removed from the respiratory tract involve: (1) direct or macrophage-mediated mechanical mucociliary translocation to the pharynx, swallowing into the gastrointestinal tract, and elimination in the feces; (2) dissolution; and (3) transverse breakage of long fibers into shorter fibers. To date, there are no clinical methods to enhance or supplement these natural methods of elimination of inhaled fibers that deposit on the epithelial surfaces of the respiratory tract.

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

The mechanisms by which repeated exposure to airborne synthetic vitreous fibers may cause pulmonary or pleural disorders are poorly understood (see Section 3.5), and there are no tested methods of interference. It is plausible that repeated exposure to the more durable synthetic vitreous fibers could also cause pulmonary or pleural disorders in humans as it has been observed to do in laboratory rodents.

## 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 synthetic vitreous fibers 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 synthetic vitreous fibers.

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.

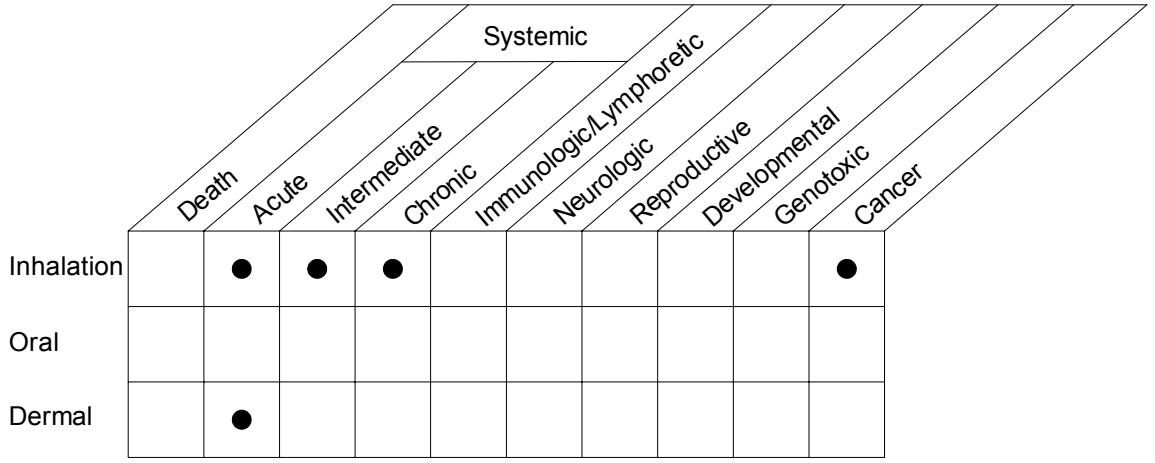
### 3.12.1 Existing Information on Health Effects of Synthetic Vitreous Fibers

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to synthetic vitreous fibers are summarized in Figure 3-2. The purpose of this figure is to illustrate the existing information concerning the health effects of synthetic vitreous fibers. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

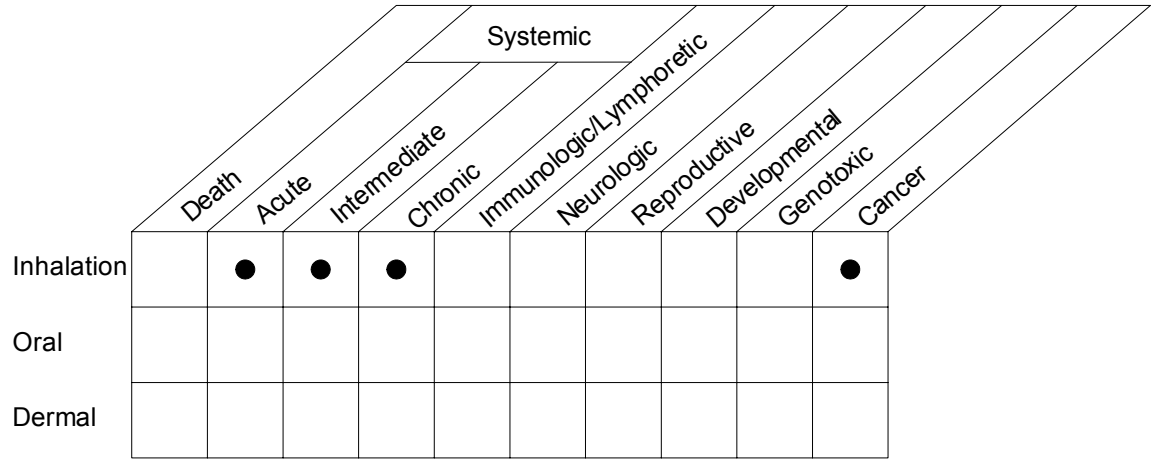
### 3.12.2 Identification of Data Needs

**Acute-Duration Exposure.** As discussed in Section 3.2, acute occupational exposure to synthetic vitreous fibers including fiberglass fabrics and insulation materials has been associated with reversible

**Figure 3-2. Existing Information on Health Effects of Synthetic Vitreous Fibers**




**Human**




**Animal**

● Existing Studies

symptoms of irritation of the upper respiratory tract (ACGIH 2001; Horvath 1995; Milby and Wolf 1969; Nasr et al. 1971; Newball and Brahim 1976; Petersen and Sabroe 1991; Thriene et al. 1996), the skin (Bendsoe et al. 1987; Bjornberg 1985; Bjornberg and Lowhagen 1977; Bjornberg et al. 1979a, 1979b, 1979c; Eun et al. 1991 Fisher 1982; Fisher and Warkentin 1969; Heisel and Hunt 1968; Kiec-Swierczynska and Szymczk 1995; Koh and Khoo, 1995; Longley and Jones 1966; Peterson and Sabroe 1991; Possick et al. 1970; Stam-Westerveld et al. 1994; Tarvainen et al. 1993; Thriene et al. 1996), and the eyes (Longley and Jones 1966; Petersen and Sabroe 1991; Stokholm et al. 1982). The skin irritation has been associated with fibers of diameter >5 μm and often becomes less pronounced with continued exposure (ACGIH 2001; Heisel and Hunt 1968; Stam Westerveld et al. 1994).

The available human data adequately identify reversible skin irritation as a concern from acute dermal exposure. The data support occupational health and public health recommendations to limit dermal contact and airborne exposure by limiting the generation of dusts from materials containing synthetic vitreous fibers and by wearing loose protective clothing, gloves, and ocular and respiratory protection when handling the material.

Acute inhalation studies in animals are limited to rodent studies with RCF1 that observed pulmonary and pleural inflammation (Everitt et al. 1994; Gelzleichter et al. 1996a, 1996c). Other studies have observed nonneoplastic and neoplastic health effects caused by injection or implantation (e.g., single acute dosing) of synthetic vitreous fibers into the intraperitioneal or intrapleural cavities of animals (Adachi et al. 1991; Davis et al. 1984; Feron et al. 1985; Mohr et al. 1984; Pickrell et al. 1983; Pigott and Ishmael 1981; Pott et al. 1987; Renne et al. 1985; Smith et al. 1987; Stanton and Wrench 1972; Stanton et al. 1977; Wright and Kuschner, 1977). Their relevance to human inhalation exposure is unclear because of the high doses and rapid dose rates used, the bypassing of the natural defense systems of the nasal and upper respiratory system, and the overloading or lack (for intraperitoneal studies) of pulmonary clearance mechanisms. No acute inhalation MRL was derived because data describing dose-response relationships for irritation of the upper respiratory tract in humans or animals are not available.

No acute-duration oral exposure studies in humans or animals were identified. The oral route of exposure is not of public health concern for synthetic vitreous fibers; therefore, no data need is identified.

**Intermediate-Duration Exposure.** Epidemiologic studies involving inhalation exposure have tended to exclude persons with intermediate-duration (<1 year) exposure, due to associated confounding

factors. In animals, multiple exposure-level experiments were conducted for RCF1, the glass wools MMVF10 and MMVF11, the rock wool MMVF21, and the slag wool MMVF22 (Hesterberg et al. 1999; Mast et al. 1995b; McConnell et al. 1994), but other fiber types were tested only at single (usually high) concentrations. The studies were designed as chronic studies, but include interim sacrifice data describing dose-response relationships for effects from intermediate-duration inhalation exposure.

Virtually all of the fibers tested caused reversible pulmonary inflammation, including the refractory ceramic fibers RCF1, RCF2, RCF3, and RCF4, the insulation glass wools MMVF10 and MMVF11, the rock wool MMVF21, the slag wool MMVF22, the durable glass fiber MMVF33, the high-temperature rock wool MMVF 34, the high-silica synthetic vitreous fiber X607, the special-purpose 104E-glass fiber, GB100R glass wool, and C102/C104 blend fibrous glass (Cullen et al. 2000; Goldstein et al. 1983; Haratake et al. 1995; Hesterberg et al. 1993c, 1998b; Kamstrup et al. 2001; Mast et al. 1995a, 1995b; McConnell et al. 1994, 1999). Only one study reported a NOAEL, for Code 104 glass wool (Muhle et al. 1987).

Interstitial or pleural fibrosis was seen in rodents exposed to the refractory ceramic fibers RCF1, RCF2, RCF3, and RCF4, the durable glass fiber MMVF33, and the special purpose 104E-glass following intermediate-duration exposure (Cullen et al. 2000; Mast et al. 1995a, 1995b; McConnell et al. 1999), but no increase in fibrosis was seen in animals exposed to MMVF10, MMVF11, MMVF34, or X607 (Hesterberg et al. 1993c, 1998b; Kamstrup et al. 2001; McConnell et al. 1999).

The available animal data adequately identify pulmonary or pleural effects as potential health hazards from intermediate-duration inhalation exposure to synthetic vitreous fibers. The data also provide adequate descriptions of dose-response relationships for these effects in rats from samples of glass wools, rock wool, slag wool, and refractory ceramic fibers.

A chronic inhalation MRL was derived for the refractory ceramic fiber, RCF1, based on pulmonary inflammation in rats as the critical effect (see Section 2.3 and Appendix A). The MRL derivation used rat and human lung deposition and clearance models to extrapolate rat exposure levels to human equivalent concentrations and was based on the assumption that the responses in rats would occur in humans at the same dose of fibers deposited in the alveolar region of the lung. The interim sacrifice data from the chronic study indicated that dose-response relationships for this effect were similar for chronic and intermediate durations. Although an intermediate inhalation MRL for refractory ceramic fibers was not

derived, the data indicate that it would be similar to the chronic MRL. It is expected that the chronic MRL can be used reliably to assess effects from intermediate-duration exposures. Additional data for intermediate-duration exposure to RCF1 do not appear to be needed.

Adequate rat data are also available for intermediate and chronic inhalation exposure to MMVF10, MMVF11, MMVF21, and MMVF22. However, no intermediate or chronic inhalation MRLs were derived because of the uncertainty in extrapolating from rats to humans in the absence of human lung deposition and clearance models for these synthetic vitreous fibers. However, when such models are available, the rat studies will provide adequate data for deriving intermediate and chronic inhalation MRLs for glass wool, rock wool, and slag wool.

No intermediate-duration oral or dermal exposure studies in humans or animals were identified. Repeated exposure by the oral route is of relatively low concern for the general population; therefore, no data need has been identified at this time. For dermal exposure, the available data demonstrating acute reversible skin irritation from direct contact with insulation materials containing synthetic vitreous is adequate to support public health recommendations to wear gloves and protective clothing (and other protective devices including eye and respiratory protection) when handling materials containing synthetic vitreous fibers. No data need has been identified for potential health effects from intermediate-duration dermal exposure.

**Chronic-Duration Exposure and Cancer.** The most biologically significant effect found in retrospective and longitudinal evaluations of the health of workers involved in the manufacture of refractory ceramic fibers in the United States (LeMasters et al. 1994; Lentz et al. 2003; Lockey et al. 1996, 2002) and Europe (Cowie et al. 2001; Trethowan et al. 1995) is a low prevalence of pleural plaques (about 3%). However, consistent statistically significant associations with exposure to refractory ceramic fibers were only found in the U.S. cohort (Lentz et al. 2003; Lockey et al. 1996, 2002). Consistent exposure-related effects on pulmonary function have not been found in these cohorts (Burge et al. 1995; Cowie et al. 2001; Lockey et al. 1998).

Adverse findings in cross-sectional health evaluation studies of workers involved in the manufacture of continuous glass fibers, glass wool, or rock and slag wool are restricted to elevated prevalences of self-reported respiratory symptoms (e.g., coughing, bronchitis) (Albin et al. 1998; Clausen et al. 1993; Engholm and von Schmalensee 1982; Kilburn et al. 1992); evidence for elevated prevalences of pleural

plaques in these workers is inadequate (Hughes et al. 1993; Kilburn and Warshaw 1991; Kilburn et al. 1992; Sanden and Jarvholm 1986; Scansetti et al. 1993; Weill et al. 1983).

Cohort mortality and case-control studies have tracked nonneoplastic and neoplastic causes of mortality among groups of workers involved in the manufacture of fibrous glass, rock wool, or slag wool without finding conclusive evidence of increased risks associated with exposure (Bayliss et al. 1976; Bertazzi et al. 1986; Boffetta et al. 1999; Buchanich et al. 2001; Chiazze et al. 1992, 1993, 1995, 1997, 2002; Enterline and Henderson 1975; Kjaerheim et al. 2001; Marsh et al. 1990, 2001a, 2001b, 2001c; Morgan 1981; Sali et al. 1999; Saracci et al. 1984; Shannon et al. 1984, 1987, 1990; Simonato et al. 1986a, 1987; Watkins et al. 1997). Similar cohort mortality or case-control studies of workers involved in the manufacture of refractory ceramic fibers are restricted to a mortality study of male workers employed at two U.S. manufacturing plants (LeMasters et al. 2003). In an initial report of the mortality experience of this cohort (about 90% of which is still alive), the only statistically significant excess mortality was for deaths associated with cancer of the urinary system. No mesotheliomas and no excess deaths associated with respiratory cancers or nonmalignant respiratory disease were found. The excess urinary cancer deaths may be a chance finding given the wide confidence interval for the SMR, the large number of statistical tests (n=46) that were conducted, and the lack of a plausible mechanistic explanation of how fibers may increase the risk for urinary cancer mortality. Continued monitoring of the mortality experience of this cohort is planned.

In animals, chronic-duration inhalation studies were primarily continuations of intermediate-duration studies, with pulmonary inflammation observed for all fibers tested and fibrosis observed for the refractory ceramic fibers and MMVF 33 (see Section 3.2). The special-purpose 104E-glass was not tested in a chronic-duration study. Although C102/C104 blend fibrous glass was not fibrogenic at 8 months, pulmonary fibrosis was observed by 18 months (Goldstein et al. 1983). Pleural mesotheliomas were observed in rodents exposed to refractory ceramic fibers (RCF1, RCF2, and RCF3), MMVF33, and 104E-glass (Cullen et al. 2000; Mast et al. 1995a; McConnell et al. 1999; Smith et al. 1987). Lung tumor incidence (adenomas, carcinomas, or the combined incidence) were elevated in rodents exposed to RCF1, RCF2, RCF3, RCF4, or 104E-glass (Cullen et al. 2000; Mast et al. 1995a, 1995b; McConnell et al. 1995), but not in studies with other synthetic vitreous fibers including MMVF10, MMVF11, MMVF 21, MMVF22, MMVF34, Code 104 glass wool, GB100R glass wool, high-silica synthetic vitreous fiber X607, or special-purpose 100/475 glass microfiber (Cullen et al. 2000; Goldstein et al. 1983; Haratake et

al. 1995; Hesterberg et al. 1993c, 1998b; Kamstrup et al. 2001; Mast et al. 1995a, 1995b; McConnell et al. 1994, 1999; Muhle et al. 1987).

As discussed in the previous section, a chronic inhalation MRL was derived for the refractory ceramic fiber, RCF1, based on pulmonary inflammation in rats as the critical effect (see Section 2.3 and Appendix A). One area of uncertainty associated with the critical study for the chronic MRL is the degree to which the dose-response relationship for pulmonary inflammation is affected by the nonfibrous particles in the aerosols to which the rats were exposed. Nonfibrous particles (with aspect ratios <3:1) have been reported to account for about 25% of the mass in RCF1 aerosols (Bellmann et al. 2001). Results from 3-week exposure studies with rats suggest that pulmonary responses to RCF1a, a material with only 2% of its mass accounted for by nonfibrous particles, are less severe than those induced by RCF1 at similar exposure levels (Bellmann et al. 2001). Additional research may be useful to quantitatively determine the effect of nonfibrous particles on the dose-response relationship for pulmonary inflammation from chronic exposure to refractory ceramic fibers.

Adequate rat data are also available for intermediate and chronic inhalation exposure to the glass wools, MMVF10 and MMVF11, a rock wool, MMVF21, and a slag wool, MMVF22. However, no intermediate or chronic inhalation MRLs were derived because of the uncertainty in extrapolating from rats to humans in the absence of human lung deposition and clearance models for these synthetic vitreous fibers. When such models are available, the rat studies will provide adequate data for deriving intermediate and chronic inhalation MRLs for glass wool, rock wool, and slag wool.

Workers involved in the installation or removal of insulation materials with synthetic vitreous fibers are expected to be exposed to higher airborne levels of fibers than manufacturing workers, but research that monitored health status and mortality patterns in groups of these types of workers is limited. Additional longitudinal monitoring of the respiratory health of insulation workers (and their exposure conditions) may be helpful in a better assessment of the health safety of their work environment.

No chronic-duration oral or dermal exposure studies in humans or animals were identified, although experimental studies with human subjects, case reports, and occupational exposure experience document the well-known acute, but reversible, skin irritation caused by direct dermal contact with insulation glass wools. Repeated exposure by these routes is not of high concern for the general public; therefore, no data needs for these routes have been identified at this time. Reinforcing the lack of concern for health effects

by oral exposure to fibrous materials, results from several studies of rats exposed for life to several types of asbestos found no convincing evidenc for nonmalignant disease in the exposed rats (Agency for Toxic Substances and Disease Registry 2001).

**Genotoxicity.** No evidence for genotoxic activity of several synthetic vitreous fibers was found in bacterial mutation assays (Chamberlain and Tarmy 1977) or sister chromatid exchange assays in cultured human cells (Casey 1983). However, cytogenetic effects induced by synthetic vitreous fibers in mammalian cells *in vitro* include chromosomal aberrations (Brown et al. 1979a, 1979b); morphological transformations (Gao et al. 1995; Hesterberg and Barrett 1984; Hesterberg et al. 1985; Oshimura et al. 1984; Whong et al. 1999); micronuclei and multinuclei (Dopp and Schiffmann 1998; Dopp et al. 1997; Hart et al. 1992; Ong et al. 1997; Peraud and Riebe-Imre 1994; Zhong et al. 1997); polyploidy (Koshi et al. 1991; Sincock et al. 1982); and DNA strand breaks and DNA-DNA interstrand crosslinks (Wang et al. 1999b). In addition, several synthetic vitreous fiber types have been demonstrated to damage isolated DNA (Donaldson et al. 1995c) and to hydroxylate 2-deoxyguanosine to 8-hydroxydeoxyguanosine, presumably via hydroxyl radicals (Leanderson et al. 1988, 1989).

There is evidence that fiber dimensions can influence *in vitro* cytogenetic activities (Hesterberg and Barrett 1984; Hesterberg et al. 1985; Ong et al. 1997) and that synthetic vitreous fibers are often less genotoxically active than asbestos fibers (e.g., Donaldson et al. 1995c; Janssen et al. 1994a; Leanderson et al. 1988, 1989; Peraud and Rieve-Imre 1994; Wang et al. 1999b). For example, thin glass fibers (diameters 0.1–0.2 μm, lengths >10 μm) were very active in transforming Syrian hamster embryo cells, whereas thick glass fibers (diameter about 0.8 μm) were much less potent (Hesterberg and Barrett 1984). Milling of the thin glass fibers to reduce the length to <1 μm diminished the transforming activity.

The available evidence is sufficient to suggest that synthetic vitreous fibers may produce cytogenetic changes in *in vitro* systems, but data regarding *in vivo* genotoxicity is lacking. *In vivo* data may be helpful to further assess the genotoxic potential of synthetic vitreous fibers.

**Reproductive Toxicity.** There are no studies in humans or animals on the potential for synthetic vitreous fibers to produce reproductive effects. Given the limited degree to which synthetic vitreous fibers are absorbed into the body, there is no mechanistic basis to suspect that reproductive effects may be of concern from exposure to synthetic vitreous fibers. No data needs have been identified at this time.

**Developmental Toxicity.** There are no studies in humans or animals on the potential for synthetic vitreous fibers to produce developmentally toxic effects. As with reproductive toxicity, there is no empirical or mechanistic basis to suspect that developmental effects may be of concern from exposure to synthetic vitreous fibers. No data needs have been identified at this time.

**Immunotoxicity.** There are no studies in humans or animals specifically designed to examine the potential for synthetic vitreous fibers to affect the immunological or lymphoreticular systems following inhalation, oral, or dermal exposures. There are several reports of immune system depression in asbestos-exposed workers who developed asbestosis or cancer (see Agency for Toxic Substance and Disease Registry 2001), but whether or not the depression was directly caused by asbestos or by the diseased state is unknown. Given the lack of increased reporting of symptoms of allergy or immune system depression in health surveillance studies of workers involved in the manufacture of refractory ceramic fibers or insulation wools (Clausen et al. 1993; Cowie et al. 2001; Ernst et al. 1987; Gross 1976; Hansen et al. 1999; Hill et al. 1973; Hughes et al. 1993; Kilburn et al. 1992; LeMasters et al. 1998; Lockey et al. 1998; Moulin et al. 1988; Nasr et al. 1971; Sanden and Jarvholm 1986; Trethowan et al. 1995; Weill et al. 1983; Wright 1968), immunological effects do not appear to be a critical public health concern from exposure to synthetic vitreous fibers. No data needs have been identified at this time.

**Neurotoxicity.** There are no studies in humans or animals on the potential for synthetic vitreous fibers to produce neurotoxic effects. As with reproductive and developmental toxicity, there is no empirical or mechanistic basis to suspect that neurotoxic effects may be of concern from exposure to synthetic vitreous fibers. No data needs have been identified at this time.

**Epidemiological and Human Dosimetry Studies.** Studies of workers predominately involved in the manufacture of fibrous glass materials have focused on the prevalence of respiratory symptoms through the administration of questionnaires, pulmonary function testing, and chest x-ray examinations (Clausen et al. 1993; Gross 1976; Hill et al. 1973; Hughes et al. 1993; Nasr et al. 1971; Weill et al. 1983; Wright 1968). In general, these studies reported no consistent evidence for increased prevalence of adverse respiratory symptoms, abnormal pulmonary functions, or chest x-ray abnormalities; however, one study reported altered pulmonary function (decreased forced expiratory volume in 1 second) in a group of Danish insulation workers compared with a group of bus drivers (Clausen et al. 1993). Longitudinal health evaluations of workers involved in the manufacture of refractory ceramic fibers, fibrous glass, rock wool, or slag wool have not found consistent evidence of exposure-related changes in chest x-rays or

pulmonary functions, with the exception that pleural plaques were found in about 3% of examined U.S. refractory ceramic fiber manufacturing workers and that pleural plaque prevalence showed statistically significant trends with increasing exposure categories (LeMasters et al. 1994; Lentz et al. 2003; Lockey et al. 1996, 2002).

Epidemiologic studies (cohort mortality and case-control studies) of causes of mortality among groups of workers involved in the manufacture of fibrous glass, rock wool, or slag wool provide no consistent evidence for increased risks of mortality from nonmalignant respiratory disease, lung cancer, or pleural mesothelioma (Bayliss et al. 1976; Bertazzi et al. 1986; Boffetta et al. 1999; Buchanich et al. 2001; Chiazze et al. 1992, 1993, 1995, 1997, 2002; Enterline and Henderson 1975; Kjaerheim et al. 2002; Marsh et al. 1990, 2001a, 2001b, 2001c; Morgan 1981; Sali et al. 1999; Saracci et al. 1984; Shannon et al. 1984, 1987, 1990; Simonato et al. 1986a, 1987; Watkins et al. 1997). In an initial report of the only available cohort mortality study of refractory ceramic fiber workers, the only statistically significant excess mortality was for deaths associated with cancer of the urinary system (LeMasters et al. 2003). No mesotheliomas and no excess deaths associated with respiratory cancers or nonmalignant respiratory disease were found. Continued monitoring of the mortality experience of this cohort is planned.

As discussed in the "Chronic-Duration Exposure and Cancer" section, workers involved in the installation or removal of insulation materials with synthetic vitreous fibers are expected to be exposed to higher airborne levels of fibers than manufacturing workers, but monitoring of the health status and mortality patterns in groups of these types of workers is limited. Additional longitudinal monitoring of the respiratory health of groups of insulation workers (and their exposure conditions) may be helpful in a better assessment of the health safety of their work environment.

### Biomarkers of Exposure and Effect.

***Exposure.*** The most pertinent parameter for measuring exposure to synthetic vitreous fibers would be retained or deposited dose of fibers in the lung, a biomarker that is invasive and impossible to determine without autopsy or resection. The detection and chemical identification of fibers in bronchoalveolar lavage or sputum samples has been proposed as less invasive biomarkers of exposure to asbestos (Agency for Toxic Substances and Disease Registry 2001) and synthetic vitreous fibers (Dumortier et al. 2001), but these methods have not been fully developed as quantitative biomarkers of exposure. Further

development of noninvasive biomarkers of exposure may be useful to monitor workers exposed to dusty working conditions when installing or removing materials containing synthetic vitreous fibers.

***Effect.*** No specific and sensitive biomarkers of disease induced by synthetic vitreous fibers are known. The chest x-ray represents the most widely used method to detect nonneoplastic and neoplastic lesions in the lung or pleura that may occur (as indicated by animal experiments) after long-term exposure to synthetic vitreous fibers (American Thoracic Society 1986). However, the chest x-ray would detect changes only after significant injury has occurred and would not indicate directly whether or not the changes were caused by synthetic vitreous fibers or some other lung toxicant such as cigarette smoke or asbestos. Computerized tomography has shown some promise for detecting early asbestos-related effects such as pleural plaques or thickening (Agency for Toxic Substances and Disease Registry 2001), and may be useful to monitor the health of workers repeatedly exposed to high levels of airborne synthetic vitreous fibers. Tests of lung function also detect relatively early signs of effects from lung toxicants, but provide only limited information regarding the possible cause. Given the evidence that pulmonary or pleural effects are not expected at airborne concentrations below current recommendations for occupational exposure limits (1 fiber/cc for insulation wools and 0.2 fiber/cc for refractory ceramic fibers; ACGIH 2001), current methods to monitor possible effects from synthetic vitreous fibers appear adequate, albeit lacking in specificity (i.e., chest x-ray, lung function tests, and computerized tomography). No data needs have been identified at this time.

**Absorption, Distribution, Metabolism, and Excretion.** As discussed in Section 3.4, rates of absorption of synthetic vitreous fibers across the epithelial layers of the respiratory tract, the gastrointestinal tract, and the skin are expected to be negligible given the relatively large physical dimensions of these elongated particles. The toxicokinetic variables of greatest relevance to the exposure route of greatest public health concern (inhalation) are: the extent and location of fiber deposition in the respiratory tract; the rates of deposited fiber removal by mucociliary transport, macrophage-mediated engulfment and clearance, and dissolution in lung fluid; and the translocation of fibers within and across the lung. These variables are of toxicological interest because fibers can accumulate in the lung leading to chronic and persistent pulmonary inflammation and, for the more durable synthetic vitreous fibers, tissue damage when rates of fiber deposition exceed rates of removal. For a variety of synthetic vitreous fibers and some amphibole fibers (which do not undergo dissolution in lung fluid), correlations have been demonstrated between the ability to induce pulmonary or pleural inflammation or tissue damage and several of these variables, including dissolution rates in synthetic lung fluid, fiber breakage rates, and

fiber lung clearance half-times (Bernstein et al. 2001a, 2001b; Eastes and Hadley 1996; Eastes et al. 2000; Hesterberg et al. 1998a).

For several types of synthetic vitreous fibers, these processes have been well studied in animals, but not directly in human subjects. The animal study results provide enough information to support the development of models that predict lung deposition and retention of inhaled refractory ceramic fibers and other synthetic vitreous fibers (glass wools and rock wools) in rats (Yu et al. 1994, 1995b, 1996, 1998a, 1998b). Good agreement has been observed between model predictions and observed concentrations of fibers in the lungs of rats exposed to aerosols of refractory ceramic fibers or insulation wools for intermediate or chronic durations. Models to predict the deposition and retention of inhaled refractory ceramic fibers in humans have been developed based on known anatomical and physiological differences between rats and humans (Yu et al. 1995a, 1997). In the only testing of the human model, it was used to predict exposure concentrations from autopsied lung concentration data for three refractory ceramic fiber manufacturing workers (Yu et al. 1997). The predicted exposure concentrations were within the range of air concentrations measured for some manufacturing plants.

Models for lung retention and clearance of other synthetic vitreous fibers have not been developed. Development of human models for insulation wools will decrease uncertainty in extrapolating from chronic inhalation data for pulmonary inflammation in rats and facilitate the derivation of intermediate- and chronic-duration inhalation MRLs for these materials. Additional research to compare predictions from the human models with lung concentration data for human subjects with known exposures may help to decrease uncertainty in the validity of the model predictions.

The lung deposition and retention models incorporate information from the animal studies that the fraction of inhaled synthetic vitreous fibers deposited on the epithelial surfaces of the respiratory tract and the region where deposition occurs are determined by fiber dimensions, fiber mass density, ventilation parameters, and the structure and airway size of the respiratory tract (Dai and Yu 1998; Lippmann 1990; Morgan 1995; Yu et al. 1995a). Fibers with aerodynamic diameters >3–5 μm are predominately deposited in the upper airways and do not travel to the lower lung where gas exchange occurs. Fibers deposited in the upper airways are quickly removed by mucociliary transport to the pharynx and swallowing. The models also incorporate information from animal studies illustrating the following features of clearance of synthetic vitreous fibers from the lower lung: (1) fibers are cleared from the lower gas exchange region by macrophage engulfment and transport; (2) fibers longer than the diameter

of macrophages are poorly engulfed and cleared (i.e., shorter fibers are more rapidly cleared than longer fibers); (3) macrophage-mediated clearance is dependent on lung burden of particles (the rate of clearance slows at high lung burdens); (4) dissolution of synthetic vitreous fibers occurs in lung fluid (the dissolution rate varies with fibers of varying chemical composition); and (5) partially dissolved fibers more readily break into shorter fibers. The models do not describe translocation of deposited fibers from the lower lung into pleural tissue or the lymphatic system, although there is evidence from animal studies that small numbers of short and thin fibers are rapidly translocated to pleural tissues (Everitt et al. 1997; Gelzleichter et al. 1996a, 1999) and that translocation to lymph nodes can be considerable only under conditions that overload macrophage-mediated clearance mechanisms (Lee et al. 1981a; Morgan et al. 1982). Additional research on the extent and rate of translocation of fibers into pleural tissue, and conditions governing this process, may be useful in providing more a specific description of the target organ dose-response relationship for pleural effects (pleural fibrosis and mesothelioma) observed in rats exposed to the most durable of synthetic vitreous fibers, refractory ceramic fibers.

There are no toxicokinetic studies in humans or animals following oral or dermal exposure. Absorption and retention in the gastrointestinal tract and the skin are expected to be negligible. No data needs are identified at this time for toxicokinetic data for these routes of exposure.

**Comparative Toxicokinetics.** As discussed in Sections 3.4 and 3.5.3, differences in respiratory tract size and geometry, ventilation rates and patterns, and macrophage size between animal species and humans are expected to influence the retention of synthetic vitreous fibers in the lung. Lung deposition and clearance models that incorporate many of these interspecies differences have been developed for refractory ceramic fibers in rats, hamsters, and humans (Dai and Yu 1998; Yu et al. 1994, 1995a, 1995b, 1996, 1997). The models assume that dissolution rates, as well as transverse breakage rates and patterns (i.e., breakage of long fibers into shorter ones), are the same in animals and humans. The models predict that for refractory ceramic fiber size ranges and concentrations encountered in workplaces, (1) mouth-breathing leads to higher fractional deposition of inhaled fibers than nose-breathing in humans; (2) fractional deposition of inhaled fibers is less in rats and hamsters than in nose-breathing humans; (3) humans have 1–2.5 times less deposited fiber per unit alveolar surface area than rats and hamster; and (4) size dimensions (length and width) of fibers deposited in human lungs are larger than those of fibers deposited in lungs of rats and hamsters (Yu et al. 1995a).

The rat model has been extended to other synthetic vitreous fibers (i.e., several types of insulation wools), but, to date, the human model has not. As discussed in the previous section, development of human models for insulation wools will decrease uncertainty in extrapolating from chronic inhalation data for pulmonary inflammation in rats and facilitate in the derivation of intermediate- and chronic-duration inhalation MRLs for these materials.

There are no comparative toxicokinetic studies in humans or animals following oral or dermal exposure. Absorption and retention in the gastrointestinal tract and the skin are expected to be negligible in animals and humans. No data needs are identified at this time for comparative toxicokinetic data for these routes of exposure.

**Methods for Reducing Toxic Effects.** Information specific to synthetic vitreous fibers regarding treatment of acute irritation effects or possible chronic effects from exposure or reduction of body burdens have not been identified, although minimizing exposure, wearing protective clothing, and rinsing of exposed areas (e.g., skin and eyes) with water are recommended (Ellenhorn et al. 1997; Goldfrank et al. 1998; Jeffress 1999; Mentzer 1999; OSHA 1999).

As discussed in Section 3.5.1, the dose of fibers retained in the lower lung is a key determinant of the potential for fibers to induce toxic effects such as pulmonary inflammation, pulmonary fibrosis, lung cancer, or mesothelioma. Lung retention of fibers is the net result of lung deposition and clearance mechanisms including direct mucociliary clearance, macrophage-mediated clearance, dissolution rates, and transverse breakage of long fibers into shorter fibers. Once fibers are inhaled and deposited in the lung, there are no known treatment options to enhance the natural clearance mechanisms and reduce body burden after exposure. Additional research on physiological and molecular details of clearance mechanisms and mechanisms governing translocation into pleural tissue may provide clues for developing treatments to enhance clearance of the more biopersistent synthetic vitreous fibers from the lower lung and pleural tissue.

Observed correlations between toxic potencies and dissolution rates for various types of vitreous and mineral fibers indicate that the dissolution of fibers in lung fluid is a key determinant of potential toxicity that is influenced by chemical composition and structure and manufacturing processes (Bernstein et al. 2001a, 2001b; Eastes and Hadley 1996; Eastes et al. 2000; Hesterberg et al. 1998a; Hesterberg and Hart 2001; Wardenbach et al. 2000). Ongoing research to develop new synthetic vitreous fibers that are less

biopersistent holds promise as a method to avert or decrease the potential for producing toxic effects. For example, vitreous fibers with relatively high alumina and silica contents have been shown to favor a relatively uniform, slower rate of dissolution, but increasing content of oxides of calcium, magnesium, and potassium can lead to nonuniform rates of dissolution, faster breakage, and faster clearance (Eastes et al. 2000; Hesterberg and Hart 2001; Morgan 1994b; Potter and Mattson 1991).

As briefly discussed in Section 3.5.2, cellular and molecular events involved in fiber-induced nonneoplastic and neoplastic effect are poorly understood, but mechanistic studies (predominately with asbestos fibers) indicate that fibers retained in lung or pleural tissue may lead to cytotoxic and cytoproliferative changes as a result of increased production of reactive oxygen species that can damage cellular macromolecules, lead to cytotoxicity, and stimulate the release of inflammatory mediators, cytokines, and growth hormones (Churg et al. 2000; Driscoll 1996; IARC Expert Panel 1996). Several other mechanisms also have been proposed. Additional research on mechanisms of fiber-induced toxicity may eventually lead to the development of therapeutic approaches for reducing toxic effects from the biopersistent synthetic vitreous fibers or more efficient screening methods to evaluate the potential toxicities of newly developed synthetic vitreous fibers.

**Children's Susceptibility.** No information was located specifically concerning health effects in children exposed to synthetic vitreous fibers, and no studies were located that have compared immature and mature animals with respect to pharmacokinetics of, or susceptibility to, inorganic fibers of any type (including asbestos) by any route of exposure. There is no indication from the available literature that the pulmonary clearance mechanism might be less active or underdeveloped in children relative to adults. Direct effects on the developing fetus are not expected given the low absorption of synthetic vitreous fibers by the lung, gastrointestinal tract, and skin. Thus, there does not appear to be a need to conduct developmental toxicity tests for synthetic vitreous fibers. Additional research comparing pulmonary and pleural responses of immature and mature animals to the more biopersistent synthetic vitreous fibers may provide relevant information regarding the relative susceptibility of adults and children to the potential toxicity of synthetic vitreous fibers. Such experiments may be difficult to perform with immature animals, however, given the stress experienced by animals when they are fitted with nose-only inhalation apparatus (McConnell 1999).

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

### 3.12.3 Ongoing Studies

Ongoing studies funded solely by the U.S. government have not been identified. Other organizations have funded several large ongoing epidemiological studies of synthetic vitreous fiber manufacturing workers and the recent extensive animal toxicology studies reported in the published literature (see Section 3.2).

# 4. CHEMICAL AND PHYSICAL INFORMATION

## 4.1 CHEMICAL IDENTITY

Synthetic vitreous fibers are inorganic substances, largely composed of aluminum and calcium silicates that are derived from rock, clay, slag, or glass (IARC 1988, 2002). While naturally occurring mineral fibers such as asbestos are crystalline in structure, synthetic vitreous fibers are amorphous materials. There are several methods of categorizing synthetic vitreous fibers based either on origin, chemical structure, morphology, application, or method of manufacturing. The most recent classification scheme proposed by the International Agency for Research on Cancer (IARC) has divided these compounds into two broad classes: filaments and wools. The filaments contain continuous glass filaments, while the wools contain glass wool, rock (stone) wool, slag wool, refractory ceramic fibers, and other newly engineered biosoluble fibers (IARC 2002). Glass wools are further subdivided into insulation wools and special purpose wools (see Figure 2-1). Continuous filament products are produced by drawing or spinning the molten mix from nozzles, while the wools are manufactured with a rotary or centrifugal process without using a nozzle (see Chapter 5 for details). Generally, the wool fibers tend to be shorter and finer than the continuous filament fibers, and their diameters may be more variable (IARC 1988). The typical chemical composition of these types of synthetic vitreous fibers is represented in Table 4-1. Special purpose glass fibers are sometimes used in high technology industries and have very specific properties that are tailored to their specific use. Although the procedures used to make these fibers are similar to those of glass wool, the operating parameters are usually adjusted to create products with extremely small diameters. One example of a special purpose glass fiber is included in Table 4-1.

Fibrous glass products are derived from powdered sand and largely consist of silicon and aluminum oxides. The final properties of the glass are dictated by the percent composition of other oxides including alkali metal oxides, alkaline earth oxides, and metal oxides like $ZrO_2$ and $Fe_2O_3$. Glass, like other insulating materials, provides a high resistance to the passage of electricity. Electrical glass (E-glass) is a continuous filament type of fibrous glass developed for electrical applications that has excellent heat and water resistance (IARC 1988, 2002). The high resistivity of E-glass is related to its low alkali oxide content. The majority of continuous filament fibrous glass produced is E-glass (IARC 1988, 2002). Other types of glass are used for certain types of specialized purposes, and relatively small changes in the

## Table 4-1. Chemical Identity of Some Types of Synthetic Vitreous Fibers[a,b]

| Percent composition | E-Glass | S-Glass | AR-Glass | Glass wool | Rock wool from basalt melted in a furnace | Rock wool from basalt and other material melted in a cupola | Slag wool melted in a cupola | RCF kaolin | RCF zirconia | Special purpose glass fiber 475 formulation[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| $SiO_2$ | 52–56 | 65 | 60.7 | 55–70 | 45–48 | 41–53 | 38–52 | 49.5–53.5 | 47.5–50 | 57–58 |
| $Al_2O_3$ | 12–16 | 25 | | 0–7 | 12–13.5 | 6–14 | 5–15 | 43.5–47 | 35–36 | 5–6 |
| $B_2O_3$ | 5–10 | | | 3–12 | | | | | | 10–11 |
| $K_2O$ | 0–2 | | 2 | 0–2.5 | 0.8–2 | 0.5–2 | 0.3–2 | <0.01 | <0.01 | 2–3 |
| $Na_2O$ | 0–2 | | | 13–18 | 2.5–3.3 | 1.1–3.5 | 0–1 | 0.5 | <0.3 | 10–11 |
| MgO | 0–5 | 10 | | 0–5 | 8–10 | 6–16 | 4–14 | <0.1 | 0.01 | 0–0.5 |
| CaO | 16–25 | | | 5–13 | 10–12 | 10–25 | 20–43 | <0.1 | <0.05 | 2–3 |
| $TiO_2$ | 0–1.5 | | | 0–0.5 | 2.5–3 | 0.9–3.5 | 0.3–1 | 2 | 0.04 | 0–0.1 |
| $Fe_2O_3$ | 0–0.8 | | | 0.1–0.5 | | | | 1 | <0.05 | 0–0.1 |
| FeO | | | | | 11–12 | 3–8 | 0–2 | | | |
| $Li_2O$ | | | 1.3 | 0–0.5 | | | | | | |
| $SO_3$ | | | | 0–0.5 | | | | | | |
| S | | | | | 0–0.2 | 0–0.2 | 0–2 | | | |
| $F_2$ | 0–1 | | | 0–1.5 | | | | | | |
| BaO | | | | 0–3 | | | | | | 5 |
| $ZrO_2$ | | | 21.5 | | | | | 0.1 | 15–17 | |
| $P_2O_5$ | | | | | | | 0–0.5 | | | |
| $Cr_2O_3$ | | | | | | | | <0.03 | <0.01 | |
| ZnO | | | | | | | | | | 4 |

[a]Navy Environmental Health Center 1997; TIMA 1993
[b]As is standard practice, the chemical composition of the elements are reported as oxides, even though no such individual crystals exist in the fibers.
[c]There are several formulations applicable to this category and formulation 475 is generally representative.

AR-glass = alkali resistant glass; E-glass = electrical glass (so called because the low alkali oxide content makes it useful for electrical applications); RCF = refractory ceramic fiber; S-glass = high tensile strength glass (stronger than E-glass)

chemical composition of the glass can result in significant changes to its optical, electrical, chemical, and mechanical properties. Chemical glass (C-glass) is highly resistant to attack by chemicals such as hydrofluoric acid, concentrated phosphoric acid (when hot), and superheated water. The chemical resistance is determined by the relative amounts of the acidic oxides ($SiO_2$, $B_2O_3$), basic oxides (CaO, MgO, $Na_2O$, $K_2O$), and amphoteric oxides ($Al_2O_3$). High-strength glass (S-glass) is almost completely composed of aluminum, silicon, and magnesium oxides and finds use in sophisticated high technology applications where high tensile strength is required; its tensile strength is typically 30–40% greater than E-glass. Alkali resistant glass (AR-glass) contains a high percentage of zirconium oxide, which makes this type of glass highly resistant to acidic and alkaline compounds.

The term mineral wool is often used to collectively refer to rock wool and slag wool, although occasionally, glass wool was included in this category. Similar to other glass fibers, the chemical composition of rock wool and slag wool are primarily aluminum and silicon oxides. However, these wools possess a higher alkaline earth oxide content (MgO and CaO) and lower alkali metal oxide content ($Na_2O$ and $K_2O$) than glass wool. Rock wool is derived from igneous rocks such as diabase, basalt, or olivine, while slag wool is derived from blast furnace slag from the steel industry (Navy Environmental Health Center 1997).

Refractory ceramic fibers are a specialized type of synthetic vitreous fiber that are highly heat resistant and thus find use in high-temperature applications. Refractory ceramic fibers contain a much higher concentration of alumina than the other fibers listed in Table 4-1 and are sometimes referred to as aluminosilicate glasses. Although refractory ceramic fibers are amorphous at low temperatures, they undergo partial crystallization (devitrification) to quartz, cristobalite, or tridymite at elevated temperatures (Maxim et al. 1999b).

## 4.2 PHYSICAL AND CHEMICAL PROPERTIES

The important physical properties that are pertinent for organic compounds are generally not applicable to inorganic materials like fibrous glass. Properties such as vapor pressure, Henry's law constant, and octanol/water partition coefficient are exceedingly low and not measurable. Even properties like melting point are difficult to define since fibrous glass products are amorphous and do not experience a distinct melting point as crystalline materials do, but soften over a fairly broad temperature range. The term softening point is used for materials that do not possess a definite melting point and is often employed

when discussing synthetic vitreous fibers. It represents the temperature at which plastic flow becomes viscous flow, and is specifically defined as the temperature at which the viscosity of the partial molten glass is $10^{7.6}$ poise (TIMA 1993). Since synthetic vitreous fibers are often used in textile products as a reinforcing material, the softening point is an important physical property. Some physical properties of the synthetic vitreous fibers listed in Table 4-1 are shown in Table 4-2. Since the final products within each class of fibers can be varied according to manufacturing specifications, the values listed in Table 4-2 should only be considered representative of the properties for each class in a very general sense.

Synthetic vitreous fibers are not actually soluble in water, but the term dissolution is often used to describe the durability of synthetic vitreous fibers, especially as it pertains to biological fluid. This should not be confused with solubility, which is the amount of material that dissolves in solution before it reaches chemical equilibrium. The dissolution rate is the rate at which a fiber reacts with a solution and is degraded in it. Under alkaline and acidic conditions, the silicate network of synthetic vitreous fibers can be attacked, resulting in the leaching of individual ions and the eventual disruption of the entire fiber network. Due to the larger surface area, fine fibers have greater dissolution rates than course fibers (see Section 3.4 for details).

Because the toxicity of fibers is related to their physical dimensions, it is important to characterize the size of synthetic vitreous fibers. In a typical glass fiber product, the average length is usually on the order of several centimeters, but the average diameter is usually on the order of a few microns. The nominal diameter is defined as the average fiber diameter in the finished product and varies according to fiber type, use, and manufacturing process involved (ACGIH 2001). The diameters of airborne fibers are an important physical property from a biological standpoint because thin fibers are considered respirable and may be deposited in the peripheral lung airways. Airborne fibers with diameters <3 μm are generally considered respirable in humans. There is also a strong correlation between the fiber diameter and the airborne fiber levels found in workplaces (Esmen and Erdal 1990; Esmen et al. 1979a, 1979b). Generally, the greater the fiber diameter, the lower the airborne fiber concentration. The nominal fiber diameter of continuous filament fibrous glass is usually in the range of 3–25 μm, depending upon the application, with typical diameters in the range of 6–15 μm (Navy Environmental Health Center 1997). The method of producing continuous filament fibers allows for excellent control of the preset fiber diameter and as a result, there is little variation in range of diameters for the resulting product. The production of rock wool, slag wool, and glass wool includes a rotary or centrifugal process resulting in nominal fiber

## Table 4-2. Physical Properties of Some Types of Synthetic Vitreous Fibers[a]

| Property | E-Glass | S-Glass | AR-Glass | Glass wool | Rock wool | Slag wool | Refractory ceramic fibers | Special purpose glass fiber 475 formulation[b] |
|---|---|---|---|---|---|---|---|---|
| Molecular weight | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Density ($g/cm^3$) | 2.60–2.65 | 2.5 | 2.52 | 2.40–2.55 | 2.7–2.9 | 2.7–2.9 | 2.6–2.7 | 2.4 |
| Softening point °C | 835–860 | 970 | 680 | 650–700 | No data | No data | 1,740–1,800 | 650 |
| Dielectric constant at 1 MHz | 5.8–6.4[c] | 4.9–5.3[c] | No data | No data | No data | No data | No data | No data |
| Modulus of elasticity (GPa) | 70–75 | 85 | 70–75 | 55–62 | 55–62 | 48–76 | 76–100[d] | No data |
| Refractive index | 1.55–1.57 | 1.52 | 1.525 | 1.51–1.54 | 1.6–1.8 | 1.6–1.8 | 1.55–1.57 | 1.53 |
| Tensile strength (MPa) | 3,400[c] | 4,590[c] | 3,700[c] | No data | 482–689[d] | 482–689[d] | 1,000–1,300[c,e] | No data |

[a]All data derived from TIMA 1993 unless otherwise noted.
[b]There are several formulations applicable to this category and formulation 475 is generally representative.
[c]Fitzer et al. 1988
[d]Navy Environmental Health Center 1997
[e]There are various commercial products of boron or silicon carbide filaments or yarns with high tensile strength, but these are crystalline fibers and technically not synthetic vitreous fibers.

N/A = not applicable

diameters in the range of about 3–7 μm for rock wool and slag wool and 3–15 μm for ordinary glass wool (Navy Environmental Health Center 1997). The smaller diameters of these fibers in comparison to continuous filament fibers, allows for the possibility that a small fraction of these fibers may be respirable when they become airborne. Special purpose glass fibers are produced by a flame attenuation process whereby the hot, molten glass is poured in front of a high temperature gas flame, resulting in fibers with a mean diameter of <3 μm and very often <1 μm. Refractory ceramic fibers (RCFs) are produced by melting and spinning or blowing of calcinated kaolin, aluminum silicates and metallic oxide blends, and high purity aluminum silicate. The typical fiber diameter of RCFs is 1–5 μm.

Christensen et al. (1993) employed light microscopy (LM) and scanning electron microscopy (SEM) to measure the length-weighted diameters of 22 synthetic vitreous fiber products obtained from 11 different manufacturers. In this study, nine different glass wool products, nine rock wool or slag wool products, three refractory ceramics, and a single special purpose glass fiber were analyzed. The results of this study are summarized in Table 4-3.

The results of a recent comprehensive workplace monitoring study using transmission electron microscopy (TEM) was reported by Mast et al. (2000), which characterized the airborne fiber dimensions of refractory ceramic fibers. Measurements of 3,357 fibers obtained at 98 workplaces yielded an airborne diameter range of 0.067–4.0 μm. The arithmetic mean and standard deviation were reported as 1.05 μm and 0.64 μm, respectively, while the geometric mean and standard deviation were reported as 0.84 μm and 2.05 (the geometric standard deviation is unitless), respectively (Mast et al. 2000). Fiber lengths ranged from 0.6 to 138 μm, with an arithmetic mean length and standard deviation of 20.6 μm and 19.3 μm, respectively. The geometric mean length and geometric standard deviation were reported as 14.1 μm and 2.48, respectively. The size distributions of airborne synthetic vitreous fibers at different locations under a variety of occupational settings were summarized in the most recent IARC monograph (IARC 2002) and these data are condensed in Table 4-4.

## Table 4-3. Measured Diameters of Glass Wool, Rock Wool, Slag Wool, Refractory Ceramic Fibers, and a Special Purpose Glass Fiber[a]

| Number of products studied | Arithmetic mean diameter range (μm) LM | Geometric mean diameter range (μm) LM | Arithmetic mean diameter range (μm) SEM | Geometric mean diameter range (μm) SEM |
|---|---|---|---|---|
| Glass wool | | | | |
| 9 | 2.4–8.1 | 1.7–6.6 | 1.2–7.7 | 0.8–6.3 |
| Special purpose glass fiber[b] | | | | |
| 1 | Not applicable[b] | Not applicable[b] | 0.6 | 0.4 |
| Mineral wool | | | | |
| 9 | 2.5–4.7 | 1.7–3.3 | 2.4–5.3 | 1.7–4.0 |
| Refractory ceramic fibers | | | | |
| 3 | 2.3–3.9 | 1.5–2.8 | 2.4–3.8 | 1.7–2.8 |

[a]Data obtained from Christensen et al. (1993); for all samples, between 400 and 490 individual fibers were measured in order to derive the statistical quantities presented in the table.
[b]A single special purpose glass wool fiber was studied with a diameter too small to be accurately measured by LM.

LM = light microscopy; SEM = scanning electron microscopy

## Table 4-4. Statistical Analysis of Airborne Fibers Under Different Occupational Settings[a]

| SVF product or setting | GM diameter (μm) | GSD diameter | GM length (μm) | GSD length | Length-diameter correlation |
|---|---|---|---|---|---|
| Rock wool production | 0.3–0.5 | 1.9–2.7 | 7.0–9.0 | 2.2–3.0 | 0.4–0.6 |
| Rock wool use | 1.2 | 2.7 | 22 | 4.0 | 0.7 |
| Glass wool use | 0.75 | 2.8 | 16 | 3.5 | 0.7 |
| Glass wool use | 0.8–1.9 | 1.4–1.9 | 9.5–30 | 1.4–2.5 | 0.2–0.7 |
| Rock wool use | 1.6–1.9 | 1.6–1.9 | 19 | 1.7–2.7 | 0.4–0.6 |
| Glass wool house prefabrication | 0.91–1.2 | 1.7–1.8 | 9.2–9.3 | 2.3–2.5 | No data |
| Rock wool house prefabrication | 1.3–1.7 | 1.9 | 12–17 | 2.5–2.8 | No data |
| Installation of SVF batts | 0.9–1.3 | 2.2 | 22–37 | 2.8–2.9 | 0.5–0.6 |
| Installation of loose SVF with binder | 1.0–2.0 | 1.8–2.2 | 30–50 | 2.3–2.6 | 0.4–0.6 |
| Installation of loose SVF without binder | 0.60 | 1.9 | 14–15 | 2.4–2.6 | 0.5–0.6 |
| RCF production and use | 0.84 | 2.05 | 14.1 | 2.5 | 0.4 |
| RCF factory | 0.96–1.2 | 1.7–1.9 | 12–19 | 2.4–2.6 | No data |
| RCF factory | 0.86 | 1.9–2.0 | 11–13 | 2.4–2.6 | No data |

[a]IARC 2002

GM = geometric mean; GSD = geometric standard deviation; RCF = refractory ceramic fiber; SVF = synthetic vitreous fiber

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

## 5.1 PRODUCTION

Synthetic vitreous fibers are unlike common minerals because they are amorphous and do not occur naturally in the environment. Fibrous glass and glass wool are made by melting sand in combination with other oxides such as lime or soda without crystallizing them. Rock wool is derived from igneous rock containing high levels of calcium, while slag wool is produced from the by-products of metal smelting. Although rock wool and slag wool were being produced in Europe in the mid to late 19$^{th}$ century, it was not until after World War I that its production within the United States became significant (IARC 1988). In 1928, there were 8 manufacturing plants in the United States that produced rock wool or slag wool, by 1939, the number had grown to 25, and in 1985, there were 58 facilities in the United States producing fibrous glass, mineral wool, and refractory ceramics (IARC 1988).

Historical U.S. production volumes for synthetic vitreous fibers are shown in Tables 5-1 and 5-2. Glass wool products comprise the vast majority of synthetic vitreous fibers produced in the United States. The Glass Manufacturing Industry Council (GMIC) reports that there are currently 10 major manufacturers operating about 40 plants around the United States, and estimates that the current production volume of glass fibers, including glass wool, is about 3 million tons ($2.72 \times 10^9$ kg) annually (GMIC 2002). The annual U.S. production of mineral wool is roughly 550,250 tons ($5.0 \times 10^8$ kg), and accounts for approximately 10–15% of the total amount of synthetic vitreous fibers produced. The total domestic production of refractory ceramic fibers was approximately 107.7 million pounds ($4.9 \times 10^7$ kg) in 1997 (Mast et al. 2000). For comparison, the total production volume of all synthetic vitreous fibers in Canada was estimated as 250–300 kilotons ($2.26 \times 10^8$–$2.71 \times 10^8$ kg) in 1991, of which 70% was glass wool, 20% was mineral wool, 10% was continuous filament glass, and <1% was refractory ceramic fibers (Environment Canada 1993).

The production of fibrous glass differs depending upon whether the final product being formed is continuous filament glass fibers or glass wool. In general, a glass-making furnace is used to melt the raw materials and a separate device is frequently used to convert the melt into marbles. The preformed marbles can be stored, distributed, and remelted for fiber formation. A direct melt process is also

## Table 5-1. Production Volumes of Glass Wool, Rock Wool, and Slag Wool Products in the United States[a]

| Product | Quantity (million kg), 1977 | Quantity (million kg), 1982 |
|---|---|---|
| Wool for insulation (homes and commercial/industrial buildings) | | |
| Loose and granulated fiber | 373.2 | 327.2 |
| Building batts, blankets, and rolls | 359.9 (R-19 or more)[b] | 530.0 (R-19 or more)[b] |
| | 403.9 (R-11 to R-18.9) | 418.4 (R-11 to R-18.9) |
| | Not available (R-10.9 or less) | 52.3 (R-10.9 or less) |
| Acoustical, such as wall and ceiling | Not available | 46.3 |
| Wool for industrial, equipment, and appliance insulation[c] | | |
| Flexible blankets, rolls, and batts (plain) | 167.8 | 173.2 |
| Flexible blankets, rolls, and batts (coated) | 16.5 | 21.4 |
| Flexible blankets, rolls, and batts (faced) | 24.0 | Not available |
| Special purpose insulation | 19.6 | 11.5 |
| Blocks and boards | 46.0 | 10.0 |
| Pipe insulation | 30.5 | 26.8 |
| Acoustical, including pads, boards, and patches | 24 | Not available |

[a]IARC 1988
[b]The R-value is the reciprocal of the amount of heat energy per area of material per degree difference between the outside and inside.
[c]Includes amounts from products produced in the same establishment as well as products purchased or transferred from other establishments.

## Table 5-2. Continuous Filament Glass Fiber Production in the United States[a]

| Year | Quantity (million kg) |
|---|---|
| 1975 | 247.88 |
| 1976 | 306.90 |
| 1977 | 357.30 |
| 1978 | 419.04 |
| 1979 | 460.36 |
| 1980 | 393.62 |
| 1981 | 472.61 |
| 1982 | 408.15 |
| 1983 | 530.27 |
| 1984 | 632.88 |

[a]IARC 1988

employed, which produces the fibers while avoiding the conversion of the melt into marbles. In the production of continuous filament fibers, nozzles are attached to the bushings on the furnace forehearth, and mechanical drawing is used to form the fibers from the melt. A fine mist of water is sprayed onto the strands as they are extruded through the bushing and a lubricating agent is applied before the strands are wound into a cake (IARC 1988).

Glass wool and mineral wool are manufactured with a rotary or centrifugal process without the use of nozzle extruders. In this process, the molten material from the furnace is transferred into a rotating spinner, and the fibers are produced as centrifugal force extrudes the material through small holes in the side of the spinning device. The final wool fibers are generally shorter and thinner than continuous filament fibers. Sometimes, a blowing process in which the melt is forced through the bushings at the bottom of the crucible by a downward directed stream of gas is used to extrude the fibers (Fitzer et al. 1988). The resultant fiber strands are usually about 3–6 μm in diameter and about 3–10 cm in length (Fitzer et al. 1988). Prior to converting the fibers to final products, binders, sizings, or lubricants are usually added. Binders are phenol-formaldehyde resins that impart structural rigidity to the fiber. Lubricating oils or paraffin oils are added to reduce dust and lint formation of the final product and reduce the amount of airborne fibers during their use. Sizings are added to promote adhesion between fibers and the matrix material in reinforced applications. Several sizings are used, including polyvinyl acetate chrome mixture, polyvinyl acetate silane, and epoxy silane (Navy Environmental Health Center 1997).

Special purpose glass fibers are usually produced with a flame attenuation process, which results in the production of very small diameter fibers. The flame attenuation method of producing fibers is a two-step procedure TIMA 1993). In the first step, the melt is drawn through the bushings of the furnace to produce strands of course fibers. The course fibers are then remelted and attenuated into several finer fibers with a high temperature gas flame, normally impinging at right angles to the primary fiber. Fibers are usually propelled by high velocity gasses through a forming tube, upon which a binder is sprayed, before producing the final wool fiber (TIMA 1993).

Refractory ceramic fibers are produced by blowing and spinning processes similar to those used in the production of wool, but the starting material is kaolin clay rather than rock or slag (IARC 1988). Since refractory fibers are relatively new materials, the exact processes used for producing these individual fibers are often considered proprietary and are not disclosed (Fitzer et al. 1988).

## 5.2 IMPORT/EXPORT

Data regarding the quantities of manmade glass filaments (including glass wool), mineral wool, and refractory ceramic goods imported and exported to and from the United States from 1998 to 2001 are summarized in Table 5-3 (USDOC 2002).

## 5.3 USE

Synthetic vitreous fibers are an important substitute for asbestos in a variety of products where thermal, acoustical, and electrical resistance is required. Fibrous glass (including glass wool) accounts for about 80% of the production of synthetic vitreous fibers in the United States (WHO 1988). The majority of this production is in the form of glass wool, which is used for insulation purposes, similar to the mineral wools. Continuous filament fibers are used as reinforcement in plastics and building products, and in industrial fabrics (ACGIH 2001). Mineral wool accounts for about 10–15% of the production of synthetic vitreous fibers in the United States (WHO 1988). Similar to glass wool, the vast majority of rock wool and slag wool is produced for thermal and acoustical insulation applications for construction of homes, buildings, and other structures (IARC 1988). Appliances and plumbing applications also use glass wool and mineral wool for insulation purposes. The end products are usually in the form of bats, boards, blankets, and sheets. Refractory ceramics fibers and special purpose fibers only account for about 2% of all synthetic vitreous fibers produced in the United States (WHO 1988). Refractory ceramic materials are very heat resistant and find use in applications that require high temperatures. Final products are often in the form of blankets, boards, felts, bulk fibers, and paper and textile products (IARC 1988). Refractory ceramic blankets or boards are often used as insulation in ships and in firewalls to contain fires or in catalytic converters in the automobile industry and in aircraft and aerospace engines (IARC 1988). Ceramic blankets and boards are commonly used as linings for furnaces and kilns. Ceramic fiber textile products such as yarns or fabrics find use in flame resistant clothing, curtains, and other materials. Specialty purpose glass fibers are very expensive to manufacture and only find use in high technology applications such as high performance insulation in the aircraft industry and specialty filtration products (WHO 1988).

## Table 5-3. U.S. Import/Export Volume of Glass Fibers (Including Glass Wool), Mineral Wool and Refractory Ceramic Goods[a]

| Year | Import quantity (kg) | Export quantity (kg) |
|---|---|---|
| Glass fibers including glass wool | | |
| 1998 | 73,074,090 | 119,386,619 |
| 1999 | 96,924,030 | 112,438,061 |
| 2000 | 103,001,680 | 119,829,077 |
| 2001 | 93,045,850 | 122,598,785 |
| Mineral wool | | |
| 1998 | 4,096,373 | 13,507,235 |
| 1999 | 4,732,083 | 12,856,177 |
| 2000 | 5,086,956 | 15,736,857 |
| 2001 | 4,330,133 | 15,760,666 |
| Refractory ceramic goods | | |
| 1998 | 26,677,254 | 21,567,397 |
| 1999 | 23,552,712 | 11,044,364 |
| 2000 | 28,520,534 | 16,464,014 |
| 2001 | 24,191,899 | 12,054,960 |

[a]USDOC 2002

## 5.4 DISPOSAL

No components in synthetic vitreous fibers are identified by the EPA as hazardous waste in Resource Conservation and Recovery Act (RCRA) (40CFR Part 261), and as such they may be disposed of in landfills; however, state and local regulations may apply. Provided that refractory ceramic fibers and other synthetic vitreous fibers have an average diameter >1 μm, the EPA agrees that these substances would not fall within the fine mineral fibers category under Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) and, thus, would not be subject to release reporting and liability requirements. Should synthetic vitreous fibers, however, have an average diameter of ≤1 μm, these substances would be considered hazardous substances and, therefore, would be subject to CERCLA requirements (EPA 1995). The U.S. Navy suggest that all synthetic vitreous fiber material be wetted before placing the material in heavy duty plastic bags or other impermeable objects before being discarded at landfills (Navy Environmental Health Center 1997).

Glass and insulating material are often recycled for further use after being removed or discarded. According to the North American Insulation Manufacturers Association (NAIMA), over 18 billion pounds of glass and insulating material have been recycled in North America since 1992 (NAIMA 2002).

# 6. POTENTIAL FOR HUMAN EXPOSURE

## 6.1 OVERVIEW

Synthetic vitreous fibers were not identified in any of the 1,647 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2004). However, the number of sites evaluated for synthetic vitreous fibers is not known. The frequency of these sites can be seen in Figure 6-1.

Like other inorganic substances, synthetic vitreous fibers do not undergo typical transformations in the environment, such as photolysis and biodegradation, which are important for organic compounds. Under acidic or alkaline conditions, synthetic vitreous fibers may undergo dissolution, whereby the silicate network may be attacked and slowly degraded. Experimental dissolution rates of tested fibers have been reported to span over 5 orders of magnitude. This degradation mechanism is more relevant in biological systems than it is in the environment (see Section 3.4 for more details). The transport and partitioning of synthetic vitreous fibers are largely governed by their size. 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 can be exposed to low levels of synthetic vitreous fibers when insulating material or other synthetic vitreous fiber-containing material such as ceiling boards are physically disturbed and fibers become suspended in the air. Home, building, and appliance insulation are often composed of glass wool, rock wool, or slag wool, and low levels of synthetic vitreous fibers have been detected in indoor air. These levels are usually on the order of about $1x10^{-4}$ fiber/cc, although higher levels are often observed during the installation of insulation in attics or ceilings; however, these levels quickly return to pre-installation levels, usually in 1 or 2 days. Low levels of synthetic vitreous fibers have also been detected in outdoor air, and available data suggest that there are little differences in the concentration of these fibers near source dominated areas (e.g., near production plants) when compared to other locations. Typical levels of synthetic vitreous fibers in outdoor ambient air can vary, but are also on the order of about $1x10^{-4}$ fiber/cc.

**Figure 6-1. Frequency of NPL Sites with Synthetic Vitreous Fiber Contamination***


Derived from HazDat 2004

*No data are available in HazDat 2004

The overwhelming majority of human exposure to synthetic vitreous fibers occurs as occupational exposure through inhalation and dermal contact. Occupational exposure is estimated to be several orders of magnitude greater than environmental exposure. Employees at manufacturing facilities where synthetic vitreous fiber products are produced, as well as workers who regularly install or come into contact with insulating material are most at risk for elevated levels of exposure. Workers involved in demolition work, as well as in building maintenance and repair, are potentially exposed to higher levels of synthetic vitreous fibers once these materials are disturbed or demolished. Workers involved in the removal of refractory ceramic fiber insulation in high temperature furnaces may also be exposed to quartz, cristobalite, and tridymite, which form as refractory ceramic fibers devitrify at elevated temperatures (Maxim et al. 1999b).

In the literature discussing data on airborne synthetic vitreous fibers, total dust or total fiber levels are occasionally reported. These levels include all types of fibers, not just the synthetic vitreous fibers, and quite often synthetic vitreous fibers only constitute a small percentage of the total concentration of fibers in the sample. The precise definition of what constitutes an actual fiber, and how these fibers should be counted under microscopic examination is not standardized, and different studies have used different counting methods (see Chapter 7). A fiber is usually defined as having length of at least 5 μm, and a length to diameter ratio (aspect ratio) of either 5:1 or 3:1 (TIMA 1993). Frequently, only the levels of respirable fibers are reported. Respirable fibers are those fibers that can be inhaled into the lower lung and usually only fibers with diameters of <3 μm are considered respirable in humans (although some authors have used larger values in older publications). It is also generally accepted that fibers longer than 200–250 μm are too large to be deposited in the lung, and are therefore not respirable (TIMA 1993). Recently, the American Conference of Governmental Industrial Hygienists (ACGIH) has defined respirable fibers as possessing a diameter <3 μm, length ≥5 μm, and an aspect ratio of ≥3:1 (ACGIH 2001). The term respirable fiber in this chapter refers to fibers possessing diameters of <3 μm, unless otherwise noted. Section 3.4 (Toxicokinetics) discusses the deposition and clearance of fibers in the lung in more detail.

Phase contrast microscopy (PCM) is most frequently used to measure fiber levels, but this method cannot detect fibers with diameters smaller than 0.25 μm. PCM uses visible light photons for analysis, and because the resolution of a microscope is a function of the wavelength of photons used for analysis and the numerical aperture of the microscope, the theoretical limit of 0.25 μm for light microscopy cannot be

improved upon. Transmission electron microscopy (TEM) or scanning electron microscopy (SEM) are often employed to improve sensitivity since these techniques can measure fibers with smaller diameters than PCM because electrons with much shorter wavelengths than visible photons are used in these experiments (see Chapter 7 for details). It is often difficult to directly compare results of early studies to more recent ones due to the methods in which fibers were sampled and analyzed. Many early monitoring studies employed a set of fiber counting rules specifying a fiber as a particle with length >5 μm and aspect ratio of ≥3:1 (counting rules A). More recent studies frequently use a counting rule in which fibers are counted if their lengths are >5 μm, their diameters are <3 μm, and their aspect ratio is ≥5:1 (counting rules B). While the differences in actual fiber counts are usually small, calculating fibers using counting rules A generally yield higher counts as compared to the counting rules B (Breysse et al. 1999; Miller et al. 1995). See Chapter 7 for more details regarding the analysis, sampling, and counting of fibers.

The Toxics Release Inventory (TRI) has not listed synthetic vitreous fibers for inclusion in its database (TRI01 2003).

## 6.2 RELEASES TO THE ENVIRONMENT

Low levels of synthetic vitreous fibers may be released to the environment during their production or use. Demolishing buildings or houses that contain synthetic vitreous fibers in insulating products, ceiling boards etc., may also release low levels of synthetic vitreous fibers locally. The majority of releases most likely arise from the disposal of material containing synthetic vitreous fiber in landfills.

### 6.2.1 Air

Very limited data are available regarding the emission of synthetic vitreous fibers to ambient air. The concentration of synthetic vitreous fibers in air emissions from fibrous glass, rock wool, and slag wool plants in Germany were on the order of 0.01 fiber/cc, and the total fibrous dust emissions from these plants were estimated as 1.8 tons/year (WHO 1988). Concentrations of respirable fibers as high as 2.7 fibers/cc were measured by PCM in stack gasses at several older glass, rock, and slag wool plants in the United States (Environment Canada 1993). Concentrations of total fibers in stack gasses measured in 1991 using TEM at four refractory ceramic fiber production plants and three refractory ceramic fiber processing facilities ranged up to 14.1 fibers/cc (Environment Canada 1993).

Synthetic vitreous fibers were not identified in any of the current or former NPL hazardous waste sites (HazDat 2004). Synthetic vitreous fibers were not included in the TRI (TRI01 2003).

### 6.2.2 Water

Few data exist regarding the frequency or levels of synthetic vitreous fibers released to water. Glass fibers were identified in samples of sewage sludge from five cities in the United States; however, the specific form and exact quantity of the glass fibers were not reported (Bishop et al. 1985).

Synthetic vitreous fibers were not identified in any of the current or former NPL hazardous waste sites (HazDat 2004). Synthetic vitreous fibers were not included in the TRI (TRI01 2003).

### 6.2.3 Soil

No data exist regarding the frequency or levels of synthetic vitreous fibers released to soil. Most of these releases are expected to be in the form of discarded construction material (e.g., insulation, ceiling boards, etc.) that have been disposed of at landfills.

Synthetic vitreous fibers were not identified in any of the current or former NPL hazardous waste sites (HazDat 2004). Synthetic vitreous fibers were not included in the TRI (TRI01 2003).

## 6.3 ENVIRONMENTAL FATE

### 6.3.1 Transport and Partitioning

The transport, distribution, and degradation of synthetic vitreous fibers in the environment have not been studied (WHO 1988). However, synthetic vitreous fibers are nonvolatile and generally insoluble, so their natural tendency is to settle out of air and water, and deposit in soil or sediment.

### 6.3.2 Transformation and Degradation

#### 6.3.2.1 Air

Synthetic vitreous fibers are not known to undergo any significant transformation or degradation in air (WHO 1988).

#### 6.3.2.2 Water

Synthetic vitreous fibers are not known to undergo any significant transformation or degradation in water (WHO 1988). The silicate network of all synthetic vitreous fibers can be attacked by acids or alkaline solutions, but this does not occur to any significant extent under environmentally relevant conditions. Using *in vitro* tests at 37 °C with simulated extracellular fluid (pH 7.4), the dissolution rates of glass, rock, and slag wools with diameters of 1 μm were reported as 0.4, 1.2, and 2.0 years, respectively (Environment Canada 1993). Lifetimes for refractory ceramic fibers were about 5 years. Because of their larger surface area, fine fibers will undergo dissolution more readily than course fibers (see Section 3.4 for more details regarding dissolution in biological media).

#### 6.3.2.3 Sediment and Soil

Synthetic vitreous fibers are not known to undergo any significant transformation or degradation in soil or sediment (WHO 1988).

## 6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

### 6.4.1 Air

Available monitoring data suggest that the concentration of synthetic vitreous fibers in the atmosphere is very low. The levels of fibrous glass in ventilation systems and in the ambient air from various locations of California were studied from 1968 to 1971, in order to investigate the erosion of fibers from air transmission systems (Balzer et al. 1971; NIOSH 1976). The concentration of fibrous glass in 36 ambient air samples collected from Berkeley, San Jose, Sacramento, the Sierra Mountains, and Los Angeles ranged from not detected to $9.0 \times 10^{-3}$ fiber/cc, with an arithmetic mean of $2.57 \times 10^{-3}$ fiber/cc, as

determined by PCM and TEM (NIOSH 1976). The fiber diameters ranged from 0.10–17.7 μm, with an arithmetic mean of 4.3 μm. The concentration of fibrous glass in 37 ventilation system samples ranged from not detected to $2.0x10^{-3}$ fiber/cc ($8.7x10^{-4}$ fiber/cc, arithmetic mean), and the fiber diameters were 0.10–17.7 μm (3.7 μm, arithmetic mean). The mean airborne concentrations of fibers were monitored at one rural location and three cities in Germany in 1981–1982 (Hohr 1985). Samples were analyzed with TEM in conjunction with energy-dispersive x-ray analysis (EDXA), and electron diffraction analysis. The fibers identified as synthetic vitreous fibers constituted about 1–5% of the inorganic fibers, with a concentration range of $4.0x10^{-5}$–$1.7x10^{-3}$ fiber/cc (Hohr 1985). The results of these, and several other past monitoring studies have been compiled and summarized in IARC (1988, 2002) and WHO (1988).

The concentration of respirable glass fibers near a large fiberglass wool manufacturing facility in Newark, Ohio ranged from below the detection limit of $1.0x10^{-5}$ fiber/cc to $1.4x10^{-4}$ fiber/cc, during four sampling periods in 1988–1989 as determined by PCM (Switala et al. 1994). These levels were similar to the measured levels in ambient air from a rural site located 10 miles away from the plant in Granville, Ohio. The range of concentrations at the rural location was from below the detection limit of $1.0x10^{-5}$ fiber/cc to $1.5x10^{-4}$ fiber/cc, during the same sampling period. Furthermore it was shown that only 16% of the 460 samples obtained at the Newark (plant) location had concentrations of glass fibers above the detection limit and only 4% of the 485 samples obtained from the Granville (rural) location had concentrations above the detection limit. Glass fibers accounted for <1% of the total respirable fibers measured at these sites. The total respirable fiber concentrations (this includes all fibers, not just synthetic vitreous fibers) at the Newark location ranged from below the detection limits to 0.02318 fiber/cc, while the levels of total respirable fibers at the Granville site ranged from below the detection limits to 0.04290 fiber/cc. The majority of non-glass fibers were reported to be pollen and trichome, seed hairs, and insect parts (Switala et al. 1994). Low levels of synthetic vitreous fibers in ambient air have also been measured in various locations in France (Gaudichet et al. 1989). The maximum concentration of respirable synthetic vitreous fibers in outdoor air at 18 locations in Paris was $1.5x10^{-5}$ fiber/cc, with a mean value of $2.0x10^{-6}$ fiber/cc as determined by PCM (Gaudichet et al. 1989).

In general, indoor air concentrations of synthetic vitreous fibers are very low under non-occupational settings, unless there is a disturbance in the fiberglass insulation system or ceiling boards of the home or building. A comprehensive study using PCM was carried out in Denmark in order to study the concentration of synthetic vitreous fibers in the indoor air of public buildings (Schneider et al. 1990). The concentration of respirable airborne synthetic vitreous fibers ranged from not detected to

$1.66x10^{-3}$ fiber/cc in air samples collected from 105 rooms using 10 different types of ceiling boards. The mean respirable levels were in the range of $2.60x10^{-5}$–$2.13x10^{-4}$ fiber/cc. The levels of nonsynthetic vitreous fibers were at least an order of magnitude greater than the levels of synthetic vitreous fibers. It was also reported that no respirable airborne levels of synthetic vitreous fibers were observed in 65 of the rooms, but that low levels of respirable synthetic vitreous fibers were found on other objects such as tables or cupboards (Schneider et al. 1990). The results of this study pertaining to the levels of airborne synthetic vitreous fibers are summarized in Table 6-1.

A recent study employing both PCM and SEM analyzed 51 residential and commercial buildings throughout the United States, and found respirable synthetic vitreous fibers were present in only 2 of the 50 samples analyzed by SEM (Carter et al. 1999). It was demonstrated that the majority of airborne fibers were organic, and that inorganic fibers, including synthetic vitreous fibers, composed <10% of the detectable respirable amount. Gaudichet et al. (1989) measured the levels of synthetic vitreous fibers at 79 indoor locations in France where synthetic vitreous fiber materials were used in a variety of applications, and found the levels of respirable synthetic vitreous fibers to be low. A range of respirable synthetic vitreous fibers were reported as not detected to $6.23x10^{-3}$ fiber/cc with a median value of $3.0x10^{-6}$ fiber/cc (Gaudichet et al. 1989). The levels of respirable fibers (diameter <3 μm and lengths >5 but <100 μm) were measured in 12 houses during the installation of rock wool or glass wool insulation material by PCM and TEM (Jaffrey 1990). Almost no differences were noticed in the pre-installation airborne levels, which were on the order of $1.0x10^{-4}$ fiber/cc, and the post insulation samples, which were taken 2 days after installation was complete. Comparable results were obtained by Miller et al. (1995) when analyzing the fiber concentrations in living spaces of 14 homes prior to installation of insulation and the evening following installation. Total fiber levels ranged from 0.0020 to 0.011 fiber/cc before installation, and from 0.0030 to 0.015 fiber/cc 1 day post-installation using PCM and counting rules A (see Chapter 7). Fiber concentrations calculated using counting rules B were slightly lower, but there were no statistically significant differences when comparing levels calculated by either the A or B counting rules. Similar results were obtained when using SEM methods and the two counting rules to measure only synthetic vitreous fibers levels, although the level of fibers classified as synthetic vitreous fibers were about an order of magnitude lower than the total fiber levels. The maximum pre-installation level of synthetic vitreous fibers was 0.001 fiber/cc, and the post-installation levels ranged from below the detection limit of 0.001 fiber/cc to 0.007 fiber/cc.

## Table 6-1. Airborne Concentrations of Synthetic Vitreous Fibers in Buildings in Denmark[a]

| Type of ceiling board[b] | Number of rooms | Water soluble binder | Respirable fiber level fibers/cc; range (mean) | Non-respirable fiber level fibers/cc; range (mean) |
|---|---|---|---|---|
| Karlit mineral | 11 | Yes | $0–1.66\times10^{-3}$ ($2.13\times10^{-4}$) | $0–3.3\times10^{-4}$ ($5.7\times10^{-5}$) |
| Hotaco mineral | 14 | Yes | $0–4.3\times10^{-4}$ ($5.6\times10^{-5}$) | $0–1.9\times10^{-4}$ ($2.1\times10^{-5}$) |
| Ny Hotaco mineral | 2 | Yes | $6–13\times10^{-5}$ ($9.5\times10^{-5}$) | Not detected |
| Other with water soluble binder | 12 | Yes | $0–3.6\times10^{-4}$ ($5.9\times10^{-5}$) | $0–7.0\times10^{-5}$ ($1.4\times10^{-5}$) |
| Soft mineral wool sealed on three sides | 13 | No | $0–3.4\times10^{-4}$ ($2.6\times10^{-5}$) | $0–1.0\times10^{-4}$ ($8.0\times10^{-6}$) |
| Hard mineral wool sealed on three sides | 9 | No | $0–1.3\times10^{-4}$ ($3.1\times10^{-5}$) | $0–7.0\times10^{-5}$ ($1.0\times10^{-5}$) |
| Unsealed mineral wool | 12 | No | $0–1.03\times10^{-3}$ ($1.8\times10^{-4}$) | $0–4.0\times10^{-4}$ ($6.7\times10^{-5}$) |
| Sealed mineral wool on all six surfaces | 9 | No | $0–6.1\times10^{-4}$ ($9.4\times10^{-5}$) | $0–2.4\times10^{-4}$ ($4.6\times10^{-5}$) |
| Batts on top of perforated panels | 11 | No | $0–1.0\times10^{-4}$ ($1.7\times10^{-5}$) | $0–6.0\times10^{-5}$ ($9.0\times10^{-6}$) |
| No synthetic vitreous fiber (control group) | 12 | Not applicable | $0–6.2\times10^{-4}$ ($6.2\times10^{-5}$) | $0–1.3\times10^{-4}$ ($1.8\times10^{-5}$) |

[a]Schneider et al. 1990
[b]Contains Danish product names

### 6.4.2 Water

No data exist regarding the ambient levels of synthetic vitreous fibers in water.

### 6.4.3 Sediment and Soil

No data exist regarding the ambient levels of synthetic vitreous fibers in soil or sediment.

### 6.4.4 Other Environmental Media

No data exist regarding the levels of synthetic vitreous fibers in foods, plants, or animals.

## 6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The exposure of the general population (non-occupational exposure) to synthetic vitreous fibers in both indoor and outdoor air is low. Persons that install their own home insulation may briefly be exposed to higher than normal levels during the installation; however, these exposures can be significantly reduced with the use of protective equipment such as ventilators and gloves. Furthermore, it has been shown that the airborne levels of synthetic vitreous fibers attenuate rapidly following installation (Jaffrey 1990; Miller et al. 1995). No exposures from food, drinking water, or other environmental media are expected. A recent study measured the density (fibers/$mm^2$) of synthetic vitreous fibers on material surfaces (desks, floors, shelves, etc.) inside 20 buildings located in Cambridge and Boston, Massachusetts (Vallarino et al. 2003). It was determined that nearly 60% of the samples collected had zero or one countable synthetic vitreous fiber when using NIOSH Method 7400 and counting rules B. Only about 4% of the samples had densities >1 fiber/$mm^2$. A second survey was undertaken that analyzed the synthetic vitreous fibers on the surface of objects inside 20 buildings located in 10 cities within the United States (Vallarino et al. 2003). In this survey, counting rules A were employed, which allows fibers possessing diameters >3 μm to be counted. Using counting rules A, the number of samples having zero countable synthetic vitreous fibers decreased from about 43 to 14%. It was also shown that surfaces seldom contacted or cleaned (tops of bookcases or high shelves) had higher fiber loadings than surfaces that received frequent contact.

Although there was a large degree of variability in the fiber loadings, it is clear that only low levels of synthetic vitreous fibers are expected to be present on common surfaces within buildings used by the general population.

The airborne levels of synthetic vitreous fibers have been shown to be higher under occupational settings as compared to ambient air levels, and thus, occupational exposure is far greater than the exposure for the general population. Esmen and Erdal (1990) concluded that occupational exposure is several orders of magnitude greater than environmental exposure. The Occupational Safety and Health Administration (OSHA) estimates that there are over 250,000 workers in the United States who are exposed to synthetic vitreous fibers in manufacturing and downstream use (OSHA 2002). This number is expected to increase as use of products containing synthetic vitreous fibers increases.

Workers involved in the installation of fiberglass insulating material are exposed to synthetic vitreous fibers through both dermal and inhalation routes. Airborne fiber levels were studied by PCM during the installation of fibrous glass insulating materials in northern California (NIOSH 1976). The concentration of fibrous glass in 40 air samples obtained during the installation of this material ranged from $5.0 \times 10^{-4}$ to 2.41 fibers/cc (0.406 fiber/cc, arithmetic mean) with diameters in the range of 0.30–25.0 μm (6.5 μm, arithmetic mean). These airborne levels were 2–3 orders of magnitude greater than levels typically found in ambient air (Balzer 1971; NIOSH 1976; Switala et al. 1994). Differences were noted in the concentration of glass fibers in personal air samples when comparing the installation of batt-type material with blown-in insulation. The arithmetic mean concentration of total glass fibers during the installation of batt-type insulation was 0.13 fiber/cc and the arithmetic mean respirable glass fiber concentration was 0.042 fiber/cc as determined by PCM (Jacob et al. 1992). The personal air concentrations were higher for applications involving blown-in insulation wool as compared to batt-type material. The arithmetic mean concentrations of total glass wool fibers were 0.68 fiber/cc (cubed blown wool) and 1.7 fibers/cc (milled blown wool) during the installation process. The corresponding arithmetic mean concentrations of respirable glass wool fibers were 0.30 fiber/cc for the milled blown wool and 0.82 fiber/cc for the cubed blown wool (Jacob et al. 1992). The levels of airborne respirable glass fibers were shown to decrease significantly after installation, with levels on the order of $1 \times 10^{-4}$ fiber/cc 1 day after installation (Jacob et al. 1992). The respirable airborne concentrations of refractory ceramic fibers, rock wool, and glass wool fibers were measured by PCM and TEM at five construction sites using products containing these materials (Perrault et al. 1992). The greatest airborne levels were observed during the removal of refractory ceramic fiber insulating material from the inside walls of industrial furnaces, with geometric

mean concentrations ranging from 0.39 to 3.51 fibers/cc. The geometric mean concentration of respirable fibers during the installation of blown in rock wool in the attic of a residential apartment building was 0.32 fiber/cc, while the geometric mean concentration was 0.15 fiber/cc for sprayed-on rock wool insulation at an industrial construction site. The lowest airborne levels were observed during the installation of fiberglass panels around ventilation ducts at an industrial construction site, with a geometric mean concentration of 0.010 fiber/cc (Perrault et al. 1992). Using TEM and PCM, the mean concentration of respirable airborne fibers were measured in the range of 0.080–1.76 fibers/cc during the installation of either glass wool or rock wool insulating material in 12 houses in England (Jaffrey 1990). The lowest airborne concentrations were observed during the installation of rock wool blanket material, and the highest level occurred during the installation of a fine glass wool blanket material, in which approximately 80% of the fibers had diameters <1 μm.

In a study of four facilities producing fibrous glass insulation and one producing fibrous glass textile products, the range of concentrations for total respirable fibers having lengths >5 μm were reported as not detected to 1.97 fibers/cc, with mean levels in the range of 0.020–0.97 fiber/cc (Johnson et al. 1969). No data were provided regarding what percentage of total fiber counts were glass fibers as opposed to other fibers, and respirable fibers in this study were defined as fibers having a diameter <5 μm, rather than the currently accepted value of <3 μm. The airborne level of fibers in various parts of 16 manufacturing facilities producing glass wool, continuous glass filament, rock and slag wool, and refractory ceramic fibers were measured by Esmen et al. (1979a, 1979b), and the details of this study have been summarized in other publications (IARC 1988, 2002; WHO 1988). Table 6-2 shows the levels of total suspended particulate matter in various regions of these 16 plants, and Table 6-3 shows the corresponding concentrations of total airborne fibers measured by PCM. The greatest airborne fiber levels of were observed at a plant producing refractory ceramic and special purpose fibers (plant 15), where the nominal fiber diameter of the product ranged from 0.050 to 1.6 μm. Additional studies employing transmission electron microscopy to detect small diameter fibers showed airborne fiber levels as high as 6.49 fibers/cc for this location. More recent monitoring data on workplace airborne levels confirm that higher concentrations are observed under occupational settings as compared to the levels observed under non-occupational conditions. In a study of airborne fiber levels during 11 different manufacturing operations involving Owens-Corning Fiberglass insulation products, the mean concentration of airborne total glass fibers ranged from 0.0020 to 0.14 fiber/cc and the mean concentration of respirable glass fibers ranged from 0.0010 to 0.071 fiber/cc as determined by PCM (Jacob et al. 1993). The airborne fiber levels were

## Table 6-2. Concentrations (mg/m$^3$) of Total Suspended Airborne Particulate Matter in 16 Facilities in the United States[a]

| Plant | Forming mean (SD) | Production mean (SD) | Manufacturing mean (SD) | Maintenance mean (SD) | Quality control mean (SD) | Shipping mean (SD) | Overall mean (SD) |
|---|---|---|---|---|---|---|---|
| 1 | 0.47 (0.47) | 1.04 (1.34) | 0.96 (0.96) | 0.71 (0.45) | 0.21 (0.12) | 0.39 (0.09) | 0.89 (1.12) |
| 2 | 1.65 (1.17) | 2.53 (2.30) | 2.28 (1.51) | 2.05 (1.32) | 1.53 (0.63) | 1.34 (0.58) | 1.94 (1.68) |
| 3 | No data | 0.51 (0.30) | No data | 0.83 (0.61) | No data | 0.70 (0.42) | 0.65 (0.46) |
| 4 | 1.22 (0.51) | 0.77 (0.49) | 1.23 (0.95) | 2.08 (4.40) | 0.52 (0.14) | 1.32 (0.96) | 1.24 (2.26) |
| 5 | 0.76 (0.25) | 0.67 (1.52) | 0.29 (0.95) | 0.55 (0.32) | 0.09 (No data) | 0.62 (0.33) | 0.60 (1.04) |
| 6 | 1.30 (0.71) | 1.77 (2.23) | 0.51 (0.39) | 2.00 (2.50) | 0.49 (0.82) | 0.45 (0.19) | 1.17 (1.72) |
| 7 | 2.18 (1.62) | 2.05 (0.31) | 4.31 (4.03) | 6.72 (7.84) | No data | 1.77 (1.02) | 4.00 (4.27) |
| 8 | No data | 8.48 (9.02) | 1.17 (0.55) | 4.64 (8.28) | No data | 0.84 (0.67) | 4.73 (8.69) |
| 9 | 1.18 (0.48) | 1.90 (1.52) | 1.14 (0.53) | 1.33 (0.57) | No data | 1.08 (0.46) | 1.33 (1.02) |
| 10 | 2.45 (0.93) | 0.75 (0.47) | 0.73 (0.33) | 1.25 (1.07) | 0.32 (0.09) | 0.69 (0.15) | 1.07 (0.91) |
| 11 | 2.18 (1.64) | 1.08 (1.82) | 0.87 (0.46) | 1.26 (0.49) | 1.25 (No data) | 1.04 (0.41) | 1.37 (1.09) |
| 12 | 0.34 (0.35) | 0.20 (0.30) | 0.28 (0.26) | 0.53 (0.26) | 0.53 (0.66) | 0.88 (0.08) | 0.21 (0.16) |
| 13 | 4.10 (No data) | 1.34 (0.46) | 1.19 (1.08) | 1.80 (1.69) | No data | 1.31 (0.59) | 1.40 (1.08) |
| 14 | 3.00 (1.37) | 0.85 (0.59) | 1.06 (0.47) | 1.57 (1.41) | No data | 0.91 (0.72) | 1.42(1.21) |
| 15 | 0.30 (0.21) | 0.61 (0.51) | 1.08 (0.80) | 1.09 (0.75) | 1.66 (0.73) | 0.54 (0.18) | 0.75 (0.67) |
| 16 | 0.77 (0.46) | 0.82 (0.69) | 0.86 (0.52) | 1.79 (1.50) | 0.44 (No data) | 0.76 (0.53) | 1.07 (1.02) |

[a]Esmen et al. 1979b; measurements obtained with phase contrast microscopy

SD = standard deviation

## Table 6-3. Concentrations (fiber(s)/cc) of Total Airborne Fibers in 16 Facilities in the United States[a]

| Plant | ND µm | Forming area mean (SD) | Production area mean (SD) | Manufacturing area mean (SD) | Maintenance area mean (SD) | Quality control area mean (SD) | Shipping area mean (SD) | Overall mean (SD) |
|---|---|---|---|---|---|---|---|---|
| 1 | 1–12 | 0.002 (0.001) | 0.38 (0.32) | 0.03 (0.02) | 0.02 (0.02) | 0.07 (0.10) | 0.01 (0.001) | 0.01 (0.25) |
| 2 | 6 | 0.07 (0.03) | 0.17 (0.14) | 0.12 (0.11) | 0.08 (0.05) | 0.19 (0.16) | 0.07 (0.06) | 0.11 (0.12) |
| 3 | 3–6 | No data | 0.02 (0.02) | No data | 0.07 (0.18) | No data | 0.005 (0.01) | 0.04 (0.1) |
| 4 | 1–6 | 0.01 (0.004) | 0.07 (0.12) | 0.04 (0.05) | 0.03 (0.02) | 0.01 (0.01) | 0.02 (0.01) | 0.04 (0.08) |
| 5 | 8 | 0.02 (0.01) | 0.03 (0.02) | 0.03 (0.02) | 0.02 (0.01) | 0.03 (No data) | 0.03 (0.01) | 0.02 (0.02) |
| 6 | 5–15 | 0.05 (0.10) | 0.01 (0.01) | 0.008 (0.01) | 0.01 (0.03) | 0.01 (0.02) | 0.005 (0.004) | 0.01 (0.03) |
| 7 | 5 | 0.15 (0.03) | 0.24 (0.12) | 0.43 (0.32) | 0.44 (0.37) | No data | 0.15 (0.17) | 0.34 (0.35) |
| 8 | 7–10 | No data | 0.03 (0.02) | 0.04 (0.03) | 0.01 (0.01) | No data | 0.01 (0.01) | 0.02 (0.02) |
| 9 | 7–10 | 0.02 (0.02) | 0.01 (0.01) | 0.02 (0.07) | 0.01 (0.006) | No data | 0.004 (0.002) | 0.02 (0.01) |
| 10 | 6–16 | 0.001 (0.001) | 0.003 (0.004) | 0.004 (0.004) | 0.002 (0.003) | 0.003 (0.003) | 0.002 (0.002) | 0.002 (0.003) |
| 11 | 7 | 0.09 (0.11) | 0.05 (0.03) | 0.04 (0.03) | 0.04 (0.04) | 0.08 (0.08) | 0.03 (0.02) | 0.05 (0.05) |
| 12 | 6–115 | 0.01 (0.01) | 0.020 (0.030) | 0.01 (0.004) | 0.01 (0.02) | 0.01 (0.003) | 0.007 (0.005) | 0.01 (0.02) |
| 13 | 7 | 0.58 (No data) | 0.08 (0.06) | 0.11 (0.17) | 0.09 (0.08) | No data | 0.03 (0.02) | 0.10 (0.10) |
| 14 | 6–13 | 0.01 (0.01) | 0.04 (0.09) | 0.05 (0.05) | 0.05 (0.13) | No data | 0.03 (0.03) | 0.04 (0.03) |
| 15 | 0.05–1.6 | 0.19 (0.22) | 0.92 (1.02) | 1.56 (3.79) | 0.11 (0.10) | 0.89 (0.33) | 0.10 (0.09) | 0.78 (2.1) |
| 16 | 6–10 | 0.02 (0.01) | 0.02 (0.02) | 0.05 (0.03) | 0.07 (0.23) | 0.04 (No data) | 0.02 (0.01) | 0.04 (0.12) |

[a]Esmen et al. 1979b

ND = nominal diameter; SD = standard deviation

also studied during the removal of pipe installation and ceiling boards. For these removal processes, the mean airborne concentration of total glass fibers was 0.10 fiber/cc and the mean airborne concentration of respirable glass fibers was 0.042 fiber/cc (Jacob et al. 1993). While these levels are greater than levels found in ambient air, they are far lower than a 1992 proposed OSHA exposure limit of 1 fiber/cc per 8-hour time-weighted-average (TWA) (OSHA 2002).

The North American Insulation Manufacturers Association (NAIMA) has recently developed a Health and Safety Partnership (HSPP) with the participation and oversight of OSHA (Marchant et al. 2002; Maxim et al. 2003a). As part of this program, a database that estimates the level of potential exposure to respirable fibers from fiber glass, rock wool, and slag wool was developed. Textile glass fibers were not included in the program because they are generally considered non-respirable due to their relatively large nominal diameters. The database contains current information regarding time-weighted average exposure levels, which are categorized by product type and specific work function. Information from this database regarding exposure by industrial sector is provided in Table 6-4. Additional exposure data categorized by product description and job description are presented in Tables 6-5 and 6-6, respectively. Maxim et al. (2003a) estimated the probable cumulative lifetime exposure (fiber-month/cc) to persons that install fiberglass or rock/slag wool insulation materials in residential, commercial and industrial buildings. This analysis concluded that due to smaller exposure times, both do it yourself and professional insulation installers had much lower lifetime exposures than workers employed in the manufacturing of fiberglass, rock/slag wool products (Maxim et al. 2003a). The authors noted that recent epidemiological studies have concluded that there is no significant increase in respiratory system cancer among the manufacturing cohorts, and therefore, there is even less risk for installers (Maxim et al. 2003a).

The concentration of respirable (defined in this study as having diameters $\leq$3 μm) refractory ceramic fibers in personal air samples in seven manufacturing plants located in France, the United Kingdom, and Germany ranged from about 0.2 to 1.0 fiber/cc as determined by PCM (Trethowan et al. 1995). The levels of respirable airborne refractory ceramic fibers were studied by PCM at five manufacturing plants located in the United States over a 6-year period to assess differences in exposure levels during different work shifts in the plants (Hall et al. 1997). The geometric mean TWA exposure for all shifts at these five plants ranged from 0.080 to 0.35 fiber/cc, and little differences were observed in the level of exposure and which shift the measurements were obtained. Based on a 2-year survey of occupational exposure to refractory ceramic fibers in the United Kingdom, some typical exposure levels categorized by process

## Table 6-4. Exposures to Synthetic Vitreous Fibers Categorized by Industrial Sector[a]

| Industrial sector | Samples | Mean (f/cc) | Standard deviation | Median | Range |
|---|---|---|---|---|---|
| Glass wool manufacturing | 1,648 | 0.23 | 0.53 | 0.03 | 0.01–4.63 |
| Glass wool fabrication | 475 | 0.28 | 0.49 | 0.10 | 0.01–3.80 |
| Glass wool installation | 344 | 0.38 | 0.73 | 0.16 | 0.01–7.49 |
| Glass wool retrofit/removal | 6 | 0.26 | 0.26 | 0.21 | 0.03–0.74 |
| All glass wool | 2,473 | 0.26 | 0.55 | 0.05 | 0.01–7.49 |
| Mineral wool manufacturing | 429 | 0.20 | 0.19 | 0.15 | 0.01–1.41 |
| Mineral wool installation | 74 | 0.15 | 0.17 | 0.09 | 0.02–0.82 |
| Mineral wool retrofit/removal | 2 | 0.10 | 0.01 | 0.10 | 0.10–0.11 |
| All mineral wool | 505 | 0.19 | 0.19 | 0.14 | 0.01–1.41 |

[a]Marchant et al. 2002. Exposures are presented as 8-hour time-weighted average (TWA) exposures.

## Table 6-5. Exposures to Synthetic Vitreous Fibers Categorized by Product Type[a]

| Product type | Samples | Mean (f/cc) | SD[b] (f/cc) | Median (f/cc) | Range (f/cc) |
|---|---|---|---|---|---|
| **Glass Wool Manufacturing** | | | | | |
| Air handling products | 12 | 0.03 | 0.03 | 0.02 | 0.01–0.13 |
| Aircraft insulation | 67 | 0.19 | 0.36 | 0.06 | 0.01–2.29 |
| Appliance insulation | 28 | 0.12 | 0.29 | 0.03 | 0.01–1.30 |
| Automotive insulation | 102 | 0.02 | 0.03 | 0.01 | 0.01–0.18 |
| Separator and filtration media | 376 | 0.80 | 0.84 | 0.51 | 0.01–4.63 |
| Blowing wool with binder | 71 | 0.04 | 0.03 | 0.03 | 0.01–0.02 |
| Blowing wool without binder | 53 | 0.11 | 0.12 | 0.08 | 0.01–0.49 |
| High-density board | 14 | 0.02 | 0.02 | 0.01 | 0.01–0.09 |
| Pipe insulation | 114 | 0.05 | 0.10 | 0.02 | 0.01–0.70 |
| Batts and blankets | 472 | 0.05 | 0.09 | 0.02 | 0.01–0.97 |
| Other[c] | 339 | 0.07 | 0.18 | 0.02 | 0.01–2.30 |
| **Glass Wool Installation** | | | | | |
| Air handling products | 11 | 0.28 | 0.34 | 0.23 | 0.02–1.23 |
| Appliance insulation | 31 | 0.08 | 0.16 | 0.02 | 0.01–0.06 |
| Automotive insulation | 17 | 0.02 | 0.02 | 0.01 | 0.01–0.05 |
| Blowing wool with binder | 19 | 0.30 | 0.30 | 0.24 | 0.04–1.13 |
| Blowing wool without binder | 133 | 0.79 | 1.02 | 0.50 | 0.01–7.49 |
| Cavity loose fill insulation | 12 | 0.15 | 0.12 | 0.11 | 0.04–0.47 |
| Pipe insulation | 28 | 0.05 | 0.05 | 0.03 | 0.01–0.19 |
| Batts and blankets | 62 | 0.17 | 0.10 | 0.16 | 0.01–0.46 |
| Other[d] | 25 | 0.05 | 0.04 | 0.02 | 0.01–0.16 |
| **Glass Wool Fabrication** | | | | | |
| Acoustical panels | 11 | 0.07 | 0.07 | 0.03 | 0.01–0.23 |
| Air handling products | 66 | 0.05 | 0.05 | 0.03 | 0.01–0.22 |
| Appliance insulation | 37 | 0.14 | 0.15 | 0.10 | 0.01–0.65 |
| Automotive insulation | 19 | 0.05 | 0.04 | 0.03 | 0.01–0.10 |
| Battery separator media | 122 | 0.55 | 0.77 | 0.20 | 0.01–3.80 |
| Air and water filters | 146 | 0.32 | 0.41 | 0.15 | 0.01–1.90 |
| Other[e] | 74 | 0.10 | 0.10 | 0.09 | 0.01–0.64 |
| **Mineral Wool Manufacturing** | | | | | |
| Ceiling panel/tile | 412 | 0.20 | 0.19 | 0.15 | 0.01–1.41 |
| Other[f] | 17 | 0.06 | 0.04 | 0.05 | 0.01–0.15 |

## Table 6-5. Exposures to Synthetic Vitreous Fibers Categorized by Product Type[a]

| Product type | Samples | Mean (f/cc) | SD[b] (f/cc) | Median (f/cc) | Range (f/cc) |
|---|---|---|---|---|---|
| **Mineral Wool Installation** | | | | | |
| Ceiling panel/tile | 33 | 0.23 | 0.21 | 0.17 | 0.02–0.82 |
| Spray–on fireproofing | 15 | 0.08 | 0.10 | 0.05 | 0.02–0.42 |
| Insulation batts/blankets | 12 | 0.09 | 0.04 | 0.08 | 0.04–0.16 |
| Other[f] | 14 | 0.11 | 0.11 | 0.06 | 0.02–0.40 |

[a]Marchant et al. 2002. Exposures are presented as 8-hour time-weighted average (TWA) exposures.
[b]Standard deviation
[c]Includes acoustical panels and nonspecified products
[d]Includes flex duct and nonspecified products
[e]Includes aircraft and pipe insulation; batts, blankets with binder, and nonspecified products
[f]Includes air handling board, appliance insulation, blowing wool with binder, cavity loose fill insulation, pipe insulation, safing blanket, and board

## Table 6-6. Exposures to Synthetic Vitreous Fibers Categorized by Job Type[a]

| Job description | Samples | Mean (f/cc) | SD[b] (f/cc) | Median (f/cc) | Range (f/cc) |
|---|---|---|---|---|---|
| **Glass Wool Manufacturing** | | | | | |
| Scrap baler/compactor | 29 | 0.05 | 0.05 | 0.04 | 0.01–0.25 |
| Batch/binder mixer | 40 | 0.18 | 0.33 | 0.04 | 0.01–1.30 |
| Cutting/hot press mold | 109 | 0.04 | 0.12 | 0.01 | 0.01–0.88 |
| Forming | 289 | 0.11 | 0.23 | 0.02 | 0.01–2.30 |
| General laborer/maintenance | 62 | 0.11 | 0.33 | 0.02 | 0.01–2.29 |
| Packaging | 890 | 0.34 | 0.67 | 0.04 | 0.01–4.63 |
| Quality control/research | 75 | 0.18 | 0.23 | 0.09 | 0.01–1.20 |
| Sewing/laminating/assembly | 91 | 0.08 | 0.11 | 0.03 | 0.01–0.62 |
| Shipping/receiving | 53 | 0.01 | 0.01 | 0.01 | 0.01–0.06 |
| Other[c] | 10 | 0.11 | 0.20 | 0.05 | 0.01–0.66 |
| **Glass Wool Installation** | | | | | |
| Assembly | 34 | 0.04 | 0.06 | 0.02 | 0.01–0.35 |
| Feeder | 63 | 0.36 | 0.37 | 0.20 | 0.01–2.18 |
| Installer | 232 | 0.45 | 0.85 | 0.18 | 0.01–7.49 |
| Other[d] | 9 | 0.16 | 0.14 | 0.07 | 0.03–0.37 |
| **Mineral Wool Manufacturing** | | | | | |
| Supervisory | 17 | 0.13 | 0.11 | 0.10 | 0.01–0.40 |
| Forming | 162 | 0.24 | 0.22 | 0.18 | 0.01–1.41 |
| Maintenance | 79 | 0.18 | 0.16 | 0.14 | 0.01–0.79 |
| Packaging | 62 | 0.25 | 0.20 | 0.23 | 0.01–1.00 |
| Quality control | 20 | 0.21 | 0.21 | 0.16 | 0.01–0.80 |
| Shipping/receiving | 55 | 0.14 | 0.14 | 0.08 | 0.01–0.57 |
| Other[e] | 34 | 0.09 | 0.10 | 0.05 | 0.01–0.42 |
| **Mineral Wool Installation** | | | | | |
| Installers | 65 | 0.16 | 0.17 | 0.10 | 0.02–0.82 |
| Other[e] | 9 | 0.09 | 0.12 | 0.05 | 0.02–0.40 |

[a]Marchant et al. 2002. Exposures are presented as 8-hour time-weighted average (TWA) exposures.
[b]Standard deviation
[c]Includes administration and blowing wool chopper operator and nodulator.
[d]Includes cutting/sawing and maintenance.
[e]Includes assembly, cutting/sawing, vehicle driver production, warehousing, feeder, and general laborer.

description or job type were compiled (Friar and Phillips 1989). The results of this survey are summarized in Table 6-7 While high levels of exposure were estimated for certain job descriptions, it was noted that over 60% of the exposure levels fall within the 0–0.5 fiber/cc range (Friar and Phillips 1989).

The results of a comprehensive 54-month workplace monitoring study for exposure to refractory ceramic fibers in the United States have been published (Mast et al. 2000; Maxim et al. 1994). Although large differences were noted in the TWA exposures to workers performing various job functions, it was reported that of the nearly 3,000 samples obtained at facilities that process or use refractory ceramic fibers, 77% of the TWA measurements were below the industry recommended exposure guideline of 0.5 fiber/cc (Mast et al. 2000). It was also reported that approximately 84% of the samples obtained at refractory ceramic fiber producing facilities were below the recommended exposure guideline. Workers involved in the removal and installation of insulation from furnaces, as well as the finishing (use of drill presses, sanding, and sawing) of refractory ceramic fibers had the highest TWA exposures, while workers involved in mixing/forming, fiber manufacturing, product assembly, and auxiliary job categories had the lowest TWA. The TWA exposures ranged from about 0.2 fiber/cc for auxiliary and assembly workers to about 1.2 fibers/cc for workers involved in the removal of refractory ceramic fiber containing insulating material (Maxim et al. 1994). A significant decrease in the TWA exposure to workers over the period of 1990–1998 was observed as engineering controls and respirator use has improved (Mast et al. 2000).

Exposure to refractory ceramic fibers may pose an additional health hazard for workers involved in the removal of ceramic fiber insulation from high temperature industrial furnaces, since refractory ceramic fibers may be partially converted to quartz, cristobalite, and tridymite at elevated temperatures (Maxim et al. 1999). Tests performed on three refractory ceramic fiber containing insulation blankets showed that between 3 and 21% of the bulk fibers had been converted to cristobalite at temperatures in the range of 500–2,550 °F, with the majority of devitrification occurring on the surface layers of the hot face (Gantner 1986). The percentage of cristobalite in corresponding air samples ranged from 4.0 to 14.7% (Gantner 1986). No quartz or tridymite was detected. An analysis of the monitoring data led to the conclusion that personal exposure to cristobalite while removing insulation from the furnaces reached or exceeded the threshold limit value of 0.05 mg/m$^3$ in about 75% of the samples (Gantner 1986). The phase changes and devitrification process of refractory ceramic fibers that occur as a function of temperature have been discussed elsewhere (Brown et al. 1992). A study was conducted to determine the level of exposure to

## Table 6-7. Typical Exposures in the Manufacture and Use of Refractory Ceramic Fibers[a]

| Process description or job | Exposure level (fiber(s)/cc) |
|---|---|
| **Manufacture** | |
| Needle operator | 0.5 |
| Baling raw fiber | 0.4 |
| Fiber chopping | 0.8 |
| Product reeling | 0.8 |
| Bagging/chopping raw fiber | 1.2 |
| Mixing during product formation | 0.4 |
| Packing products | 0.02 |
| **Use** | |
| Wrapping refractory ceramic fiber blanket around pipe weld | 0.8 |
| Stripping and relining furnace panel | 1.2 |
| Kiln building | 1.75 |
| Handling blanket refractory ceramic fiber | 1.0 |
| Machining and ventilation control of refractory ceramic fiber fireboard | 0.6 |
| Insulation work using blanket | 1.0 |
| Handling operations; manual handling, but with little cutting or machining | 0.1 |

[a]Friar and Phillips 1989

refractory ceramic fibers during the installation and removal of insulation in 13 furnaces situated in 6 refineries and 2 chemical plants located in the United States (Cheng et al. 1992). The majority of exposures to refractory ceramic fibers were found to be low, with 8-hour TWA exposure levels of ≤0.2 fiber/cc for most of the tasks involved. However, airborne levels as high as 17 fibers/cc were observed when removing refractory ceramic fiber containing blankets inside of furnaces or when welders cut through crude oil furnace tubes when cutting away damaged metal parts while repairing a furnace (Cheng et al. 1992). Furthermore, the study found that workers who replaced worn out refractory ceramic fiber modules from the furnaces had exposure to cristobalite in dust samples ranging from 0.03 to 0.2 mg/m$^3$, with a geometric mean of 0.06 mg/m$^3$, which is above the OSHA established permissible exposure limit (PEL) of 0.05 mg/m$^3$ (Cheng et al. 1992). A more recent study conducted from 1993 to 1998 found that respirable quartz was detectable in only 14 of the 158 samples taken during the removal of insulation from industrial furnaces, respirable cristobalite was only detectable in 3 samples, and respirable tridymite was only detected in 1 sample (Maxim et al. 1999). However, the short sampling time of many of these collections led to relatively poor limits of detection due to the low volume of air collected during the analysis, and longer sampling times would likely indicate a higher percentage of detectable crystalline silica 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 Section 3.7 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children may be exposed to low levels of synthetic vitreous fibers in the same ways that adults are exposed outside the workplace. This exposure primarily occurs from inhaling low levels of synthetic

vitreous fibers from ambient and household air, or air from schools and other public buildings. 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). A study conducted by Schneider et al. (1996) attempted to evaluate the personal exposure of individuals residing in different parts of Europe to organic and inorganic fibers. It was determined that out of the four groups studied (suburban school children, rural retired persons, office workers, and taxi drivers), schoolchildren had the greatest exposure to total fiber counts. The mean concentration of total respirable fibers in the personal air samples of schoolchildren was 0.02 fiber/cc (Schneider et al. 1996). However, it was shown that the majority of respirable fibers were organic fibers and inorganic fibers other than synthetic vitreous fibers (particularly gypsum), and the level of exposure to fibers consistent with synthetic vitreous fibers was very low.

The airborne fiber concentration in kindergartens in Denmark was studied to determine if there was a correlation between respiratory problems and fiber concentrations in the schools (Rindel et al. 1987; Schneider 1986). The mean concentrations of respirable fibers in schools with ceiling boards containing synthetic vitreous fibers with water-soluble binders and resin binders were $1.1 \times 10^{-4}$ and $9.7 \times 10^{-5}$ fiber/cc, respectively. The mean concentration in kindergartens using ceiling boards that did not contain synthetic vitreous fibers was $4.1 \times 10^{-5}$ fiber/cc. It was concluded that no correlation existed between respiratory symptoms or disease and synthetic vitreous fibers exposure (Rindel et al. 1987; Schneider 1986).

Since children tend to play on carpets and floors, they may also be exposed to synthetic vitreous fibers that have been deposited on theses surfaces, but the levels are expected to be very low (Schneider et al. 1990).

## 6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The people most likely to have high exposure to synthetic vitreous fibers are workers who come into contact with products containing these fibers while on the job. This includes people involved in the manufacture of synthetic vitreous fiber-containing products, and also people who install, service, remove,

or use these products. Workers engaged in the demolition of buildings with synthetic vitreous fiber-containing materials are also potentially exposed. Workers involved in the installation or servicing of furnaces that contain refractory ceramic fiber insulation may also be exposed to quartz, cristobalite, and tridymite. Workers may also carry home deposited synthetic vitreous fibers from their clothing or in their hair, resulting in exposure of family members; however, this is not likely to be of concern at the present.

Lung tissue samples were obtained from the autopsies of 145 former employees of 17 synthetic vitreous fiber plants located in the United States (McDonald et al. 1990). Levels of total fibers were approximately 60% greater in workers than in people who were not occupationally exposed, but the majority of detectable fibers were not synthetic vitreous fibers. While certain fibers were classified as synthetic vitreous fibers, no further identification as to exact type of synthetic vitreous fibers was possible. Furthermore, only four individuals that were occupationally exposed had synthetic vitreous fibers lung concentrations >0.2 fiber/μg lung tissue (one worker had a concentration of 1 fiber/μg), the rest had concentrations below 0.2 fiber/μg (McDonald et al. 1990). The geometric mean fiber length, fiber diameter, and aspect ratio were 7.5 μm, 1.0 μm, and 8.0, respectively, for those occupationally exposed, while the values for the referents were 6.6 μm, 1.2 μm, and 6.1, respectively. Autopsy reports indicated that synthetic vitreous fibers were not detected in the lung tissue of one female and eight male subjects who were employed in glass wool production plants for at least 1 year between 1946 and 1978 (Gibbs et al. 1996). These findings suggest that glass wool and other types of synthetic vitreous fibers do not have a prolonged durability in human lung tissue.

Although data are scarce, current monitoring data do not support the assumption that persons residing near plants where synthetic vitreous fibers are produced will be exposed to higher levels of these fibers in the ambient air than persons who reside distal from such plants (Switala et al. 1994). It is noted that in 1990, the EPA intended to regulate all synthetic vitreous fibers under the Clean Air Act, but instead chose to list only those mineral fibers having an average diameter less than 1 μm, following an industry-funded study, which showed that emissions of such fibers from synthetic vitreous fiber producing facilities were insignificant (EPA 1992).

## 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 synthetic vitreous fibers is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of synthetic vitreous fibers.

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 synthetic vitreous fibers are generally well characterized (see Chapter 4), and there does not appear to be a need for further research in this area. However, continuing characterization of new fibers, particularly the physical dimensions of the fibers and products, will be necessary as they are produced.

**Production, Import/Export, Use, Release, and Disposal.** Data regarding the import and export volumes of glass fibers, refractory ceramic goods, and mineral wool exist (USDOC 2002). Although some production volume data are available for synthetic vitreous fibers (GMIC 2002; Mast et al. 2000), more recent data would be useful. There is also a data need to have an estimate of the annual amount of synthetic vitreous fiber containing material that is either disposed of at landfills or incinerated at hazardous waste incinerators. Synthetic vitreous fibers are primarily used for insulation purposes and reinforcing other materials (IARC 1988, 2002; WHO 1988).

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 offsite transfer information to the EPA. TRI, which contains this information for 2001, became available in 2003. This database is updated yearly and provides a list of industrial facilities producing, processing, and using friable asbestos and their emissions.

**Environmental Fate.** Synthetic vitreous fibers are fundamentally inert and are not considered to undergo transport or degradative processes in the environment analogous to organic pollutants (WHO 1988). 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 that apply to all particulate matter, and these processes are reasonably well understood (WHO 1988).

**Bioavailability from Environmental Media.** Synthetic vitreous fibers are generally insoluble and are not absorbed following dermal exposure. Most exposures occur to fibers in air, so the effect of matrices such as soil or food is 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 whether this is biologically significant would be helpful.

**Food Chain Bioaccumulation.** No data were located on synthetic vitreous fiber 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. No data needs have been identified at this time.

**Exposure Levels in Environmental Media.** Data exist regarding the levels of synthetic vitreous fibers in ambient air (Balzer et al. 1971; NIOSH 1976; Switala et al. 1994) and indoor air (Gantner 1986; Jacob et al. 1992, 1993; Schneider et al. 1990; Trethowan et al. 1995). Generally, these levels are very low, with the exception of indoor air concentrations when insulating material is being installed (Jacob et al. 1993). No data exist regarding the levels of synthetic vitreous fibers in other environmental media such as water or soil. It would be useful to have airborne measurements of synthetic vitreous fibers near municipal landfills where construction material containing synthetic vitreous fibers are often discarded. Airborne levels in the vicinity of waste incinerators where synthetic vitreous fiber containing material may be burned would also be useful.

**Exposure Levels in Humans.** The general population is exposed to low levels of synthetic vitreous fibers from ambient and indoor air (Balzer et al. 1971; Gantner 1986; Jacob et al. 1992, 1993; NIOSH 1976; Switala et al. 1994). Occupational exposure is several orders of magnitude greater than exposure to

the general population (Esmen and Erdal 1990). There are few data regarding the levels of synthetic vitreous fibers in human tissue due to the difficulty in analyzing for these substances (Dumortier et al. 2001; McDonald et al. 1990; Roggli 1989; Schneider and Stockholm 1981). Body burden data, particularly for workers frequently exposed to synthetic vitreous fibers occupationally, would be useful to better evaluate human exposure.

**Exposures of Children.** No data exist regarding the levels of synthetic vitreous fibers in children. It was shown that exposure of children residing in Europe to synthetic vitreous fibers is significantly lower than exposure to organic and other inorganic fibers (Schneider et al. 1996). Other studies have indicated that there is no correlation between respiratory problems in children and synthetic vitreous fibers concentrations in schools (Rindel et al. 1987; Schneider 1986). Children may be exposed to these substances in the same ways that adults are exposed outside the workplace, from synthetic vitreous fibers in the air. Just as children are exposed to synthetic vitreous fibers in the same way as non-occupationally exposed adults, there are no childhood-specific means to decrease exposure. Because childhood exposure to synthetic vitreous fibers is considered low and it is difficult to analyze for synthetic vitreous fibers in humans, there is no data need to conduct body burden studies at this time.

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 synthetic vitreous fibers were located. These substances are not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. These substances 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 synthetic vitreous fibers.

### 6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2002) 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.

A light-scattering-based optical sensor is being developed for the online analysis of fiber diameters during the manufacturing and production process of fiberglass, by Mission Research Corporation, Santa Barbara, California. Such a sensor will allow for the rapid measurement of fiber diameters and allow for improved production efficiency and control (FEDRIP 2002). The Vortec Corporation (J.G. Hnat, principal investigator) is developing an advanced coal-fired incinerator/glass melter as a means of eliminating the solid/hazardous waste disposal problems associated with the production of insulation products and enabling glass manufacturers to use an abundant and inexpensive fuel.

# 7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring synthetic vitreous fibers, its metabolites, and other biomarkers of exposure and effect to synthetic vitreous fibers. 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, synthetic vitreous fibers are not a single chemical entity, but rather a group of amorphous polysilicates. Because the toxicity of fibrous particles appears to be related primarily to fiber size and chemical durability, modern analytical methods focus on providing information on these parameters, as well as on total number of fibers. 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. A complicating factor in the analysis of synthetic vitreous fibers is distinguishing small fibrous particles from asbestos or other inorganic fibers, and identifying and quantifying the various forms of synthetic vitreous fibers. NIOSH methods for determining fiber concentrations are geared to counting fibers of certain dimensions utilizing detailed rules as to how to count different objects (e.g., objects with split ends or attached particles) (NIOSH 1994a).

***Light Microscopic Methods.*** Phase contrast microscopy (PCM) is most frequently employed to measure the levels of synthetic vitreous fibers. Currently, the standard method for the determination of airborne fibrous particles in the workplace is NIOSH Method 7400, Asbestos and Other Fibers by Phase Contrast Microscopy (NIOSH 1994a). In NIOSH Method 7400, samples are collected on 25 mm cellulose ester filters (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. Different counting rules may be employed when analyzing for synthetic vitreous fibers as compared to asbestos (termed counting rules A and B,

respectively), and these different counting rules often make comparing data from various studies difficult. The details of these counting rules are available in the NIOSH Manual of Analytical Methods (1994). Briefly, when using counting rules B, only fibers <3 μm in diameter and >5 μm in length with aspect ratios of ≥5:1 are counted. The rules further specify the counting of fiber ends only, with sufficient fields to yield at least 200 fiber ends. The counting of fibers in a minimum of 20 fields is also required for statistical validity. When using counting rules A, fibers with diameters >3 μm may be counted as well as fibers possessing an aspect ratio of ≥3:1. A recent study has concluded that using the A counting rules generally gives higher fiber counts than the B counting rules when analyzing the same samples (Breysse et al. 1999). Another recent study recommends using counting rules A in order to decrease the number of non-detects when analyzing for synthetic vitreous fibers on contact surfaces such as desks, floors, bookshelves, etc. inside of office buildings (Vallerino et al. 2003). Fiber concentrations in air are usually reported as fibers/mL or fibers/cc, although fibers/$m^3$ or fibers/L are occasionally employed. Fiber densities are used to quantify the amount of synthetic vitreous fibers on the surface of objects; these units are usually given in fibers/$mm^2$ (Vallerino et al. 2003).

Although the PCM method is relatively fast and inexpensive, it does not specifically distinguish between the various forms of synthetic vitreous fibers, and it not sensitive to enough to detect fibers possessing very small diameters. The resolution of a microscope (the ability to distinguish between two very closely spaced objects) is limited by the wavelength of light used for analysis and the numerical aperture of the microscope (Hecht 1989). Because PCM uses visible light of approximately 400–700 nm, the maximum resolution than can be achieved is about 0.25 μm. Frequently, synthetic vitreous fibers can be distinguished from other fibers, like asbestos, based upon their morphology (Switala et al. 1994). Glass fibers have clean, well defined, mostly parallel sides, while other fibers such as asbestos usually have irregular sides or hair-like appendages emanating from the sides (Switala et al. 1994). The ends of glass fibers have three distinctive features that can be useful in their identification: (1) The edges possess a clean break that occurs transverse to the fiber length; (2) the ends exhibit a notch-type break; and (3) the ends will taper similar to that of a sharpened pencil. Other materials will fan or fry, and therefore, the morphology of glass fibers is often distinctive from that of other fiber types. When morphology alone cannot distinguish between synthetic vitreous fibers and other fibers, or greater sensitivity is required, other microscopic techniques may be employed to augment the analysis.

Since synthetic vitreous fibers are amorphous substances, polarized light microscopy is often employed to distinguish synthetic vitreous fibers from natural minerals with a crystalline structure. In this technique,

linear polarized radiation is used to illuminate the sample and a second polarizer placed after the sample is used to analyze the light that is transmitted as the sample is rotated in various spatial directions (NIOSH Method 9002). Amorphous samples like synthetic vitreous fibers have the same refractive index in each direction, while anisotropic materials such as asbestos have optical properties that vary with the orientation of incident light with the crystallographic axes, and demonstrate a range of refractive indices depending both on the propagation direction of light through the substance and on the vibrational plane coordinates.

If improved resolution is required to analyze fibrous samples, transmission electron microscopy (TEM) (NIOSH Method 7402) or scanning electron microscopy (SEM) are often employed. Fibers with diameters as small as 0.05 and 0.005 μm can be counted by SEM and TEM methods, respectively. In the TEM experiment, the wavelength of a 100 KeV electron is 0.0037 nm, which is about 143,000 times smaller than the wavelength of light used in PCM. Hence, using electrons for analysis rather than visible light photons leads to much better resolution than can be achieved with light microscopy. Identification techniques such as energy-dispersive x-ray analysis (EDXA) can be used with SEM and TEM to identify fibers on the basis of elemental composition (Spurny 1994). Because EDXA only identifies the elemental composition of the fibers, it can only distinguish between organic and inorganic fibers, as well as things such as silicate or nonsilicate type fibers. In the TEM experiment, it is also possible to measure the diffraction of electrons by crystalline structures that are traversed by the electron beam. This technique can be useful to distinguish between crystalline structures and amorphous fibers like synthetic vitreous fibers.

Methods for preparing biological and environmental samples for microscopy are described below.

## 7.1 BIOLOGICAL MATERIALS

The analysis of fibers in biological samples involves digesting the biological material in a strong base (e.g., potassium hydroxide) or a powerful oxidant (e.g., hypochlorite). The insoluble residue (including the fibrous portion) 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.

Methods for sampling fibrous particles in biological tissue are not standardized and it is often difficult to compare results of one laboratory with another (WHO 1988). There is also evidence that indicates that digestion of biological materials with potassium hydroxide or sodium hypochlorite can cause substantial loss of synthetic vitreous fibers in the samples (McDonald et al. 1990). A review on the methods of sampling, analysis, and identification of fibers in lung tissue has been published (Davis et al. 1986). It was concluded that low temperature ashing in the presence of nascent oxygen is a superior extraction method than chemical digestion alone (Davis et al. 1986). A method for the sampling and identification of nonrespirable fibers in the eyes of workers frequently exposed to synthetic vitreous fibers has been published (Schneider and Stockholm 1981). In this procedure, mucous threads and dried mucous samples were ashed in a low temperature asher and examined by PCM. A correlation was reported between synthetic vitreous fibers levels in the eyes and total dust samples in the workplace. The techniques used to analyze synthetic vitreous fibers in biological samples are summarized in Table 7-1.

## 7.2 ENVIRONMENTAL SAMPLES

For the analysis of 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. Two types of filters are commonly employed for air sample collection, cellulose ester membrane filters (MF) and polycarbonate (Nuclepore) filters (NPF) (Spurny 1994). The NPF is a surface filter that retains fibers on the exterior of the filter, while the MF is a spongy depth type filter. The sensitivity of the methods depends on the volume of air drawn through the filter, the filtration procedure, and the microscopic method employed. Filtration studies have shown that an MF with pore size of 0.8 μm and an NPF with a pore size of 0.4 μm are capable of collecting most fibers in the workplace (Spurny 1994). Air samples obtained using NPFs can be applied directly for SEM or EDXA analysis without further preparation; however, specimen preparation for TEM analysis is more complex. In the workplace, where PCM is the standard method, the working range of countable fibers for a short-term sample (15 minutes) is around 0.5–0.04 fiber/cc, but may be reduced to 0.001 fiber/cc using an 8-hour sample because a larger volume of air is collected (NIOSH 1976). Improvements in filter preparation procedures now allow for viewing at higher magnification (1,250x), resulting in a several-fold improvement in sensitivity for these fibers (Pang et al. 1989). Recently, detection limits of $1x10^{-5}$ f/cc have been obtained using a 12-hour sampling procedure (Switala et al. 1994). It is important to keep in mind that only fibers with diameters >0.25 μm can be counted by PCM, while fibers with diameters as small as 0.05 and 0.005 μm can be

## Table 7-1. Analytical Methods for Determining Synthetic Vitreous Fibers in Biological Samples

| Sample matrix | Preparation method | Analytical method | Sample detection limit | Percent recovery | Reference |
|---|---|---|---|---|---|
| Broncho-alveolar fluid | Digestion with sodium hypochlorite; membrane filter; dry | PCM | No data | No data | Spurny 1994 |
| Urine | Membrane filtration followed by ashing and dispersion in 1% acetic acid followed by nuclepore filtration (0.1 µm) | TEM | No data | No data | Spurny 1994 |
| Eye mucous | Low temperature ashing | PCM | No data | No data | Schneider and Stockholm 1981 |
| Lung tissue | Low temperature ashing in a plasma asher; filtration with 0.2 µm nuclepore | TEM | 0.04 µm (diameter) 0.09 µm (length) | No data | McDonald et al. 1990 |

PCM = phase contrast microscopy; TEM = transmission electron microscopy

counted by SEM and TEM methods, respectively (WHO 1988). The techniques used to analyze synthetic vitreous fibers in air samples are summarized in Table 7-2.

While no methods were located for the analysis of synthetic vitreous fibers in water, TEM-based methods exist that can quantify asbestos concentrations in water samples, and these methods should also be applicable toward the measurement of synthetic vitreous fibers (Brackett et al. 1992; Melton et al. 1978). No methods were located for the analysis of asbestos or synthetic vitreous fibers 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 synthetic vitreous fibers is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of synthetic vitreous fibers.

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

### 7.3.1 Identification of Data Needs

**Methods for Determining Biomarkers of Exposure and Effect.** Standardized techniques to evaluate the levels of synthetic vitreous fibers in biological tissues do not exist. In general, biological tissues are subject to digestion with a strong base or oxidizing agent, followed by ashing. The tissue is then analyzed by microscopic examination. A method for the sampling and identification of nonrespirable fibers in the eyes of workers frequently exposed to synthetic vitreous fibers has been published (Schneider and Stockholm 1981). A data need exists to develop reliable methods to analyze for synthetic vitreous fibers in human tissue.

## Table 7-2. Analytical Methods for Determining Synthetic Vitreous Fibers in Environmental Samples

| Sample matrix | Preparation method | Analytical method | Sample detection limit[a] | Percent recovery | Reference |
|---|---|---|---|---|---|
| Air | Pump air through filter membrane; convert to optically transparent gel | PCM | 0.01 f/cc | ±35 | ASTM 1988 |
| Air | Filter with 0.45–1.2 µm cellulose ester membrane filter | NIOSH 7400; PCM | 0.003 f/cc | No data | Jacob et al. 1993; NIOSH 1994a |
| Air | Filter with 0.45–1.2 µm cellulose ester membrane filter | PCM; polarized light microscopy | $1x10^{-5}$ f/cc | No data | Switala et al. 1994 |
| Air | Filter with 0.45–1.2 µm cellulose ester membrane filter | NIOSH 7402; TEM | 0.001 f/cc | No data | NIOSH 1994a; Spurny 1994 |
| Surfaces | Collect samples using 12.56 or 50.24 $mm^2$ finger-print lifters; transfer to microscope slide | NIOSH 7400 | 0.06–0.24 f/$mm^2$ | No data | Vallarino et al. 2003 |

[a]Sample detection limits in air are a function of the volume of air collected and thus the sampling time. Detection limits on the surface of an object are a function of the number of fibers collected per unit area.

f/cc = fibers per cubic centimeter; NIOSH = National Institute for Occupational Safety and Health; PCM = phase contrast microscopy; TEM = transmission electron microscopy

***Exposure.*** Uncoated or coated fibers in bronchoalveolar lavage fluid samples or in autopsied or surgically resected lung tissue samples are the principal biomarkers of exposure to biopersistent asbestos fibers (Agency for Toxic Substances and Disease Registry 2001).[1] However, similar biomarkers to identify or quantify human exposure to synthetic vitreous fibers, which are less biopersistent than asbestos fibers, have not been developed for routine clinical use. Nevertheless, aluminum-silicate fibers with chemical compositions consistent with synthetic vitreous fibers have been detected in human lung tissues (McDonald et al. 1990; Roggli 1989; Sébastien et al. 1994) and in bronchoalveolar lavage samples (Dumortier et al. 2001).

Among 1,800 bronchoalveolar samples submitted to a Belgium hospital between 1992 and 1997 for fiber analysis, pseudoasbestos bodies were detected in samples from nine patients (0.5%) (Dumortier et al. 2001). In samples from these nine patients (all of whom had occupational experience with furnaces or welding), fibers of composition consistent with refractory ceramic fiber composition were detected in 42% of core fibers analyzed (Dumortier et al. 2001). Other nonasbestos fibers and asbestos fibers accounted for 28% and 30% of the core fibers analyzed in these samples.

***Effect.*** Epidemiological studies of synthetic vitreous fiber manufacturing workers have not found consistent evidence for increased risks of malignant or nonmalignant respiratory or pleural effects, but results from animal experiments indicate that repeated inhalation exposure to synthetic vitreous fibers may result in pulmonary or pleural fibrosis, lung cancer, or mesothelioma, depending on fiber dimensions, fiber durability in the lung, duration of exposure, and exposure levels.

The chest x-ray is the most common means of detecting the onset of pleural or pulmonary changes that may precede or accompany fibrosis (i.e., irreversible scarring of lung or pleural tissue that can lead to restricted breathing). The International Labour Office (ILO) established a classification system for profusion of opacities in chest x-rays 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). The American Thoracic Society (1986) recommends that chest x-rays be scored for pleural and pulmonary changes separately because of the experience with asbestos-exposed workers indicating that pleural and pulmonary fibrosis have differences in "epidemiology, clinical features, and prognosis." Lung function

[1] Particles or fibers that are deposited in the lung and are too large to be phagocytized by alveolar macrophages may become coated with an iron-rich protein coat. The generic term for these structures is ferruginous bodies. When the core fiber is asbestos, the resultant structure is termed an asbestos body (Agency for Toxic Substances and Disease Registry 2001). Ferruginous bodies having the appearance of asbestos bodies under light microscopy and a nonasbestos core fiber have been termed pseudoasbestos bodies (Dumortier et al. 2001).

tests are also useful to characterize the development of pulmonary or pleural fibrosis; forced vital capacity is diminished with increasing severity of pulmonary or pleural fibrosis.

Development of sensitive and specific chemical or biochemical tests for synthetic vitreous fibers effects would be useful.

**Methods for Determining Parent Compounds and Degradation Products in Environmental Media.** Methods are available to measure synthetic vitreous fibers in air (Jacob et al. 1993; NIOSH 1994a; Spurny 1994; Switala et al. 1994). These methods are precise, and are sensitive enough to detect levels that are frequently encountered in both occupational and non-occupational settings. No specific methods of measuring the levels of synthetic vitreous fibers in other environmental media such as soil, water, and sediment exist. Since exposure to synthetic vitreous fibers primarily occurs through inhaling air, no data need has been identified at this time.

### 7.3.2 Ongoing Studies

No data were found regarding ongoing studies involving analytical methods for the detection of synthetic vitreous fibers.

# 8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding synthetic vitreous fibers in air, water, and other media are summarized in Table 8-1.

The U.S. Department of Health and Human Services, National Toxicology Program (NTP 1998, 2000, 2002) classified glass wool (respirable size) as *reasonably anticipated to be a human carcinogen*, based on sufficient evidence of carcinogenicity in experimental animals. This assessment was originally prepared in 1993–1994 for the *7th Report on Carcinogens* (NTP 1994), but has not been updated since then in the *8th, 9th, or 10th Reports on Carcinogens* (NTP 1998, 2000, 2002). Continuous filament glass, rock wool, slag wool, or refractory ceramic fibers were not listed or assessed for carcinogenicity in the *7th, 8th, 9th, or 10th Report on Carcinogens* (NTP 1994, 1998, 2000, 2002).

The International Agency for Research on Cancer (IARC 2002) concluded that epidemiologic studies published since the previous IARC (1988) assessment provided no evidence of increased risks of lung cancer or of mesothelioma from occupational exposure during the manufacture of man-made vitreous fibers and inadequate evidence overall of any excess cancer risk. IARC (2002) concluded that there was (1) sufficient evidence in experimental animals for the carcinogenicity of certain special purpose glass fibers and of refractory ceramic fibers; (2) limited evidence in experimental animals for the carcinogenicity of insulation glass wool, rock (stone) wool, and slag wool; and (3) inadequate evidence in experimental animals for the carcinogenicity of continuous glass filament and certain newly developed, less biopersistent fibers such as X-607 and MMVF34. Insulation glass wool, rock (stone) wool, slag wool, and continuous filament glass were classified in Group 3, not classifiable as to carcinogenicity to humans because of the inadequate evidence of carcinogenicity in humans and the relatively low biopersistence of these materials. In contrast, refractory ceramic fibers and certain special-purpose glass fibers (104 E-glass and 475 glass fibers) not used as insulating materials were classified in Group 2B, possibly carcinogenic to humans, because of their relatively high biopersistence.

The U.S. EPA Integrated Risk Information System (IRIS) (2004) has not classified the potential carcinogenicity of glass wool, continuous filament glass, rock wool, or slag wool, but assigned refractory ceramic fibers to Group B2, probable human carcinogen, based on no data on carcinogenicity in humans and sufficient evidence of carcinogenicity in animal studies. Currently, EPA is developing a cancer

## Table 8-1. Regulations and Guidelines Applicable to Synthetic Vitreous Fibers

| Agency | Description | Information | References |
|---|---|---|---|
| INTERNATIONAL | | | |
| Guidelines: | | | |
| IARC | Carcinogenicity classification | | |
| | Insulation glass wool, rock (stone) wool, slag wool, and continuous filament glass | Group 3[a] | IARC 2002 |
| | Refractory ceramic fibers and certain special-purpose glass wools not used as insulating materials | Group 2B[b] | IARC 2002 |
| NATIONAL | | | |
| Regulations and Guidelines: | | | |
| a. Air | | | |
| ACGIH | TLV (8-hour TWA) | | |
| | Synthetic vitreous fibers | | ACGIH 2001 |
| | Continuous filament glass fibers, glass wool fibers, rock wool fibers, slag wool fibers, special purpose glass fibers | 1.0 fibers/cc[c] | |
| | Continuous filament glass (inhalable fraction) | 5 mg/m$^3$ | |
| | Refractory ceramic fibers | 0.2 fibers/cc[c] | |
| NIOSH | REL (10-hour TWA) | | |
| | Fibrous glass dust (fiber glas®, fiberglass, glass fibers, and glass wool); fibers ≤3.5 µm in diameter and ≥10 µm in length) | 3 fibers/cc | NIOSH 1992 |
| | Total fibrous glass dust | 5 mg/m$^3$ | |
| | Refractory ceramic fibers | No data | NIOSH 1992 |
| OSHA | PEL (8-hour TWA) | | |
| | Fiberglass and mineral wool (glass wool, rock wool, and slag wool) | 1.0 fiber/cc *voluntary* | OSHA 1999 |
| | Synthetic vitreous fibers as an inert or nuisance dust | | OSHA 2001b |
| | Respirable fraction | 5 mg/m$^3$ | |
| | Total dust | 15 mg/m$^3$ | |
| b. Water | No data | | |
| c. Food | No data | | |
| d. Other | | | |
| ACGIH | Carcinogenicity classification | | |
| | Synthetic vitreous fibers | | ACGIH 2001 |
| | Continuous filament glass fibers (respirable fibers and inhalable fraction) | Group A4[d] | |

## Table 8-1. Regulations and Guidelines Applicable to Synthetic Vitreous Fibers

| Agency | Description | Information | References |
|---|---|---|---|
| NATIONAL *(cont.)* | | | |
| ACGIH | Glass wool fibers, rock wool fibers, slag wool fibers, and special purpose glass fibers | Group A3[e] | |
| | Refractory ceramic fibers | Group A2[f] | |
| EPA | Carcinogenicity classification | | |
| | Glass wool, continuous filament glass, rock wool, and slag wool | No data | IRIS 2002 |
| | Refractory ceramic fibers | Group B2[g] | IRIS 2002 |
| | Inhalation unit risk | No data | |
| | Oral slope factor | No data | |
| NTP | Carcinogenicity classification | | |
| | Glass wool (respirable size) | Reasonably anticipated to be a human carcinogen | NTP 2002 |
| | Continuous filament glass, rock wool, slag wool, and refractory ceramic fibers | No data[h] | NTP 2002 |
| STATE | | | |
| Regulations and Guidelines: | | | |
| a. Air | | No data | |
| b. Water | | No data | |
| c. Food | | No data | |
| d. Other | | No data | |

[a]Group 3: not classifiable as to carcinogenicity to humans, based on inadequate evidence of carcinogenicity in humans and inadequate or limited evidence in experimental animals
[b]Group 2B: possibly carcinogenic to humans, based on limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals
[c]Respirable fibers: length >5 µm; aspect ratio ≥3:1, as determined by the membrane filter method at 400–450X magnification (4-mm objective), using phase-contrast illumination.
[d]Group A4: not classifiable as a human carcinogen
[e]Group A3: confirmed animal carcinogen with unknown relevance to humans
[f]Group A2: suspected human carcinogen, based on limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals with relevance to humans
[g]Group B2: probable human carcinogen, based on sufficient evidence of carcinogenicity in animals
[h]Not listed or assessed in the 9th Report on Carcinogens (NTP 2001)

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; 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; TWA = time-weighted average

assessment for refractory ceramic fibers based on recent multiple-exposure chronic inhalation animal bioassays. The assessment is considering the development of quantitative inhalation unit risk estimates for refractory ceramic fibers based on the animal tumorigenic responses, but, as of February 2004, the assessment was not completed.

In 1999, a Health and Safety Partnership Program was established as a voluntary workplace safety program for workers involved in the manufacture, fabrication, installation, and removal of glass wool, rock wool, and slag wool products (Marchant et al. 2002; OSHA 1999). The program was established as a result of negotiations between OSHA, the North American Insulation Manufacturers Association, the National Insulation Association, and the Insulation Contractors Association of America. The program established a voluntary eight-hour time-weighted average (TWA) permissible exposure limit (PEL) of 1 respirable fiber/cc. Respirable fibers are counted as particles with length >5 μm, diameter <3 μm, and aspect ratio ≥3:1. The agreement specifies that when the PEL is exceeded in a workplace (such as when insulation is blown into attics or removed), workers will wear NIOSH certified dust respirators.

# 9. REFERENCES

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(1):91-99.

ACGIH. 1992. Fibrous glass dust. American Conference of Government Industrial Hygienists. Cincinnati, OH.

ACGIH. 1998. Asbestos, all forms. American Conference of Government Industrial Hygienists. Cincinnati, OH.

*ACGIH. 2001. Synthetic vitreous fibers. Supplement to documentation of the threshold limit values and biological exposure indices. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

Adachi S, Kawamura K, Takemoto K. 2001. A trial on the quantitative risk assessment of man-made mineral fibers by the rat intraperitoneal administration assay using the JFM standard fibrous samples. Ind Health 39(2):168-174.

*Adachi S, Takemoto K, Kimura K. 1991. Tumorigenicity of fine man-made fibers after intratracheal administrations to hamsters. Environ Res 54(1):52-73.

*Adamson IYR, Bakowska J, Bowden DH. 1994. Mesothelial cell proliferation: A nonspecific response to lung injury associated with fibrosis. Am J Respir Cell Mol Biol 10:253-258.

*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.

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

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

*Agency for Toxic Substances and Disease Registry. 2001. Toxicological profile for asbestos (Update). Department of Health and Human Services, Atlanta, GA.

Alam W. 1998. Manufactured mineral fibers. In: Hamilton & Hardy's industrial toxicology. St Louis: Mosby Publishers, 571-573.

*Cited in text

## 9. REFERENCES

*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.

Alexander IC, Brown RC, Jubb GA, et al. 1994. Durability of ceramic and novel man-made mineral fibers. Environ Health Perspect 102:67-71.

*Altman PL, Dittmer DS. 1974. Biological handbooks: Biology data book. Vol. III. 2nd ed. Bethesda, MD: Federation of American Societies for Experimental Biology, 1987-2008, 2041.

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

*Andersen A, Langmark F. 1986. Incidence of cancer in the mineral-wool producing industry in Norway. Scand J Work Environ Health 12:72-77.

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

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

Antonsson A-B, Runmark S. 1987. Airborne fibrous glass and dust originating from worked reinforced plastics. Am Ind Hyg Assoc J 48(8):684-687.

Ares J. 1990. Exposure to non-asbestos refractory materials: Corrections to fiber counts for comparable risk assessment. Bull Environ Contam Toxicol 45:783-788.

*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.

Aufderheide M, Riebe-Imre M, Straub M, et al. 1994a. Cellular effects of mineral fibers. In: Dungworth DL, Mauderly JL, Oberdorster G, eds. Toxic and carcinogenic effects of solid particles in the respiratory tract. Washington, DC: ILSI Press, 575-580.

Aufderheide M, Riebe-Imre M, Straub M, et al. 1994b. Differences in the biological effects of crocidolite asbestos and two glass fibres on epithelial lung cells. Exp Toxicol Pathol 45(8):467-472.

Balzer JL. 1976. Environmental data; Airborne concentrations found in various operations. Occupational exposure to fibrous glass. Proceedings of a symposium sponsored by NIOSH, April 1976.

*Balzer JL, Cooper WC, Fowler DP. 1971. Fibrous glass-lined air transmission systems: An assessment of their environmental effects. Am Ind Hyg Assoc J 32:512-518.

*Barchowsky A, Lannon BM, Elmore LC, et al. 1997. Increased focal adhesion kinase- and urokinase-type plasminogen activator receptor-associated cell signaling in endothelial cells exposed to asbestos. Environ Health Perspect 105:1131-1137.

## 9. REFERENCES

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

Baron PA. 1996. Application of the thoracic sampling definition to fiber measurement. Am Ind Hyg Assoc J 57(9):820-824.

Baron PA. 2001. Measurement of airborne fibers: A review. Ind Health 39:39-50.

*Bayliss DL, Dement JM, Wagoner JK, et al. 1976. Mortality patterns among fibrous glass production workers. Ann N Y Acad Sci 271:324-335.

Beck EG, Holt PF, Manojlovic N. 1972. Comparison of effects on macrophage cultures of glass fibre, glass powder, and chrysotile asbestos. Br J Ind Med 29:280-286.

Bellmann B, Konig H, Muhle H, et al. 1986. Chemical durability of asbestos and of man-made mineral fibres *in vivo*. J Aerosol Sci 17(3):341-345.

*Bellmann B, Muhle H, Creutzenberg O, et al. 2001. Effects of nonfibrous particles on ceramic fiber (RCF1) toxicity in rats. Inhal Toxicol 13(10):877-901.

Bellmann B, Muhle H, Creutzenberg O, et al. 2003. Calibration study on subchronic inhalation toxicity of man-made vitreous fibers in rats. Inhal Toxicol 15:1147-1177.

*Bellmann B, Muhle H, Kamstrup O, et al. 1994a. Investigation on the durability of man-made vitreous fibers in rat lungs. Environ Health Perspect Suppl 102(5):185-189.

*Bellmann B, Muhle H, Kamstrup O, et al. 1995. Investigation on the biodurability of chemically different stone wool fibres. Exp Toxicol Pathol 47(2-3):195-201.

*Bellmann B, Muhle H, Pott F. 1994b. Investigation of the biodurability and carcinogenicity of different man-made mineral fibres. NATO ASI Ser H 85:299-304.

*Bender JR. 1993. Pulmonary effects of exposure to fine fiberglass: Irregular opacities and small airways obstruction. Br J Ind Med 50(4):381.

Bender JR, Hadley JG. 1994. Glass fiber manufacturing and fiber safety: The producer's perspective. Environ Health Perspect 102(Suppl 6):37-40.

*Bendsoe N, Bjornberg A, Lowhagen G-B, et al. 1987. Glass fibre irritation and protective creams. Contact Dermatitis 17(2):69-72.

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

Bermudez E, Mangum JB, Moss OR, et al. 2003. Pleural dosimetry and pathobiological responses in rats and hamsters exposed subchronically to MMVF 10a fiberglass. Toxicol Sci 74:165-173.

*Bernard A, Hermans C. 1997. Biomonitoring of early effects on the kidney or the lung. Sci Total Environ 199:205-211.

9. REFERENCES

Bernstein DM. 1993. An evaluation of the use of an inhalation model versus intraperitoneal injection model for the assessment in rats of the carcinogenicity of natural and man-made vitreous fibers. Zentralbl Arbeitsmed Arbeitsshutz Prophyl Ergon 43(4):120-128.

Bernstein DM, Chevalier J, Smith P. 2003. Comparison of calidria chrysotile asbestos to pure tremolite: Inhalation biopersistence and histopathology following short-term exposure. Inhal Toxicol 15:1387-1419.

*Bernstein DM, Morscheidt C, Grimm H-G, et al. 1996. Evaluation of soluble fibers using the inhalation biopersistence model. A nine-fiber comparison. Inhal Toxicol 8:345-385.

*Bernstein DM, Morscheidt C, Tiesler H, et al. 1995. Evaluation of the biopersistence of commercial and experimental fibers following inhalation. Inhal Toxicol 7(7):1031-1058.

*Bernstein DM, Riego Sintes JM, Ersboell BK, et al. 2001b. Biopersistence of synthetic mineral fibers as a predictor of chronic inhalation toxicity in rats. Inhal Toxicol 13(10):823-849.

*Bernstein DM, Riego Sintes JM, Ersboell BK, et al. 2001a. Biopersistence of synthetic mineral fibers as a predictor of chronic intraperitoneal injection tumor response in rats. Inhal Toxicol 13(10):851-875.

Berrigan D. 2002. Respiratory cancer and exposure to man-made vitreous fibers: A systematic review. Am J Ind Med 42:354-362.

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.

*Bertazzi PA, Zocchetti C, Riboldi L, et al. 1986. Cancer mortality of an Italian cohort of workers in man-made glass-fiber production. Scand J Work Environ Health 12(1):65-71.

Bertrand R, Pezerat H. 1980. Fibrous glass: Carcinogenicity and dimensional characteristics. IARC Sci Publ 30:901-911.

Bignon J. 1983. Lung diseases and non-asbestos fibres. Eur J Respir Dis 64:397-402.

Bignon J. 1989. Mineral fibres in the non-occupational environment. In: Bignon J, Peto J, Saracci R, eds. Non-occupational exposure to mineral fibres. IARC Publication No. 90. Lyon, France.

Bignon J, Brochard P, Brown R, et al. 1995. Assessment of the toxicity of man-made fibres. A final report of a workshop held in Paris, France, 3-4, February 1994. Ann Occup Hyg 39(1):89-106.

Bignon J, Monchaux G, Chameaud J, et al. 1983. Incidence of various types of thoracic malignancy induced in rats by intrapleural injection of 2 mg of various mineral dusts after inhalation of $^{222}$Ra. Carcinogenesis 4(5):621-628.

*Bishop K, Ring SJ, Zoltai T, et al. 1985. Identification of asbestos and glass fibers in municipal sewage sludges. Bull Environ Contam Toxicol 34:301-308.

*Bjornberg A. 1985. Glass fiber dermatitis. Am J Ind Med 8(4-5):395-400.

## 9. REFERENCES

*Bjornberg A, Lowhagen G-B. 1977. Patch testing with mineral wool (rockwool). Acta Derm Venereol (Stockh) 57(3):257-260.

*Bjornberg A, Lowhagen G-B, Tengberg J-E. 1979c. Does occupational exposure to glass-fibres increase the general skin reactivity to irritants? Contact Dermatitis 5(3):175-177.

*Bjornberg A, Lowhagen G, Tengberg JE. 1979b. Relationship between intensities of skin test reactions to glass-fibres and chemical irritants. Contact Dermatitis 5(3):171-174.

*Bjornberg A, Lowhagen G-S, Tengberg JE. 1979a. Skin reactivity in workers with and without itching from occupational exposure to glass fibers. Acta Derm Venereol (Stockh) 59(1):49-54.

*Boffetta P, Andersen A, Hansen J, et al. 1999. Cancer incidence among European man-made vitreous fiber production workers. Scand J Work Environ Health 25(3):222-226.

*Boffetta P, Sali D, Kolstad H, et al. 1998. Mortality of short-term workers in two international cohorts. J Occup Environ Med 40(12):1120-1126.

*Boffetta P, Saracci R, Andersen A, et al. 1992. Lung cancer mortality among workers in the European production of man-made mineral fibers- a Poisson regression analysis. Scand J Work Environ Health 18(5):279-286.

*Boffetta P, Saracci R, Andersen A, et al. 1997. Cancer mortality among man-made vitreous fiber production workers. Epidemiology 8(3):259-268.

Bolton RE. 1983. Fibres and fibrogenesis. Eur J Respir Dis 64:403-405.

Bolton RE, Davis JMG, Donaldson K, et al. 1982. Variations in the carcinogenicity of mineral fibres. Ann Occup Hyg 26(1-4):569-582.

Borm PJA. 2002. Particle toxicology: From coal mining to nanotechnology. Inhal Toxicol 14:311-324.

Botham SK, Holt PF. 1973. Comparison of effects of glass fibre and glass powder on guinea-pig lungs. Br J Ind Med 30:232-236.

Bottin MC, Vigneron JC, Rousseau R, et al. 2003. Man-made mineral fiber hazardous properties assessment using transgenic rodents: Example of glass fiber testing. Inhal Toxicol 15:1017-1027.

*Brackett KA, Clark PJ, Millette JR. 1992. Method for the analysis of asbestos fibers in water using MCE filters. Microscope 40:159-163.

*Breysse PN, Lees PSJ, Rooney BC. 1999. Comparison of NIOSH Method 7400 A and B counting rules for assessing synthetic vitreous fiber exposures. Am Ind Hyg Assoc J 60(4):526-532.

Breysse PN, Lees PSJ, Rooney BC, et al. 2001. End-user exposures to synthetic vitreous fibers: II. Fabrication and installation fabrication of commercial products. Appl Occup Environ Hyg 16:464-470.

Brochard P, Pairon JC, Bignon J. 1994. The occupational physician's point of view: The model of man-made vitreous fibers. Environ Health Perspect 102:31-36.

## 9. REFERENCES

*Brody AR, Roe MW. 1983. Deposition pattern of inorganic particles at the alveolar level in the lungs of rats and mice. Am Rev Respir Dis 128(4):724-729.

Brown RC. 1991. Carcinogenicity of the insulation wools: Reassessment of the IARC evaluation. Regul Toxicol Pharmacol 14:12-23.

Brown RC. 2000. Influence of non-fibrous particles in the animal testing of refractory ceramic fibres. In: Rammlmair D, Mederer J, Pentinghaus H, eds. Applied mineralogy: In research, economy, technology, ecology and culture. Gottingen, Germany: Balkema Publishers.

*Brown DM, Beswick PH, Bell KS, et al. 2000. Depletion of glutathione and ascorbate in lung lining fluid by respirable fibres. Ann Occup Hyg 44(2):101-108.

*Brown DM, Beswick PH, Donaldson K. 1999. Induction of nuclear translocation of NF-*K*B in epithelial cells by respirable mineral fibres. J Pathol 189:258-264.

*Brown DM, Fisher C, Donaldson K. 1998. Free radical activity of synthetic vitreous fibers: Iron chelation inhibits hydroxyl radical generation by refractory ceramic fiber. J Toxicol Environ Health A 53(7):545-561.

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.

*Brown RC, Chamberlain M, Davies R, et al. 1979a. In vitro biological effects of glass fibers. J Environ Pathol Toxicol 2(6):1369-1383.

*Brown RC, Chamberlain M, Skidmore JW. 1979b. *In vitro* effects of man-made mineral fibres. Ann Occup Hyg 22(2):175-179.

Brown RC, Hoskins JA, Miller K, et al. 1990. Pathogenetic mechanisms of asbestos and other mineral fibres. Mol Aspects Med 11(5):325-349.

Brown RC, Poole A, Turver CJ. 1986. *In vitro* correlates of mineral dust toxicity. Food Chem Toxicol 24(6-7):535-538.

*Brown RC, Sara EA, Hoskins JA, et al. 1992. The effects of heating and devitrification on the structure and biological activity of aluminosilicate refractory ceramic fibres. Ann Occup Hyg 36(2):115-129.

*Brown RC, Sebastien P, Bellmann B, et al. 2000. Particle contamination in experimental fiber preparations. Inhal Toxicol 12(3):99-107.

*Brüske-Hohlfeld I, Moehner M, Pohlabein H, et al. 2000. Occupational lung cancer risk for men in Germany: Results from a pooled case-control study. Am J Epidemiol 151(4):384-395.

*Buchanich JM, Marsh GM, Youk AO. 2001. Historical cohort study of US man-made vitreous fiber production workers: V. Tobacco-smoking habits. J Occup Environ Med 43(9):793-802.

Bunn WB, Bender JR, Hesterberg TW, et al. 1993. Recent studies of man-made vitreous fibers. J Occup Med 35(2):101-113.

## 9. REFERENCES

Bunn WB, Versen RA, Chase GR. 1991. An update on the health effects of man-made vitreous fibers and potential fiber exposures. Tappi J June 1991:136-143.

*Burge PS, Calvert IA, Trethowan WM, et al. 1995. Are the respiratory health effects found in manufacturers of ceramic fibres due to the dust rather than the exposure to fibres? Occup Environ Med 52:105-109.

Camilucci L, Campopiano A, Casciardi S, et al. 2001. [Exposure to artificial mineral fibers in public buildings.] Med Lav 92(1):32-38. (Italian)

*Carpenter RL, Wilson CL. 1999. The inhalation toxicity of glass fibers- a review of the scientific literature. Naval Health Research Center Detachment (Toxicology) (NHRC/TD).

*Carter CM, Axten CW, Byers CD, et al. 1999. Indoor airborne fiber levels of MMVF in residential and commercial buildings. Am Ind Hyg Assoc J 60(6):794-800.

Carthew P, Edwards RE, Dorman BM, et al. 1995. Intrapleural administration of vitreous high duty ceramic fibres and heated devitrified ceramic fibres does not give rise to pleural mesothelioma in rats. Hum Exp Toxicol 14(8):657-661.

Casciardi S, Camppoiano A, Fioravanti F, et al. 2003. [An example of size characterization of synthetic vitreous fibers.] Med Lav 94:542-555. (Italian)

*Casey G. 1983. Sister-chromatid exchange and cell kinetics in CHO-K1 cells, human fibronblasts and lymphoblastoid cells exposed in vitro to asbestos and glass fibre. Mutat Res 116:369-377.

*Chamberlain M, Tarmy EM. 1977. Asbestos and glass fibres in bacterial mutation tests. Mutat Res 43:159-164.

*Cheng RT, McDermott HJ, Gia GM, et al. 1992. Exposures to refractory ceramic fiber in refineries and chemical plants. Appl Occup Environ Hyg 7(6):361-367.

Cherrie J, Dodgson J. 1986. Past exposures to airbrone fibers and other potential risk factors in the European man-made mineral fiber production industry. Scand J Work Environ Health 12:26-33.

Cherrie J, Dodgson J, Groat S, et al. 1987. Environmental surveys in the European man-made mineral fiber production. Scand J Work Environ Health 12:18-25.

*Chiazze L, Watkins DK, Fryar C. 1992. A case-control study of malignant and non-malignant respiratory disease among employees of a fiberglass manufacturing facility. Br J Ind Med 49:326-331.

*Chiazze L, Watkins DK, Fryar C, et al. 1993. A case-control study of malignant and non-malignant respiratory disease among employees of a fiberglass manufacturing facility II. Exposure assessment. Br J Ind Med 50(8):717-725.

*Chiazze L, Watkins DK, Fryar C. 1995. Adjustment for the confounding effect of cigarette smoking in an historical cohort mortality study of workers in a fiberglass manufacturing facility. J Occup Environ Med 37(6):744-748.

## 9. REFERENCES

*Chiazze L, Watkins DK, Fryar C. 1997. Historical cohort mortality study of a continuous filament fiberglass manufacturing plant. I. White men. J Occup Environ Med 39(5):432-441.

*Chiazze L, Watkins DK, Fryar C, et al. 2002. Mortality from non-malignant respiratory disease in the fibreglass manufacturing industry. Occup Environ Med 59:369-372.

*Christensen VR, Eastes W, Hamilton RD, et al. 1993. Fiber diameter distributions in typical MMVR wool insulation products. Am Ind Hyg Assoc J 54(5):232-238.

*Christensen VR, Jensen SL, Guldberg M, et al. 1994. Effect of chemical composition of man-made vitreous fibers on the rate of dissolution in vitro at different pHs. Environ Health Perspect 102:83-86.

*Churg A, Stevens B. 1995. Enhanced retention of asbestos fibers in the airways of human smokers. Am J Respir Crit Care Med 151:1409-1413.

Churg A, Warnock ML, Bensch KG. 1978. Malignant mesothelioma arising after direct application of asbestos and fiber glass to the pericardium. Am Rev Respir Dis 118(2):419-424.

*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 J, Gilks B, et al. 2000. Pathogenesis of fibrosis produced by asbestos and man-made mineral fibers: What makes a fiber fibrogenic? Inhal Toxicol 12:15-26.

Class P, Deghilage P, Brown RC. 2001. Dustiness of different high-temperature insulation wools and refractory ceramic fibres. Ann Occup Hyg 45(5):381-384.

*Claude J, Frentzel-Beyme R. 1984. A mortality study of workers employed in a German rock wool factory. Scand J Work Environ Health 10:151-157.

*Claude J, Frentzel-Beyme R. 1986. Mortality of workers in a German rock-wool factory-A second look with extended follow-up. Scand J Work Environ Health 12:53-60.

*Clausen J, Netterstrom B, Wolff C. 1993. Lung function in insulation workers. Br J Ind Med 50:252-256.

Cleland LG, Vernon-Roberts B, Smith K. 1984. Fibre glass induced synovitis. Ann Rheum Dis 43:530-534.

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

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.

Clupper DC, Gough JE, Hall MM, et al. 2003. In vitro bioactivity of S520 glass fibers and initial assessment of osteoblast attachment. J Biomed Mater Res 67A:285-294.

9. REFERENCES

*Colborn T, Clement C, eds. 1992. Chemically-induced alterations in sexual and functional development: The wildlife-human connection. In: Advances in modern environmental toxicology. Vol. XXI, Princeton, NJ: Princeton Scientific Publishing.

Collier CG, Morris KJ, Launder KA, et al. 1994. The behavior of glass fibers in the rat following intraperitoneal injection. Regul Toxicol Pharmacol 20:S89-S103.

Collier CG, Morris KJ, Launder KA, et al. 1995. The durability and distribution of glass fibres in the rat following intra-peritoneal injection. Ann Occup Hyg 39(5):699-704.

Corn M, Hammad Y, Whittier D, et al. 1976. Employee exposure in airborne fiber and total particulate matter in two mineral wool facilities. Environ Res 12:59-74.

*Cowie HA, Wild P, Beck J, et al. 2001. An epidemiological study of the respiratory health of workers in the European refractory ceramic fibre industry. Occup Environ Med 58:800-810.

Cullen RT, Miller BG, Clark S, et al. 2002. Tumorigenicity of cellulose fibers injected into the rat peritoneal cavity. Inhal Toxicol 14:685-703.

*Cullen RT, Searl A, Buchanan D, et al. 2000. Pathogenicity of a special-purpose glass microfiber (E Glass) relative to another glass microfiber and amosite asbestos. Inhal Toxicol 12(10):959-977.

Cummings KM, Hastrup JL, Streck RJ, et al. 2000a. Correspondence Re: Cummings et al., consumer perception of risk associated with filters contaminated with glass fibers. Cancer Epidemiol Biomarkers Prev 10(4):417-418.

Cummings KM, Hastrup JL, Swedrock T, et al. 2000b. Consumer perception of risk associated with filters contaminated with glass fibers. Cancer Epidemiol Biomarkers Prev 9(9):977-979.

*Dai YT, Yu CP. 1998. Alveolar deposition of fibers in rodents and humans. J Aerosol Med 11(4):247-258.

Davies R. 1980. The effect of mineral fibres on macrophages. In: Wagner JC, Davis W, eds. Biological effects of mineral fibres. IARC Scientific Publication No. 30. Lyon, France, 419-425.

Davies L, Cherrie JW. 1992. Airborne fiber concentrations in a glass continuous filament factory. Ann Occup Hyg 36(6):609-627.

Davis JMG. 1972. The fibrogenic effects of mineral dusts injected into the pleural cavity of mice. Br J Exp Pathol 53:190-201.

Davis JMG. 1986. A review of experimental evidence for the carcinogenicity of man-made vitreous fibers. Scand J Work Environ Health 12:12-17.

Davis JA, Kalinowski MR. 1989. Development of LM/SEM/TEM methods for the quantitative analysis of airborne glass fiber levels. In: Russell PE, ed. 29th annual meeting of the Microbeam Analysis Society. San Francisco, CA: San Francisco Press, Inc., 427-428.

## 9. REFERENCES

*Davis JMG, Addison RE, Bolton K, et al. 1984. The pathogenic effects of fibrous ceramic aluminum silicate glass administered to rats by inhalation and peritoneal injection. In: Biological effects of man-made mineral fibers. Proceedings of a WHO/IARC Conference, Vol. 2, Copenhagen, Denmark, April 20-22, 1982, 303-322.

*Davis JMG, Brown DM, Cullen RT, et al. 1996. A comparison if methods of determining and predicting the pathogenicity of mineral fibers. Inhal Toxicol 8(8):747-770.

*Davis JMG, Gylseth B, Morgan A. 1986. Assessment of mineral fibres from human lung tissue. Thorax 41:167-175.

Dement JM. 1975. Environmental aspects of fibrous glass production and utilization. Environ Res 9:295-312.

Denizeau F, Marion M, Chevalier G, et al. 1985. Absence of genotoxic effect of nonasbestos mineral fibers. Cell Biol Toxicol 1(2):23-32.

Deren G. 1995. Refractory-ceramic-fiber furnace linings. Am Ceram Soc Bull 74(5):65-68.

DeVuyst P, Dumortier P, Swaen GMH, et al. 1995. Respiratory health effects of man-made vitreous (mineral) fibres. Eur Resp J 8(12):2149-2173.

Dodgson J, Ottery J, Cherrie JW, et al. 1980. Fibre concentrations and size distributions of airborne fibres in several European man-made mineral fibre plants. IARC Sci Publ 30:913-925.

Donaldson K. 1994. Biological activity of respirable industrial fibres treated to mimic residence in the lung. Toxicol Lett 72(1-3):299-305.

Donaldson K. 2001. The toxicology of respirable industrial fibres: An overview. Toxicol Lett 123:11.

Donaldson K, Tran CL. 2002. Inflammation caused by particles and fibers. Inhal Toxicol 14:5-27.

Donaldson K, Brown DM, Miller BG, et al. 1995a. Bromo-deoxyuridine (BRDU) uptake in the lungs of rats inhaling amosite asbestos or vitreous fibers at equal airborne fibre concentrations. Exp Toxicol Pathol 47(2-3):207-211.

*Donaldson K, Gilmour PS, Beswick PH. 1995c. Supercoiled plasmid DNA as a model target for assessing the generation of free radicals at the surface of fibres. Exp Toxicol Pathol 47(4):235-237.

*Donaldson K, Hill IM, Beswick PH. 1995b. Superoxide anion release by alveolar macrophages exposed to respirable industrial fibres: modifying effect of fibre opsonisation. Exp Toxicol Pathol 47(4):229-231.

*Dopp E, Schiffmann D. 1998. Analysis of chromosomal alteration induced by asbestos and ceramic fibers. Toxicol Lett 96:155-162.

Dopp E, Nebe B, Hahnel C, et al. 1995. Mineral fibers induce apoptosis in Syrian hamster embryo fibroblasts. Pathobiology 63:213-221.

9. REFERENCES

*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.

Dörger M, Allmeling A-M, Neuber A, et al. 1997. Interspecies comparison of rat and hamster alveolar macrophage antioxidative and oxidative capacity. Environ Health Perspect 105:1309-1312.

*Dörger M, Munzing S, Allmeling A-M, et al. 2000. Comparison of the phagocytic response of rat and hamster alveolar macrophages to man-made vitreous fibers *in vitro*. Hum Exp Toxicol 19(11):635-640.

*Dörger M, Munzing S, Allmeling AM, et al. 2001. Differential responses of rat alveolar and peritoneal macrophages to man-made vitreous fibers *in vitro*. Environ Res 85:207-214.

*Driscoll KE. 1996. Effects of fibres on cell proliferation, cell activation and gene expression. IARC Sci Publ 140:73-96.

*Driscoll KE, Carter JM, Hassenbein DG, et al. 1997. Cytokines and particle-induced inflammatory cell recruitment. Environ Health Perspect 105(5):1159-1164.

*Dufresne A, Perrault G, Yamato H, et al. 1999. Clearance of man made mineral fibres from the lungs of sheep. Occup Environ Med 56:684-690.

*Dumortier P, Broucke I, DeVuyst P. 2001. Pseudoasbestos bodies and fibers in bronchoalveolar lavage of refractory ceramic fiber users. Am J Respir Crit Care Med 164(3):499-503.

*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.

Eastes W, Hadley JG. 2001. Comment on "Long man-made fibers and lung cancer risk." Regul Toxicol Pharmacol 33(2):268.

*Eastes W, Morris KJ, Morgan A, et al. 1995. Dissolution of glass fibers in the rat lung following intratracheal instillation. Inhal Toxicol 7:197-213.

*Eastes W, Potter RM, Hadley JG. 2000. Estimating in vitro glass fiber dissolution rate from composition. Inhal Toxicol 12(4):269-280.

*Ellenhorn MJ. 1997. Man-made mineral fibers (MMMF). In: Ellenhorn's medical toxicology, 1515-1518.

Engholm G, Englund A, Fletcher AC, et al. 1987. Respiratory cancer incidence in Swedish construction workers exposed to man-made mineral fibres and asbestos. Ann Occup Hyg 31(48):663-675.

*Engholm G, vonSchmalensee G. 1982. Bronchitis and exposure to man-made mineral fibres in non-smoking construction workers. Eur J Respir Dis 118:73-78.

9. REFERENCES

England EC, Carlton GN, Krevonick PL. 2000. The impact of ventilation systems on worker exposures during advanced composite material and fiberglass repair operations on military aircraft. Appl Occup Environ Hyg 15(5):391-396.

*Enterline PE. 1990. Role of manmade mineral fibres in the causation of cancer. Br J Ind Med 47:145-145.

*Enterline PE, Henderson V. 1975. The health of retired fibrous glass workers. Arch Environ Health 30:113-116.

*Enterline PE, Marsh GM, Esmen NA. 1983. Respiratory disease among workers exposed to man-made mineral fibers. Am Rev Respir Dis 128(1):1-7.

*Enterline PE, Marsh GM, Henderson V, et al. 1987. Mortality update of a cohort of U.S. man-made mineral fibre workers. Ann Occup Hyg 31(4B):625-656.

*Environment Canada. 1993. Mineral fibres (man-made vitreous fibres). Priority Substances List Assessment Report.

*EPA. 1980. Man-made vitreous fibers and health. In: Proceedings of the National Workshop on Substitutes for Asbestos. U.S. Environmental Protection Agency. EPA560380001.

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

*EPA. 1992. ARARs fact sheet: Compliance with the clean air act and associated air quality requirements. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response. EPA9234222FS.

*EPA. 1995. Reportable Quantity Adjustments; final rule. Fed Regist 60(112):30925.

*EPA. 1997. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. EPA630R96012.

*Ernst P, Shapiro S, Dales RE, et al. 1987. Determinants of respiratory symptoms in insulation workers exposed to asbestos and synthetic mineral fibres. Br J Ind Med 44:90-95.

*Esmen NA, Erdal S. 1990. Human occupational and nonoccupational exposure to fibers. Environ Health Perspect 88:277-286.

*Esmen NA, Corn M, Hammad YY, et al. 1979a. Exposure of employees to man-made mineral fibers: Ceramic fiber production. Environ Res 19:265-278.

*Esmen N, Corn M, Hammad Y, et al. 1979b. Summary of measurements of employee exposure to airborne dust and fiber in sixteen facilities producing man-made mineral fibers. Am Ind Hyg Assoc J 40:108-117.

*Esmen NA, Hammad YY, Corn M, et al. 1978. Exposure to employees to man-made mineral fibers: Mineral wool production. Environ Res 15:262-277.

9. REFERENCES

Estes W, Morris KJ, Morgan A, et al. 1995. Dissolution of glass fibers in the rat lung following intratracheal instillation. Inhal Toxicol 7(2):197-213.

*Eun HC, Lee HG, Paik NW. 1991. Patch test responses to rockwool of different diameters evaluated by cutaneous blood flow measurement. Contact Dermatitis 24(4):270-273.

Everest Consulting Associates. 1996. Particulate-to-fiber ratios and fiber size distributions in the RCC maximum and tolerated dose (MTD) study and in the workplace. Presented to the U.S. Environmental Protection Agency. Prepared by Everest Consulting Associates, Cranbury, NJ.

*Everitt J, Bermudez E, Mangum J, et al. 1994. Acute pleural response of hamsters and rats to inhaled ceramic fibers. In: Dungworth DL, Mauderly JL, Oberdorster G, eds. Toxic and carcinogenic effects of solid particles in the respiratory tract. Washington DC: ILSI Press, 599-602.

*Everitt JI, Gelzleichter TR, Bermudez E, et al. 1997. Comparison of pleural responses of rats and hamsters to subchronic inhalation of refractory ceramic fibers. Environ Health Perspect 105:1209-121.

Fallentin B, Kamstrup O. 1993. Simulation of past exposure in slag wool production. Ann Occup Hyg 37(4):419-433.

Faux SP, Houghton CE, Hubbard A, et al. 2001. Increased expression of epidermal growth factor receptor in rat pleural mesothelial cells correlates with carcinogenicity of mineral fibres. Carcinogenesis 12(12):2275-2280.

Fayerweather WE, Bender JR, Hadley JG, et al. 1997. Quantitative risk assessment for a glass fiber insulation product. Regul Toxicol Pharmacol 25:103-120.

Fayerweather WE, Eastes W, Cereghini F, et al. 2002. Quantitative risk assessment of durable glass fibers. Inhal Toxicol 14:553-568.

*FEDRIP. 2002. Federal Research in Progress Database. National Technical Information Service, Springfield, VA.

*Feron VJ, Scherrenberg PM, Immel HR, et al. 1985. Pulmonary response of hamsters to fibrous glass: chronic effects of repeated intratracheal instillation with or without benzo[a]pyrene. Carcinogenesis 6:1495-1499.

*Fisher AA. 1982. Fiberglass vs mineral wool (rockwool) dermatitis. Cutis 29:412-513.

*Fisher BK, Warkentin JD. 1969. Fiber glass dermatitis. Arch Dermatol 99:717-719.

*Fitzer E, Kleinholz R, Tiesler H, et al. 1988. Fibers, synthetic inorganics. In: Gerhartz W, Yamamoto YS, Elvers B, et al., eds. Ullmann's encyclopedia of industrial chemistry, 1-66.

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.

Forget G, Lacroix MJ, Brown RC, et al. 1986. Response of perifused alveolar macrophages to glass fibers: Effect of exposure duration and fiber length. Environ Res 39:124-135.

*Forrester BG. 1997. Reactive airway dysfunction syndrome: Occurrence after exposure to a refractory ceramic fiber-phosphoric acid binder mixture. South Med J 90(4):447-450.

Fowler DP, Balzer JL, Cooper WC. 1971. Exposure of insulation workers to airborne fibrous glass. Am Ind Hyg Assoc J 32(2):86-91.

Foy JWD, Collier C, Swauger JE. 2003. A comparison of mathematical methods for the determination of in vitro dissolution constants for glass fibers. Inhal Toxicol 15:167-179.

*Fraire AE, Greenberg SD, Spjut HJ, et al. 1994. Effect of fibrous glass on rat pleural mesothelium. Am J Respir Crit Care Med 1509:521-527.

*Friar JJ, Phillips AM. 1989. Exposure to man-made mineral fibres. In: Bignon J, Peto J, Saracci R, eds. Non-occupational exposure to mineral fibres. IARC Scientific Publication No. 90. Lyon, France, 299-303.

Friemann J, Muller KM, Pott F. 1990. Mesothelial proliferation due to asbestos and man-made fibres. Experimental studies on rat omentum. Pathol Res Pract 186(1):117-123.

Fujoino A, Hori H, Higashi T, et al. 1995. In-vitro biological study to evaluate the toxic potentials of fibrous materials. Int J Occup Environ Health 1:21-28.

Fustinoni S, Colosio C, Colombi A, et al. 1998. Albumin and hemoglobin adducts as biomarkers of exposure to styrene in fiberglass-reinforced-plastics workers. Int Arch Occup Environ Health 70:35-41.

*Gantner BA. 1986. Respiratory hazard from removal of ceramic fiber insulation from high temperature industrial furnaces. Am Ind Hyg Assoc J 47(9):530-534.

*Gao H, Brick J, Ong S-h, et al. 1997. Selective hyperexpression of c-*jun* oncoprotein by glass fiber- and silica-transformed BALB/c-3T3 cells. Cancer Lett 112(1):65-69.

*Gao HG, Whong W-Z, Jones WG, et al. 1995. Morphological transformation induced by glass fibers in BALB/c-3T3 cells. Teratog Carcinog Mutagen 15(2):63-71.

Gardner IT, Uff JS. 1978. "Blue bodies" in a case of cryptogenic fibrosing alveolitis (desquamative type)- an ultra-structural study. Thorax 33:806-813.

Gardner MJ, Magnani C, Pannett B, et al. 1988. Lung cancer among glass fibre production workers: a case-control study. Br J Ind Med 45(9):613-618.

*Gardner MJ, Winter PD, Pannett B, et al. 1986. Mortality study of workers in the man-made mineral fiber production industry in the UK. Scand J Work Environ Health 12:85-93.

## 9. REFERENCES

*Gaudichet A, Petit G, Billon-Galland MA, et al. 1989. Levels of atmospheric pollution by man-made fibres in buildings. In: Bignon J, Peto J, Saracci R, eds. Non-occupational exposure to mineral fibres. International Agency for Research on Cancer. IARC Scientific Publication No. 90. Lyon, France, 291-298.

Geiser M, Matter M, Maye I, et al. 2003. Influence of airspace geometry and surfactant on the retention of man-made vitreous fibers (MMVF 10a). Environ Health Perspect 111(7):895-901.

*Gelzleichter TR, Bermudez E, Mangum JB, et al. 1996a. Pulmonary and pleural responses in Fischer 344 rats following short-term inhalation of a synthetic vitreous fiber. I. Quantitation of lung and pleural fiber burdens. Fundam Appl Toxicol 30(1):31-38.

*Gelzleichter TR, Bermudez E, Mangum JB, et al. 1996b. Pulmonary and pleural responses in Fischer 344 rats following short-term inhalation of a synthetic vitreous fiber (II) Pathobiologic responses. Fundam Appl Toxicol 30(1):39-46.

*Gelzleichter TR, Bermudez E, Mangum JB, et al. 1999. Comparison of pulmonary and pleural responses of rats and hamsters to inhaled refractory ceramic fibers. Toxicol Sci 49(1):93-101.

*Gelzleichter TR, Mangum JB, Vermudez E, et al. 1996c. Pulmonary and pleural leukocytes from F344 rats produce elevated levels of fibronectin following inhalation of refractory ceramic fibers. Exp Toxicol Pathol 48(6):487-489.

*Gibbs AR, Pooley FD, Griffiths DM, et al. 1996. A histopathological and mineralogical study of lung tissues from workers engaged in glass wool manufacture. In: Sixth international meeting on the toxicology of natural and man-made fibrous and non-fibrous particles: Lake Placid, NY Spetember 15-18, 1996. 157.

*Gilmour PS, Beswick PH, Brown DM, et al. 1995. Detection of surface free radical activity of respirable industrial fibres using supercoiled phiX174 plasmid DNA. Carcinogenesis 16(12):2973-2979.

*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(5):1313-1317.

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

Glass LR, Brown RC, Hoskins JA. 1995. Health effects of refractory ceramic fibres: scientific issues and policy considerations. Occup Environ Med 52(7):433-440.

*GMIC. 2002. Overview of the U.S. glass industry. Glass Manufacturing Industry Council. http://www.gmic.org/. May 07, 2002.

Goldberg MS, Parent ME, Siemiatycki J. 2001. A case-control study of the relationship between the risk of colon cancer in men and exposures to occupational agents. Am J Ind Med 39:531-546.

*Goldfrank LR. 1998. The pathophysiologic basis of medical toxicology. Part C. In: Goldfrank's toxicologic emergencies, 482.

9. REFERENCES

Goldsmith JR. 1986. Comparative epidemiology of men exposed to asbestos and man-made mineral fibers. Am J Ind Med 10(5-6):543-552.

*Goldsmith JR, Goldsmith DF. 1993. Fiberglass or silica exposure and increased nephritis or ESRD (end-stage renal disease). Am J Ind Med 23:873-881.

*Goldstein B, Rendall REG, Webster I. 1983. A comparison of the effects of exposure of baboons to crocidolite and fibrous-glass dusts. Environ Res 32:344-359.

Gradon L, Podgorski A. 1992. Experimental study on fibrous particle deposition in the human nasal cast. J Aerosol Sci 23:S469-S472.

Greim H, Brinkmann B, Pohlenz-Michel C, et al. 2000. The necessity of developing new criteria for carcinogen classification of fibers by the MAK commission. Inhal Toxicol 12:419-425.

*Greim H, Brom P, Schins R, et al. 2001. Toxicity of fibers and particles-report of the workshop held in Munich, Germany, 26-27 October 2000. Inhal Toxicol 13(9):737-754.

Greim HA, Ziegler-Skylakakis K. 1997. Strategies for setting occupational exposure limits for particles. Environ Health Perspect 105:1357-1361.

Griffis LC, Pickerell JA, Carpenter RL, et al. 1983. Deposition of crocidolite asbestos and glass microfibers inhaled by the beagle dog. Am Ind Hyg Assoc J 44(3):216-222.

Grimm HG, Bernstein DM, Attia M, et al. 2002. Experience from a long-term carcinogenicity study with intraperitoneal injection of biosoluble synthetic mineral fibers. Inhal Toxicol 14:855-882.

*Gross P. 1976. The biologic categorization of inhaled fiber glass dust. Arch Environ Health 31:101-107.

*Gross P. 1981. Consideration of the aerodynamic equivalent diameter of respirable mineral fibers. Am Ind Hyg Assoc J 42(6):449-452.

Gross P, Stanton MF. 1973. Tumors of the pleura induced with asbestos and fibrous glass. J Natl Cancer Inst 51(1):315-319.

Gross P, Davis JMG, Harley RA, et al. 1973. Lymphatic transport of fibrous dust from the lungs. J Occup Med 15(3):186-189.

Gross P, deTreville RTP, Cralley LJ. 1968. Pulmonary ferruginous bodies. Developed in response to filamentous dusts and a method of isolation and concentration. Arch Pathol 85:539-546.

Gross P, deTreville RTP, Cralley LJ, et al. 1970. The pulmonary response to fibrous dusts of diverse compositions. Am Ind Hyg Assoc J 31:125-132.

Gross P, Harley RA, Davis JMG, et al. 1974a. Mineral fiber content of human lungs. Am Ind Hyg Assoc J 35(3):148-151.

Gross P, Harley RA, Swinburne LM, et al. 1974b. Ingested mineral fibers. Do they penetrate tissue or cause cancer? Arch Environ Health 29:341-347.

Gross P, Kaschak M, Tolker EB, et al. 1970. The pulmonary reaction to high concentrations of fibrous glass dust. Arch Environ Health 20:696-704.

Gross P, Theodos PA, Murphy RLH. 1976. The pulmonary response to fiberglass dust- Report to the Committee on Environmental Health. American College of Chest Physicians. Chest 69(2):216-219.

Gross P, Tuma J, DeTrebille RTP. 1971. Lungs of workers exposed to fiber glass. Arch Environ Health 23:67-76.

Gross P, Westrick ML, Schrenk HH, et al. 1956. The effects of a synthetic ceramic fiber dust upon the lungs of rats. AMA Arch Ind Health 13(2):161-166.

Guldberg M, Jensen SL, Knudsen T, et al. 2002. High-alumina low-silica HT stone wool fibers: A chemical compositional range with high biosolubility. Regul Toxicol Pharmacol 35:217-226.

Gulumian M, Van Wyk JA. 1987. Hydroxyl radical production in the presence of fibres by a fenton-type reaction. Chem Biol Interact 62:89-97.

*Gustavsson P, Plato N, Axelson O, et al. 1992. Lung cancer risk among workers exposed to man-made mineral fibers (MMMF) in the Swedish prefabricated house industry. Am J Ind Med 21(6):825-834.

Gutknecht MHG. 1999. [Results of workplace exposure measurements of refractory ceramic fibers.] Geharstoffe Reinhalt Luft 59(5):171-177. (German)

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

*Hall GS, Rice CH, Lockey JE, et al. 1997. A comparison of exposures to refractory ceramic fibres over multiple work shifts. Ann Occup Hyg 41(5):555-560.

Hamilton RD, Miiler WC, Christensen DR, et al. 1994. Characterization of exposure and dose of man made vitreous fiber in experimental studies. Environ Health Perspect 102:109-112.

Hammad YY, Attieh B. 1989. Pulmonary deposition of MMMF. J Aerosol Sci 20(8):1329-1332.

Hammad YY, Atieh B. 1994. Long-term clearance of ceramic fibers from guinea pig lungs. In: Dungworth DL, Mauderly JL, Oberdorster G, eds. Toxic and carcinogenic effects of solid particles in the respiratory tract. Washington, DC: ILSI Press, 477-449.

Hammad YY, Atieh B. 1995. Long-term clearance of ceramic fibers from guinea-pig lungs. Exp Toxicol Pathol 47:192-194.

Hammad Y, Diem J, Craighead J, et al. 1982. Deposition of inhaled man made mineral fibres in the lungs of rats. Ann Occup Hyg 26(1):179-187.

Hansen ES. 2002. Comments on a nested case-control study of lung cancer among European rock and slag wool production workers. Int J Occup Environ Health 8:281-283.

## 9. REFERENCES

*Hansen E, Rasmussen F, Hardt F, et al. 1999. Lung function and respiratory health of long-term fiber-exposed stonewool factory workers. Am J Respir Crit Care Med 160(2):466-472.

Hansen J, Boffetta P, Anderson A, et al. 1997. Comparison of information on occupation and lifestyle habits obtained from European man-made vitreous fibre production workers and their relatives. Int J Epidemiol 26(5):1009-1016.

Hanton DY, Furtak H, Grimm HG. 1998. Preparation and handling conditions of MMVF for in-vivo experiments. Aerosol Sci Technol 29(5):449-456.

*Haratake J, Yamato H, Hori H, et al. 1995. Histopathologic examinations of rats treated by chronic inhalation exposures to glass fibers. Inhal Toxicol 7:343-352.

*Hart GA, Kathman LM, Hesterberg TW. 1994. *In vitro* cytotoxicity of asbestos and man-made vitreous fibers: Roles of fiber length, diameter and composition. Carcinogenesis 15(5):971-977.

*Hart GA, Newman MM, Bunn WB, et al. 1992. Cytotoxicity of refractory ceramic fibres to Chinese hamster ovary cells in culture. Toxicol in Vitro 6(4):317-326.

Hashish AH, Fleming JS, Conway J, et al. 1998. Lung deposition of particles by airway generation in healthy subjects: three-dimensional radionuclide imaging and numerical model prediction. J Aerosol Sci 29(1/2):205-215.

*HazDat. 2004. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA. http://www.atsdr.cdc.gov/hazdat.html. January 12, 2004.

*Hecht E. 1989. Optics. Second edition. Spatz B, ed. Reading, MA: Addison-Wesley Publishing Company, Inc., 191-192.

Heise H, Mattheus A. 1971. [Skin reactions to insulators: I. Epicutaneous testing of mineral fibers.] Dermatol Monatsschr 157(1):52-61. (German)

Heise H, Mattheus A. 1971. [Skin reactions to insulators: II. Relationships to frequent allergens.] Dermatol Monatsschr 157(1):62-67. (German)

*Heisel EB, Hunt FE. 1968. Further studies in cutaneous reactions to glass fibers. Arch Environ Health 17:705-711.

*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, Chase GR. 1995. Commentary on "Fibrous glass and lung cancer". Letter to the editor. Am J Ind Med 30:111-112.

Hesterberg TW, Hart GA. 1994. A comparison of human exposures to fiberglass with those used in a recent rat chronic inhalation study. Regul Toxicol Pharmacol 20:S35-S46.

*Hesterberg TW, Hart GA. 1998. Health and safety aspects of fiber glass. Nonwoven Conference and Trade Fair, St. Petersburg, FL, March 9-11, 1998. Atlanta, GA: TAPPI Press, 269-288.

## 9. REFERENCES

*Hesterberg TW, Hart GA. 2000. Lung biopersistence and in vitro dissolution rate predict the pathogenic potential of synthetic vitreous fibers. Inhal Toxicol 12:91-97.

*Hesterberg TW, Hart GA. 2001. Synthetic vitreous fibers: A review of toxicology research and its impact on hazard classification. Crit Rev Toxicol 31(1):1-53.

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(5):1223-1229.

*Hesterberg TW, Axten C, McConnell EE, et al. 1999. Studies on the inhalation toxicology of two fiberglasses and amosite asbestos in the Syrian golden hamster. Part I. Results of a subchronic study and dose selection for a chronic study. Inhal Toxicol 11(9):747-784.

Hesterberg TW, Butterick CJ, Oshimura M. 1986. Role of phagocytosis in Syrian hamster cell transformation and cytogenetic effects induced by asbestos and short and long glass fibers. Cancer Res 46(11):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, Chase G, Axten C, et al. 1999. Erratum: Biopersistence of synthetic vitreous fibers and amosite asbestos in the rat lung following inhalation. Toxicol Appl Pharmacol 155:292.

*Hesterberg TW, Hart GA, Bunn WB. 1993a. In vitro toxicology of fibers: mechanistic studies and possible use for screening assays. In: Warheit DB, ed. Fiber toxicology. Chapter 7. San Diego, CA: Academic Press, Inc., 139-170.

*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, Hart GA, Miiller WC, et al. 2002. Use of short-term assays to evaluate the potential toxicity of two new biosoluble glasswool fibers. Inhal Toxicol 14:217-246.

Hesterberg TW, Miiller WC, Anderson R. 1993b. Chronic inhalation studies of man-made vitreous fibers. Proceedings of the 22nd DOE/NRC Nuclear Air Cleaning Conference 1992. Vol 1:191-204.

Hesterberg TW, Miiller WC, Mast R, et al. 1994. Relationship between lung biopersistence and biological effects of man-made vitreous fibers after chronic inhalation in rats. Environ Health Perspect 102:133-137.

*Hesterberg TW, Miiller WC, McConnell EE, et al. 1993c. Chronic inhalation toxicity of size-separated glass fibers in Fischer 344 rats. Fundam Appl Toxicol 20:464-476.

*Hesterberg TW, Miiller WC, McConnell EE, et al. 1994. Chronic inhalation toxicity of man-made vitreous fibers: Relationship to lung burden and lung retention. In: Dungworth DL, Mauderly JL, Oberdorster G, eds. Toxic and carcinogenic effects of solid particles in the respiratory tract. Washington, DC: ILSI Press., 455-459.

9. REFERENCES

*Hesterberg TW, Miiller 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, Oshimura M, Barrett JC. 1985. In: Beck EG, Bignon J, eds. In vitro effects of mineral dusts. Third International Workshop. Berlin: Springer-Verlag, 185-196.

Hill IM, Beswick PH, Donaldson K. 1996. Enhancement of the macrophage oxidative burst by immunoglobulin coating of respirable fibers: Fiber-specific differences between asbestos and man-made fibers. Exp Lung Res 22(2):133-148.

*Hill JW, Whitehead WS, Cameron JD, et al. 1973. Glass fibres: absence of pulmonary hazard in production workers. Br J Ind Med 30:174-179.

Hinnen U, Elsner P, Barraud M, et al. 1997. Foreign body granuloma of the penis caused by occupational glass fibre exposure. Genitourin Med 73:577-578.

Hippeli S, Dornisch K, Kaiser S, et al. 1997. Biological durability and oxidative potential of a stonewool mineral fibre compared to crocidolite asbestos fibers. Arch Toxicol 71(8):532-535.

*Hirvonen A. 1997. Combinations of susceptible genotypes and individual responses to toxicants. Environ Health Perspect 105(suppl 4):755-757.

Hirvonen A, Mattson K, Karjaiainen T, 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, Saarikoski ST, Linnainmaa K, et al. 1996. Gluthione *S*-transferase and *N*-acetyltransferase genotypes and asbestos-associated pulmonary disorders. J Natl Cancer Inst 88(24):1853-1856.

Hoch-Ligetti C, Sass B, Sobel HJ, et al. 1983. Endocardial tumors in rats exposed to durable fibrous materials. J Natl Cancer Inst 71(5):1067-1071.

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

*Hohr D. 1985. [Investigations by transmission electron microscopy of fibrous particles in ambient air.] Staub Reinhalt Luft 45:171-174. (German)

Holmes A, Morgan A, Davison W. 1983. Formation of pseudo-asbestos bodies on sized glass fibres in the hamster lung. Ann Occup Hyg 27(3):301-313.

Hori H, Ishimatsu S, Oyabu T, et al. 1999. A clearance model of inhaled man-made fibers in rat lungs. Ind Health 37(1):103-107.

Horowitz LD. 1978. NIOSH Criteria Document on fibrous glass. J Occup Med 20(11):718, 720.

*Horvath HP. 1995. Health effects of man-made mineral fibers. Cleve Clin J Med 62(1):8-19.

Hoskins JA, Brown RC. 1994. Contamination of the air with mineral fibers following the explosive destruction of buildings and fire. Drug Metab Rev 26(4):663-673.

Howden PJ, Faux SP. 1996a. Fibre-induced lipid peroxidation leads to DNA adduct formation in *Salmonella typhimurium* TA104 and rat lung fibroblasts. Carcinogenesis 17(3):413-419.

Howden PJ, Faux SP. 1996b. Glutathione modulates the formation of 8-hydroxdeoxyguanosine in isolated DNA and mutagenicity in *Salmonella typhimurium* TA 100 induced by mineral fibres. Carcinogenesis 17(10):2275-2277.

Huang JQ, Ji CM. 1994. A survey of the health effect of continuous filament glass fibre on long-term exposed workers. Ann Occup Hyg 38:763-768.

Huff J. 2002. IARC monographs, industrial influence, and upgrading, downgrading, and under-grading chemicals. Int J Occup Environ Health 8:249-270.

*Hughes JM, Jones RN, Glindmeyer HW, et al. 1993. Follow up study of workers exposed to man made mineral fibres. Br J Ind Med 50:658-667.

*Hunting KL, Welch LS. 1993. Occupational exposure to dust and lung disease among sheet metal workers. Br J Ind Med 50(5):432-442.

IARC. 1987. Asbestos. IARC monographs programme on the evaluation of carcinogenic risks to humans. International Agency for Research on Cancer. http://193.51.164.11/htdocs/Monographs/Suppl7/Asbestos.html. May 07, 2002.

*IARC. 1988. IARC monographs of the evaluation of carcinogenic risks to human. International Agency for Research on Cancer. Lyon, France: World Health Organization. IARC Sci Publ 43:39-171.

*IARC. 2001. Man-made mineral fibres. IARC monographs programme on the evaluation of carcinogenic risks to humans. International Agency for Research on Cancer. http://193.51.164.11/htdocs/Monographs/Vol43/43-01.htm. May 07, 2002.

*IARC. 2002. Man-made mineral fibres. IARC monographs programme on the evaluation of carcinogenic risks to humans. International Agency for Research on Cancer. http://193.51.164.11/htdocs/monographs/vol81/81.html. Feburary 02, 2004.

*IARC Expert Panel. 1996. Congress report. In: Kane AB, Boffetta P, Saracci R, et al., eds. Mechanisms of fibre carcinogenesis. International Agency for Research on Cancer. Scientific Publications No. 140, 1-9.

Infante PF, Schuman LD, Dement J, et al. 1994a. Fibrous glass and cancer. Am J Ind Med 26:559-584.

Infante PF, Schuman LD, Dement J, et al. 1994b. Fibrous glass and cancer: Commentary. Am J Ind Med 26:559-584.

Infante PF, Schuman LD, Huff J. 1996. Fibrous glass insulation and cancer: Response and rebuttal. Am J Ind Med 30:113-120.

*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.

ILSI. 2000. The relevance of the rat lung response to particle overload for human risk assessment: A workshop concensus report. ILSI Risk Science Institute Workshop. International Life Sciences Institute. Inhal Toxicol 12:1-17.

*IRIS. 2004. Integrated Risk Information System. http://www.epa.gov/iris. January 08, 2004.

Ishihara Y. 2001. *In vitro* studies on biological effects of fibrous minerals. Ind Health 39:94-105.

Ishimatsu S, Oyabu T, Hori H, et al. 1999. A new digestion method for recovery of MMMFs from lungs. Ind Health 37(3):307-312.

Iwata T, Yano E. 2003. Reactive oxygen metabolite production induced by asbestos and glass fibers: Effect of fiber milling. Ind Health 41:32-38.

*Jacob TR, Hadley JG, Bender JR, et al. 1992. Airborne glass fiber concentrations during installation of residential insulation. Am Ind Hyg Assoc J 53(8):519-523.

*Jacob TR, Hadley JG, Bender JR, et al. 1993. Airborne glass fiber concentrations during manufacturing operations involving glass wool insulation. Am Ind Hyg Assoc J 54(6):320-326.

Jacobsen M. 1983. Do we know enough from epidemiology to prevent asbestosis? Eur J Respir Dis 64:407-408.

*Jaffrey TSAM. 1990. Levels of airborne man-made mineral fibres in UK dwellings. I. Fibre levels during and after installation of insulation. Atmos Environ 24A(1):133-141.

Janssen YMV, Borm PJA, Marsh JP, et al. 1994b. The role of active oxygen species in lung toxicity induced by mineral fibers and particulates. Adv Environ Sci Technol 28:445-457.

*Janssen YMW, Heintz NH, Marsh JP, et al. 1994a. Induction of c-fos and c-jun proto-oncogenes in target cells of the lung and pleura by carcinogenic fibers. Am J Respir Cell Mol Biol 11:522-530.

*Jarvholm B, Jarliden A-K, Lilja B-G, et al. 1995. Occurrence of pleural plaques in workers with exposure to mineral wool. Int Arch Occup Environ Health 67(5):343-346.

Jaurand M-C. 1997. Mechanisms of fiber-induced genotoxicity. Environ Health Perspect Suppl 105(5):1073-1084.

Jaurand MC, Magne L, Bignon J, et al. 1980. Effects of well-defined fibres on red blood cells and alveolar macrophages. In: Wagner JC, Davis W, eds. Biological effects of mineral fibres. IARC Scientific Publication No. 30. Lyon, France.

*Jeffress CN. 1999. Written communication (May 18, 1999) to Kenneth Mentzer, Executive Vice President, OSHA regarding expression of support for the “Health and Safety Partnership Program” to help protect employees involved in manufacturing, installing, and removing products containing synthetic vitreous fibers.

*Jensen CG, Watson M. 1999. Inhibition of cytokinesis by asbestos and synthetic fibres. Cell Biol Int 23(12):829-840.

*Johanson CE. 1980. Permeability and vascularity of the developing brain: Cerebellum vs cerebral cortex. Brain Res 190:3-16.

Johnson NF. 1993. The limitations of inhalation, intratracheal, and intracoelomic routes of administration for identifying hazardous fibrous materials. In: Warheit DB, ed. Fiber toxicology. Chapter 3. San Diego, CA: Academic Press, Inc., 43-72.

Johnson NF. 1994. An overview of animal models for assessing synthetic vitreous fibers (SVFs) safety. Regul Toxicol Pharmacol 20:S7-S21.

Johnson NF. 1994. Phasgosomal pH and glass fiber dissolution in cultured nasal epithelial cells and alveolar macrophages: A preliminary study. Environ Health Perspect 102:97-102.

Johnson NF, Hahn FF. 1996. Induction of mesothelioma after intrapleural inoculation of F344 rats with silicon carbide whiskers or continuous ceramic filaments. Occup Environ Med 53(12):813-816.

*Johnson NF, Jaramillo RJ. 1997. p53, Cip 1, and Gadd 153 expression following treatment of A549 cells with natural and man-made vitreous fibers. Environ Health Perspect 105:1143-1145.

*Johnson NF, Wagner JC. 1980. A study by electron microscopy of the effects of chrysotile and man-made mineral fibres on rat lungs. In: Wagner JC, Davis W, eds. Biological effects of mineral fibers. IARC Sci Publ 30:293-303.

*Johnson DL, Healey JJ, Ayer EA, et al. 1969. Exposure to fibers in the manufacture of fibrous glass. Am Ind Hyg Assoc J 30:545-550.

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(6):807-823.

Jolanki R, Makinen I, Suuronen K, et al. 2002. Occupational irritant contact dermatitis from synthetic mineral fibres according to Finnish statistics. Contact Dermatitis 47:329-333.

*Jones AD. 1993. Respirable industrial fibres: Deposition, clearance and dissolution in animal models. Ann Occup Hyg 37(2):211-226.

Julier F, Tiesler H, Zindler G. 1993. [Measurement of fibrous dust concentrations when handling mineral-wool insulations on industrial building sites.] Staub Reinhalt Luft 53(6):245-250. (German)

*Kamstrup O, Davis JMG, Ellehauge A, et al. 1998. The biopersistence and pathogenicity of man-made vitreous fibres after short- and long-term inhalation. Ann Occup Hyg 42(3):191-199.

*Kamstrup O, Ellehauge A, Chevalier J, et al. 2001. Chronic inhalation studies of two types of stone wool fibers in rats. Inhal Toxicol 13(7):603-621.

Kamstrup O, Ellehauge A, Collier CG, et al. 2002. Carcinogenicity studies after intraperitoneal injection of two types of stone wool fibres in rats. Ann Occup Hyg 46:135-142.

*Kane AB. 1996. Mechanisms of mineral fibre carcinogenesis. In: Kane AB, Bofetta P, Saracci R, et al., eds. Mechanisms of fibre carcinogenesis. International Agency for Research on Cancer, 11-34.

Keegan TE, Simmons JE, Pegram RA. 1998. NOAEL and LOAEL determinations of acute hepatotoxicity for chloroform and bromodichloromethane delivered in an aqueous vehicle to F344 rats. J Toxicol Environ Health A 55(1):65-75.

Kelly JT, Kimbell JS, Asgharian B. 2001. Particle deposition in a rat nasal mold. CIIT Activities. Research Triangle Park, NC: CIIT Centers for Health Professionals, 1-6.

*Kelsey KT, Nelson HN, Wiencke JK, et al. 1997. The glutathione S-transferase Θ and μ deletion polymorphisms in asbestosis. Am J Ind Med 31:274-279.

*Kiec-Swierczynska M, Szymczk W. 1995. The effect of the working environment on occupational skin disease development in workers processing rockwool. Int J Occup Med Environ Health 8(1):17-22.

*Kiec-Swierczynska M, Wojtczak J. 2000. Occupational ceramic fibres dermatitis in Poland. Occup Med 50(5):337-342.

Kilburn KH. 1993. Pulmonary effects of exposure to fine fiberglass: irregular opacities and small airways obstruction. Reply to comments. Br J Ind Med 50(4):383-384.

*Kilburn KH, Warshaw RH. 1992. Difficulties of attribution of effect in workers exposed to fiberglass and asbestos. Am Ind Hyg Assoc J 20(6):745-751.

*Kilburn KH, Powers D, Warshaw RH. 1992. Pulmonary effects of exposure to fine fiberglass: irregular opacities and small airways obstruction. Br J Ind Med 49:714-720.

Kim J-H, Chang H-S, Kim K-Y, et al. 1999. Environmental measurements of total dust and fiber concentration in manufacturer and user of man-made mineral fibers. Ind Health 37(3):322-328.

Kim K-A, Lee WK, Kim JK, et al. 2001. Mechanism of refractory ceramic fiber- and rock wool-induced cytotoxicity in alveolar macrophages. Int Arch Occup Environ Health 74(1):9-15.

*Kjaerheim K, Boffetta P, Hansen J, et al. 2002. Lung cancer among rock and slag wool production workers. Epidemiology 13:445-453.

Klingholz R. 1977. Technology and production of man-made mineral fibres. Ann Occup Hyg 20:153-159.

*Knudsen T, Guldberg M, Christensen VR, et al. 1996. New type of stone wool (HT fibres) with a high dissolution rate at pH=4.5. Glastech Ber 69(10):331-337.

Koenig AR, Axten CW. 1995. Exposures to airborne fiber and free crystalline silica during installation of commercial and industrial mineral wool products. Am Ind Hyg Assoc J 56(10):1016-1022.

*Koh D, Khoo NY. 1995. Environmental glass fibre counts and skin symptoms. Contact Dermatitis 32(3):185.

*Koh D, Aw TC, Foulds IS. 1992. Fiberglass dermatitis from printed circuit boards. Am J Ind Med 21:193-198.

9. REFERENCES

*Komori M, Nishio K, Kitada M, et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human livers. Biochemistry 29:4430-4433.

Konzen J. 1975. Observations on fibrous glass in relation to health. In: Zenz C, ed. Occupational medicine. Principles and practical applications. Chapter 13. Chicago, IL: YearBook Medical Publishers, Inc., 231-238.

Konzen JL. 1980. Man-made vitreous fibers and health. Proceedings National Workshop on Substitutes for Asbestos. EPA560380001.

Konzen JL. 1994. Comment on: Occupational exposure to dust and lung disease among sheet metal workers. Br J Ind Med 50(5):432-442.

*Koshi K, Kohyama N, Myojo T, et al. 1991. Cell toxicity hemolytic action and clastogenic activity of asbestos and its substitutes. Ind Health 29(2):37-56.

Krantz S. 1988. Exposure to man-made mineral fibers at ten production plants in Sweden. Scand J Work Environ Health 14:49-51.

*Krishnan K, Andersen ME. 1994. Physiologically based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. Principles and methods of toxicology. 3rd ed. New York, NY: Raven Press, Ltd., 149-188.

*Krishnan K, Andersen ME, Clewell HJ III, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures: Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

Kudo Y, Watanabe M, Okada M, et al. 2003. Comparative cytotoxicity study of rock wool and chrysotile by cell magnetometric evaluation. Inhal Toxicol 15:1275-1295.

Lafuma J, Morin M, Poncy JL, et al. 1980. Mesothelioma induced by intrapleural injection of different types of fibres in rats; synergistic effect of other carcinogens. In: Wagner JC, Davis W, eds. Biological effects of mineral fibres. IARC Sci Publ 30:311-320.

Lambre C, Schorsch F, Blanchard O, et al. 1998. An evaluation of the carcinogenic potential of five man-made vitreous fibers using the intraperitoneal test. Inhal Toxicol 10(11):995-1021.

Law BD, Bunn WB, Hesterberg TW. 1990. Solubility of polymeric organic fibers and manmade vitreous fibers in gambles solution. Inhal Toxicol 2(4):321-339.

Law BD, Bunn WB, Hesterberg TW. 1991. Dissolution of natural mineral and man-made vitreous fibers in Karnovsky's and formalin fixatives. Inhal Toxicol 3(3):309-321.

*Lea CS, Hertz-Picciotto I, Andersen A, et al. 1999. Gender differences in the healthy worker effect among synthetic vitreous fiber workers. Am J Epidemiol 150(10):1099-1106.

Leadbetter MR, Corn M. 1972. Particle size distribution of rat lung residues after exposure to fiberglass dust clouds. Am Ind Hyg Assoc J 33(8):511-522.

9. REFERENCES

*Leanderson P, Tagesson C. 1989. Cigarette smoke potentiates the DNA-damaging effect of manmade mineral fibers. Am J Ind Med 16(6):697-706.

*Leanderson P, Soderkvist P, Tagesson C, et al. 1988. Formation of 8-hydroxydeoxyguanosine by asbestos and man made mineral fibres. Br J Ind Med 45:309-311.

*Leanderson P, Soderkvist P, Tagesson C. 1989. Hydroxyl radical mediated DNA base modification by manmade mineral fibres. Br J Ind Med 46:435-438.

*LeBouffant L, Daniel H, Henin JP, et al. 1987. Experimental study on long-term effects of inhaled MMMF on the lungs of rats. Ann Occup Hyg 31(48):765-790.

*Lee J-M, Hennekens CH, Trichopoulos D, et al. 1995. Man-made vitreous fibers and risk of respiratory system cancer: A review of the epidemiologic evidence. J Occup Environ Med 37(6):725-738.

Lee KP, Barras CE, Griffith FD. 1979. Pulmonary response to glass fiber by inhalation exposure. Lab Invest 40(2):123-133.

*Lee KP, Barras CE, Griffith FD, et al. 1981b. Comparative pulmonary responses to inhaled inorganic fibers with asbestos and fiberglass. Environ Res 24:167-191.

*Lee KP, Barras CE, Griffith FD, et al. 1981a. Pulmonary response and transmigration of inorganic fibers by inhalation exposure. Am J Pathol 102(3):314-323.

*Lee WJ, Baris D, Jarvholm B, et al. 2003. Multiple myeloma and diesel and other occupational exposures in Swedish construction workers. Int J Cancer 107:134-138.

*Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: Implications for practice. Pediatr Clin North Am 44(1):55-77.

Lees PSJ, Breysse PN, McArthur BR, et al. 1993. End user exposures to man-made vitreous fibers: I. Installation of residential insulation products. Appl Occup Environ Hyg 8(12):1022-1030.

*Leikauf GD, Fink SP, Miller M, et al. 1995. Refractory ceramic fibers activate alveolar macrophage eicosanoid and cytokine release. J Appl Physiol 78(1):164-171.

Lemaire I, Dionne PG, Nadeau D, et al. 1989. Rat lung reactivity to natural and man-made fibrous silicates following short-term exposure. Environ Res 48:193-210.

*Lemasters G, Lockey J, Levin L, et al. 1998. An industry-wide pulmonary study of men and women manufacturing refractory ceramic fibers. Am J Epidemiol 148(9):910-919.

Lemasters G, Lockey J, Levin L, et al. 2001. A longitudinal study of chest radiographic changes and mortality of workers in the refractory ceramic fiber industry. Am J Epidemiol 153(11):S264.

*Lemasters G, Lockey J, Rice C, et al. 1994. Radiographic changes among workers manufacturing refractory ceramic fibre and products. Ann Occup Hyg 38:745-751.

*Lemasters G, Lockey J, Yiin JH, et al. 2003. Mortality of workers occupationally exposed to refractory ceramic fibers. J Occup Environ Med 45:440-450.

Lemen RA. 2001. Fiberglass. In: Bingham E, Cohrssen B, Powell CH, eds. Patty's toxicology. John Wiley & Sons, 575-582.

Lentz TJ, Rice CH, Lockey JE. 1999. Potential significance of airborne fiber dimensions measured in the US refractory ceramic fiber manufacturing industry. Am J Ind Med 36(2):286-298.

*Lentz TJ, Rice CH, Succop PA, et al. 2003. Pulmonary deposition modeling with airborne fiber exposure data: A study of workers manufacturing refractory ceramic fibers. Appl Occup Environ Hyg 18:278-288.

*Leung H-W. 1993. Physiologically-based pharmacokinetic modeling. In: Ballentine B, Marro T, Turner P, eds. General and applied toxicology. Vol. 1. New York, NY: Stockton Press, 153-164.

Lindgren F, Sjosstrom M, Berglind R, et al. 1996. Modeling of the biological activity for a set of ceramic fibre materials: A QSAR study. SAR QSAR Environ Res 5:299-310.

*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.

*Livingston, AL. 1978. Forage plant estrogens. J Toxicol Environ Health 4:301-324.

Lockey JE. 1996. Man-made fibers and nonasbestos fibrous silicates. In: Harber P, Scheneker MB, Balmes JR, eds. Occupational and respiratory disease. Chapter 21. Mosby-Year Book, Inc., 330-344.

*Lockey JE, Lemasters GK, Levin L, et al. 2002. A longitudinal study of chest radiographic changes of workers in the refractory ceramic fiber industry. Chest 121:2044-2051.

*Lockey J, Lemasters G, Rice C, et al. 1996. Refractory ceramic fiber exposure and pleural plaques. Am J Respir Crit Care Med 154(5):1405-1410.

*Lockey JE, Levin LS, Lemasters GK, et al. 1998. Longitudinal estimates of pulmonary function in refractory ceramic fiber manufacturing workers. Am J Respir Crit Care Med 157(4 Pt 1):1226-1233.

*Longley EO, Jones RC. 1966. Fiberglass conjunctivitis and keratitis. Arch Environ Health 13:790-793.

Luce D, Leclerc A, Begin D, et al. 2002. Sinonasal cancer and occupational exposures: A polled analysis of 12 case-control studies. Cancer Causes Control 13:147-157.

Luoto K, Holopainen M, Perander M, et al. 1996. Cellular effects of particles-impact of dissolution on toxicity of man-made mineral fibers. Cent Eur J Public Health 4:29-32.

*Luoto K, Holopainen M, Sarataho M, et al. 1997. Comparison of cytotoxicity of man-made vitreous fibres. Ann Occup Hyg 41(1):37-50.

9. REFERENCES

Luoto K, Holopainen M, Savolainen K. 1994. Scanning electron microscopic study on the changes in the cell surface morphology of rat alveolar macrophages after their exposure to man-made vitreous fibers. Environ Res 66:198-207.

Luoto K, Holopainen M, Savolainen K. 1995. Durability of man-made vitreous fibres as assessed by dissolution of silicon, iron and aluminium in rat alveolar macrophages. Ann Occup Hyg 39(6):855-867.

Ma Z, Otsuki T, Tomokuni A, et al. 1999. Man-made mineral fibers induce apotosis of human peripheral blood mononuclear cells similarly to chrysotile B. Int J Mol Med 4(6):633-637.

Maltoni C, Minardi F, Soffritti M, et al. 1991. Long-term carcinogenicity bioassays on industrial chemicals, and man-made mineral fibers, at the Bentivoglio (BT) Laboratories of the Bologna Institute of Oncology: Premises, programs, and results. Toxicol Ind Health 7(516):63-94.

*Marchand JL, Luce D, Lecierc A, et al. 2000. Laryngeal and hypopharyngeal cancer and occupational exposure to asbestos and man-made vitreous fibers: Results of a case-control study. Am J Ind Med 37(6):581-589.

*Marchant GE, Amen MA, Bullock CH, et al. 2002. A synthetic vitreous fiber (SVF) occupational exposure database: Implementing the SVF health and safety partnership program. Appl Occup Environ Hyg 17:276-285.

Marconi A, Corradetti E, Mannozzi A. 1987. Concentrations of man-made vitreous fibres during installation of insulation materials aboard ships at Ancona naval dockyards. Ann Occup Hyg 31(4B):595-599.

*Marks-Konczalik J, Gillissen A, Jaworska M, et al. 1998. Induction of manganese superoxide dismutase gene expression in bronchoepithelial cells after rockwool exposure. Lung 176(3):165-180.

*Marsh GM, Buchanich JM, Youk AO. 2001a. Historical cohort study of US man-made vitreous fiber production workers. VI. Respiratory system cancer standardized mortality ratios adjusted for the confounding effect of cigarette smoking. J Occup Environ Med 43(9):803-808.

*Marsh GM, Enterline PE, Stone RA, et al. 1990. Mortality among a cohort of U.S. man-made mineral fiber workers: 1985 follow-up. J Occup Environ Med 32:594-604.

*Marsh GM, Gula MJ, Youk AO, et al. 2001b. Historical cohort study of U.S. man-made vitreous fiber production workers: II. Mortality from mesothelioma. J Occup Environ Med 43(9):757-766.

Marsh GM, Stone RA, Youk AO, et al. 1997. Cancer mortality among man-made vitreous fiber production workers. Letter to the editor. Epidemiology 9(2):218-220.

*Marsh GM, Youk AO, Stone RA, et al. 2001c. Historical cohort study of US man-made vitreous fiber production workers: I. 1992 fiberglass cohort follow-up: Initial findings. J Occup Environ Med 43(9):741-756.

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(5):207-209.

9. REFERENCES

*Mast RW, Maxim LD, Utell MJ, et al. 2000. Refractory ceramic fiber: Toxicology, epidemiology, and risk analyses- A review. Inhal Toxicol 12(5):359-399.

*Mast RW, McConnell EE, Hesterberg TW, et al. 1995b. Multiple-dose chronic inhalation toxicity study of size-separated kaolin refractory ceramic fiber in male Fischer 344 rats. Inhal Toxicol 7(4):469-502.

*Mast RW, McConnell EE, Anderson R, et al. 1995a. Studies on the chronic toxicity (inhalation) of four types of refractory ceramic fiber in male Fischer 344 rats. Inhal Toxicol 7:425-467.

*Mattson SM. 1994. Glass fiber dissolution in simulated lung fluid and measures needed to improve consistency and correspondence to in vivo dissolution. Environ Health Perspect 102:87-90.

*Maxim LD, McConnell EE. 2001. Interspecies comparisons of the toxicity of asbestos and synthetic vitreous fibers: A weight-of-the-evidence approach. Regul Toxicol Pharmacol 33(3):319-342.

*Maxim LD, Allshouse JN, Chen SH, et al. 2000a. Workplace monitoring of refractory ceramic fiber in the United States. Regul Toxicol Pharmacol 32(3):293-309.

Maxim LD, Allshouse JN, Kelly WP, et al. 1997. A multiyear workplace-monitoring program for refractory ceramic fibers: Findings and conclusions. Regul Toxicol Pharmacol 26(2):156-171.

Maxim LD, Allshouse JN, Venturin DE. 2000b. The random-effects model applied to refractory ceramic fiber data. Regul Toxicol Pharmacol 32(2):190-199.

Maxim LD, Boymel P, Chase GR, et al. 2002. Indices of fiber biopersistence and carcinogen classification for synthetic vitreous fibers (SVFs). Regul Toxicol Pharmacol 35:357-378.

*Maxim LD, Eastes W, Hadley JG, et al. 2003a. Fiber glass and rock/slag wool exposure of professional and do-it-yourself installers. Regul Toxicol Pharmacol 37:28-44.

*Maxim LD, Kelly WP, Walters T, et al. 1994. A multiyear workplace-monitoring program for refractory ceramic fibers. Regul Toxicol Pharmacol 20:S200-S215.

Maxim LD, Mast RW, Utell MJ, et al. 1999a. Hazard assessment and risk analysis of two new synthetic vitreous fibers. Regul Toxicol Pharmacol 30(1):54-74.

*Maxim LD, Venturin D, Allshouse JN. 1999b. Respirable crystalline silica exposure associated with the installation and removal of RCF and conventional silica-containing refractories in industrial furnaces. Regul Toxicol Pharmacol 29(1):44-63.

*Maxim LD, Yu CP, Oberdorster G, et al. 2003b. Quantitative risk analyses for RCF: Survey and synthesis. Regul Toxicol Pharmacol 38:400-416.

*Mayr U, Butsch A, Schneider S. 1992. Validation of two in vitro test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. Toxicology 74:135-149.

McClellan RO. 1994. Assessing health risks of synthetic vitreous fibers: An integrative approach. Regul Toxicol Pharmacol 20(9):S121-S134.

McClellan RO, Hesterberg TW. 1994. Role of biopersistence in the pathogenicity of man-made fibers and methods for evaluating biopersistence: A summary of two round-table discussions. Environ Health Perspect 102:277-283.

McConnell EE. 1996. Commentary on "Fibrous glass and lung cancer". Letter to the editor. Am J Ind Med 30:109-110.

McConnell EE. 2000. A science-based paradigm for the classification of synthetic vitreous fibers. Regul Toxicol Pharmacol 32(1):14-21.

*McConnell EE, Axten C, Hesterberg TW, et al. 1999. Studies on the inhalation toxicology of two fiberglasses and amosite asbestos in the Syrian golden hamster. Part II. Results of chronic exposure. Inhal Toxicol 1(9):785-835.

*McConnell EE, Kampstrup O, Musselman R, et al. 1994. Chronic inhalation study of size-separated rock and slag wool insulation fibers in Fischer 344/N rats. Inhal Toxicol 6:571-614.

*McConnell EE, Mast RW, Hesterberg TW, et al. 1995. Chronic inhalation toxicity of a kaolin-based refractory ceramic fiber in Syrian golden hamsters. Inhal Toxicol 7:503-532.

*McDonald AD, McDonald JC, Rando RJ, et al. 2001. Cohort mortality study of North American industrial sand workers. I. Mortality from lung cancer, silicosis and other causes. Ann Occup Hyg 45(3):193-199.

McDonald JC. 1998. Mineral fibre persistence and carcinogenicity. Ind Health 36:372-375.

*McDonald JC, Armstrong BG, Edwards CW, et al. 2001. Case-referent survey of young adults with mesothelioma: I. Lung analyses. Ann Occup Hyg 45(7):513-518.

*McDonald JC, Case BW, Enterline PE, et al. 1990. Lung dust analysis in the assessment of past exposure of man-made mineral fibre workers. Ann Occup Hyg 34:427-441.

*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. San Francisco, CA.

*Melton CW, Anderson SJ, Dye CF, et al. 1978. Development of a rapid analytical method for determining asbestos in water. Gov Rep Announce Index (U.S.) 1979, 79(11), 80.

*Mentzer, KD. 1999. Written communication (May 18, 1999) to Dr. Adam Finkel, Director of Health Standards, OSHA regarding voluntary health and safety partnership program for fiber glass, rock and slag wool fiber products.

Miettinen OS, Rossiter CE. 1990. Man-made mineral fibers and lung cancer. Scand J Work Environ Health 16(4):221-231.

*Milby TH, Wolf CR. 1969. Respiratory tract irritation from fibrous glass inhalation. J Occup Med 11(8):409-410.

9. REFERENCES

Miller BG, Jones AD, Searl A, et al. 1999. 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. 1999. 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, Hudspith BN, Meredith C. 1994. The effect of MMMF on the kinetics of cytokine expression in murine lung populations: Role in fibre-induced disease. NATO ASI Ser H 85:79-90.

*Miller ME, Lees PSJ, Breysse PN. 1995. A comparison of airborne man-made vitreous fiber concentrations before and after installation of insulation in a new construction housing. Appl Occup Environ Hyg 10(3):182-187.

Milton DK, Walters MD, Hammond K, et al. 1996a. Worker exposure to endotoxin, phenolic compounds, and formaldehyde in a fiberglass insulation manufacturing plant. Am Ind Hyg Assoc J 57:889-896.

Milton DK, Wypij D, Kriebel D, et al. 1996b. Endotoxin exposure-response in a fiberglass manufacturing facility. Am J Ind Med 29:3-13.

*Minamoto K, Nagano M, Inaoka T, et al. 2002. Skin problems among fiber-glass reinforced plastics factory workers in Japan. Ind Health 40:42-50.

Mirer FE, Park RM. 1993. A case-control study of malignant and non-malignant disease among employees of a fiberglass manufacturing facility. Comments. Br J Ind Med 50(3):287.

Mitchell RI, Donofrio DJ, Moorman WJ. 1986. Chronic inhalation toxicity of fibrous glass in rats and monkeys. J Am Coll Toxicol 5(6):545-575.

Miyamoto K, Hiramatsu K, Ohtaki Y, et al. 1995. Effects of gomisin A on the promotor action and serum bile acid concentration in hepatocarcinogenesis induced by 3'-methyl-4-dimethylamino-azobenzene. Biol Pharm Bull 18(10):1443-1445.

*Mohr U, Pott F, Vonnahme FJ. 1984. Morphological aspects of mesotheliomas after intratracheal instillations of fibrous dusts in Syrian golden hamsters. Exp Pathol 26(3):179-183.

Monchaux G, Bignon J, Hirsch A, et al. 1982. Translocation of mineral fibres through the respiratory system after injection into the pleural cavity of rats. Ann Occup Hyg 26(1-4):309-318.

*Monchaux G, Bignon J, Jaurand MC, et al. 1981. Mesotheliomas in rats following inoculation with acid-leached chrysotile asbestos and other mineral fibers. Carcinogenesis 2(3):229-236.

Moolgavkar SH, Brown RC, Turim J. 2001a. Biopersistence, fiber length, and cancer risk assessment for inhaled fibers. Inhal Toxicol 13(9):755-772.

Moolgavkar SH, Luebeck EG, Turim J, et al. 2000. Lung cancer risk associated with exposure to man-made fibers. Drug Chem Toxicol 23(1):223-242.

Moolgavkar SH, Turim J, Brown RC, et al. 2001b. Long man-made fibers and lung cancer risk. Regul Toxicol Pharmacol 33:138-146.

Moore MA, Boymel PM, Maxim LD. 2002. Categorization and nomenclature of vitreous silicate wools. Regul Toxicol Pharmacol 35(1):1-13.

*Morgan RW. 1981. Mortality study of fibrous glass production workers. Arch Environ Health 36:179-183.

Morgan A. 1994. In vivo evaluation of chemical biopersistence of man-made mineral fibers. Environ Health Perspect 102:127-131.

*Morgan A. 1995. Deposition of inhaled asbestos and man-made mineral fibers in the respiratory tract. Ann Occup Hyg 39(5):747-758.

*Morgan A, Holmes A. 1980. Concentrations and dimensions of coated and uncoated asbestos fibres in the human lung. Br J Ind Med 37:25-32.

Morgan A, Holmes A. 1984. Solubility of rockwool fibres *in vivo* and the formation of pseudo-asbestos bodies. Ann Occup Hyg 28(3):307-314.

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, Black A, Evans N, et al. 1980. Deposition of sized glass fibres in the respiratory tract of the rat. Ann Occup Hyg 23:353-366.

*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 182-190.

Morgan A, Davis JA, Mattson SM, et al. 1994b. Effect of chemical composition on the solubility of glass fibres *in vivo* and *in vitro*. Ann Occup Hyg 38:609-617.

*Morgan A, Holmes A, Davison W. 1982. Clearance of sized glass fibres from the rat lung and their solubility in vivo Ann Occup Hyg 25(3):317-331.

*Morgan A, Morris KJ, Launder KA, et al. 1994a. Retention of glass fibers in the rat trachea following administration by intratracheal instillation. Inhal Toxicol 6:241-251.

*Morgan A, Talbot RJ, Holmes A. 1978. Significance of fibre length in the clearance of asbestos fibres from the lung. Br J Ind Med 35:146-153.

Morimoto Y, Tanaka I. 2001. *In vivo* studies of man-made mineral fibers- Fibrosis-related factors. Ind Health 39(2):106-113.

*Morimoto Y, Kido M, Tanaka I, et al. 1993. Synergistic effects of mineral fibres and cigarette smoke on the production of tumour necrosis factor by alveolar macrophages of rats. Br J Ind Med 50(10):955-960.

9. REFERENCES

Morimoto Y, Tsuda T, Hirohashi M, et al. 1999. Effects of mineral fibers on the gene expression of proinflammatory cytokines and inducible nitric-oxide synthase in alveolar macrophages. Ind Health 37(3):329-334.

Morimoto Y, Tsuda T, Hori H, et al. 1999. Combined effect of cigarette smoke and mineral fibers on the gene expression of cytokine mRNA. Environ Health Perspect 107(6):495-500.

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(5):1247-1251.

Morimoto Y, Tsuda T, Yamato H, et al. 2001. Comparison of gene expression of cytokines mRNA in lungs of rats induced by intratracheal instillation and inhalation of mineral fibers. Inhal Toxicol 13(7):589-601.

Morris GF, Brody AR. 1999. Stressing fibrogenesis in cell culture. Am J Respir Cell Mol Biol 21(4):447-448.

Morris KJ, Collier CG, Eastes W, et al. 1996. Comparison of biopersistence of experimental glass fibres in the lung and peritoneal cavity. Exp Toxicol Pathol 48(6):490-493.

*Morris KJ, Launder KA, Morgan A, et al. 1995. Preliminary data from investigations of the in vivo biopersistence of three experimental glass fibres of varying chemical composition. Exp Toxicol Pathol 47(2-3):179-182.

*Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. Clin Pharmacokin 5:485-527.

Morton WE. 2002. Comment on historical cohort study of U.S. man-made vitreous fiber production workers. Letters to the editor. J Occup Environ Med 44(2):106-108.

Mossman BT. 1988. Carcinogenic potential of asbestos and nonasbestos fibers. J Environ Sci Health Part C Environ Carcinogen Rev 6(2):151-195.

*Mossman BT, Churg A. 1998. Mechanisms in the pathogenesis of asbestosis and silicosis. Am J Respir Crit Care Med 157:1666-1680.

Moulin JJ, Mur JM, Wild P, et al. 1986. Oral cavity and laryngeal cancers among man-made mineral fiber production workers. Scand J Work Environ Health 12(9):27-31.

*Moulin JJ, Wild P, Mur JM, et al. 1988. Respiratory health assessment by questionnaire of 2024 workers involved in man-made miner fiber production. Int Arch Occup Environ Health 61(3):171-178.

*Muhle H, Bellmann B. 1995. Biopersistence of man-made vitreous fibres. Ann Occup Hyg 39(5):655-660.

*Muhle H, Bellmann B. 1997. Significance of the biodurability of man-made vitreous fibers to risk assessment. Environ Health Perspect 105:1045-1047.

9. REFERENCES

Muhle H, Mangelsdorf I. 2003. Inahalation toxicity of mineral particles: Critical appraisal of endpoints and study design. Toxicol Lett 140-141:223-228.

Muhle H, Pott F. 2000. Asbestos as reference material for fibre-induced cancer. Int Arch Occup Environ Health 73:S53-S59.

Muhle H, Bellmann B, Pott F. 1994. Comparative investigations of the biodurability of mineral fibers in the rat lung. Environ Health Perspect 102:163-168.

*Muhle H, Pott F, Bellman B, Takenaka S, et al. 1987. Inhalation and injection experiments in rats to test the carcinogenicity of MMMF. Ann Occup Hyg 31(4B):755-764.

Murata-Kamiya N, Tsutsui T, Fujino A, et al. 1997. Determination of carcinogenic potential of mineral fibers by 8-hydroxydeoxyguanosine as a marker of oxidative DNA damage in mammalian cells. Int Arch Occup Environ Health 70:321-326.

Murphy GB. 1961. Fiber glass pneumoconiosis. Arch Environ Health 3:102-108.

Musselman R. 1992. A case-control study of lung cancer in a cohort of workers potentially exposed to slog wool fibres. Br J Ind Med 49(6):454.

*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., eds. 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(5):139-143.

*Myojo T. 1987. Deposition of fibrous aerosol in model bifurcating tubes. J Aerosol Sci 18(3):337-347.

Myojo T. 1990. The effect of length and diameter on the disposition of fibrous aerosol in a model lung bifurcation. J Aerosol Sci 21(5):651-659.

Myojo T, Takaya M. 2001. Estimation of fibrous aerosol deposition in upper bronchi based on experimental data with model bifurcation. Ind Health 39:141-149.

Nadeau D, Fouquette-Couture L, Paradis D, et al. 1987. Cytotoxicity of respirable dusts from industrial minerals; comparison of two naturally occurring and two man-made silicates. Drug Chem Toxicol 10:49-86.

*NAIMA. 2002. Fiber glass and slag wool insulations- materials for a sustainable planet. North American Insulation Manufacturers Association. Publication No. 12.

*NAS/NRC. 1989. Report of the oversight committee. In: Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press.

*Nasr ANM, Ditchek T, Scholtens PA. 1971. The prevalence of radiographic abnormalities in the chests of fiber glass workers. J Occup Med 13(8):371-376.

## 9. REFERENCES

*Navy Environment Health Center. 1997. Man-made vitreous fibers. Technical Manual NEHC-TM6290-1. Rev. A.

Nejjari A, Fournier J, Pezerat H, et al. 1993. Mineral fibres: Correlation between oxidizing surface activity and DNA base hydroxylation. Br J Ind Med 50(6):501-504.

*Newball HH, Brahim SA. 1976. Respiratory response to domestic fibrous glass exposure. Environ Res 12:201-207.

*NIOSH. 1976. Occupational exposure to fibrous glass. Proceedings of a Symposium. Washington, DC: National Institute for Occupational Safety and Health, 33-61, 83-89, 193-204.

*NIOSH. 1977. Occupational exposure to fibrous glass-criteria for a recommended standard. National Institute for Occupational Safety and Health.

*NIOSH. 1992. Pocket guide to chemical hazards. National Institute for Occupational Safety and Health.

*NIOSH. 1994a. Asbestos (bulk) by PLM. NIOSH Manual of Analytical Methods (NMAM), Fourth Edition, 8/15/94. National Institute for Occupational Safety and Health.

NIOSH. 1994b. NIOSH manual of analytical methods. NIOSH method 7400. 4th ed. National Institute for Occupational Safety and Health.

*NIOSH. 1999. Work-related lung disease surveillance report 1999. U.S. Department of Health and Human Services, Division of Respiratory Disease Studies. National Institute for Occupational Safety and Health. Washington, DC.

*NIOSH. 2002. NIOSH pocket guide to chemical hazards. National Institute for Occupational Safety and Health. Wysiwyg://157//http://www.cdc.gov/nIOSH/npg/npg.html. May 07, 2002.

*NRC. 1993. National Research Council. Pesticides in the diets of infants and children. Washington, DC: National Academy Press.

*NRC Subcommittee on Manufactured Vitreous Fibers. 2000. Review of the U.S. Navy's Exposure Standard for manufactured vitreous fibers. National Academy of Sciences, National Research Council, Washington, DC: National Academy Press.

*NTP. 1994. 7th Report on carcinogens. National Toxicology Program. http://ntp-server.niehs.nih.gov/Main_pages/NTP_7RoC_pg.html. May 07, 2002.

*NTP. 1998. 8th Report on carcinogens. National Toxicology Program. http://ntp-server.niehs.nih.gov/Main_pages/NTP_8RoC_pg.html. May 07, 2002.

*NTP. 2000. 9th Report on carcinogens. National Toxicology Program. http://ehp.niehs.nih.gov/roc/toc9.html. May 07, 2002.

*NTP. 2002. 10th Report on carcinogens. National Toxicology Program. http://ehp.niehs.nih.gov/roc/toc9.html. January 17, 2004.

*Oberdörster G. 1994. Respiratory tract dosimetry of particles: implications for setting of exposure concentrations and extrapolation modeling. Proceedings of an international symposium: IPCS Joint Series No. 18, 83-110.

*Oberdörster G. 2000. Determinants of the pathogenicity of man-made vitreous fibres (MMVF) Int Arch Occup Environ Health 73:S60-S68.

Oberdörster G. 2002. Toxicokinetics and effects of fibrous and nonfibrous particles. Inhal Toxicol 14:29-56.

Ohyama M, Otake T, Morinaga K. 2000. The chemiluminescent response from human monocyte-derived macrophages exposed to various mineral fibers of different sizes. Ind Health 38(3):289-293.

Ohyama M, Otake T, Morinaga K. 2001. Effect of size of man-made and natural mineral fibers on chemiluminescent response in human monocyte-derived macrophages. Environ Health Perspect 109(10):1033-1038.

Ojajarvi IA, Partanen TJ, Ahblom A, et al. 2000. Occupational exposures and pancreatic cancer: A meta-analysis. Occup Environ Med 57(5):316-324.

*Okabe K, Murthy GGK, Vallarino JA, et al. 1997. Deposition efficiency of inhaled fibers in the hamster lung. Inhal Toxicol 9(2):85-98.

Okabe K, Vallarino JA, Murthy GGK, et al. 1996. Dissolution of slagwool fibers in the filter clearing and mounting step in preparation for counting. Inhal Toxicol 8(3):263-270.

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.

*Olsen JH, Jensen OM. 1984. Cancer incidence among employees in one mineral wool production plant in Denmark. Scand J Work Environ Health 10:17-24.

*Olsen JH, Jensen OM, Kampstrup O. 1986. Influence of smoking habits and place of residence on the risk of lung cancer among workers in one rock-wool producing plant in Denmark. Scand J Work Environ Health 12:48-52.

*Ong T, Lui Y, Zhong B-Z, et al. 1997. Induction of micronucleated and mutinucleated cells by man-made fibers in vitro in mammalian cells. J Toxicol Environ Health 50(4):409-414.

Osgood CJ. 1994. Refractory ceramic fibers (RFCs) induce germline aneuploidy in Drosophila oocytes. Mutat Res 324(1-2):23-27.

*OSHA. 1992. U.S. Department of Labor, Occupational Safety and Health Administration. 57:7877-7878, 24310-24331, 49657-49661.

*OSHA. 1999. OSHA endorses major agreement to protect workers exposed to fiberglass insulation. Occupational Safety and Health Administration. http://www.osha-slc.gov/media/oshanews/may99/trade-19990518.html. May 07, 2002.

9. REFERENCES

OSHA. 2001a. Asbestos. Occupational safety and health standards. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1001. http://www.osha.gov/pls/oshaweb/owa...ARDS&p-id=9995&p-text-version=FALSE. May 07, 2002.

*OSHA. 2001b. Synthetic mineral fibers. Occupational Safety and Health Administration. http://www.osha.gov/SLTC/syntheticmineralfibers/index.html. May 07, 2002.

*OSHA. 2002. Synthetic mineral fibers. Occupational Safety and Health Administration. http://www.osha.gov/oshinfo/priorities/synthetic.html. May 07, 2002.

*Oshimura M, Hesterberg TW, Tsutsui T, et al. 1984. Correlation of asbestos-induced cytogenic effects with cell transformation of Syrian hamster embryo cells in culture. Cancer Res 44(11):5017-5022.

*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.

Pang TWS. 2000. Precision and accuracy of asbestos fiber counting by phase contrast microscopy. Environ Sci Technol 61(4):529-538.

*Pang TWS, Schonfeld-Starr FA, Patel K. 1989. An improved membrane filter technique for evaluation of asbestos fibers. Am Ind Hyg Assoc J 50(3):174-190.

Pelin K, Kivipensas P, Linnainmaa K. 1995. 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.

*Peraud A, Riebe-Imre M. 1994. Toxic and chromosomal-damaging effects of natural and man-made mineral fibers in epithelial lung cells in vitro. In: Dungworth DL, Mauderly JL, Oberdorster G, eds. Toxic and carcinogenic effects of solid particles in the respiratory tract. Washington, DC: ILSI Press, 569-574.

*Perrault G, Dion C, Cloutier Y. 1992. Sampling and analysis of mineral fibers on construction sites. Appl Occup Environ Hyg 7(5):323-326.

*Petersen R, Sabroe S. 1991. Irritative symptoms and exposure to mineral wool. Am J Ind Med 20(1):113-122.

*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.

*Pickrell JA, Hill JO, Carpenter RL, et al. 1983. *In vitro* and *in vivo* response after exposure to man-made mineral and asbestos insulation fibers. Am Ind Hyg Assoc J 44(8):557-561.

Pigott GH, Ishmael J. 1981. An assessment of the fibrogenic potential of 2 refractory fibers by intraperitoneal injection in rats. Toxicol Lett 8(3):153-164.

Pigott GH, Ishmael J. 1992. The effects of intrapleural injections of alumina and aluminosilicate (ceramic) fibers. Int J Exp Pathol 73:137-146.

## 9. REFERENCES

*Plato N, Gustavsson P, Krantz S. 1997. Assessment of past exposure to man-made vitreous fibers in the Swedish prefabricated house industry. Am J Ind Med 32(4):349-354.

Plato N, Krantz S, Andersson L, et al. 1995a. Characterization of current exposure to man-made vitreous fibres (MMVF) in the prefabricated house industry in Sweden. Ann Occup Hyg 39(2):167-179.

Plato N, Krantz S, Gustavsson P, et al. 1995b Fiber exposure assessment in the Swedish rock wool and slag wool production industry in 1938-1990. Scand J Work Environ Health 21(5):345-352.

*Plato N, Westerholm P, Gustavsson P, et al. 1995c. Cancer incidence, mortality and exposure-response among Swedish man-made vitreous fiber production workers. Scand J Work Environ Health 21(5):353-361.

*Pohlabein H, Jockel K-H, Bruske-Hohlfeld I, et al. 2000. Lung cancer and exposure to man-made vitreous fibers: Results from a pooled case-control study in Germany. Am J Ind Med 37:469-477.

*Possick PA, Gellin GA, Key MM. 1970. Fibrous glass dermatitis. Am Ind Hyg Assoc J 37:12-15.

Pott F. 1980. Animal experiments on biological effects of mineral fibres. In: Wagner JC, Davis W, eds. Biological effects of mineral fibers. IARC Sci Publ 30:261-272.

Pott F. 1995. Detection of mineral fibre carcinogenicity with the intraperitoneal test recent results and their validity. Ann Occup Hyg 39(5):771-779.

Pott F, Roller M. 1998. [How far can carcinogenicity studies of fiber types be substituted by data on their biopersistence?] Geharstoffe Reinhalt Luft 58(3):85-91. (German)

Pott F, Dungworth DL, Heinrich U, et al. 1994. Lung tumours in rats after intratracheal instillation of dusts. Ann Occup Hyg 38:357-363.

Pott F, Friedrichs KH, Huth F. 1975. [Carcinogenic effects of fibrous dusts.] EUR 2:715-724. (German)

*Pott F, Freidrichs K-H, Huth F. 1976. Results of animal experiments concerning the carcinogenic effect of fibrous dusts and their interpretation with regard to the carcinogenesis in humans. Zbl Bakt Hyg I Abt Orig B 162:467-505.

Pott F, Huth F, Friedrichs KH. 1974. Tumorigenic effect of fibrous dusts in experimental animals. Environ Health Perspect 9:313-315.

Pott F, Huth F, Spurny K. 1980. Tumour induction after intraperitoneal injection of fibrous dusts. In: Wagner JC, Davis W, eds. Biological effects of mineral fibres. IARC Sci Publ 30:337-342.

Pott F, Roller M, Kamino K, et al. 1994. Significance of durability of mineral fibers for their toxicity and carcinogenic potency in the abdominal cavity of rats in comparison with the low sensitivity of inhalation studies. Environ Health Perspect 102:145-150.

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.

## 9. REFERENCES

*Pott F, Schllipkoter HW, Ziem U. 1984. New results from implantation experiments with mineral fibres. Proceedings of the World Health Organization Conference, 286-302.

Pott F, Ziem U, Mohr U. 1983. Lung carcinomas and mesotheliomas following intratracheal instillation of glass fibres and asbestos. Report held on the VI$^{th}$ International Pneumoconiosis Conference, September 20-23, 1983.

*Pott F, Ziem L, Reiffer FJ, et al. 1987. Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats. Exp Pathol 32:129-152.

*Potter RM, Mattson SM. 1991. Glass fibre dissolution in a physiological saline solution. Glastech Ber 64:16-28.

*Quinn MM, Smith TJ, Youk AO, et al. 2001. Historical cohort study of US man-made vitreous fiber production workers: VIII. Exposure-specific job analysis. J Occup Environ Med 43:824-834.

Randall REG, DuToit RSJ. 1994. The retention and clearance of glass fibre and different varieties of asbestos by the lung. Ann Occup Hyg 38:757-761.

*Renne RA, Eldridge SR, Lewis TR, et al. 1985. Fibrogenic potential of intratracheally instilled quartz, ferric oxide, fibrous glass, and hydrated alumina in hamsters. Toxicol Pathol 13:306-314.

Rice CH, Lockey JE, Lemasters GK, et al. 1997. Estimation of historical and current employee exposure to refractory ceramic fibers during manufacturing and related operations. Appl Occup Environ Hyg 12(1):54-61.

Riebe-Imre M, Aufderheide M, Emura M, et al. 1994. Comparative studies with natural and man-made mineral fibres in vitro and in vivo. NATO ASI Ser H 85:273-284.

*Rindel A, Bach E, Breum NO, et al. 1987. Correlating health effects with indoor air quality in kindergartens. Int Arch Occup Environ Health 59:363-373.

*Robinson CF, Dement JM, Ness GO, et al. 1982. Mortality patterns of rock and slag mineral wool production workers: an epidemiological and environmental study. Br J Ind Med 39(1):45-53.

*Rodelsperger K, Woitowitz HJ. 1995. Airborne fibre concentrations and lung burden compared to the tumour response in rats and humans exposed to asbestos. Ann Occup Hyg 39(5):719-725.

*Rodelsperger K, Jockel K-H, Pohlabein H, et al. 2001. Asbestos and man-made vitreous fibers as risk factors for diffuse malignant mesothelioma: Results from a German hospital-based case-control study. Am J Ind Med 39(3):262-275.

*Roggli VL. 1989. Nonasbestos mineral fibers in human lungs. Microbeam Analysis 24:57-59.

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 Suppl 105(5):1253-1256.

Rood AP. 1988. Size distribution of airborne ceramic fibres as determined by transmission electron microscopy. Ann Occup Hyg 32(2):237-240.

Rood AP, Streeter RR. 1985. Size distributions of airborne superfine man-made mineral fibers determined by transmission electron microscopy. Am Ind Hyg Assoc J 46(5):257-261.

Rossiter CE. 1993. Pulmonary effects of exposure to fine fiberglass: irregular opacities and small airways obstruction. Br J Ind Med 50:382-383.

*Rossiter CE, Gilson JC, Sheers G, et al. 1994. Refractory ceramic fibre production workers. Analysis of radiograph readings. Ann Occup Hyg 38:731-738.

Rouyer E, Lehuede P, Chopinet M-H. 1995. Corrosion mechanisms of glass fibers by physiological fluid in in-vitro tests. Verre 1:621-624.

Rowe JN, Springer JA. 1986. Asbestos lung cancer risks: Comparison of animal and human extrapolations. Risk Anal 6(2):171-180.

Ruotsalainen M, Hirvonen M-R, Luoto K. 1999. Production of reactive oxygen species by man-made vitreous fibres in human polymorphonuclear leukocytes. Hum Exp Toxicol 18(6):354-362.

Rutten A, Bermudez E, Mangum J, et al. 1994a. Pleural pathology in hamsters and rats exposed to instilled man-made vitreous fibers. In: Dungworth DL, Mauderly JL, Oberdorster G, eds. Toxic and carcinogenic effects of solid particles in the respiratory tract. Washington, DC: ILSI Press, 595-598.

Rutten AA, Bermudez E, Mangum JB, et al. 1994b. Mesothelial cell proliferation induced by intrapleural instillation of man-made fibers in rats and hamsters. Fundam Appl Toxicol 23(1):107-117.

Saffiotti U. 1998. Respiratory tract carcinogenesis by mineral fibres and dusts: models and mechanisms. Monaldi Arch Chest Dis 53(2):160-167.

Sahle W, Laszlo I. 1996. Airborne inorganic fibre level monitoring by transmission electron microscope (TEM): Comparison of direct and indirect sample transfer methods. Ann Occup Hyg 40(1):29-44.

*Sali D, Boffetta P, Andersen A, et al. 1999. Non-neoplastic mortality of European workers who produce man made vitreous fibres. Occup Environ Med 56:612-617.

*Sanden A, Jarvholm B. 1986. Pleural plaques, respiratory symptoms and respiratory function in shipyard workers exposed to man-made mineral fibres. J Soc Occup Med 36:86-89.

Saracci R. 1986. Ten years of epidemiologic investigations on man-made mineral fibers and health. Scand J Work Environ Health 12:5-11.

*Saracci R, Simonato L, Acheson ED, et al. 1984. Mortality and incidence of cancer of workers in the man made vitreous fibres producing industry: an international investigation at 13 European plants. Br J Ind Med 41:425-436.

*Scansetti G, Pira E, Botta GC, et al. 1993. Asbestos exposure in a steam-electric generating plant. Ann Occup Hyg 37(6):645-655.

9. REFERENCES

*Schneider T. 1986. Manmade mineral fibers and other fibers in the air and settled dust. Environ Int 12:61-65.

Schneider T, Skotte J. 1990. Fiber exposure reassessed with the new indices. Environ Res 51:108-116.

*Schneider T, Stokholm J. 1981. Accumulation of fibres in the eyes of workers handling man-made mineral fiber products. Scand J Work Environ Health 7(7):271-276.

*Schneider T, Burdett G, Martinon L, et al. 1996. Ubiquitous fiber exposure in selected sampling sites in Europe. Scand J Work Environ Health 22(4):274-284.

Schneider T, Gibbs GW, Burdett G, et al. 1997. Testing fibre release from insulation products: Report on a workshop. Ann Occup Hyg 41(5):605-607.

Schneider T, Husemoen T, Olsen E, et al. 1993. Airborne fibre concentration during standardized building insulation with bonded man-made vitreous fibre insulation material having different nominal diameters and oil content. Ann Occup Hyg 37(6):631-644.

*Schneider T, Nielsen O, Bredsdorff P, et al. 1990. Dust in buildings with man-made mineral fiber ceiling boards. Scand J Work Environ Health 16:434-439.

Schneider T, Skotte J, Nissen P. 1985. Man-made mineral fiber size fractions and their interrelation. Scand J Work Environ Health 11(2):117-122.

*Scholze H, Conradt R. 1987. An in vitro study of the chemical durability of siliceous fibres. Ann Occup Hyg 31(4B):683-692.

Schuman LD, Infante PF. 1993. Synthetic mineral fibers. J Occup Med 35(12):1173-1177.

*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, Cullen RT. 1997. An enzymatic tissue digestion method for fibre biopersistence studies. Ann Occup Hyg 41(6):721-727.

*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, Vergnon JM, Blanchard O, et al. 1994. Durability of ceramic fibres in the human lung. Preliminary results. Ann Occup Hyg 38:723-730.

Sernau R, Cortina T, Zito M, et al. 1984. Genotoxicity of asbestos and fiberglass in the Chinese hamster ovary (CHO) HGRPT forward mutation and sister chromatid exchange assays. Environ Mutagen 6:422-423.

*Setchell BP, Waites GMH. 1975. The blood-testis barrier. In: Creep RO, Astwood EB, Geiger SR, eds. Handbook of physiology: Endocrinology V. Philadelphia, PA: WB Saunders, 222-238.

*Shannon HS, Hayes M, Julian JA, et al. 1984. Mortality experience of glass fibre workers. Br J Ind Med 41:35-38.

*Shannon HS, Jamieson E, Julian JA, et al. 1987. Mortality experience of Ontario glass fibre workers - extended follow-up. Ann Occup Hyg 31(4B):657-662.

*Shannon HS, Jamieson E, Julian JA, et al. 1990. Mortality of glass filament (textile) workers. Br J Ind Med 47(5):533-536.

Shaw GR, Connell DW. 1994. Prediction and monitoring of the carcinogenicity of polycyclic aromatic compounds (PACs). Rev Environ Contam Toxicol 135:1-62.

*Simonato L, Fletcher AC, Cherrie J, et al. 1986a. The man-made mineral fiber European historical cohort study. Scand J Work Environ Health 12:34-47.

Simonato L, Fletcher AC, Cherrie J, et al. 1986b. Updating lung cancer mortality among a cohort of man-made mineral fibre production workers in seven European countries. Cancer Lett 30(2):189-200.

*Simonato L, Fletcher AC, Cherrie JW, et al. 1987. The International Agency for Research on Cancer historical cohort study of MMMF production workers in seven European countries: Extension of the follow-up. Ann Occup Hyg 31(4B):603-623.

*Sincock AM, Delhanty JDA, Casey G. 1982. A comparison of the cytogenetic response to asbestos and glass fibre in Chinese hamster and human cell lines. Mutat Res 101(3):257-268.

*Sjogren B. 2000. Non-neoplastic mortality of European workers who produce man-made vitreous fibres. Occup Environ Med 57:284-288.

*Smith DM, Ortiz LW, Archuleta RF, et al. 1987. Long-term health effects in hamsters and rats exposed chronically to man-made vitreous fibres. Ann Occup Hyg 31(4B):731-754.

*Smith TJ, Quinn MM, Marsh GM, et al. 2001. Historical cohort study of US man-made vitreous fiber production workers: VII. Overview of the exposure assessment. J Occup Environ Med 43(9):809-823.

*Spruny KR. 1994. Sampling, analysis, identification and monitoring of fibrous dusts and aerosols. Analyst 119:41-51.

Spurny KR, Pott F, Stober W, et al. 1983. On the chemical changes of asbestos fibers and MMMFs in biologic residence and in the environment: Part I. Am Ind Hyg Assoc J 44(11):833-845.

*Stam-Westerveld EB, Coenraads PJ, vanderValk PGM, et al. 1994. Rubbing test responses of the skin to man-made mineral fibres of different diameters. Contact Dermatitis 31:1-4.

*Stanton MF, Wrench C. 1972. Mechanisms of mesothelioma induction with asbestos and fibrous glass. J Natl Cancer Inst 48:797-822.

*Stanton WF, Layard M, Tegeris A, et al. 1977. Carcinogenicity of fibrous glass: Pleural response in the rat in relation to fiber dimension. J Natl Cancer Inst 58(3):587-597.

Steenland K, Stayner L. 1997. Silica, asbesots, man-made mineral fibers, and cancer. Cancer Causes Control 8:491-503.

9. REFERENCES

*Stöber W. 1972. Dynamic shape factors of nonspherical aerosol particles. In: Mercer TT, Morrow PE, Stober W, eds. Assessment of airborne particles. Springfield: Charles C. Thomas, 249-289.

*Stöber 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(6):539-598.

*Stockholm J, Norn M, Schneider T. 1982. Ophthalmologic effects of man-made mineral fibers. Scand J Work Environ Health 8(3):185-190.

Stone RA, Marsh GM, Youk AO, et al. 1996. Statistical estimation of exposure to fibres in jobs for which no direct measurements are available. Occup Hyg 3:91-101.

*Stone RA, Youk AO, Marsh GM, et al. 2001. Historical cohort study of US man-made vitreous fiber production workers: IV Quantitative exposure-response analysis of the nested case-control study of respiratory system cancer. J Occup Environ Med 43(9):779-792.

Strubel G, Fraij B, Rodelsperger K, et al. 1986. Man-made mineral fibers in the working environment. Letter to the editor. Am J Ind Med 10(1):101-102.

*Switala ED, Harlan RC, Schlaudecker DG, et al. 1994. Measurement of respirable glass and total fiber concentrations in the ambient air around a fiberglass wool manufacturing facility and a rural area. Regul Toxicol Pharmacol 20(3 part 2):S76-S88.

Takahashi T, Munakata M, Takekawa H, et al. 1996. Pulmonary fibrosis in a carpenter with long-lasting exposure to fiberglass. Am J Ind Med 30:596-600.

Tanaka I, Oyabu T, Ishimatsu S. 1994a. Pulmonary deposition and clearance of glass fiber in rat lungs after long-term inhalation. Environ Health Perspect 102:215-216.

Tanaka I, Shutou T, Ishimatsu S. 1994b. Pulmonary deposition and clearance of glass fibre in rats after continuous inhalation. Ann Occup Hyg 38:753-756.

Tanaka I, Yamato H, Oyabu T, et al. 2001. Biopersistence of man-made fibers by animal inhalation experiments in recent reports. Ind Health 39(2):114-118.

*Tarvainen K, Jolanki R, Forsman-Gronholm L, et al. 1993. Exposure, skin protection and occupational skin diseases in the glass-fibre-reinforced plastics industry. Contact Dermatitis 29(3):119-127.

*Teppo L, Kojonen E. 1986. Mortality and cancer risk among workers exposed to man-made mineral fibers in Finland. Scand J Work Environ Health 12:61-64.

*Thriene B, Sobottka A, Willer H, et al. 1996. Man-made mineral fibre boards in buildings- health risks caused by quality deficiencies. Toxicol Lett 88(1-3):299-303.

*TIMA Inc. 1993. Man-made vitreous fibers: Nomenclature, chemical and physical properties, Stamford, CT: TIMA Inc., 1-70.

*Timbrell V. 1965. The inhalation of fibrous dusts. Ann N Y Acad Sci 132:255-273.

Timbrell V. 1972. Inhalation and biological effects of asbestos. In: Mercer TT, Morrow PE, Stober W, eds. Assessment of airborne particles fundamentals, applications and implications to inhalation toxicity. Springfield, IL: Charles C Thomas, 429-445.

*Timbrell V. 1982. Deposition and retention of fibres in the human lung. Ann Occup Hyg 26(1-4):347-369.

Tran CL, Jones AD, Miller BG, et al. 2003. Modeling the retention and clearance of manmade vitreous fibers in the rat lung. Inhal Toxicol 15:553-587.

*Trethowan WN, Burge PS, Rossiter CE. 1995. Study of the respiratory health of employees in seven European plants that manufacture ceramic fibres. Occup Environ Med 52:97-104.

*TRI01. 2003. 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/. May 08, 2001.

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(5):1173-1178.

*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.

*Turim J, Brown RC. 2003. A dose-response model for refractory ceramic fibers. Inhal Toxicol 15:1103-1118.

Unfried K, Roller M, Pott F, et al. 1997. Fiber-specific molecular features of tumors induced in rat peritoneum. Environ Health Perspect Suppl 105(5):1103-1108.

*USDOC. 2002. US General exports and imports. United States Department of Commerce.
USITC. 1995. Industry and trade summary. Manmade fibers. USITC Publication 2874.

Valberg PA, Blanchard JD. 1991. Pulmonary macrophage physiology: Origin, motility, endocytosis. In: Parent RA, ed. Comparative biology of the normal lung. Vol 1, Chapter 36. Boca Raton, FL: CRC Press, Inc.

*Vallarino J, Spengler JD, Buck R, et al. 2003. Quantifying synthetic vitreous fiber surface contamination in office buildings. Am Ind Hyg Assoc J 64:80-87.

van den Bergen EA, Rocchi PSJ, Boogaard PJ. 1994. Ceramic fibers and other respiratory hazards during the renewal of the refractory lining in a large industrial furnace. Appl Occup Environ Hyg 9(1):32-35.

Van Graft M, Spit BJ, Immel HR, et al. 1986. Pulmonary response of hamsters to fibrous glass. Clearance and morphology after a single intratracheal instillation. Exp Pathol 29(4):197-209.

VanOrden DR. 2000. Counting rules for vitreous fiber exposures. Am Ind Hyg Assoc J 61(4):454.

9. REFERENCES

*Veblin DR, Wylie AG. 1993. Mineralogy of amphiboles and 1:1 layer silicates. In: Gutherie GD, Mossman BT, eds. MSA reviews in mineralogy, Volume 28. Health effects of mineral dusts, 61-137.

*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.

Vu VT. 1994. Assessment of the potential health effects of natural and man-made fibers and their testing needs: Perspectives of the U.S. Environmental Protection Agency. In: Dungworth DL, Mauderly JL, Oberdörster G, eds. Toxic and carcinogenic effects of solid particles in the respiratory tract. Washington, DC: ILSI Press, 367-384.

Vu VT, Dearfield KL. 1993. Biological effects of fibrous materials in experimental studies and related regulatory aspects. In: Warheit D, ed. Fiber toxicology. Chapter 18. San Diego, CA: Academic Press, Inc., 449-492.

Vu VT, Lai DY. 1997. Approaches to characterizing human health risks of exposure to fibers. Environ Health Perspect 105: 1329-1336.

Wagner JC, Berry G, Timbrell V. 1973. Mesotheliomata in rats after inoculation with asbestos and other materials. Br J Cancer 28(2):173-185.

Walker AM, Maxim LD, Utell M. 2002. Risk analysis for mortality from respiratory tumors in a cohort of refractory ceramic fiber workers. Regul Toxicol Pharmacol 35(1):95-104.

Wang Q-E, Han C-H, Wu W-D, et al. 1999a. Biological effects of man-made mineral fibers (1) Reactive oxygen species production and calcium homeostasis in alveolar macrophages. Ind Health 37(1):62-67.

*Wang Q-E, Han C-H, Yang Y-P, et al. 1999b. Biological effects of man-made mineral fibers (II) Their genetic damages examined by *in vitro* assay. Ind Health 37(3):342-347.

*Wardenbach P, Pott F, Woitowitz H-J. 2000. Differences between the classification of man-made vitreous fibers (MMVF) according to the European directive and German legislation: analysis of scientific data and implications for worker protection. Eur J Oncol 5:111-118.

Warheit DB. 1989. Interspecies comparisons of lung responses to inhaled particles and gases. CRC Crit Rev Toxicol 20:1-29.

Warheit DB, Hart GA, Hesterberg TW, et al. 2001. Potential pulmonary effects of man-made organic fiber (MMOF) dusts. Crit Rev Toxicol 31(6):697-736.

*Wastiaux A, Blanchard O, Honnons S. 1994. Possible application of urinary analysis to estimate dissolution of some man-made vitreous fibers. Environ Health Perspect 102:217-219.

Waterman LS, Purnell CJ, Anderson PWP. 1992. Airborne fibre levels associated with the use of MMMF brazing mats during welding operations. Ann Occup Hyg 34(1):97-99.

*Watkins DK, Chiazze L, Fryar C. 1997. History cohort mortality study of a continuous filament fiberglass manufacturing plant. II. Women and minorities. J Occup Environ Med 39(6):548-555.

Wedge R, Abt E, Bakshi K, et al. 2001. Review of the U.S. Navy's exposure standard for manufactured vitreous fibers. Inhal Toxicol 12(1):103-108.

*Weill H, Hughes JM, Hammad YY, et al. 1983. Respiratory health in workers exposed to man-made vitreous fibers. Am Rev Respir Dis 128:104-112.

Weiss W. 1993. Pulmonary effects of exposure to fine fibreglass: irregular opacities and small airways obstruction. Correspondence. Br J Ind Med 50:1054.

Weiss W. 1996. Epidemiology of fibrous glass and lung cancer: Letter to the editor. Am J Ind Med 30:105-108.

*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.

*Westerholm P, Bolander A-M. 1986. Mortality and cancer incidence in the man-made mineral fiber industry in Sweden. Scand J Work Environ Health 12 (Suppl 1):78-84.

*WHO. 1985. Reference methods for measuring synthetic mineral fibers (MMMF). WHO/EURO Technical Committee for evaluating MMMF. WHO, Copenhagen.

*WHO. 1988. Man-made mineral fibers. Environmental Health Criteria. Vol. 77. Geneva: World Health Organization.

*Whong W-Z, Gao H-G, Zhou G, et al. 1999. Genetic alterations of cancer-related genes in glass fiber-induced transformed cells. J Toxicol Environ Health A 56(6):397-404.

*Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Bronner F, eds. Mineral metabolism: An advanced treatise. Volume II. The elements Part A. New York: Academic Press.

*Wilson R, Langer AM, Nolan RP. 1999. A risk assessment for exposure to glass wool. Regul Toxicol Pharmacol 30:96-109.

Wong O, Musselman RP. 1994. An epidemiological and toxicological evaluation of the carcinogenicity of man-made vitreous fiber, with a consideration of coexposures. J Environ Pathol Toxicol 13(3):169-180.

*Wong O, Foliart D, Trent LS. 1991. A case-control study of lung cancer in a cohort of workers potentially exposed to slag wool fibres. Br J Ind Med 48:818-824.

Woodworth CD, Mossman BT, Craighead JE. 1983. Induction of squamous metaplasia in organ cultures of hamster trachea by naturally occurring and synthetic fibers. Cancer Res 43:4906-4912.

*Wright GW. 1968. Airborne fibrous glass particles. Arch Environ Health 16:175-181.

*Wright GW, Kuschner M. 1977. The influence of varying lengths of glass and asbestos on tissue response in guinea pigs. Ann Occup Hyg 2:455-474.

9. REFERENCES

Wu J-D, Milton DK, Hammond K, et al. 1999. Hierarchical cluster analysis applied to workers' exposures in fiberglass insulation manufacturing. Ann Occup Hyg 43(1):43-55.

*Wylie AG, Verkouteren JR. 2000. Amphibole asbestos from Libby, Montana: aspects of nomenclature. Am Mineral 85:1540-1542.

Xie C, Reusse A, Dai J, et al. 2000. TNF-α increases tracheal epithelial asbestos and fiberglass binding via a NF-kB-dependent mechanism. Am J Physiol Lung Cell Mol Physiol 2000:L608-L614.

*Xu GB, Yu CP. 1986. Effects of age on deposition of inhaled aerosols in the human lung. Aerosol Sci Technol 5:349-357.

Yamato H, Tanaka I, Higashi T, et al. 1992. Determinant factor for clearance of ceramic fibres from rat lungs. Br J Ind Med 49(3):182-185.

Yamato H, Tanaka I, Higashi T, et al. 1994. Clearance of inhaled ceramic fibers from rat lungs. Environ Health Perspect 102:169-171.

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(11):2751-2758.

*Yokosaki Y, Morimoto Y, Yamato H, et al. 1991. Cellular changes induced in rats lungs by inhalation of ceramic fibres. Toxicol Ind Health 7(5-6):479-483.

*Youk AO, Marsh GM, Stone RA, et al. 2001. Historical cohort study of US man-made vitreous fiber production workers: III. Analysis of exposure-weighted measures of respirable fibers and formaldehyde in the nested case-control study of respiratory system cancer. J Occup Environ Med 43(9):767-778.

*Yu CP, Oberdörster G. 2000. Dose-response and human cancer and non-cancer risk assessment of inhaled refractory ceramic fibers (RCF). Unpublished report to Dr. David Y. Lai. Washington, DC: U.S. Envirronmental Protection Agency.

Yu CP, Asgharian B, Yen BM. 1986. Impaction and sedimentation deposition of fibers in airways. Am Ind Hyg Assoc J 47(2):72-77.

*Yu CP, Dai T, Boymel PM, et al. 1998a. A clearance model of man-made vitreous fibers (MMVFs) in the rat lung. Inhal Toxicol 10(4):253-274.

*Yu CP, Dai YT, Ding YJ. 1998b. A retention model of man-man vitreous fibers (MMVFs) inhaled by rats. Aerosol Sci Technol 29(2):152-162.

*Yu, CP, Ding J, Zhang L, et al. 1995b. Deposition and clearance modeling of inhaled kaolin refractory ceramic fibers (RCF) in hamsters- comparison between species. Inhal Toxicol 7(2):165-177.

*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(1):151-159.

*Yu C, Ding Y, Zhang L, et al. 1997. Retention modeling of refractory ceramic fibers (RCF) in humans. Regul Toxicol Pharmacol 25:18-25.

9. REFERENCES

*Yu CP, Zhang L, Oberdörster G, et al. 1994. Clearance of refractory ceramic fibers (RCF) from the rat lung: Development of a model. Environ Res 65(2):243-253.

*Yu CP, Zhang L, Oberdörster G, et al. 1995a. Deposition of refractory ceramic fibers (RCF) in the human respiratory tract and comparison with rodent studies. Aerosol Sci Technol 23:291-300.

Zanjanian MH, Sahu A 1981. Anaphylactic reaction to fiber glass. Ann Allergy 47:157-158.

*Zhong B-Z, Ong T, Whong W-Z. 1997. Studies on the relationship between treatment condition and micronucleus induction in V79 cells exposed to silica and glass fibers. Mutat Res 39:111-116.

*Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12:29-34.

*Zoitos BK, DeMeringo A, Rouyer E, et al. 1997. In vitro measurement of fiber dissolution rate relevant to biopersistence at neutral pH: An interlaboratory round robin. Inhal Toxicol 9:525-540.

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.

*Zoltai, T. 1979. Asbestiform and acicular mineral fragments. Ann NY Acad Sci 330:621-643.

*Zoltai T. 1981. Amphibole asbestos mineralogy. In: Veblen DR, ed. Amphiboles and other hydrous particles. MSA reviews in mineralogy. Volume 28, 235-278.

# 10. GLOSSARY

**Absorption—**The taking up of liquids by solids, or of gases by solids or liquids.

**Acute Exposure—**Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

**Adsorption—**The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

**Adsorption Coefficient ($K_{oc}$)—**The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

**Adsorption Ratio (Kd)—**The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

**Benchmark Dose (BMD)—**Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD10 would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

**Benchmark Dose Model—**A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

**Bioconcentration Factor (BCF)—**The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

**Biomarkers—**Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

**Cancer Effect Level (CEL)—**The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

**Carcinogen—**A chemical capable of inducing cancer.

**Case-Control Study—**A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

**Case Report—**Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

**Case Series—**Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

**Ceiling Value—**A concentration of a substance that should not be exceeded, even instantaneously.

**Chronic Exposure—**Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

**Cohort Study—**A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

**Cross-sectional Study—**A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

**Data Needs—**Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

**Developmental Toxicity—**The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

**Dose-Response Relationship—**The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

**Embryotoxicity and Fetotoxicity—**Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

**Environmental Protection Agency (EPA) Health Advisory—**An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

**Epidemiology—**Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

**Genotoxicity—**A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

**Half-life—**A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

**Immediately Dangerous to Life or Health (IDLH)—**The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

**Incidence—**The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

**Intermediate Exposure—**Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

**Immunologic Toxicity—**The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

**Immunological Effects—**Functional changes in the immune response.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

**Lethal Concentration(LO) ($LC_{LO}$)—**The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

**Lethal Concentration(50) ($LC_{50}$)—**A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

**Lethal Dose(LO) ($LD_{LO}$)—**The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

**Lethal Dose(50) ($LD_{50}$)—**The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time(50) ($LT_{50}$)—**A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

**Lowest-Observed-Adverse-Effect Level (LOAEL)—**The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

**Lymphoreticular Effects—**Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

**Malformations—**Permanent structural changes that may adversely affect survival, development, or function.

**Minimal Risk Level (MRL)—**An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

**Modifying Factor (MF)—**A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

**Morbidity—**State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

**Mortality—**Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

**Mutagen—**A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

**Necropsy—**The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

**Neurotoxicity—**The occurrence of adverse effects on the nervous system following exposure to a chemical.

**No-Observed-Adverse-Effect Level (NOAEL)—**The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

**Octanol-Water Partition Coefficient ($K_{ow}$)—**The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

**Odds Ratio (OR)—**A means of measuring the association between an exposure (such as toxic substances and a disease or condition) 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 group.

**Organophosphate or Organophosphorus Compound—**A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

**Permissible Exposure Limit (PEL)—**An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

**Pesticide—**General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

**Pharmacokinetics—**The 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, whereas the physiologically-based model compartments represent real anatomic regions of the body.

**Physiologically Based Pharmacodynamic (PBPD) Model—**A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end

points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

**Physiologically Based Pharmacokinetic (PBPK) Model—**Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

**Prevalence—**The number of cases of a disease or condition in a population at one point in time.

**Prospective Study—**A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

**q1*—**The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The $q_1$* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/$m^3$ for air).

**Recommended Exposure Limit (REL)—**A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

**Reference Concentration (RfC)—**An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/$m^3$ or ppm.

**Reference Dose (RfD)—**An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL-from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

**Reportable Quantity (RQ)—**The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

**Reproductive Toxicity—**The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

**Retrospective Study—**A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

**Risk—**The possibility or chance that some adverse effect will result from a given exposure to a chemical.

**Risk Factor—**An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

**Risk Ratio—**The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

**Short-Term Exposure Limit (STEL)—**The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

**Standardized Mortality Ratio (SMR)—**A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

**Target Organ Toxicity—**This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

**Teratogen—**A chemical that causes structural defects that affect the development of an organism.

**Threshold Limit Value (TLV)—**An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

**Time-Weighted Average (TWA)—**An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

**Toxic Dose(50) (TD50)—**A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

**Toxicokinetic—**The study of the absorption, distribution, and elimination of toxic compounds in the living organism.

**Uncertainty Factor (UF)—**A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-

observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

**Xenobiotic—**Any chemical that is foreign to the biological system.

# APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Refractory Ceramic Fibers
CAS Number: None
Date: July 13, 2004
Profile Status: Final Post Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [ X ] Chronic
Graph Key: 78
Species: Fischer 344 Rats

Minimal Risk Level: 0.03 [ ] mg/kg/day [ ] ppm [X] WHO fiber/cc

References:

Mast RW, McConnell EE, Anderson R, et al. 1995a. Studies on the chronic toxicity (inhalation) of four types of refractory ceramic fiber in male Fischer 344 rats. Inhal Toxicol 7:425-467.

Mast RW, McConnell EE, Hesterberg TW, et al. 1995b. Multiple dose chronic inhalation toxicity study of size-separated kaolin refractory ceramic fiber in male Fischer 344 rats. Inhal Toxicol 7(4):469-502.

Bernstein DW, Sintes JMR, Ersboell BK, et al. 2001b. Biopersistence of synthetic mineral fibers as a predictor of chronic inhalation toxicity in rats. Inhal Toxicol 13:823-849.

Maxim LD, Yu CP, Oberdörster G, et al. 2003. Quantitative risk analyses for RCF: survey and synthesis. Regul Toxicol Pharmacol 38:400-416.

Experimental design and effects noted:

In the multiple-exposure level study (Mast et al. 1995b), four groups of about 140 male F344 rats were exposed via nose-only inhalation to 0 (filtered air controls), 3, 9, or 16 mg/m$^3$ of a refractory ceramic fiber called RCF1, 6 hours/day, 5 days/week for up to 24 months. The companion study (Mast et al. 1995a) exposed two groups of about 140 male F344 rats to 0 or 30 mg/m$^3$ RCF1 (from the same lot as the multiple-exposure level study) via the same protocol.

The RCF1 test material was prepared from a bulk sample of kaolin-based refractory ceramic fiber obtained from Carborundum Company, Niagara Falls, New York. The bulk material was separated (before aerosol generation) to concentrate the numbers of fibers with a targeted nominal arithmetic mean diameter of 1 µm and length of 20–30 µm. These dimensions were chosen based on results of an unpublished simulated workplace exposure study showing airborne fibers to be principally of this size range. The generated aerosols had the characteristics listed in Table A-1. In addition to fibers (i.e., particles with length:diameter ≥3:1), the aerosols contained nonfibrous particles, often referred to as "shot". In the experimental aerosols, the ratios of nonfibrous particles (with diameters <3 µm) to total fibers or to WHO fibers were reported by Mast et al. (1995b) to range from 0.9 to 1.5 or from 1.3 to 1.96, respectively (Table A-1).

## Table A-1. RCF1 Aerosol Characteristics in the 2-Year Inhalation Bioassays with F344 Rats (Mast et al. 1995a, 1995b)

| Character (mean [± standard deviation]) | 3 mg/m$^3$ | 9 mg/m$^3$ | 16 mg/m$^3$ | 30 mg/m$^3$ |
|---|---|---|---|---|
| Gravimetric concentration (mg/m$^3$) | 3.0±0.4 | 8.8 ±0.7 | 16.5±1.1 | 29.1±5.2 |
| Total fibers/cc (L:D≥3) | 36±17 | 91±34 | 162±37 | 234±35 |
| WHO fibers/cc (L>5 µm; D<3 µm; L:D≥3) | 26±12 | 75±35 | 120±35 | 187±53 |
| Diameter (D) range (µm) | 0.08–5.32 | 0.08–5.37 | 0.07–4.83 | 0.12–4.53 |
| Length (L) range (µm) | 0.77–93.93 | 1.09–98.25 | 1.24–97.88 | 1.30–76.6 |
| Arithmetic mean D (µm) | 1.02±0.73 | 1.02±0.71 | 1.02±1.70 | 0.98±0.61 |
| Geometric mean D (µm) | 0.80±2.06 | 0.80±2.03 | 0.82±1.99 | 0.82±1.89 |
| Arithmetic mean L (µm) | 20.2±18.10 | 20.3±17.1 | 19.6±16.5 | 22.3±17.0 |
| Geometric mean L (µm) | 13.5±2.60 | 13.9±2.50 | 13.8±2.4 | 15.9±2.4 |
| Nonfibrous particle counts | | | | |
| ≤1 µm/cc | 28.3±19.3 | 85.7± 63.2 | 88.0±52.4 | 17±154 |
| 1–3 µm/cc | 23.0±11.8 | 54.8±38.4 | 68.4±24.2 | 135±45 |
| 3 µm/cc | 17.1±8.4 | 43.6±25.2 | 58.6±27.1 | 81±29 |
| Ratio nonfibrous particles (<3 µm):total fibers | 1.41 | 1.54 | 0.97 | 1.31 |
| Ratio nonfibrous particles (<3 µm):WHO fibers | 1.96 | 1.87 | 1.30 | 1.63 |

Groups of 3–6 rats from each exposure group were killed at 3, 6, 12, 18, and 24 months of exposure. Additional groups of 3–6 rats were removed from exposure at 3, 6, 12, and 18 months and exposed to filtered air until they were sacrificed at 24 months. Remaining rats exposed for 24 months (15–32 rats per group) were held without further exposure until 30 months when survivors were killed. All rats were necropsied. Lung tissues were removed, and weighed, and the left lung was prepared for routine histopathology that included staining for collagen deposition. Other tissues processed for histopathology included the nasal cavity, larynx, trachea, bronchi, mediastinal and mesenteric lymph nodes, liver, spleen, kidneys, heart, and all tissues with grossly visible lesions. The concentration and size distributions of fibers in lung tissue were determined after ashing of accessory lung lobes. All fibers detected in lungs had diameters <3 µm. Concentrations were expressed as total fibers per mg dry lung (length:diameter >3) or WHO fibers per mg dry lung (length >5 µm, diameter <3 µm, and length:diameter ≥3).

Observed nonneoplastic lung lesions were classified with two different grading scales. One scale (the Wagner scale) contained eight grades ranging from a normal grade of 1 (with no lesions observed), through "cellular change" grades 2 and 3 (few to conspicuous macrophages in terminal bronchioles and alveoli and no collagen deposition at the bronchiolo-alveolar junction), to five "fibrosis" grades. The fibrosis grades increased in severity as follows: grade 4 (minimal), minimal collagen deposition at the bronchoalveolar junction, increased bronchiolization, and associated mucoid debris; grade 5 (mild), interlobular linking of collagen deposition; grade 6 (moderate), early consolidation and decrease in parenchyma tissue; grade 7 (severe), marked fibrosis and consolidation; and grade 8, complete obstruction of most airways. The other scale contained five grades (0=normal; 1=minimal; 2=mild; 3=moderate; 4=marked; 5=severe) and was applied to specific histopathological findings (macrophage aggregation, bronchiolization, granuloma presence, interstitial [i.e., pulmonary] fibrosis, and pleural fibrosis).

Survival was not statistically significantly affected in any of the exposed groups compared with controls. Body weights and body weight gains were not affected in the two lowest exposure groups (3 and

9 mg/m$^3$). At sporadic intervals of exposure, rats exposed to 16 or 30 mg/m$^3$ displayed statistically significant decreases in body weight, compared with controls. The decreases were not >10% of control values, and are not considered an adverse effect. In 16- and 30-mg/m$^3$ rats, absolute and relative lung weights were significantly greater than in control rats, as early as after 3 months of exposure. After 24 months of exposure, mean absolute lung weights in these groups were respectively increased by 32 and 65%, compared with controls. The lung weight changes are considered to be an indicator of pulmonary inflammation from repeated exposure to RCF1.

Lung fiber concentrations increased with increasing exposure duration and concentration. At 24 months, mean values of WHO fibers/mg lung were $4.29 \times 10^4$, $15.60 \times 10^4$, $22.10 \times 10^4$, and $27.50 \times 10^4$ for the 3-, 9-, 16-, and 30-mg/m$^3$ groups, respectively. Mean values for total fibers/mg lung were 5.55±1.71, 18.80±3.59, 27.80±6.06, and 37.00±8.01, respectively.

Exposure-related nonneoplastic histopathological lesions were restricted to the lung or pleura. Signs of pulmonary inflammation (macrophage aggregation, bronchiolization, and granuloma presence) were observed in all exposed groups after 3 months of exposure, whereas these lesions did not occur in the control rats at any interval (see Table A-2). At 24 months, mean scores (on the five-grade scale) in the 3- and 30-mg/m$^3$ groups ranged from 2 to 3.2 for macrophage aggregation, from 1.2 to 2.7 for bronchiolization, and from 1.5 to 2 for granuloma presence (Table A-2). The mean scores reflect progression of the severity of the inflammatory lesions with increasing exposure concentration (Table A-2). There is also some evidence of progression of the severity of the inflammatory lesions with increasing duration of exposure, most notably between 3 and 12 months (Table A-2).

Signs of interstitial (i.e., pulmonary) fibrosis and pleural fibrosis appeared in rats exposed to concentrations ≥9 mg/m$^3$ (Table A-2). The five-grade scores for interstitial fibrosis and pleural fibrosis (see note about these scores below) showed some progression in severity with exposure duration and concentrations, but the average severity scores for the exposed groups did not progress beyond a score of 3 (moderate) for pulmonary fibrosis or a score of 2 (mild) for pleural fibrosis (Table A-2). Signs of fibrosis did not appear until 12 months of exposure. Using the eight-grade Wagner scale to classify the pulmonary cellular changes and fibrosis, the mean scores at 24 months were 1.0 (normal), 3.2, 4.0, 4.2, and 4.0 for the control, 3-, 9-, 16-, and 30-mg/m$^3$ groups, respectively. In rats exposed for 24 months and allowed to live without exposure to 30 months, respective mean scores were 1.0, 2.9, 3.8, 4.0, and 4.3 (Table A-2). These scores indicate that the pulmonary lesions produced by 24 months of exposure showed only minor, if any, regression and that, on average, the most severe nonneoplastic lesions formed were classified as minimal to mild fibrosis. It was reported that the principal difference between 24-month exposed rats killed at 24 and 30 months was a reduction in the number of pulmonary macrophages and granulomas in the 30-month rats; pulmonary or pleural fibrosis showed no signs of regression.

In a later published report, Bernstein et al. (2001b) reported that the pathologist, who originally scored the histological slides from the RCF1 2-year bioassay, had provided scores for collagen deposition at the bronchoalveolar junction. This lesion was scored in each rat on a five-scale system as follows:

> 0=normal;
> 1=minimal–very few (1 or 2 foci) and very small foci of collagen deposition of insufficient severity to score as Grade 4 in the eight-grade Wagner scale;
> 2=mild–slight, but easily detected, few, small foci of collagen deposition, minimally sufficient to classify in Grade 4 of the Wagner scale;
> 3=moderate–easily detected foci of collagen deposition in considerably enlarged areas, corresponding to Grade 4 of the Wagner scale;

4=marked–marked, obvious, or extensive foci of collagen deposition extending into the interstitium, and corresponding to Grade 4 of the Wagner scale;
5=severe–widespread collagen deposition with consolidation at the bronchoalveolar junction, sometimes with interlobular linking, corresponding to Grade 4 to 5 of the Wagner scale.

In accordance with this scale, collagen deposition at the bronchoalveolar junction is taken as an early response at the site where fibrosis can develop. The lesion is not classified as pulmonary fibrosis at a minimal score of 1, but is classified as minimal to mild fibrosis at scores of 2–5. The mean scores (±standard deviations) for the collagen deposition scores reported by Bernstein et al. (2001b) for the six rats in each of the groups sacrificed at 24 months were: control (n=12), 0 (normal); 3 mg/m$^3$, 0.67±0.8; 9 mg/m$^3$, 2.0±0; 16 mg/m$^3$, 2.83±0.4; and 30 mg/m$^3$, 2.17±0.4. These mean scores for collagen deposition are identical to the mean scores for the lesion named "pulmonary fibrosis" in the Mast et al. (1995a, 1995b) report and shown in Table A-2. Thus, the scores for "pulmonary fibrosis" shown in Table A-2 are actually for collagen deposition as per the original pathology reports.

Neoplastic lesions (lung adenomas, lung carcinomas, and mesotheliomas) were found most prominently in rats exposed to 30 mg/m$^3$. The tumors appeared predominately late in life. The first adenoma occurred in rats sacrificed at 18 months; carcinomas and mesotheliomas were detected only in the 30-month-sacrifice animals. Incidences for rats (that survived to 12 months) with bronchoalveolar hyperplasia were 8/129, 10/123, 16/127, 13/124, and 17/123 for the control through high-exposure groups. Combined incidences for lung adenomas or carcinoma were 1/129, 2/123, 5/127, 2/124, and 16/123. Incidences for mesothelioma were 0/129, 0/123, 1/127, 0/124, and 2/123. Incidences for mesothelial proliferation were 1/129, 0/123, 1/127, 1/124, and 9/123.

## Table A-2. Mean Severity Scores for Pulmonary Lesions in F344 Rats Exposed to RCF1 (Mast et al. 1995a, 1995b)[a]

| Exposure level/ sacrifice month | Number of rats | Macrophage Aggregation (0–5 scale) | Bronchio-lization (0–5 scale) | Granuloma (0–5 scale) | Pulmonary fibrosis (0–5 scale) | Pleural fibrosis (0–5 scale) | 8-Grade Wagner scale score |
|---|---|---|---|---|---|---|---|
| Control | | | | | | | |
| 3 | 3 | 0 | 0 | 0 | 0 | 0 | 1.0 |
| 6 | 3 | 0 | 0 | 0 | 0 | 0 | 1.0 |
| 12 | 6 | 0 | 0 | 0 | 0 | 0.3 | 1.0 |
| 18 | 6 | 0 | 0 | 0 | 0 | 0 | 1.0 |
| 24 | 6 | 0 | 0 | 0 | 0 | 0 | 1.0 |
| 30[b] | 32 | 0.1 | 0.1 | 0 | 0 | 0 | 1.0 |
| 3 mg/m$^3$ | | | | | | | |
| 3 | 3 | 1.7 | 0 | 0.7 | 0 | 0 | 2.0 |
| 6 | 3 | 1.7 | 0 | 1 | 0 | 0 | 2.0 |
| 12 | 6 | 2 | 1 | 1.3 | 0.2 | 0 | 3.0 |
| 18 | 6 | 2 | 1.2 | 1.7 | 0.7 | 0.7 | 3.2 |
| 24 | 6 | 2 | 1.2 | 1.5 | 0.7 | 0.5 | 3.2 |
| 30[b] | 23 | 2.4 | 1.7 | 1.5 | 0.8 | 0.5 | 2.9 |
| 9 mg/m$^3$ | | | | | | | |
| 3 | 3 | 2 | 0.3 | 1.3 | 0 | 0 | 2.3 |
| 6 | 3 | 2 | 0.7 | 2 | 0 | 0.3 | 2.7 |
| 12 | 6 | 2.3 | 1.2 | 2.2 | 1.7 | 0.2 | 4.0 |

**Table A-2. Mean Severity Scores for Pulmonary Lesions in F344 Rats Exposed to RCF1 (Mast et al. 1995a, 1995b)[a]**

| Exposure level/ sacrifice month | Number of rats | Macrophage Aggregation (0–5 scale) | Bronchio-lization (0–5 scale) | Granuloma (0–5 scale) | Pulmonary fibrosis (0–5 scale) | Pleural fibrosis (0–5 scale) | 8-Grade Wagner scale score |
|---|---|---|---|---|---|---|---|
| 18 | 6 | 2.3 | 1.8 | 2.2 | 1.8 | 0.7 | 4.0 |
| 24 | 6 | 2.5 | 1.8 | 2.2 | 2 | 0 | 4.0 |
| 30[b] | 25 | 2.7 | 1.7 | 1.7 | 1.7 | 0.5 | 3.8 |
| 16 mg/m$^3$ | | | | | | | |
| 3 | 3 | 2 | 1 | 2 | 0 | 0 | 3.0 |
| 6 | 3 | 2.3 | 1.3 | 2 | 0 | 0 | 3.0 |
| 12 | 6 | 3 | 1.8 | 2.8 | 2.8 | 0.7 | 4.0 |
| 18 | 6 | 3 | 2.7 | 2.7 | 2.2 | 1.2 | 4.0 |
| 24 | 6 | 3 | 2.7 | 2.7 | 2.8 | 1.5 | 4.2 |
| 30[b] | 20 | 3 | 2.5 | 2.1 | 2 | 1 | 4.0 |
| 30 mg/m$^3$ | | | | | | | |
| 3 | 3 | 2 | 1 | 2 | 2 | 0 | 3.3 |
| 6 | 3 | 2.7 | 2 | 2 | 2 | 0 | 4.0 |
| 12 | 6 | 3 | 2.3 | 2.5 | 2.5 | 1.5 | 4.0 |
| 18 | 3 | 3 | 2 | 2.3 | 2.3 | 1 | 4.3 |
| 24 | 6 | 3.2 | 2.7 | 2 | 2 | 0.5 | 4.0 |
| 30[b] | 15 | 2.8 | 2.9 | 1.9 | 1.9 | 1.3 | 4.3 |

[a]0–5 Scale for different types of lesions: 0=normal; 1=minimal; 2=mild; 3=moderate; 4=marked: 5=severe. 8-Grade Wagner Scale for pulmonary cellular change and fibrosis: 1=normal; 2 or 3=cellular change consistent with inflammation; 4=minimal fibrosis with collagen deposition, bronchiolization, and mucoid debris; 5=mild fibrosis with some interlobular linking of collagen; 6=moderate fibrosis with consolidation and parenchymal decrease; 7=severe fibrosis and consolidation; 8=complete obstruction of airways.
[b]Exposed for 24 months and sacrificed at 30 months.
[c]Bernstein et al. (2001b) reported that the original pathologist's score for this lesion was for collagen deposition at the bronchoalveolar junction, not for pulmonary fibrosis; in the five-grade scale used for collagen deposition, a minimal score of 1 is of insufficient severity to be classified as minimal fibrosis (Grade 4 on the Wagner scale).

Dose and end point used for MRL derivation:

Benchmark concentration analysis was conducted for lung weights (absolute weight expressed as percent of control), macrophage aggregation scores, bronchiolization scores, and scores for collagen deposition at the bronchoalveolar junction. Changes in the first three variables are taken as signs of pulmonary inflammation induced by refractory ceramic fibers deposited in the lung. ATSDR policy considers pulmonary fibrosis to be a serious adverse effect that is inappropriate for MRL derivation. Scores for collagen deposition at the bronchoalveolar junction were included in the analysis, because a score of 1 for this lesion is not of sufficient severity to be considered fibrosis; only scores $\geq$2 were classified as pulmonary fibrosis.

Continuous-variable models available in the EPA Benchmark Dose Software were fit to the lung weight, macrophage, bronchiolization, and bronchoalveolar collagen deposition data shown in Table A-3. Each of these end points was increasingly affected with increasing exposure level and increasing concentrations of fibers in the lungs at 24 months (Table A-3). Group means and standard deviations of the lung weight, macrophage aggregation scores, and bronchiolization scores were obtained from a report of an analysis of

the Mast et al. (1995a, 1995b) 24-month-sacrifice data by Yu and Oberdörster (2000). The mean scores and standard deviations for collagen deposition at the bronchoalveolar junction were obtained from data in the report by Bernstein et al. (2001b). The published report by Mast et al. (1995a, 1995b) only cited mean values and did not cite standard deviations. Dr. Yu's analysis did not include scores (and standard deviations) for granuloma presence.

The benchmark response level for lung weight was set at 10% increase in weight. Percentage change below this value is assumed to be nonadverse. Benchmark response levels for scores for macrophage aggregation, bronchiolization, and bronchoalveolar collagen deposition were set at 1.0 (minimal rating on the 0–5 scale, where 0=normal).

## Table A-3. Non-neoplastic Lung Responses in F344 Rats Exposed for 24 Months to RCF1 (Mast et al. 1995a, 1995b)

| Exposure level | Fiber concentrations in lungs at 24 months | Lung weight | Mean score±standard deviation (0–5 Scale) | | |
|---|---|---|---|---|---|
| (total fibers/cc) | (mean total fibers per mg lung x$10^4$) | (Percent of control) | Macrophage aggregation | Bronchio-lization | Collagen deposition at the bronchoalveolar junction |
| 0 (n=12) | NR | 100.0±14.0 | 0±0 | 0±0 | 0±0 |
| 36 (n=6) | 5.55±1.71 | 116.8±12.3 | 2.0±0 | 1.2±0.4 | 0.7±0.82 |
| 91 (n=6) | 18.80±3.59 | 110.9±8.1 | 2.5±0.6 | 1.8±0.4 | 2±0 |
| 162 (n=6) | 27.80±6.06 | 131.8±15.3 | 3.0±0 | 2.7±0.5 | 2.8±0.4 |
| 234 (n=6) | 37.00±8.01 | 164.7±44.2 | 3.2±0.4 | 2.7±0.5 | 2.2±0.4 |

0–5 Scale: 0=normal; 1=minimal; 2=mild; 3=moderate; 4=marked; 5=severe; NR= not reported

[ ] NOAEL [ ] LOAEL [X] Benchmark Concentration: Lower 95% confidence limits on benchmark concentrations (BMCLs = lower 95% confidence limit on the estimated concentrations associated with a mean score of 1.0 for macrophage aggregation, bronchiolization, or collagen deposition, or 10% increase in lung weight) were considered for selection of the point of departure for the MRL. The rat exposure-response data for these four end points were first fit to continuous-variable models. The best-fitting models were then used to calculate rat BMCLs for each of the end points. The point of departure for the MRL was selected from the rat BMCLs. The selected rat BMCL was then converted to a $BMCL_{HEC}$ using a cross-species scaling factor derived from the lung deposition and clearance models developed for RCF1 in rats and humans (Maxim et al. 2003b; Yu and Oberdörster 2000; Yu et al. 1995a, 1995b, 1996, 1997, 1998a, 1998b).

*Benchmark Concentration Modeling Results.* Available continuous-variable models in the EPA Benchmark Dose Software (linear, polynomial, power, and Hill models; BMDS version) were fit to the data shown in Table A-3.

*Lung Weight.* Adequate fits to the data (as assessed by chi-square residuals and log-likelihood ratio fit tests in the BMDS) were obtained with the linear, polynomial, power, and Hill models with constant variance assumed. Statistical tests indicated that variances were not constant across exposure groups (this is reflected in the standard deviations listed in Table A-3). Models with non-homogeneous variance (i.e., variance as a power function of dose) generally provided improved fits to the data as assessed with Aikake's Information Criteria, AIC (Table A-4). Comparing across models, a better fit is indicated by a lower AIC. The best-fitting model, as indicated by the AIC, was the power model with non-homo-

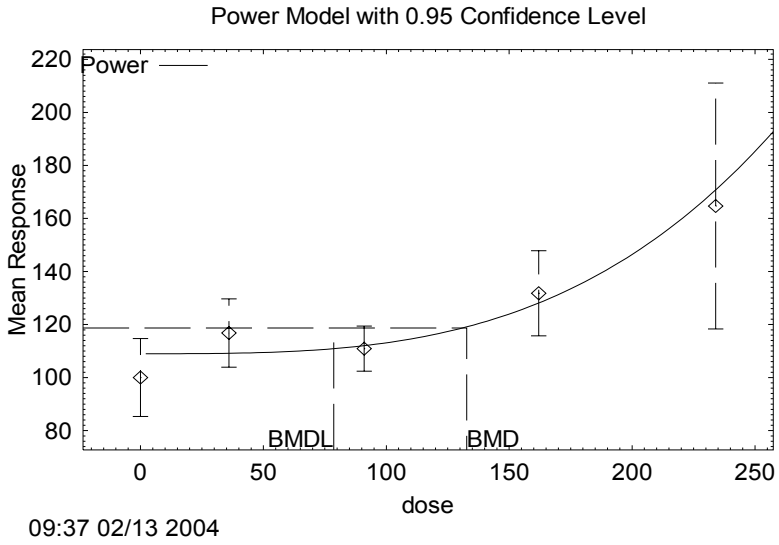
geneous variance, which predicted a rat BMC and BMCL of 133 and 79 total fibers/cc, respectively (Figure A-1).

**Table A-4. BMC Modeling Results for Lung Weights in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a, 1995b)**

| Model | BMC (total fibers/cc) | BMCL (total fibers/cc) | AIC-fitted |
|---|---|---|---|
| Linear | 40 | 30 | 220.12 |
| Linear-nonhomogeneous | .9 | 32 | 213.51 |
| Polynomial | 95 | 34 | 220.08 |
| Polynomial-nonhomogeneous | 94 | 43 | 211.52 |
| Power | 110 | 35 | 222.00 |
| Power-nonhomogeneous* | 133* | 79* | 209.30* |
| Hill | 10 | 35 | 224.00 |
| Hill-nonhomogeneous | 60 | 6 | 228.90 |

*Best Fitting Model

**Figure A-1. Predicted (Power Model with Nonhomogeneous Variance) and Observed Lung Weights in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a, 1995b) (Dose Refers To Rat Exposure Concentrations, Total Fibers/cc)**



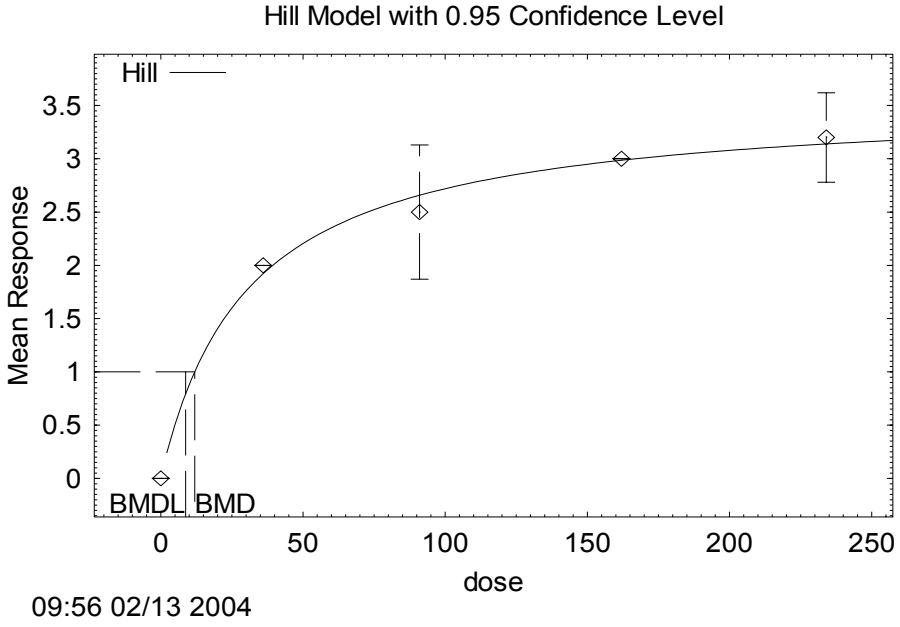

*Macrophage Aggregation Scores.* Adequate fits to the data (as assessed by chi-square residuals and log-likelihood fit tests in the BMDS) were obtained with the polynomial, power, and Hill models with constant variance assumed. Models with variance as a power function of dose did not improve the fits to the data. As assessed by AIC (Table A-5), the Hill model provided the best fit to the data, yielding a rat BMC and BMCL of 12 and 9 total fibers/cc, respectively (Figure A-2).

**Table A-5. BMC Modeling Results for Scores for Pulmonary Macrophage Aggregation in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a, 1995b)**

| Model | BMC (total fibers/cc) | BMCL (total fibers/cc) | AIC-fitted |
|---|---|---|---|
| Hill* | 12* | 9* | -33.05* |
| Polynomial | 21 | 13 | -12.08 |
| Polynomial-nonhomogeneous | 13 | 0 | -8.44 |
| Power | 6 | 0 | 13.67 |
| Power-nonhomogeneous | 51 | 0 | 15.02 |

*Best Fitting Model

**Figure A-2. Predicted (Polynomial Model with Constant Variance) and Observed Scores for Pulmonary Macrophage Aggregation in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a, 1995b) (Dose Refers to Rat Exposure Concentrations, Total Fibers/cc)**



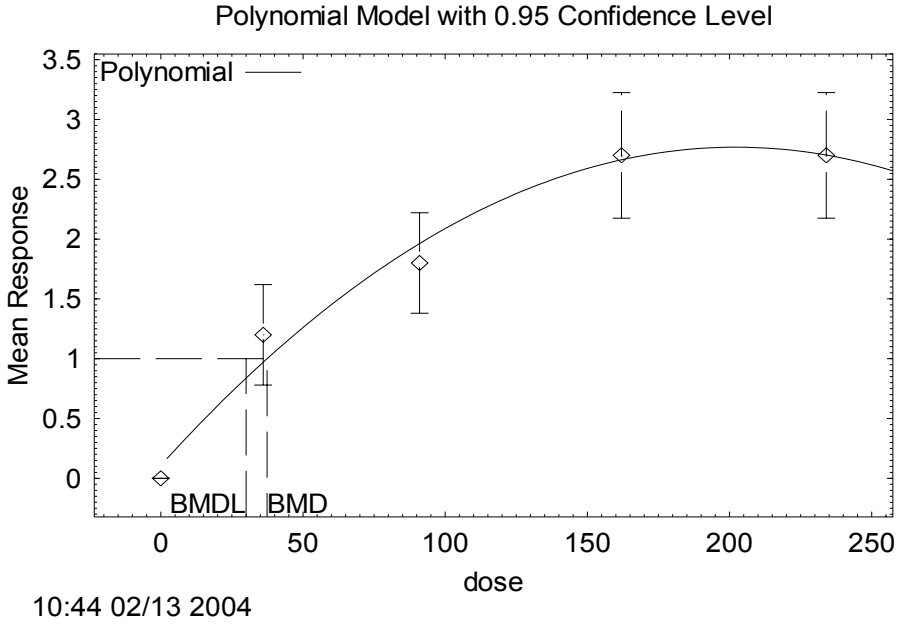

*Bronchiolization Scores.* Adequate fits to the data (as assessed by chi-square residuals and log-likelihood fit tests in the BMDS) were obtained with the polynomial and Hill models with constant variance assumed. Benchmark concentration calculations failed when models with variance as a power function of dose were fit to the data. The best-fitting model, as assessed by AIC, was the polynomial (2-degree) model (Table A-6), which yielded a rat BMC and BMCL of 37 and 30 total fibers/cc, respectively (Figure A-3).

**Table A-6. BMC Modeling Results for Scores for Bronchiolization in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a 1995b)**

| Model | BMC (total fibers/cc) | BMCL (total fibers/cc) | AIC-fitted |
|---|---|---|---|
| Polynomial* | 37* | 30* | -19.91* |
| Hill | 30 | 22 | -18.28 |

*Best Fitting Model

**Figure A-3. Predicted (Polynomial Model with Constant Variance) and Observed Scores for Bronchiolization in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a, 1995b) (Dose Refers to Rat Exposure Concentrations, Total Fibers/cc)**



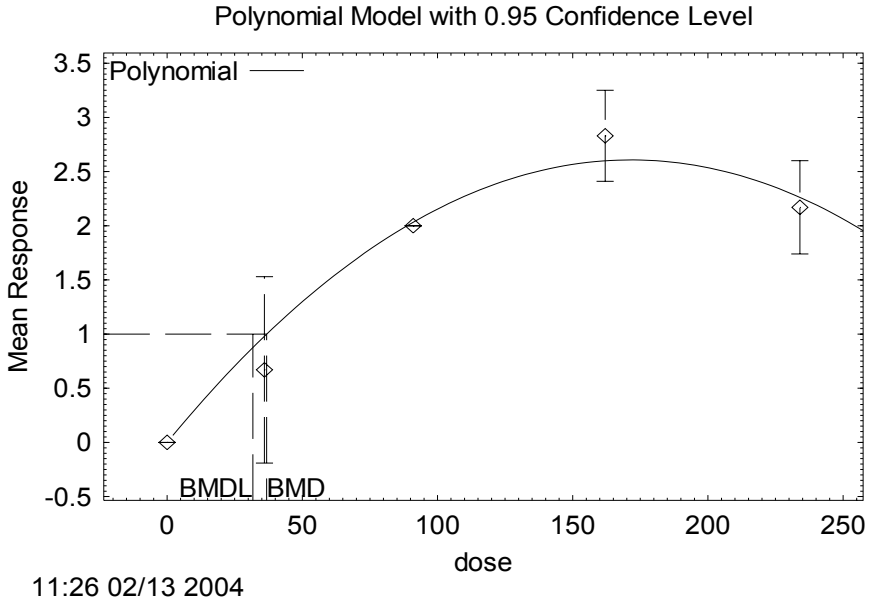

*Collagen Deposition Scores.* Adequate fits to the data (as assessed by chi-square residuals and log-likelihood ratio fit tests in the BMDS) were obtained with the polynomial and Hill models with constant variance assumed. Benchmark concentration calculations failed when models with variance as a power function of dose were fit to the data. The best-fitting model, as assessed by AIC, was the polynomial (2-degree) model (Table A-7), which yielded a rat BMC and BMCL of 37 and 32 total fibers/cc, respectively (Figure A-4).

**Table A-7. BMC Modeling Results for Scores for Collagen Deposition at the Bronchoalveolar Junction in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a, 1995b)**

| Model | BMC (total fibers/cc) | BMCL (total fibers/cc) | AIC-fitted |
|---|---|---|---|
| Polynomial* | 37* | 32* | -12.52* |
| Hill | 45 | 37 | -5.25 |

*Best Fitting Model

**Figure A-4. Predicted (Polynomial Model with Constant Variance) and Observed Scores for Collagen Deposition at the Bronchoalveolar Junction in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a, 1995b) (Dose Refers to Rat Exposure Concentrations, Total Fibers/cc)**




*Selection of Point of Departure for the MRL.* BMCs and BMCLs for the four modeled end points are shown in Table A-8. The BMCL for lung weight represents the 95% lower confidence limit on the concentration estimated to increase lung weight by a mean of 10% over control values. The BMCLs for the pulmonary lesion scores represent the 95% lower confidence limits on the concentration estimated to produce a mean score of 1 (minimal severity) for each lesion.

## Table A-8. BMCs and BMCLs for Lung Weight and Pulmonary Lesion Scores in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a, 1995b).

| End point | BMC (total fiber/cc) | BMCL (total fiber/cc) |
|---|---|---|
| Lung weight | 133 | 79 |
| Pulmonary macrophage aggregation | 12 | 9 |
| Bronchiolization | 37 | 30 |
| Collagen deposition at the bronchoalveolar junction | 37 | 32 |

The rat BMCL of 9 total fiber/cc for pulmonary macrophage aggregation was selected as the point of departure for the MRL, because this lesion is the most sensitive among those measured in the bioassay (as indicated by having the lowest BMCL in Table A-8). ATSDR considers minimal pulmonary inflammation a reversible response to fibers and nonfibrous particles that, although near the boundary between adverse and nonadverse, is an appropriate critical effect on which to base the MRL. As shown in the data in Table A-3, the severity of pulmonary macrophage aggregation in rats in the principal study showed a clear increase in severity with increasing exposure levels of RCF1, as well as with increasing concentrations of fibers in the lungs of the rats sacrificed after 24 months of exposure.

*Dosimetric Adjustment of Rat Benchmark Concentrations to Human Equivalent Concentrations (HECs)*
The BMC and BMCL for pulmonary aggregation in rats were converted to human equivalent exposure levels using an average scaling factor derived from rat and human lung deposition and clearance models for RCF1 developed by Dr. C.P. Yu and colleagues (Yu et al. 1995a, 1995b, 1996, 1997, 1998a, 1998b). Equations for deposition in the models are functions of fiber length, fiber diameter, and time. The equations for mechanical macrophage-mediated clearance rate are functions of fiber length, alveolar macrophage volume, and lung burden (total accumulated volume of fibers and particles). The clearance models include dissolution-rate and transverse breakage-rate equations.

Values for key parameters in the dosimetric models included the following (Maxim et al. 2003b;Yu and Oberdörster 2000):

Rat lung weight: 1.48 g; Human lung weight: 1,000 g
Rat lung surface area: $4.3 \times 10^3$ $cm^2$; Human lung surface area: $6.5 \times 10^5$ $cm^2$
Rat macrophage volume per lung: 26 $mm^3$; Human macrophage volume per lung: $1.75 \times 10^4$ $mm^3$
Rat macrophage diameter: 10.68 μm; Human macrophage diameter: 16.82 μm
Dissolution rate (same in rats and humans): $6.46 \times 10^{-5}$ (μm/day) or 0.73 ng/$cm^2$/hour
Breakage rate and scheme: same in rats and humans
Size distribution of refractory ceramic fibers in the human model:
Bivariate lognormal distribution (geometric mean±standard deviation) similar to workplace RCF size data: fiber diameter: 0.84 μm (±2.05); fiber length: 14.1 μm (±2.48)
Rat model: retained volume of nonfibrous plus fibrous particles (lung burden) impacts clearance rate
Human model: only retained fibrous particle volume impacts clearance rate.

Initially, Yu and Oberdörster (2000) calculated HECs from the rat exposure levels, using number of WHO fibers per $cm^2$ of lung surface area as the cross species lung burden normalization unit. The rat models were set to the exposure scenarios experienced by rats in the Mast et al. (1995a, 1995b) bioassays (6 hours/day, 5 days/week for 2 years), and two human exposure scenarios were examined, one involving continuous, lifetime (70-year) exposure assuming a tidal volume of 750 cc and nasal breathing with a respiratory frequency of 14.5 per minute, and a second involving occupational exposure (8 hours/day,

5 days/week, 50 weeks/year for 40 years) assuming a tidal volume of 1290 cc and nasal breathing with a respiratory frequency of 15.5 per minute. Calculated HECs for the two human exposure scenarios from the rat exposure levels are shown in Table A-9. The mean ratios of the rat:human equivalent exposure concentrations were 14.7 for the continuous exposure scenario and 7.3 for the occupational exposure scenario. From these ratios, mean rat-to-human dosimetric scaling factors are 0.07 (1/14.7) for the continuous exposure scenario and 0.13 (1/7.3) for the occupational exposure scenario.

**Table A-9. HECs Calculated for Two Human Exposure Scenarios from Rat Exposure Levels Using WHO Fibers per $cm^2$ of Lung Surface area for Cross-Species Normalization. (Source: Tables 7.1 and 7.2; Yu and Oberdörster, 2000)**

| Human exposure scenario | Rat exposure levels (total fibers/cc) | | | | | Mean ratio rat:human (±SD) |
|---|---|---|---|---|---|---|
| | 0 | 36 | 91 | 162 | 234 | |
| | HECs (WHO fibers/cc) | | | | | |
| Continuous | 0 | 2.4 | 8.1 | 11.0 | 13.2 | 14.7 ±2.7 |
| Occupational | 0 | 4.7 | 16.2 | 22.3 | 27.1 | 7.3 ±1.3 |

More recently, Maxim et al. (2003) showed that selection of the cross species lung burden normalization unit (i.e., number of fibers per cm2 of lung surface area versus number of fibers per mg dry weight of lung) is a key determinant in species conversion of exposure levels when using the lung and deposition models developed by Yu and colleagues. Using a human occupational exposure scenario assuming a tidal volume of 1,060 cc and nasal breathing with a respiratory frequency of 12.74 per minute and a minute ventilation of 13.5 L per minute, human equivalent concentrations corresponding to a rat exposure level of 36 total fiber/cc were calculated to be 5.7 total fiber/cc, based on a WHO fibers per $cm^2$ of lung surface area normalization, compared with 33.8 total fibers/cc, based on a WHO fibers per lung mg dry weight normalization. The ratios of rat:human equivalent exposure concentrations for these occupational exposure scenarios were 6.3 on a lung surface area basis (similar to the mean of 7.3 shown in Table A-9) and 1.1 on a lung dry weight basis. For this occupational exposure scenario, rat-to-human dosimetric scaling factors based on lung surface area normalization or lung dry weight normalization are 0.16 (i.e., 1/6.3) and 0.9 (1/1.1), respectively, indicating an approximate 6-fold difference between lung surface area and lung dry weight normalizations.

A rat-to-human scaling factor of 0.07, based on a human continuous exposure scenario and lung surface area cross-species normalization, was used to convert the rat BMC and BMCL of 12 and 9 total fibers/cc to human equivalent concentrations of 0.8 and 0.6 WHO fibers/cc, respectively. This scaling factor was used, because data are not available to confirm which cross-species lung burden normalization method is more accurate, and calculations of mean rat-to-human dosimetric scaling factors, based on lung dry weight normalization with continuous exposure scenarios, are not available. It is recognized that the analysis by Maxim et al. (2003) indicates that an alternative scaling factor, based on lung dry weight cross species normalization, could be about 6-fold higher. The point of departure for the MRL is the BMCLHEC of 0.6 WHO fibers/cc, rounded to 1 WHO fibers/cc.

Uncertainty Factors used in MRL derivation:

[X] 3 for interspecies extrapolation with dosimetric adjustment. The dosimetric adjustment takes into account physiological differences between rats and humans expected to influence deposition and clearance of refractory ceramic fibers from the lung. It is recognized that the cross species dosimetric scaling factor used (based on fiber per lung surface area normalization) may underestimate the human equivalent concentration associated with the development of pulmonary lesions, compared with a scaling factor based on a fiber per lung dry weight basis. As such, the scaling factor based on lung surface area

normalization is likely to be protective of the public health, and an additional factor to account for this dosimetric uncertainty is unnecessary. The derivation assumes that rats and humans are equally responsive to retained fibers in the lung, in the absence of conclusive evidence to indicate otherwise. The uncertainty factor of 3 accounts for the uncertainty associated with this assumption of interspecies pharmacodynamic equivalence.

[ ] 10 for use of a LOAEL: No uncertainty factor was necessary for the use of a BMCLHEC for minimal pulmonary macrophage aggregation, an effect just above the boundary between nonadverse and adverse.

[ X ] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

Was a conversion used from intermittent to continuous exposure? Yes. The human lung and deposition model used a continuous, 70-year, exposure scenario, whereas the rat lung and deposition model used the experimental exposure conditions, 6 hours/day, 5 days/week for 2 years.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: See previous discussion of the derivation of the rat-to-human dosimetric scaling factor of 0.07.

Other additional studies or pertinent information which lend support to this MRL: The Mast et al. (1995a, 1995b) study provides the best available data describing exposure-response relationships for nonneoplastic lesions in the lung and pleura from chronic inhalation exposure to refractory ceramic fibers. The study identifies pulmonary inflammation as the critical nonneoplastic end point of concern and identifies other more serious effects at higher exposure levels (pulmonary and pleural fibrosis and cancer of the lung and pleura). Other studies of rats exposed to RCF1 by inhalation provide strong support for pulmonary inflammation as the critical end point (Bellman et al. 2001; Everitt et al. 1997; Gelzleichter et al. 1999; McConnell et al. 1995), as well as other animal inhalation studies of other refractory ceramic fibers (Mast et al. 1995a) and other synthetic vitreous fibers such as insulation glass wools, MMVF10 and MMVF11 (Hesterberg et al.1993c; McConnell et al. 1999), slag wool MMVF22 (McConnell et al. 1994), and rock wool MMVF21 (McConnell et al. 1994).

There are distinct differences between laboratory animal species and humans in respiratory tract size and geometry, ventilation rate and pattern, and macrophage sizes that influence the retention (the net result of deposition and clearance) of fibers in the lung. Yu and colleagues (Yu et al. 1995a, 1995b, 1996, 1997, 1998a, 1998b) have developed lung retention models for RCF1 in rats and humans that incorporate many of these interspecies differences. Although these models significantly decrease uncertainty in extrapolating doses from rats to humans, in vivo human data on internal doses of inhaled synthetic vitreous fibers are limited, and validation exercises with the human model are correspondingly limited.

Several reviewers of draft versions of this Toxicological Profile disagreed with ATSDR's selection of macrophage aggregation as the critical effect for the MRL. Reasons for not selecting macrophage aggregation included: (1) this end point is not a response that is specific to fibers (nonfibrous particles can also cause this effect), and (2) it is a reversible and adaptive effect and therefore nonadverse. The ATSDR MRL Workgroup acknowledged that although there were confounding effects from nonfibrous particles in the principal study, the data in Table 2 show that there was a clear relationship between concentrations of fibers in the lung and increasing severity of macrophage aggregation. The MRL Workgroup acknowledged the reversibility of macrophage aggregation, but does not consider reversibility as a criterion for not selecting a critical effect for MRL derivation.

The ATSDR MRL Workgroup discussed an alternative MRL derivation with collagen deposition as the critical effect, but preferred selection of macrophage aggregation as the critical effect. If collagen deposition was selected as the critical effect for the MRL, an alternative MRL of 0.02 WHO fibers/cc was derived as follows (using a benchmark response=a concentration that would produce an average score of 1 for bronchoalveolar collagen deposition in a population and a total uncertainty factor of 90: 3 for cross-species extrapolation, 10 for human variability, and 3 for the selection of a potentially serious adverse effect as the critical effect):

1. [Rat $BMCL_{collagen\ deposition}$] x [cross-species scaling factor] = $BMCL_{collagen\ depositionHEC}$

   32 total fiber/cc x 0.07 = 2.24 WHO fibers/cc = 2 WHO fibers/cc (rounded)

2. MRL = $BMCL_{collagen\ depositionHEC}$ ÷ 90 = 2 ÷ 90 = 0.02 WHO fibers/cc.

The Workgroup noted the similarity of the values of the MRLs based on macrophage aggregation (0.03 WHO fibers/cc) or collagen deposition (0.02 WHO fibers/cc). The approximate 3-fold difference in the benchmark concentrations (9 total fibers/cc for macrophage aggregation and 32 total fibers/cc for collagen deposition) was offset by the 3-fold difference in the total uncertainty factors (30 for macrophage aggregation and 90 for collagen deposition).

The MRL derivation assumes that rats and humans are equally sensitive to the inflammatory effects of refractory ceramic fibers. Understanding of the relative pharmacodynamic sensitivity of rodents and humans to synthetic vitreous fibers, asbestos fibers, or nonfibrous particulate matter is poor. Varying opinions on the relative sensitivity of rodents and humans to deposited fibers have been expressed by Rodelsperger and Woitowitz (1995), Rowe and Springer (1986), Yu and Oberdörster (2000), Maxim and McConnell (2001), and Maxim et al. (2003). The uncertainty factor of 3 is used in the MRL derivation to account for the uncertainty of the assumption of pharmacodynamic equivalence between rats and humans.

Available comparative data with other refractory ceramic fibers (e.g., data for RCF2, RCF3, and RCF4 reported by Mast et al. 1995a) suggest that RCF1 is as potent or more potent in inducing various pulmonary effects than other refractory ceramic fibers. Thus, the chronic MRL based on RCF1 data is expected to be protective of the public health for exposure to other refractory ceramic fibers.

A significant contributing factor to the high potency of RCF1 relative to other refractory ceramic fibers is the high content of nonfibrous particles in RCF1. Bellmann et al. (2001) have reported that the mass concentration of total fibers (particles with aspect ratio >3:1) and nonfibrous particles (with aspect ratios <3:1) in RCF1 are 0.76 and 0.26 ng/ng RCF1, respectively. Evidence that the presence of the nonfibrous particles can enhance the effects on the lung was provided by comparing responses in rats exposed by inhalation for 3 weeks to concentrations of about 125 fibers (with lengths >20 μm)/cc of either RCF1 or a sample of refractory ceramic fibers, called RCF1a, in which only 2% of the mass was accounted for by nonfibrous particles (Bellmann et al. 2001). Expressed as WHO fibers/cc, the respective mean concentrations were 481 fibers/cc for RCF1a and 679 fibers/cc for RCF1. Pulmonary clearance ability was markedly depressed by RCF1, but not by RCF1a, and indices of pulmonary inflammation were more persistently increased by RCF1 than by RCF1a (Bellmann et al. 2001).

The ratio of nonfibrous particles:fibers for the RCF1 material used in the 2-year rat bioassay (Mast et al., 1995a, 1995b) has been reported to be about 3:1 by Bellmann et al. (2001), about 1-2:1 from data reported by Mast et al. (1995a, 1995b), and 9:1 by Maxim et al. (1997) and Mast et al. (2000). In contrast, workplace air samples (n=10) showed a ratio of about 0.5:1 (Mast et al. 2000; Maxim et al. 1997). Thus, a key uncertainty associated with the MRL is that the nonfibrous particles likely contributed

to the observed lung responses to some undetermined degree. As such, the MRL may underestimate the daily human exposure that is likely to be without appreciable risk of adverse noncancer health effects, and is expected to be protective of public health.

Bernstein et al. (2001b) conducted an analysis to determine if there was a statistically significant relationship between scores for collagen deposition at the bronchoalveolar junction and lung fiber concentrations (of various size classes) in the data collected in chronic rat bioassays with five types of synthetic vitreous fibers (RCF1, MMVF21—a stone wool, MMVF 11—an insulation glass wool, MMVF10—an insulation glass wool, and MMVF22—a slag wool). In the analysis, logistic and proportional odds regression models were fit to data for scores for collagen deposition at the broncho-alveolar junction and associated lung fiber concentrations in the rats sacrificed after 24 months of exposure. In these analyses, lesion score was the dependent variable and lung fiber concentration (of various size classes) was the explanatory variable. Bernstein et al. (2001b; Figure 2) noted that the score for collagen deposition showed a statistically significant relationship with increasing lung concentrations of the five types of fibers with lengths >20 μm (and not with lung concentrations of fibers in smaller length categories).

In comments provided to ATSDR (ATSDR Docket No. ATSDR-187; January 23, 2003), Dr. Bernstein noted that his analysis extended to 10 other pulmonary end points evaluated in these bioassays (including scores for macrophage aggregation and bronchiolization), and that he did not find statistically significant relationships for these scores with the concentrations of the various types of fibers in the lungs of the rats. Dr. Bernstein's analysis indicates that only the scores for collagen deposition (and not the other pulmonary end points) showed a statistically significant relationship with lung burden across the five types of synthetic vitreous fibers included in the analysis. Dr. Bernstein interpreted this to mean that, among the 11 pulmonary end points evaluated in these bioassays and this analysis, only collagen deposition had a statistically significant relationship with fiber lung burden at 24 months. Dr. Bernstein proposed that one reason for selecting bronchoalveolar collagen deposition as the critical end point for MRL derivation is that there was a lack of association for the other end points with lung fiber concentration at 24 months. An alternative interpretation of Dr. Bernstein's analysis is that it shows that only the most biopersistent of the fibers evaluated (i.e., those, such as RCF1, that accumulated to a sufficiently high level in the lung after 2 years) produced moderate collagen deposition and that all of the fiber types included in the analysis induced the other less adverse responses (such as macrophage aggregation and bronchiolization) to degrees that were indistinguishable between fiber types. The data from the principal RCF1 study shown in Table A-3 clearly show that the severity of all of the pulmonary end points (including scores for macrophage aggregation and bronchiolization) increased with increasing exposure level and with increasing lung fiber concentration at 24 months. Thus, even though the nonfibrous particles in the RCF1 atmospheres may have contributed to the pulmonary responses in the rats, the data show a clear relationship between the severity of macrophage aggregation (and other more severe end points) and the internal dose of fibers deposited in the lung. As such, it appears reasonable to select macrophage aggregation as the critical effect for MRL derivation.

The chronic MRL is expected to be appropriately applied to intermediate-duration exposure scenarios, based on evidence from interim sacrifice data from the Mast et al. (1995b) bioassay that exposure-response relationships for pulmonary inflammation and chronic exposure are similar to those for intermediate-duration exposure. Scores for pulmonary inflammation progressed to only a limited degree with progression from intermediate to chronic duration. For example, mean scores for macrophage aggregation in rats exposed to 3, 9, 16, and 30 mg/m$^3$ at 3 months were 1.7, 2, 2, and 2, respectively. The respective scores were 2, 2.3, 3, and 3 at 12 months and 2, 2.5, 3, and 3.2 at 24 months.

Exposure-response relationships for pulmonary inflammation from acute inhalation exposure to synthetic vitreous fibers are inadequately characterized for deriving an acute inhalation MRL for any type of synthetic vitreous fiber.

Any use of the MRL for refractory ceramic fibers in assessing health hazards from the insulation wools should acknowledge the evidence that many of the insulation wools are markedly less durable and less potent than refractory ceramic fibers (Bernstein et al. 2001a, 2001b; Eastes and Hadley 1996; Eastes et al. 2000; Hesterberg et al. 1998a). There are data from multiple-exposure-level 2-year rat inhalation bioassays on the glass wools, MMVF10 and MMVF11 (Hesterberg et al.1993c; McConnell et al. 1999), the slag wool MMVF22 (McConnell et al. 1994), and the rock wool MMVF21 (McConnell et al. 1994) that adequately describe exposure-response relationships for nonneoplastic pulmonary effects from intermediate- and chronic-duration exposure to these materials. However, lung deposition and clearance models for these synthetic vitreous fibers (such as those developed by C.P. Yu and colleagues for RCF1) are not yet fully developed to carry out physiologically based dosimetric calculations of human equivalent concentrations. When these models are available, they could be used to convert rat exposure concentrations to human equivalent concentrations, and use the data for MMVF10, MMVF11, MMVF22, and MMVF21 to derive inhalation MRLs for insulation wools.

There are no adequate data (from multiple-exposure level studies) for deriving inhalation MRLs for the other types of synthetic vitreous fibers (special applications glass fibers or continuous filament glass fibers that are woven).

Agency Contact (Chemical Manager): Malcolm Williams, D.V.M., Ph.D.

# APPENDIX B. USER'S GUIDE

## Chapter 1

### Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

## Chapter 2

### Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

### Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) Tables.

**Chapter 3**

**Health Effects**

**Tables and Figures for Levels of Significant Exposure (LSE)**

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

**LEGEND**

**See Sample LSE Table 3-1 (page B-6)**

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data 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 two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure 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 “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

**LEGEND**

**See Sample Figure 3-1 (page B-7)**

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in $mg/m^3$ or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38r is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the

EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels ($q_1$*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

**SAMPLE**

**Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

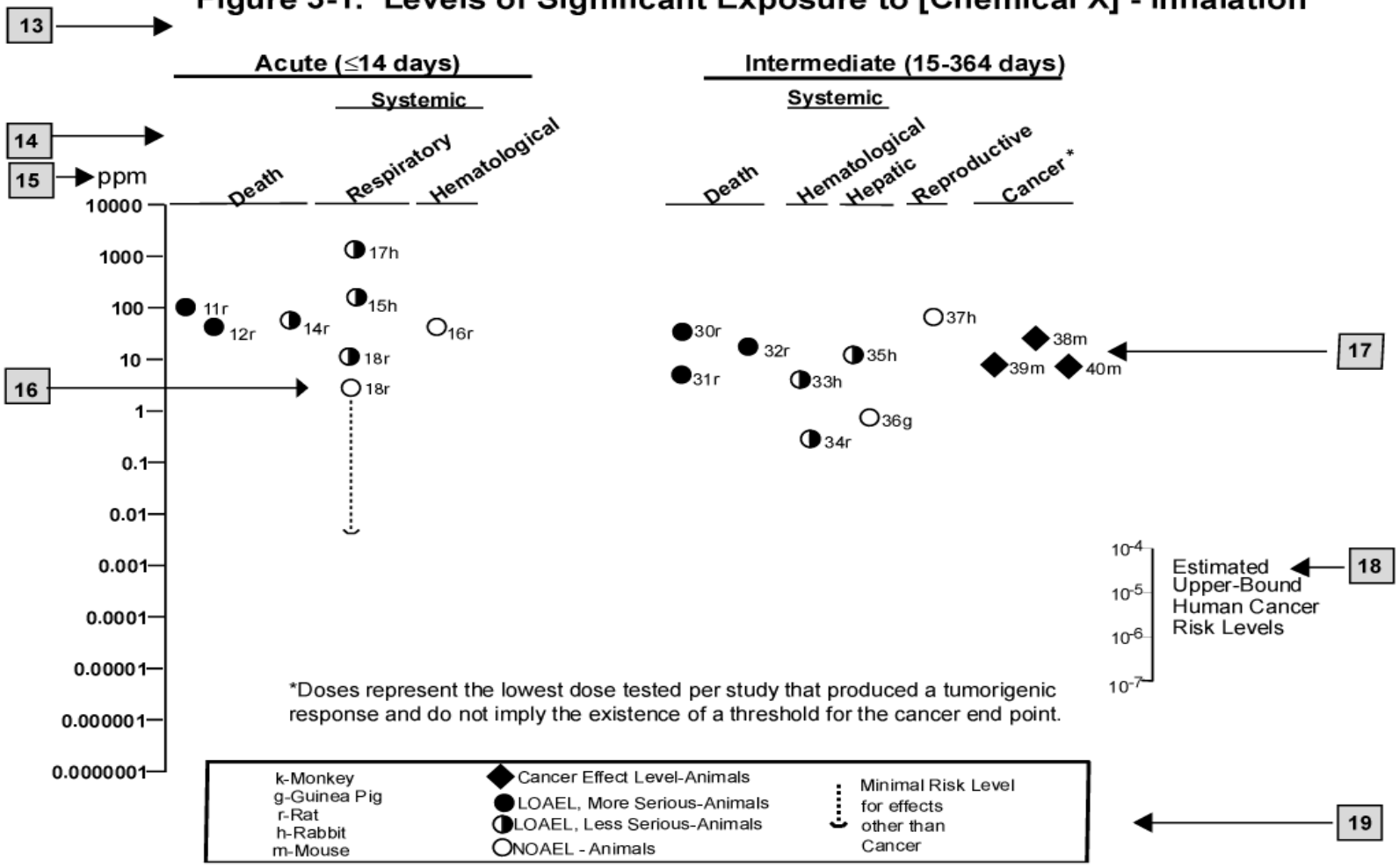
| Key to figure[a] | Species | Exposure frequency/ duration | System | NOAEL (ppm) | LOAEL (effect) | | Reference |
|---|---|---|---|---|---|---|---|
| | | | | | Less serious (ppm) | Serious (ppm) | |
| INTERMEDIATE EXPOSURE | | | | | | | |
| | 5 | 6 | 7 | 8 | 9 | | 10 |
| Systemic | ↓ | ↓ | ↓ | ↓ | ↓ | | ↓ |
| 18 | Rat | 13 wk<br>5 d/wk<br>6 hr/d | Resp | 3[b] | 10 (hyperplasia) | | Nitschke et al. 1981 |
| CHRONIC EXPOSURE | | | | | | | |
| Cancer | | | | | 11 | | |
| | | | | | ↓ | | |
| 38 | Rat | 18 mo<br>5 d/wk<br>7 hr/d | | | 20 | (CEL, multiple organs) | Wong et al. 1982 |
| 39 | Rat | 89-104 wk<br>5 d/wk<br>6 hr/d | | | 10 | (CEL, lung tumors, nasal tumors) | NTP 1982 |
| 40 | Mouse | 79-103 wk<br>5 d/wk<br>6 hr/d | | | 10 | (CEL, lung tumors, hemangiosarcomas) | NTP 1982 |

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

b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5 \times 10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

**SAMPLE**

## Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



# APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

| | |
|---|---|
| ACGIH | American Conference of Governmental Industrial Hygienists |
| ACOEM | American College of Occupational and Environmental Medicine |
| ADI | acceptable daily intake |
| ADME | absorption, distribution, metabolism, and excretion |
| AED | atomic emission detection |
| AFID | alkali flame ionization detector |
| AFOSH | Air Force Office of Safety and Health |
| ALT | alanine aminotransferase |
| AML | acute myeloid leukemia |
| AOAC | Association of Official Analytical Chemists |
| AOEC | Association of Occupational and Environmental Clinics |
| AP | alkaline phosphatase |
| APHA | American Public Health Association |
| AST | aspartate aminotransferase |
| atm | atmosphere |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| AWQC | Ambient Water Quality Criteria |
| BAT | best available technology |
| BCF | bioconcentration factor |
| BEI | Biological Exposure Index |
| BMD | benchmark dose |
| BMR | benchmark response |
| BSC | Board of Scientific Counselors |
| C | centigrade |
| CAA | Clean Air Act |
| CAG | Cancer Assessment Group of the U.S. Environmental Protection Agency |
| CAS | Chemical Abstract Services |
| CDC | Centers for Disease Control and Prevention |
| CEL | cancer effect level |
| CELDS | Computer-Environmental Legislative Data System |
| CERCLA | Comprehensive Environmental Response, Compensation, and Liability Act |
| CFR | Code of Federal Regulations |
| Ci | curie |
| CI | confidence interval |
| CL | ceiling limit value |
| CLP | Contract Laboratory Program |
| cm | centimeter |
| CML | chronic myeloid leukemia |
| CPSC | Consumer Products Safety Commission |
| CWA | Clean Water Act |
| DHEW | Department of Health, Education, and Welfare |
| DHHS | Department of Health and Human Services |
| DNA | deoxyribonucleic acid |
| DOD | Department of Defense |
| DOE | Department of Energy |
| DOL | Department of Labor |
| DOT | Department of Transportation |

| | |
|---|---|
| DOT/UN/NA/IMCO | Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code |
| DWEL | drinking water exposure level |
| ECD | electron capture detection |
| ECG/EKG | electrocardiogram |
| EEG | electroencephalogram |
| EEGL | Emergency Exposure Guidance Level |
| EPA | Environmental Protection Agency |
| F | Fahrenheit |
| $F_1$ | first-filial generation |
| FAO | Food and Agricultural Organization of the United Nations |
| FDA | Food and Drug Administration |
| FEMA | Federal Emergency Management Agency |
| FIFRA | Federal Insecticide, Fungicide, and Rodenticide Act |
| FPD | flame photometric detection |
| fpm | feet per minute |
| FR | Federal Register |
| FSH | follicle stimulating hormone |
| g | gram |
| GC | gas chromatography |
| gd | gestational day |
| GLC | gas liquid chromatography |
| GPC | gel permeation chromatography |
| HPLC | high-performance liquid chromatography |
| HRGC | high resolution gas chromatography |
| HSDB | Hazardous Substance Data Bank |
| IARC | International Agency for Research on Cancer |
| IDLH | immediately dangerous to life and health |
| ILO | International Labor Organization |
| IRIS | Integrated Risk Information System |
| Kd | adsorption ratio |
| kg | kilogram |
| kkg | metric ton |
| $K_{oc}$ | organic carbon partition coefficient |
| $K_{ow}$ | octanol-water partition coefficient |
| L | liter |
| LC | liquid chromatography |
| $LC_{50}$ | lethal concentration, 50% kill |
| $LC_{Lo}$ | lethal concentration, low |
| $LD_{50}$ | lethal dose, 50% kill |
| $LD_{Lo}$ | lethal dose, low |
| LDH | lactic dehydrogenase |
| LH | luteinizing hormone |
| LOAEL | lowest-observed-adverse-effect level |
| LSE | Levels of Significant Exposure |
| $LT_{50}$ | lethal time, 50% kill |
| m | meter |
| MA | *trans,trans*-muconic acid |
| MAL | maximum allowable level |
| mCi | millicurie |
| MCL | maximum contaminant level |

| | |
|---|---|
| MCLG | maximum contaminant level goal |
| MF | modifying factor |
| MFO | mixed function oxidase |
| mg | milligram |
| mL | milliliter |
| mm | millimeter |
| mmHg | millimeters of mercury |
| mmol | millimole |
| mppcf | millions of particles per cubic foot |
| MRL | Minimal Risk Level |
| MS | mass spectrometry |
| NAAQS | National Ambient Air Quality Standard |
| NAS | National Academy of Science |
| NATICH | National Air Toxics Information Clearinghouse |
| NATO | North Atlantic Treaty Organization |
| NCE | normochromatic erythrocytes |
| NCEH | National Center for Environmental Health |
| NCI | National Cancer Institute |
| ND | not detected |
| NFPA | National Fire Protection Association |
| ng | nanogram |
| NHANES | National Health and Nutrition Examination Survey |
| NIEHS | National Institute of Environmental Health Sciences |
| NIOSH | National Institute for Occupational Safety and Health |
| NIOSHTIC | NIOSH's Computerized Information Retrieval System |
| NLM | National Library of Medicine |
| nm | nanometer |
| nmol | nanomole |
| NOAEL | no-observed-adverse-effect level |
| NOES | National Occupational Exposure Survey |
| NOHS | National Occupational Hazard Survey |
| NPD | nitrogen phosphorus detection |
| NPDES | National Pollutant Discharge Elimination System |
| NPL | National Priorities List |
| NR | not reported |
| NRC | National Research Council |
| NS | not specified |
| NSPS | New Source Performance Standards |
| NTIS | National Technical Information Service |
| NTP | National Toxicology Program |
| ODW | Office of Drinking Water, EPA |
| OERR | Office of Emergency and Remedial Response, EPA |
| OHM/TADS | Oil and Hazardous Materials/Technical Assistance Data System |
| OPP | Office of Pesticide Programs, EPA |
| OPPT | Office of Pollution Prevention and Toxics, EPA |
| OPPTS | Office of Prevention, Pesticides and Toxic Substances, EPA |
| OR | odds ratio |
| OSHA | Occupational Safety and Health Administration |
| OSW | Office of Solid Waste, EPA |
| OTS | Office of Toxic Substances |
| OW | Office of Water |

| | |
|---|---|
| OWRS | Office of Water Regulations and Standards, EPA |
| PAH | polycyclic aromatic hydrocarbon |
| PBPD | physiologically based pharmacodynamic |
| PBPK | physiologically based pharmacokinetic |
| PCE | polychromatic erythrocytes |
| PEL | permissible exposure limit |
| pg | picogram |
| PHS | Public Health Service |
| PID | photo ionization detector |
| pmol | picomole |
| PMR | proportionate mortality ratio |
| ppb | parts per billion |
| ppm | parts per million |
| ppt | parts per trillion |
| PSNS | pretreatment standards for new sources |
| RBC | red blood cell |
| REL | recommended exposure level/limit |
| RfC | reference concentration |
| RfD | reference dose |
| RNA | ribonucleic acid |
| RQ | reportable quantity |
| RTECS | Registry of Toxic Effects of Chemical Substances |
| SARA | Superfund Amendments and Reauthorization Act |
| SCE | sister chromatid exchange |
| SGOT | serum glutamic oxaloacetic transaminase |
| SGPT | serum glutamic pyruvic transaminase |
| SIC | standard industrial classification |
| SIM | selected ion monitoring |
| SMCL | secondary maximum contaminant level |
| SMR | standardized mortality ratio |
| SNARL | suggested no adverse response level |
| SPEGL | Short-Term Public Emergency Guidance Level |
| STEL | short term exposure limit |
| STORET | Storage and Retrieval |
| $TD_{50}$ | toxic dose, 50% specific toxic effect |
| TLV | threshold limit value |
| TOC | total organic carbon |
| TPQ | threshold planning quantity |
| TRI | Toxics Release Inventory |
| TSCA | Toxic Substances Control Act |
| TWA | time-weighted average |
| UF | uncertainty factor |
| U.S. | United States |
| USDA | United States Department of Agriculture |
| USGS | United States Geological Survey |
| VOC | volatile organic compound |
| WBC | white blood cell |
| WHO | World Health Organization |

| | |
|---|---|
| > | greater than |
| ≥ | greater than or equal to |
| = | equal to |
| < | less than |
| ≤ | less than or equal to |
| % | percent |
| α | alpha |
| β | beta |
| γ | gamma |
| δ | delta |
| μm | micrometer |
| μg | microgram |
| $q_1^*$ | cancer slope factor |
| – | negative |
| + | positive |
| (+) | weakly positive result |
| (–) | weakly negative result |

# APPENDIX D. INDEX