

**DRAFT  
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 2002

## **DISCLAIMER**

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## **UPDATE STATEMENT**

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

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



## FOREWORD

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

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

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

Each profile includes the following:

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

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

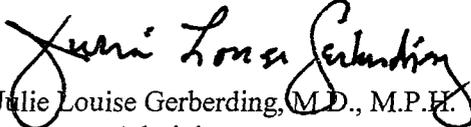
Comments should be sent to:

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Background Information

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on October 25, 2001 (66 FR 54014). 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); and October 21, 1999 (64 FR 56792). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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

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

## QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

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### *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 Synthetic Vitreous Fibers Affect Children?**
- Section 1.7**     **How Can Families Reduce the Risk of Exposure to Synthetic Vitreous Fibers?**
- 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**

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### **ATSDR Information Center**

**Phone:** 1-888-42-ATSDR or (404) 498-0110     **Fax:** (404) 498-0057  
**E-mail:** [atsdric@cdc.gov](mailto:atsdric@cdc.gov)     **Internet:** <http://www.atsdr.cdc.gov>

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

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

*Toxicity*; and numerous chemical-specific case studies.

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

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

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### ***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.

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### ***Referrals***

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

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

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### 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  
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2. Morton Lippmann, Ph.D.  
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3. John A. Pickrell, Ph.D., D.V.M.  
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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.



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## 1. PUBLIC HEALTH STATEMENT

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

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Synthetic vitreous fibers have not been detected in the 1,613 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which synthetic vitreous fibers are found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

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

If you are exposed to 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 are made from rock, clay, slag, or glass. These fibers differ from natural mineral fibers such as asbestos because they do not have a molecular structure that is crystalline. The randomly oriented molecular structure of synthetic vitreous fibers is called an amorphous structure. There are three categories of synthetic vitreous fibers: (1) glass fibers, including glass wool and continuous filament (textile) glass; (2) mineral wool, which contains stone wool and

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slag wool; and (3) refractory ceramic fibers. The primary uses of synthetic vitreous fibers are for heat and sound insulating purposes and to reinforce other materials. Insulation that is used in almost all homes and buildings is composed of synthetic vitreous fibers. 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  $\mu\text{m}$ ), 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 the fiber is also an important property because very thin fibers can be breathed in and deposited deep in the lungs. Fibers with diameters less than 3  $\mu\text{m}$  are usually considered able to be breathed into the lower respiratory tract of humans, while fibers that have diameters greater than 3  $\mu\text{m}$  are usually not. The World Health Organization (WHO) defines fibers as being greater than 5  $\mu\text{m}$  long, thinner than 3  $\mu\text{m}$ , and having an aspect ratio of  $\geq 3:1$ . 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. This is also important because fibers that have small diameters tend to have higher airborne concentrations than fibers with large 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. Small diameter fibers and fiber-containing particles may remain suspended in the air for a long time and be carried long

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distances by wind or water currents before settling. Larger diameter fibers and particles tend to settle more quickly. Synthetic vitreous fibers are not able 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.

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.

Workers that are involved in replacing insulation that contains refractory ceramic fibers in high temperature furnaces may also be exposed to three forms of crystalline silica called quartz, cristobalite, and tridymite. These crystalline materials are not synthetic vitreous fibers and are not initially in the refractory ceramic fiber insulation; however, they are formed at the very high temperatures that occur in the furnaces. Exposure to these three compounds is important because they can cause serious health effects, including lung fibrosis (silicosis).

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

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**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 eventually excreted in the feces.

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 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. PUBLIC HEALTH STATEMENT

**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 wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

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 to cause 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 come 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 in their lungs. 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 on the ability to breathe. 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 glass and stone wool manufacturing workers are not consistently different from what is found in the general U.S. population. Mesothelioma is a cancer of the membrane lining the lung.

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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, 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 that surrounds 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. These factors are 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

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the length and diameter of the fibers. Fibers with diameters greater than about 3  $\mu\text{m}$  are not inhaled into the deepest regions of the lungs. Fibers with lengths greater than about 15–20  $\mu\text{m}$  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 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) has 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 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.

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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 adults. It is not likely that these differences may 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 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.

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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 officer at work can and should tell you whether chemicals you work with are dangerous and likely to be carried home on your clothes, body, or tools, and whether you should be showering and changing clothes before you leave work, storing your street clothes in a separate area of the workplace, or laundering your work clothes at home separately from other clothes. Your employer should have Material Safety Data Sheets (MSDSs) for many of the chemicals used at your place of work, as required by the Occupational Safety and Health Administration (OSHA). Information on these sheets should include chemical names and hazardous ingredients, important properties (such as fire and explosion data), potential health effects, how you get the chemical(s) in your body, how to handle the materials properly, and what to do in an emergency. Your employer is legally responsible for providing a safe workplace and should freely answer your questions about hazardous chemicals. Either OSHA or your OSHA-approved state occupational safety and health program can answer any further questions and help your employer identify and correct problems with hazardous substances. OSHA and/or your OSHA-approved state occupational safety and health program will listen to your formal complaints about workplace health hazards

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and inspect your workplace when necessary. Employees have a right to seek safety and health on the job without fear of punishment.

### **1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO SYNTHETIC VITREOUS FIBERS?**

There are no tests specific for 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.

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

The federal government develops regulations and recommendations to protect public health.

Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA).

Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

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

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that

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provides it. Some regulations and recommendations for synthetic vitreous fibers include the following:

OSHA sets permissible exposure limits (PELs) to protect workers against the health effects of exposure to hazardous substances. The PEL for synthetic vitreous fibers as inert or nuisance dust is 5 milligrams per cubic meter ( $\text{mg}/\text{m}^3$ ) (for the respirable fraction) and  $15 \text{ mg}/\text{m}^3$  (for total dust). The voluntary PEL for fiberglass and mineral wool is 1.0 fiber per cubic centimeter (fiber/cc).

NIOSH has set recommended exposure limits (RELs) based on the time-weighted average (TWA) that you might be exposed to in 10-hours. For fibrous glass dust, the REL (10 hour TWA) is 3 fibers/cc. For total fibrous glass dust, the REL (10 hour TWA) is  $5 \text{ mg}/\text{m}^3$ .

### 1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

Agency for Toxic Substances and Disease Registry  
Division of Toxicology  
1600 Clifton Road NE, Mailstop E-29  
Atlanta, GA 30333  
Web site: <http://www.atsdr.cdc.gov>

\* Information line and technical assistance

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

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

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\* To order toxicological profiles, contact

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

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

Synthetic vitreous fibers are inorganic substances, primarily composed of aluminum and calcium silicates that are derived from rock, clay, slag, or glass. One of the characteristics that distinguishes these substances from other naturally occurring inorganic fibers is that synthetic vitreous fibers have amorphous molecular structures, while naturally occurring mineral fibers, such as asbestos, possess crystal structures. Synthetic vitreous fibers are broadly classified into three separate categories: fibrous glass; rock wool and slag wool (sometimes collectively referred to as mineral wool); and refractory ceramic fibers. Fibrous glass can either be continuous filament glass fibers (sometimes called textile fibers) or glass wool depending upon how it was produced.

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 are largely used to reinforce plastics, cement, papers, and roofing materials or woven into industrial fabrics. Refractory ceramic fibers are primarily used in insulating materials that require very high temperature 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, 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. Depending on

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the dose, durability, and dimensions of the material, as well as the duration of exposure, the deposited material may lead to lung inflammation and, for the most durable materials, lung tissue cell damage, lung tissue scarring, and cancer of the lung or pleural membrane. 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  $\geq 5 \mu\text{m}$  and a length:diameter ratio (aspect ratio) of  $\geq 3:1$  or  $\geq 5:1$ . The World Health Organization (WHO) defines fibers as being  $>5 \mu\text{m}$  long, thinner than  $3 \mu\text{m}$ , and having an aspect ratio of  $\geq 3:1$ . The National Institute for Occupational Safety and Health (NIOSH) defines fibers as particles with lengths  $>5 \mu\text{m}$  and aspect ratios  $\geq 3:1$ . 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 of  $<3 \mu\text{m}$ . 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).

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  $\#0.0001$  fiber/cc. In workplaces that manufacture synthetic vitreous fibers, reported air concentrations have mostly been reported to be  $<0.1$ – $1$  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.

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**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 fiber/cc for continuous filament glass fibers, glass wool, rock wool, slag wool, and special-purpose glass fibers or 0.2 fibers/cc for refractory ceramic fibers.

Possible health hazards from long-term exposure to airborne refractory ceramic fibers, fibrous glass, rock wool, or slag wool include effects associated with occupational exposure to asbestos (pulmonary or pleural fibrosis [i.e., tissue scarring], lung cancer, and pleural or peritoneal mesothelioma), but available evidence from epidemiologic and animal studies indicates that these materials, as a class, are much less potent than asbestos. Epidemiological studies of workers involved in the manufacture of fibrous glass, rock wool, or slag wool have found no consistent evidence for exposure-related increased risks of dying from nonmalignant respiratory disease, lung cancer, or mesothelioma. 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:

- (1) the amount of material deposited in the alveolar region of the lung (fibers with diameters  $>3 \mu\text{m}$  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);
- (2) 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  $\mu\text{m}$ ); and

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(3) the extent of movement of deposited fibers from the alveoli to the lung interstitium and the pleural cavity (fibers with diameters  $>0.3\text{--}0.4\ \mu\text{m}$  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  $>5\ \mu\text{m}$  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  $>1\ \text{fiber/cc}$ ) 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 populations working with fibrous glass materials 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. These studies, while informative, do not account for workers who had ceased exposure before the study and provide no information regarding possible exposure-response relationships.

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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 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.

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. Similar cohort mortality or case-control studies of workers involved in the manufacture of refractory ceramic fibers have not been conducted.

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 fiber/cc. This concentration is the current occupational exposure limit for synthetic vitreous fibers recommended by the American Conference of Governmental Industrial Hygienists. The most extensively studied refractory ceramic fiber, RCF1, caused minimal-to-mild pulmonary inflammation in rats and hamsters at concentrations as low as 36 fibers/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 0–4 grade scale where 0 was "normal" and 4 was "marked") even with exposure for 24 months to a concentration of 234 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 206–268 fiber/cc. The insulation glass wool MMVF10 caused pulmonary inflammation at concentrations as low as 36 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 46 fibers/cc of the glass wool, MMVF11, 44 fibers/cc of the rock wool, MMVF21, and 33 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 durable glass fiber, MMVF33, at

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318 WHO fibers/cc, the high-temperature stone wool, MMVF34, at 400 fibers/cc, the high-silica synthetic vitreous fiber, X607, at 180 fibers/cc, the special-purpose microfiber, 104E-glass, at 1,022 fibers/cc, and GB100R glass wool at 2.2 mg/m<sup>3</sup> (concentration expressed as fiber number per cc was not reported). An intermediate-duration study in male baboons reported that, 1,122 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 exposed female Wistar rats to 576 fibers/cc of Code 104 glass wool for 12 months.

Pulmonary or pleural fibrosis has been observed in animals following intermediate- or chronic-duration inhalation exposure to several refractory ceramic fibers, RCF1, RCF2, RCF3, and RCF4, in the concentration range of 208–268 fibers/cc, the durable (i.e., biopersistent) glass fiber, MMVF33, at 310 WHO fibers/cc, the insulation rock wool, MMVF21, at 185 fibers/cc, the special microfiber, 104E-glass, at 1,022 fibers/cc, and C102/104 blend fibrous glass at 1,122 fibers/cc. Dose-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 >91 fibers/cc, but not at 36 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 273–339 fibers/cc range, the slag wool, MMVF22, at 245 fibers/cc, the high-temperature stone wool, MMVF34, at 400 fibers/cc, and the high-silica synthetic vitreous fiber, X607, at 180 fibers/cc.

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 have been observed in hamsters and rats exposed to the refractory ceramic fiber, RCF1, at concentrations as low as 91 fibers/cc, in rats exposed to RCF2, RCF3,

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or RCF4 at concentrations between 206 and 268 fibers/cc, in hamsters exposed to the durable glass fiber, MMVF33, at 256 fibers/cc, and in rats exposed to the special applications microfiber, 104E-glass, at 1,022 fibers/cc. The carcinogenic response to 104E-glass in rats was observed after only 1 year of exposure, in contrast to another special purpose glass microfiber, 100/475, which did not induce cancer in rats exposed to 1,022 fibers/cc for 1 year.

No other synthetic vitreous fiber types have exhibited 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 287 or 273 fibers/cc; the insulation rock wool, MMVF21, at 264 fibers/cc of MMVF21; the slag wool, MMVF22, at 245 fibers/cc; the high-temperature stone wool, MMVF34, at 400 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 MMVF10 at 339 WHO fibers. Although no tumors were found in male baboons exposed to 1,122 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 listed in the 7<sup>th</sup> *Report on Carcinogens*, but has not been updated since then in the 8<sup>th</sup> or 9<sup>th</sup> *Reports on Carcinogens*. Continuous filament glass, rock wool, slag wool, or refractory ceramic fibers were not listed or assessed for carcinogenicity in the 9<sup>th</sup> *Report on Carcinogens*.

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In 2001, the International Agency for Research on Cancer (IARC) convened a scientific working group of 19 experts from 11 countries to review a new monograph on “man-made vitreous fibers” that will replace the previous IARC (1988) monograph on these materials. However, as of June 2002, the monograph had not been published, and the *List of IARC Evaluations* on IARC’s Web site (<http://193.51.164.11/monoeval/grlist.html>) had not been updated to reflect the new classifications noted below. As reported in an IARC (2001) press release, the new monograph and the working group concluded that epidemiologic studies published since the previous IARC (1988) 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. 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 wools 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 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 June 2002, the assessment is not completed.

### 2.3 MINIMAL RISK LEVELS

#### *Inhalation MRLs*

- C A minimal risk level (MRL) of 0.03 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 dose-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

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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 rates 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. These models significantly decrease uncertainty in extrapolating doses from rats to humans.

In deriving the MRL, the models were used to convert the rat exposure levels in the Mast et al. (1995a, 1995b) bioassay to human equivalent concentrations (see Appendix A for more details). The human equivalent concentrations and data for three indicators of pulmonary inflammation (lung weight, macrophage aggregation score, and bronchiolization score) were modeled with four continuous-variable models available in the EPA Benchmark Dose Software. The derivation assumes that rats and humans are equally sensitive to the inflammatory effects of refractory ceramic fibers. Macrophage aggregation score was selected as the most sensitive of these indicators to serve as the basis of the MRL. The point of departure for the MRL was the approximate median value (1 fiber/cc) of 95% lower limits on predicted concentrations (from several models) associated with an average score for minimal pulmonary macrophage aggregation. This value of 1 fiber/cc was divided by an uncertainty factor of 30 (3 for extrapolation from rats to humans with dosimetric adjustment and 10 for human variability) to arrive at the MRL of 0.03 fiber/cc.

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 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. In addition to its relatively high durability, a 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

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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. 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).

The chronic MRL is also 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<sup>3</sup> at 3 months were 1.7, 2, 2, and 2, respectively. At 12 and 24 months, the respective scores were: 2, 2.3, 3, and 3; and 2, 2.5, 3, and 3.2.

Dose-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 dose-response relationships for nonneoplastic pulmonary effects (i.e., pulmonary inflammation) from intermediate- and chronic-duration exposure to these materials. However, lung retention models for these synthetic vitreous fibers are not yet fully developed to carry out physiologically based dosimetric calculations of human equivalent concentrations.

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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

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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.

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#### 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 cardiovascular, gastrointestinal, hepatic, and renal systems may be indirectly affected.

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

Generally, quantitative exposure data for human studies are not available or are based on estimates made with occupation-history information. Thus, Table 3-1 and Figure 3-1 are restricted to reliable NOAEL and LOAEL values from animal studies. Quantitative comparison of data from animal inhalation studies of airborne fibers have been complicated by the use of different methods to describe units of exposure. Gravimetric measurements (i.e., mg/m<sup>3</sup>) typically include the weight of nonfibrous particles present in the test sample. The most frequent unit of exposure is fibers/cc (or total fibers/cc). 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 Chapters 6 and 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). Because only respirable fibers (those fibers that

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can be inhaled into the lower lung) are expected to cause health effects, many studies have limited reporting to fibers with dimensions likely to be respirable. A commonly used unit of exposure for this measure of exposure is WHO fibers, defined by WHO (1985) as fibers with length  $>5 \mu\text{m}$ , diameter  $\leq 3 \mu\text{m}$ , and a length/diameter ratio  $\geq 3$ .

The units presented in Table 3-1 and Figure 3-1 are (total) fibers/cc. When fibers/cc were not reported but WHO fibers/cc were, these units were used instead.

#### **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.

The most significant biological effects associated with chronic exposure to refractory ceramic fibers are pleural changes (Cowie et al. 2001; Lemasters et al. 1994; Lockey et al. 1996; Trethowan et al. 1995); they may contribute to decreased pulmonary function, but have not been mechanistically linked to increased risks of lung fibrosis or lung cancer (Agency for Toxic Substances and Disease Registry 2001). Like other synthetic vitreous fibers, symptoms of dry cough, runny nose, wheezing, and breathlessness have been reported (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

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effects have been demonstrated. Although participation rates are high, these studies have been limited by small cohort sizes and relatively short exposure durations.

A U.S. study of 627 current and 200 former refractory ceramic fiber production workers identified pleural changes in 23 men (23 pleural plaques, 2 pleural thickening) (Lemasters et al. 1994). Even after adjusting for potential asbestos exposure, a significant association remained between time since first employment and pleural plaques.

A retrospective cohort study of 652 workers from five U.S. refractory ceramic fiber plants detected 20 cases of pleural plaques (Lockey et al. 1996). A nested-case control study (20 cases and 63 controls) found statistically significant odds ratios (ORs) for three exposure variables: >20 years since first exposure (OR=9.5, 95% confidence interval (CI) 1.9–48.2), >10 years of exposure (for 10–20 years, OR=6.1, 95% CI=1.2–29.7; for >20 years, OR=22.3, 95% CI=3.6–137), and estimated exposures >15 fibers/cc-month (ORs ranging from 15.4 to 24.2). Regression analysis of data from the case-control study confirmed that asbestos exposure did not account for the increased risk.

Initial studies (Rossiter et al. 1994; Trethowan et al. 1995) and a follow-up study (Cowie et al. 2001) of 774 ceramic fiber production workers from six European plants found no association between exposure and pleural plaque incidence (for 1/0+ opacities, OR=1.02, 95% CI=0.76–1.37; for 0/1+ opacities, OR=1.18, 95% CI=0.98–1.43). However, a statistically significant association between increased cumulative exposure indices and decreased pulmonary function (forced expiratory volume in 1 second and forced midexpiratory flow) was found among exposed smokers but not exposed nonsmokers. The authors concluded that fiber exposure was not detrimental to nonsmokers, but may have potentiated the effects of cigarette smoke. The estimated mean cumulative exposure index for respirable refractory ceramic fibers was 4.9 fibers/cc-year (range 0.01–36).

A prospective study of 361 current U.S. refractory ceramic fiber production workers found a statistically significant (but not biologically significant) decrease in forced vital capacity 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 significant in longitudinal analyses conducted until 1994. Because airborne concentrations of fibers decreased in the plant over this 7-year time period, these results are inconclusive.

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***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

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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 one 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 are 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 (Weill et al. 1983), and a follow-up 7 years later (Hughes et al. 1993), 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; both plants produced very fine fibers. No progression was observed during the 7-year interval, and opacity incidence did not correlate with decreased spirometry. Two studies observed opacities 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,

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or slag wool in the United States (Bayliss et al. 1976; Chiazze et al. 1997; 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 several 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), the relevance of this artificial route of exposure to human health is controversial. Studies that exposed animals by inhalation to well-measured levels or 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.

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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 (Muhle et al. 1987). In the lungs, an immediate inflammatory response has been observed in rats and mice at the lowest exposure-levels tested, approximately 30–40 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. 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-acetylglucosaminidase, 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. 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, which may result in reduced gas exchange, have been seen following exposure to 160–200 fibers/cc of synthetic vitreous fibers (Hesterberg et al. 1994; Mast et al. 1995a, 1995b; 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).

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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, RCF4 is an “after-service” kaolin-based fiber previously exposed to high temperatures, and X607 is a high-silica synthetic vitreous fiber with physical characteristics similar to fiberglass and a manufacturing process similar to refractory ceramic fibers. Most studies have focused on RCF1, which is comparable to RCF3 (Mast et al. 1995a) and more toxic than RCF2, RCF4 (Mast et al. 1995a), or X607 (Hesterberg et al. 1998b).

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 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 6,206 fibers/cc of RCF1 (55% fiber; 89 mg/m<sup>3</sup>; 2,645 WHO fibers/cc) following 5 days of exposure or 4 weeks postexposure exhibited pulmonary and pleural inflammation, consisting of a dramatic and transient increase in bronchoalveolar levels of neutrophils, a delayed increase in pleural monocyte and eosinophil numbers, and sustained (for 4 weeks) increased 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, female Wistar rats, and male Syrian Golden hamsters have verified the observations of pulmonary and pleural inflammation, and have also seen signs of progressive fibrosis.

In male Fischer 344 rats, concentrations of RCF1 as low as 36 fibers/cc (26 WHO fibers/cc; 3 mg/m<sup>3</sup>) 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 91 fibers/cc (75 WHO

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fibers/cc; 9 mg/m<sup>3</sup>) 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), resulting in decreased gas exchange. No fibrosis was seen in rats exposed to 36 fibers/cc of RCF1; 91 fibers/cc caused minimal-to-mild interstitial fibrosis by 12 months, and 234 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-acetylglucosaminidase, total protein, and fibronectin]) as well as pleural mesothelial cell proliferation following at least 4 weeks of exposure to 650 fibers/cc (45.6 mg/m<sup>3</sup>) (Everitt et al. 1997; Gelzleichter et al. 1999).

Exposure of male Fischer 344 rats to single exposure levels of RCF2, RCF3, and RCF4 (268, 213, and 206 fibers/cc, respectively, equivalent to 30 mg/m<sup>3</sup> 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). Another study in male Fischer 344 rats with another refractory ceramic fiber, X607, reported that exposure to 180 WHO fibers/cc (equivalent to 30 mg/m<sup>3</sup>; total fibers/cc not reported), 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 (Hesterberg et al. 1998b).

Pulmonary inflammation and slight interstitial fibrosis were also seen in female Wistar rats exposed to 130 fibers/cc of either RCF1 or RCF1a for 3 weeks (Bellmann et al. 2001; Brown et al. 2000). 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, bronchioalveolar 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 (130 fibers/cc) 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.

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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 256 fibers/cc (30 mg/m<sup>3</sup>; 215 WHO fibers/cc) 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 650 fibers/cc of RCF1 (46 mg/m<sup>3</sup>) 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 36 fibers/cc of RCF1 (26 WHO fibers/cc; 3 mg/m<sup>3</sup>) 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, and RCF4 (268, 213, and 206 fibers/cc, respectively, equivalent to 30 mg/m<sup>3</sup> 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. The fiber X607 did not cause fibrosis, but did induce pulmonary inflammation (alveolar macrophage aggregation, microgranulation, and bronchiolization) in male Fischer 344 rats exposed to 180 WHO fibers/cc (30 mg/m<sup>3</sup>, total fiber counts not reported) for 2 years (Hesterberg et al. 1998b).

No nonmalignant respiratory effects were reported for male Syrian hamsters or female Osborne-Mendel rats exposed to 200 fibers/cc (12 mg/m<sup>3</sup>) of an unspecified refractory ceramic fiber (diameter 1.8 µm) for 2 years, but these results are inconclusive due to data limitations (Smith et al. 1987). Male Syrian Golden hamsters exposed for 15 or 18 months to 256 fibers/cc (30 mg/m<sup>3</sup>; 215 WHO fibers/cc) of RCF1 exhibited dramatic pulmonary inflammation (bronchioalveolar infiltration of macrophages,

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accompanied by the appearance of microgranulomas, alveolar bronchiolization), as well as mild-to-moderate interstitial and pleural fibrosis (McConnell et al. 1995).

**Glass Wool.** No acute-duration glass wool inhalation studies in animals were identified. All but one (Temstran 475, Code 104 fiber) of the glass wools induced pulmonary inflammation following inhalation in animals (Muhle et al. 1987; others). However, the only glass wools to induce fibrosis were MMVF3 (with intermediate- and chronic exposures) and C102/C104 blend fibrous glass (with chronic but not intermediate exposure) (Goldstein et al. 1983; McConnell et al. 1999).

The glass wools best characterized in animal inhalation studies are MMVF10, MMVF11, and MMVF33 (Hesterberg et al. 1993c, 1999; McConnell et al. 1999). Short-duration multiple-exposure-level studies with MMVF10 in male Syrian Golden hamsters observed minimal pulmonary inflammation (macrophage infiltration and microgranuloma formation) at the lowest levels tested, 36 and 316 WHO fibers/cc for 13 and 5 weeks, respectively (3.2 and 30.5 mg/m<sup>3</sup>) (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 206 WHO fibers/cc [16.5 mg/m<sup>3</sup>]) (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<sup>3</sup>; fiber/cc counts not reported) of GB100R glass wool (Haratake et al. 1995) and in male Fischer rats exposed to 36 and 46 fibers/cc (29 and 41 WHO fibers/cc; 3.1 and 4.8 mg/m<sup>3</sup>) 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, 287 and 273 fibers/cc (232 and 246 WHO fibers/cc; 27.8 and 28.3 mg/m<sup>3</sup>), 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<sup>3</sup>; total fibers/cc not reported) (Hesterberg et al. 1999; 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 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;

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alveolar bronchiolization), beginning at 13 weeks. Both glass fibers induced mesothelial (but not bronchoalveolar) hyperplasia at 18 months (not measured at previous timepoints).

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/cc of a C102–C104 blend of fibrous glass (7.54 mg/m<sup>3</sup>; 5.80 mg/m<sup>3</sup> 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 576 fibers/cc of Tempstran 475 (code 104) glass wool 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<sup>3</sup> 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

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this study are inconclusive, because reporting was very limited. The concentrations were 300 or 3,000 fibers/cc of a 0.45  $\mu\text{m}$  diameter glass (0.3 or 3.0  $\text{mg}/\text{m}^3$ ), 100 fibers/cc of a 3.1  $\mu\text{m}$  diameter glass (10  $\text{mg}/\text{m}^3$ ), 10 or 100 fibers/cc of a 5.4  $\mu\text{m}$  diameter glass (1.2 or 12  $\text{mg}/\text{m}^3$ ), and 25 fibers/cc of 6.1  $\mu\text{m}$  diameter glass (9  $\text{mg}/\text{m}^3$ ).

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). 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 were exposed nose-only to MMVF21, a traditional basalt-based stone/rock wool for 24 months with interim sacrifices, minimal pulmonary inflammation was seen at levels as low as 44 fibers/cc (34 WHO fibers/cc, 3.1  $\text{mg}/\text{m}^3$ ) by 3 months, and severity increased with increasing exposure (Kamstrup et al. 2001; McConnell et al. 1994). No fibrosis was seen at 44 fibers/cc, but interstitial fibrosis and pleural collagen deposition were seen at 185 fibers/cc and above (150 WHO fibers/cc; 16.1  $\text{mg}/\text{m}^3$ ) as early as 3 months.

In male Fischer 344 rats exposed nose-only to a single concentration of 400 fibers/cc (291 WHO fibers/cc; 30.1  $\text{mg}/\text{m}^3$ ) of MMVF34/HT, a high-temperature stone wool, for 2 years, inflammation (increased absolute and relative lung weight, macrophage infiltration and microgranuloma formation, alveolar bronchiolization) were seen as early as 3 months (Kamstrup et al. 1998, 2001). Minimal bronchoalveolar collagen deposition were seen at 6 and 18 (but not at 12 or 24) months, but the authors did not consider this evidence of fibrosis, based on their overall analysis of lung histopathology.

Exposure of Fischer rats to 10  $\text{mg}/\text{m}^3$  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).

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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<sup>3</sup>) 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 exposures. No fibrosis or effects in the pleura were seen at levels up to 245 fibers/cc (213 WHO fibers/cc; 29.9 mg/m<sup>3</sup>).

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<sup>3</sup>) (Smith et al. 1987); other end points were not described.

**Continuous Filament Glass.** Only one inhalation study in animals with continuous glass filaments was 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).

In male Wistar rats exposed whole-body at 1,022 fibers/cc to E-glass or 100/475 glass (two biopersistent special-purpose microfibers) for 1 year, both fibers caused “considerable” pulmonary inflammation (macrophage infiltration associated with alveolar wall thickening), and minimal alveolar and bronchiolar fibrosis (Cullen et al. 2000). Additionally, rats exposed for 1 year and allowed to recover for an additional year exhibited bronchoalveolar hyperplasia and fibrosis more advanced than in animals sacrificed immediately after exposure.

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

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**Cardiovascular Effects.** Concern for risk of cardiovascular disease resulting from inhalation exposure to synthetic vitreous fibers is based on observations with asbestos (Agency for Toxic Substances and Disease Registry 2001). Lung damage, including chronic inflammation and fibrosis, may cause increased resistance of blood through the alveolar capillary beds, leading to hypertension and other compensatory changes (Sjogren 2000).

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 authors speculate that the workers may have been at higher risk for the primary known causes of ischemic heart disease (e.g., heat, carbon monoxide, physical strain), unrelated to exposure.

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).

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

Key to <sup>a</sup> figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
<b>ACUTE EXPOSURE</b>							
<b>Systemic</b>							
1	Rat (Fischer- 344)	5 d 6 hr/d	Resp		1700 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		6206 M (pulmonary and pleural inflammation)		Gelzleichter et al. 1996a, 1996c RCF1
3	Hamster (Golden Syrian)	5 d 6 hr/d	Resp		1700 M (pulmonary and pleural inflammation; increased lung mesothelial cell proliferation)		Everitt et al. 1994 RCF1

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SYNTHETIC VITREOUS FIBERS

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

Key to <sup>a</sup> figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
<b>INTERMEDIATE EXPOSURE</b>							
<b>Systemic</b>							
4	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 application glass fiber
5	Rat (Wistar)	12 mo 5 hr/d 4 d/wk	Resp	576			Muhle et al. 1987 Code 104 glass
6	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk	Resp Bd Wt		36 M (minimal pulmonary inflammation)		Hesterberg et al. 1993 MMVF10 glass wool
7	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk	Resp Bd Wt		36 M (minimal-to-mild pulmonary inflammation)		Hesterberg et al. 1993 MMVF10 glass wool
8	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk	Resp Bd Wt		36 M (minimal-to-mild pulmonary inflammation)		Hesterberg et al. 1993 MMVF10 glass wool
9	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk	Resp Bd Wt		46 M (minimal pulmonary inflammation)		Hesterberg et al. 1993 MMVF11 glass wool

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

Key to figure <sup>a</sup>	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
10	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk	Resp		46 M (minimal-to-mild pulmonary inflammation)		Hesterberg et al. 1993  MMVF11 glass wool
			Bd Wt	273 M			
11	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk	Resp		46 M (minimal-to-mild pulmonary inflammation)		Hesterberg et al. 1993  MMVF11 glass wool
			Bd Wt	273 M			
12	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk	Resp		44 M (pulmonary inflammation)		McConnell et al. 1994  MMVF21 rock wool
			Cardio	264 M			
			Hepatic	264 M			
			Renal	264 M			
			Bd Wt	264 M			
13	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk	Resp		44 M (pulmonary inflammation)		McConnell et al. 1994  MMVF21 rock wool
			Cardio	264 M			
			Hepatic	264 M			
			Renal	264 M			
			Bd Wt	264 M			

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

Key to <sup>a</sup> figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
14	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk	Resp		44 M (pulmonary inflammation)		McConnell et al. 1994
			Cardio	264 M			MMVF21 rock wool
			Hepatic	264 M			
			Renal	264 M			
15	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk	Resp		33 M (pulmonary inflammation)		McConnell et al. 1994
			Cardio	245 M			MMVF22 slag wool
			Hepatic	245 M			
			Renal	245 M			
16	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk	Resp		33 M (pulmonary inflammation)		McConnell et al. 1994
			Cardio	245 M			MMVF22 slag wool
			Hepatic	245 M			
			Renal	245 M			
17	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk	Resp		33 M (pulmonary inflammation)		McConnell et al. 1994
			Cardio	245 M			MMVF22 slag wool
			Hepatic	245 M			
			Renal	245 M			
			Bd Wt	245 M			

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

Key to figure <sup>a</sup>	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious	Serious	
					total fibers/cc	total fibers/cc	
18	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk	Resp		400 M (minimal pulmonary inflammation)		Kamstrup et al. 2001
			Bd Wt	400 M		MMVF34 rock wool	
19	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk	Resp		400 M (minimal-to-slight pulmonary inflammation; bronchoalveolar collagen deposition without fibrosis)		Kamstrup et al. 2001
			Bd Wt	400 M		MMVF34 rock wool	
20	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk	Resp		400 M (minimal-to-slight pulmonary inflammation)		Kamstrup et al. 2001
			Bd Wt	400 M		MMVF34 rock wool	
21	Rat (Wistar)	3 wk 6 hr/day 5 d/wk	Resp			130 F (very slight interstitial fibrosis, pulmonary inflammation, reduced alveolar clearance)	Bellman et al. 2001 RCF1
22	Rat (Fischer- 344)	4 wk 4 hr/d 5 d/wk	Resp		650 M (pulmonary and pleural inflammation; incr. lung and diaphragm mesothelial cell proliferation)		Everitt et al. 1997 RCF1
23	Rat (Fischer- 344)	12 wk 4 hr/d 5 d/wk	Resp		650 M (pulmonary and pleural inflammation; incr. lung and diaphragm mesothelial cell proliferation)		Everitt et al. 1997 RCF1

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

Key to figure <sup>a</sup>	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
24	Rat (Fischer- 344)	12 wk 4 hr/d 5d/wk	Resp		647 M (pulmonary and pleural inflammation)		Gelzleichter et al. 1999 RCF1
25	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk	Resp		36 M (minimal-to-mild pulmonary inflammation)		Mast et al. 1995a, 1995b RCF1
			Cardio	234 M			
			Hepatic	234 M			
			Renal	234 M			
26	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk	Resp		36 M (minimal-to-mild pulmonary inflammation)	234 M (minimal-to-mild interstitial fibrosis, pulmonary inflammation)	Mast et al. 1995a, 1995b RCF1
			Cardio	234 M			
			Hepatic	234 M			
			Renal	234 M			
27	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk	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			
28	Rat (Wistar)	3 wk 6 hr/day 5 d/wk	Resp			130 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 <sup>a</sup> figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
29	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk	Resp		268 M (minimal-to-mild pulmonary inflammation)		Mast et al. 1995a
			Cardio	268 M			RCF2
			Hepatic	268 M			
			Renal	268 M			
			Bd Wt	268 M			
30	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk	Resp		268 M (minimal-to-mild pulmonary inflammation)		Mast et al. 1995a
			Cardio	268 M			RCF2
			Hepatic	268 M			
			Renal	268 M			
			Bd Wt	268 M			
31	Rat (Fischer- 344)	9 mo 6 hr/d 5 d/wk	Resp		268 M (minimal-to-mild interstitial fibrosis, minimal pleural fibrosis, pulmonary inflammation)		Mast et al. 1995a
			Cardio	268 M			RCF2
			Hepatic	268 M			
			Renal	268 M			
			Bd Wt	268 M			
32	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk	Resp		268 M (mild interstitial fibrosis, pulmonary inflammation)		Mast et al. 1995a
			Cardio	268 M			RCF2
			Hepatic	268 M			
			Renal	268 M			
			Bd Wt	268 M			

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

Key to <sup>a</sup> figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
33	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk	Resp		213 M (minimal-to-mild pulmonary inflammation)		Mast et al. 1995a  RCF3
			Cardio	213 M			
			Hepatic	213 M			
			Renal	213 M			
34	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk	Resp			213 M (minimal-to-mild interstitial fibrosis, pulmonary inflammation)	Mast et al. 1995a  RCF3
			Cardio	213 M			
			Hepatic	213 M			
			Renal	213 M			
35	Rat (Fischer- 344)	9 mo 6 hr/d 5 d/wk	Resp			213 M (mild interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a  RCF3
			Cardio	213 M			
			Hepatic	213 M			
			Renal	213 M			
			Bd Wt	213 M			

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

Key to <sup>a</sup> figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
36	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk	Resp			213 M (mild-to-moderate interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF3
			Cardio	213 M			
			Hepatic	213 M			
			Renal	213 M			
37	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk	Resp		206 M (minimal-to-mild pulmonary inflammation)		Mast et al. 1995a RCF4
			Cardio	206 M			
			Hepatic	206 M			
			Renal	206 M			
			Bd Wt	206 M			
38	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk	Resp		206 M (minimal-to-mild pulmonary inflammation)		Mast et al. 1995a RCF4
			Cardio	206 M			
			Hepatic	206 M			
			Renal	206 M			
			Bd Wt	206 M			
39	Rat (Fischer- 344)	9 mo 6 hr/d 5 d/wk	Resp		206 M (minimal-to-mild pulmonary inflammation)		Mast et al. 1995a RCF4
			Cardio	206 M			
			Hepatic	206 M			
			Renal	206 M			
			Bd Wt	206 M			

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

Key to <sup>a</sup> figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
40	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk	Resp			206 M (minimal-to-mild interstitial fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF4
			Cardio	206 M			
			Hepatic	206 M			
			Renal	206 M			
41	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk	Resp		180 <sup>b</sup> M (pulmonary inflammation)		Hesterberg et al. 1998b
			Hepatic	180 <sup>b</sup> M			X607 RCF
			Renal	180 <sup>b</sup> M			
			Bd Wt	180 <sup>b</sup> M			
42	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk	Resp		180 <sup>b</sup> M (pulmonary inflammation)		Hesterberg et al. 1998b
			Hepatic	180 <sup>b</sup> M			X607 RCF
			Renal	180 <sup>b</sup> M			
			Bd Wt	180 <sup>b</sup> M			
43	Rat (Fischer- 344)	1 yr 6 hr/d 5 d/wk	Resp		180 <sup>b</sup> M (pulmonary inflammation)		Hesterberg et al. 1998b
			Hepatic	180 <sup>b</sup> M			X607 RCF
			Renal	180 <sup>b</sup> M			
			Bd Wt	180 <sup>b</sup> M			

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

Key to figure <sup>a</sup>	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
44	Hamster (Golden Syrian)	7 wk 6 hr/d 5 d/wk	Resp		316 <sup>b</sup> M (pulmonary inflammation)		Hesterberg et al. 1999  MMVF10 glass wool
45	Hamster (Golden Syrian)	13 wk 6 hr/d 5 d/wk	Resp		36 <sup>b</sup> M (pulmonary inflammation)		Hesterberg et al. 1999  MMVF10 glass wool
46	Hamster (Golden Syrian)	3 mo 6 hr/d 5 d/wk	Resp		339 <sup>b</sup> M (minimal-to-moderate pulmonary inflammation)		McConnell et al. 1999
			Bd Wt	339 <sup>b</sup> M			MMVF10a glass wool
47	Hamster (Golden Syrian)	6 mo 6 hr/d 5 d/wk	Resp		339 <sup>b</sup> M (minimal-to-mild pulmonary inflammation)		McConnell et al. 1999
			Bd Wt	339 <sup>b</sup> M			MMVF10a glass wool
48	Hamster (Golden Syrian)	12 mo 6 hr/d 5 d/wk	Resp		339 <sup>b</sup> M (minimal-to-mild pulmonary inflammation)		McConnell et al. 1999
			Bd Wt	339 <sup>b</sup> M			MMVF10a glass wool
49	Hamster (Golden Syrian)	3 mo 6 hr/d 5 d/wk	Resp		310 <sup>b</sup> M (minimal-to-mild pulmonary inflammation)		McConnell et al. 1999
			Bd Wt	310 <sup>b</sup> M			MMVF33 glass wool

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

Key to figure <sup>a</sup>	Species (strain)	Exposure/duration/frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
50	Hamster (Golden Syrian)	6 mo 6 hr/d 5 d/wk	Resp			310 <sup>b</sup> M (minimal-to-mild pulmonary and pleural fibrosis, pulmonary inflammation)	McConnell et al. 1999
			Bd Wt	310 <sup>b</sup> M			MMVF33 glass wool
51	Hamster (Golden Syrian)	6 mo 6 hr/d 5 d/wk	Resp			310 <sup>b</sup> M (mild pulmonary and pleural fibrosis, pulmonary inflammation)	McConnell et al. 1999
			Bd Wt	310 <sup>b</sup> M			MMVF33 glass wool
52	Hamster (Golden Syrian)	4 wk 4 hr/d 5 d/wk	Resp		650 M (pulmonary and pleural inflammation; incr. lung and diaphragm mesothelial cell proliferation)		Everitt et al. 1997 RCF1
53	Hamster (Golden Syrian)	12 wk 4 hr/d 5 d/wk	Resp			650 M (pulmonary and pleural inflammation; incr. lung and diaphragm mesothelial cell proliferation; early signs of pleural fibrosis)	Everitt et al. 1997 RCF1
54	Hamster (Golden Syrian)	12 wk 4 hr/d 5d/wk	Resp		647 M (pulmonary and pleural inflammation)		Gelzleichter et al. 1999 RCF1

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

Key to <sup>a</sup> figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
55	Hamster (Golden Syrian)	3 mo 5 d/wk 6 hr/d	Resp		256 M (mild-to-moderate pulmonary inflammation)		McConnell et al. 1995
			Cardio	256 M			RCF1
			Hepatic	256 M			
			Renal	256 M			
			Bd Wt	256 M			
56	Baboon	8 mo 7 hr/d 5 d/wk	Resp		1122 M (pulmonary inflammation, scant ferruginous bodies)		Goldstein et al. 1983
							C102-C104 blend glass wool
							<b>Cancer</b>
57	Rat (Wistar)	1 yr 7 hr/d 5 d/wk				1022 M (CEL: pleural mesotheliomas, lung adenomas and carcinomas)	Cullen et al. 2000 104 E-glass special application glass fiber
58	Hamster (Golden Syrian)	40 wk 5 d/wk 6 h/d				256 M (CEL: pleural mesotheliomas)	McConnell et al. 1995  RCF1

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

Key to figure <sup>a</sup>	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
<b>CHRONIC EXPOSURE</b>							
<b>Systemic</b>							
59	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk	Resp		36 M (minimal-to-mild pulmonary inflammation)		Hesterberg et al. 1993
			Bd Wt	287 M			MMVF10 glass wool
60	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk	Resp		36 M (minimal-to-mild pulmonary inflammation)		Hesterberg et al. 1993
			Bd Wt	287 M			MMVF10 glass wool
61	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk	Resp		46 M (minimal-to-mild pulmonary inflammation)		Hesterberg et al. 1993
			Bd Wt	273 M			MMVF11 glass wool
62	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk	Resp		46 M (minimal-to-mild pulmonary inflammation)		Hesterberg et al. 1993
			Bd Wt	273 M			MMVF11 glass wool
63	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk	Resp			185 M (mild pulmonary fibrosis, pulmonary inflammation)	McConnell et al. 1994
			Cardio	264 M			MMVF21 rock wool
			Hepatic	264 M			
			Renal	264 M			
			Bd Wt	264 M			

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

Key to figure <sup>a</sup>	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form	
					Less serious total fibers/cc	Serious total fibers/cc		
64	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk	Resp				185 M (mild pulmonary fibrosis, pulmonary inflammation)	McConnell et al. 1994
			Cardio	264 M				MMVF21 rock wool
			Hepatic	264 M				
			Renal	264 M				
			Bd Wt	264 M				
65	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk	Resp		33 M (pulmonary inflammation)			McConnell et al. 1994
			Cardio	245 M				MMVF22 slag wool
			Hepatic	245 M				
			Renal	245 M				
			Bd Wt	245 M				
66	Rat (Fischer- 344)	24 mo 6 hr/d 5 d/wk	Resp		33 M (pulmonary inflammation)			McConnell et al. 1994
			Cardio	245 M				MMVF22 slag wool
			Hepatic	245 M				
			Renal	245 M				
			Bd Wt	245 M				
67	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk	Resp		400 M (minimal-to-slight pulmonary inflammation)			Kamstrup et al. 2001
			Bd Wt	400 M				MMVF34 rock wool

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

Key to figure <sup>a</sup>	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
68	Rat (Fischer- 344)	24 mo 6 hr/d 5 d/wk	Resp		400 M (minimal-to-moderate pulmonary inflammation)		Kamstrup et al. 2001
			Bd Wt	400 M			MMVF34 rock wool
69	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk	Resp		36 M (minimal-to-mild pulmonary inflammation)		Mast et al. 1995a, 1995b
			Cardio	234 M		91 M (minimal-to-mild interstitial fibrosis)	RCF1
			Hepatic	234 M			
			Renal	234 M			
			Bd Wt	234 M			
70	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk	Resp		36 <sup>c</sup> M (minimal-to-mild pulmonary inflammation)		Mast et al. 1995a, 1995b
			Cardio	234 M		91 M (minimal-to-mild interstitial fibrosis)	RCF1
			Hepatic	234 M			
			Renal	234 M			
			Bd Wt	234 M			
71	Rat (Fischer- 344)	15 mo 6 hr/d 5 d/wk	Resp			268 M (mild interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a
			Cardio	268 M			RCF2
			Hepatic	268 M			
			Renal	268 M			
			Bd Wt	268 M			

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

Key to figure <sup>a</sup>	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
72	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk	Resp			268 M (mild interstitial fibrosis, minimal pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF2
			Cardio	268 M			
			Hepatic	268 M			
			Renal	268 M			
			Bd Wt	268 M			
73	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk	Resp			268 M (mild-to-moderate interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF2
			Cardio	268 M			
			Hepatic	268 M			
			Renal	268 M			
			Bd Wt	268 M			
74	Rat (Fischer- 344)	15 mo 6 hr/d 5 d/wk	Resp			213 M (mild interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF3
			Cardio	213 M			
			Hepatic	213 M			
			Renal	213 M			
			Bd Wt	213 M			

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

Key to figure <sup>a</sup>	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form	
					Less serious total fibers/cc	Serious total fibers/cc		
75	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk	Resp				213 M (mild interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF3
			Cardio	213 M				
			Hepatic	213 M				
			Renal	213 M				
			Bd Wt	213 M				
76	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk	Resp				213 M (mild-to-moderate interstitial fibrosis, minimal pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF3
			Cardio	213 M				
			Hepatic	213 M				
			Renal	213 M				
			Bd Wt	213 M				
77	Rat (Fischer- 344)	15 mo 6 hr/d 5 d/wk	Resp				206 M (minimal-to-mild interstitial fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF4
			Cardio	206 M				
			Hepatic	206 M				
			Renal	206 M				
			Bd Wt	206 M				

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

Key to figure <sup>a</sup>	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
78	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk	Resp			206 M (minimal-to-mild interstitial fibrosis, minimal pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF4
			Cardio	206 M			
			Hepatic	206 M			
			Renal	206 M			
79	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk	Resp			206 M (minimal-to-mild interstitial fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF4
			Cardio	206 M			
			Hepatic	206 M			
			Renal	206 M			
80	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk	Resp		180 <sup>b</sup> M (pulmonary inflammation)		Hesterberg et al. 1998b
			Hepatic	180 <sup>b</sup> M			X607 RCF
			Renal	180 <sup>b</sup> M			
			Bd Wt	180 <sup>b</sup> M			
81	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk	Resp		180 <sup>b</sup> M (pulmonary inflammation)		Hesterberg et al. 1998b
			Hepatic	180 <sup>b</sup> M			X607 RCF
			Renal	180 <sup>b</sup> M			
			Bd Wt	180 <sup>b</sup> M			

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

Key to figure <sup>a</sup>	Species (strain)	Exposure/duration/frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious	Serious	
					total fibers/cc	total fibers/cc	
82	Hamster (Golden Syrian)	18 mo 6 hr/d 5 d/wk	Resp		339 <sup>b</sup> M (minimal-to-mild pulmonary inflammation)		McConnell et al. 1999
			Bd Wt	339 <sup>b</sup> M			MMVF10a glass wool
83	Hamster (Golden Syrian)	18 mo 6 hr/d 5 d/wk	Resp			310 <sup>b</sup> M (mild pleural and interstitial fibrosis; mesothelial hyperplasia)	McConnell et al. 1999
			Bd Wt	310 <sup>b</sup> M			MMVF33 glass wool
84	Hamster (Golden Syrian)	18 mo 5 d/wk 6 hr/d	Resp			256 M (mild-to-moderate interstitial fibrosis, moderate-to-marked pleural fibrosis, pulmonary inflammation, mesothelial hyperplasia)	McConnell et al. 1995 RCF1
			Cardio	256 M			
			Hepatic	256 M			
			Renal	256 M			
			Bd Wt	256 M			
85	Baboon	18 mo 7 hr/d 5 d/wk	Resp			1122 M (focal peribronchiolar fibrosis; numerous pulmonary ferruginous bodies)	Goldstein et al. 1983 C102-C104 blend glass wool
86	Baboon	30 mo 7 hr/d 5 d/wk	Resp			1122 M (focal peribronchiolar fibrosis; numerous pulmonary ferruginous bodies)	Goldstein et al. 1983 C102-C104 blend glass wool

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

Key to figure <sup>a</sup>	Species (strain)	Exposure/ duration/ frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
<b>Cancer</b>							
87	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk					234 M (CEL: pulmonary adenomas and carcinomas) Mast et al. 1995a, 1995b RCF1
88	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk					91 M (CEL: pleural mesothelioma) Mast et al. 1995a, 1995b RCF1
89	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk					268 M (CEL: pulmonary carcinomas, pleural mesotheliomas) Mast et al. 1995a RCF2
90	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk					213 M (CEL: pulmonary adenomas and carcinomas, pleural mesotheliomas) Mast et al. 1995a RCF3
91	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk					206 M (CEL: pleural mesothelioma) Mast et al. 1995a RCF4
92	Hamster (Golden Syrian)	78 wk 6 hr/d 5 d/wk					310 <sup>b</sup> M (CEL: pleural mesothelioma) McConnell et al. 1999 MMVF33 glass wool
93	Hamster (Golden Syrian)	24 mo 6 hr/d 5 d/wk					200 (CEL: pleural mesothelioma) Smith et al. 1987 RCF

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

Key to figure <sup>a</sup>	Species (strain)	Exposure/duration/frequency	System	NOAEL total fibers/cc	LOAEL		Reference Chemical Form
					Less serious total fibers/cc	Serious total fibers/cc	
94	Hamster (Golden Syrian)	18 mo 5 d/wk 6 hr/d				256 M (CEL: pleural mesotheliomas)	McConnell et al. 1995  RCF1

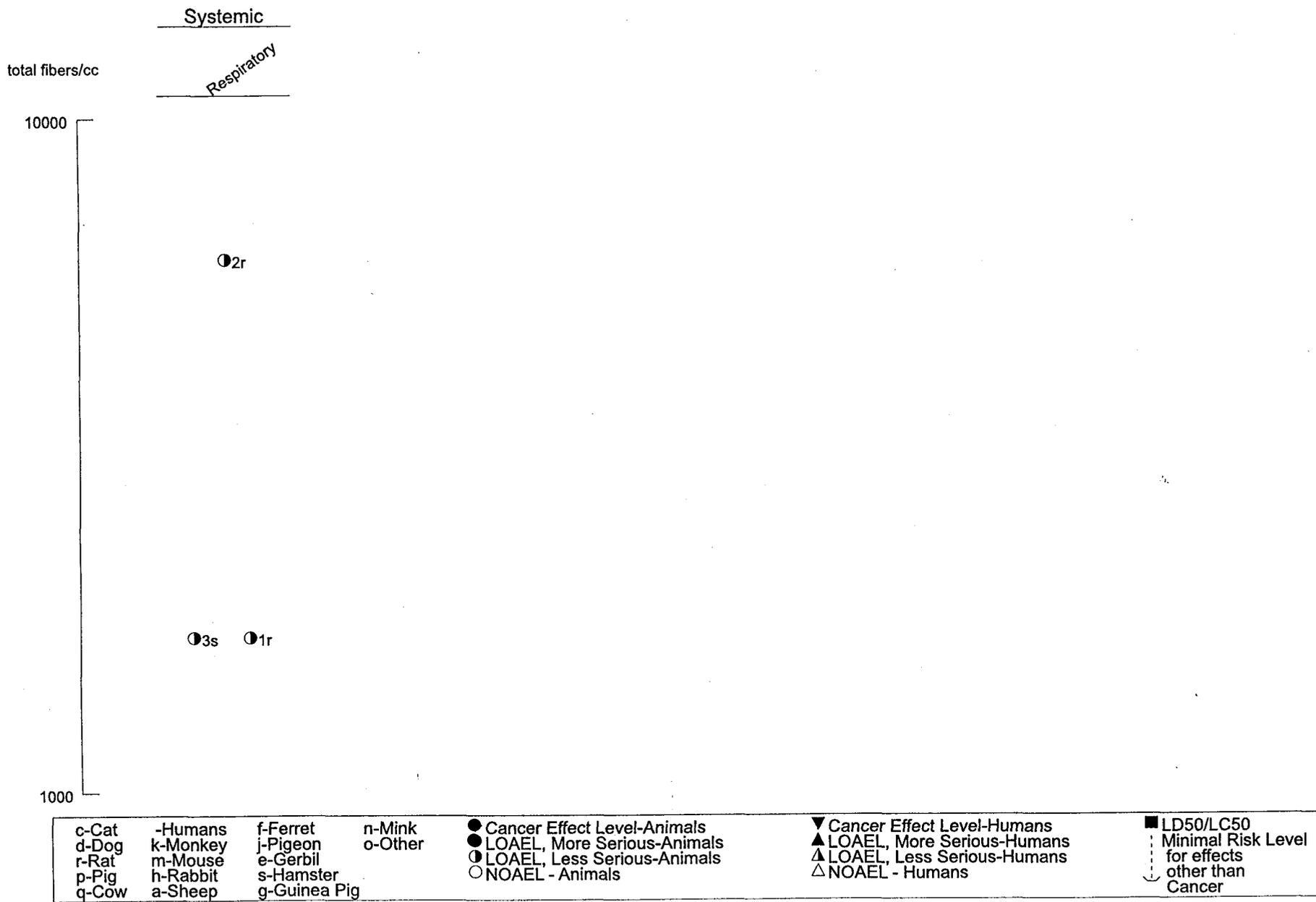
<sup>a</sup>The number corresponds to entries in Figure 3-1.

<sup>b</sup>WHO fibers (defined by WHO (1985) as fibers with length > 5 μm, diameter < 3 μm, and a length/width ratio > 3:1)

<sup>c</sup>Used to derive a chronic inhalation minimal risk level (MRL) for refractory ceramic fibers, as described in detail in Appendix A. The rat exposure concentrations (total fibers/cc) were converted to human exposure concentrations using the rat and human lung deposition and clearance models developed by Yu et al. (1995a, 1996, 1997, 1998). The human equivalent concentrations and data for three indicators of pulmonary inflammation (lung weight, macrophage aggregation score, and bronchiolization score) were modeled with four continuous-variable models available in the EPA Benchmark Dose Software. Macrophage aggregation score was selected as the most sensitive of these indicators to serve as the basis of the MRL. The point of departure for the MRL was the approximate median value (1 fiber/cc) of 95% lower limits on predicted concentrations (from several models) associated with an average score of 1.0 ("minimal") for pulmonary macrophage aggregation. This value of 1 fiber/cc was divided by an uncertainty factor of 30 (3 for extrapolation from rats to humans with dosimetric adjustment and 10 for human variability) to arrive at the MRL of 0.03 fiber/cc.

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)



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Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (Continued)  
Intermediate (15-364 days)

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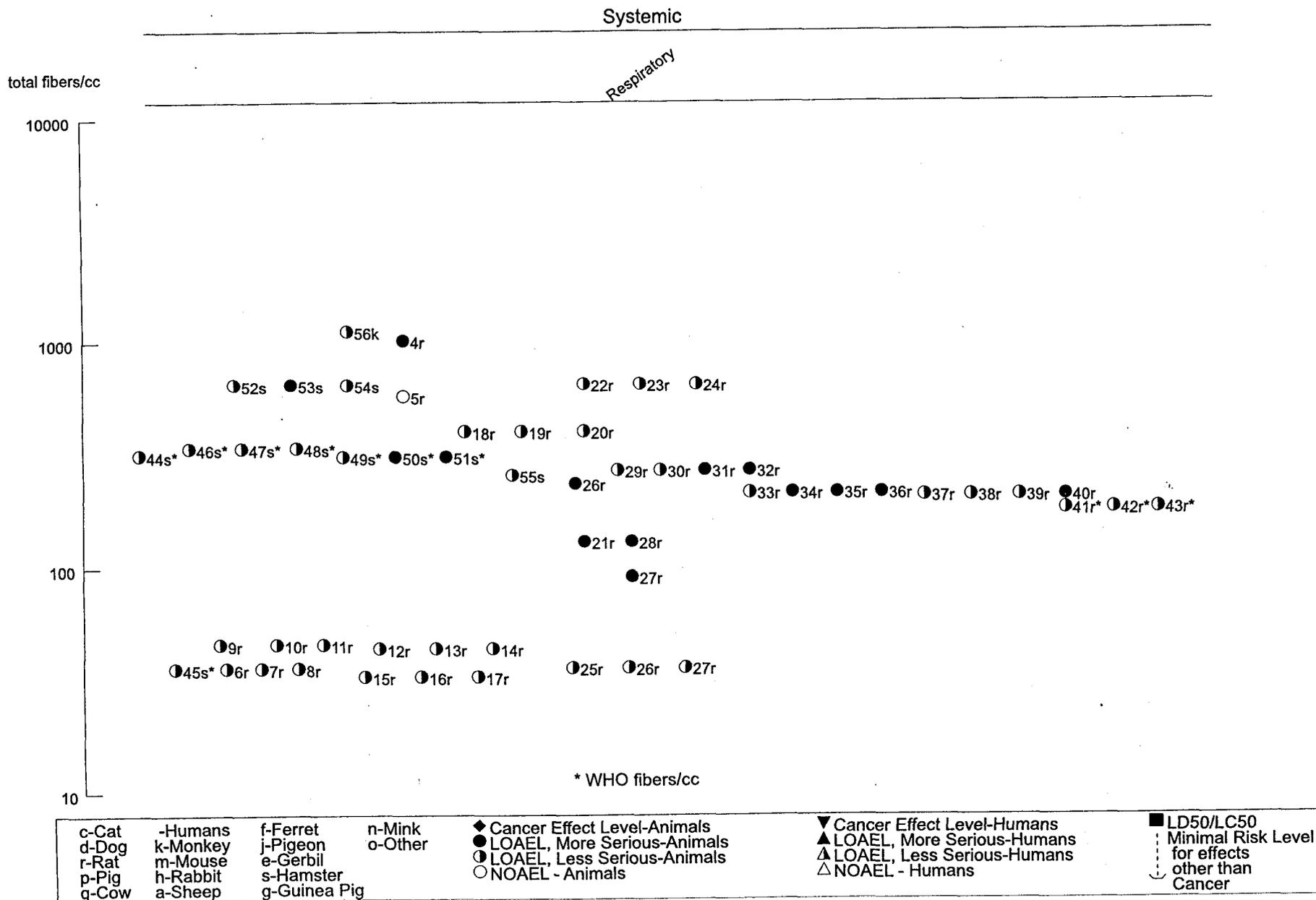
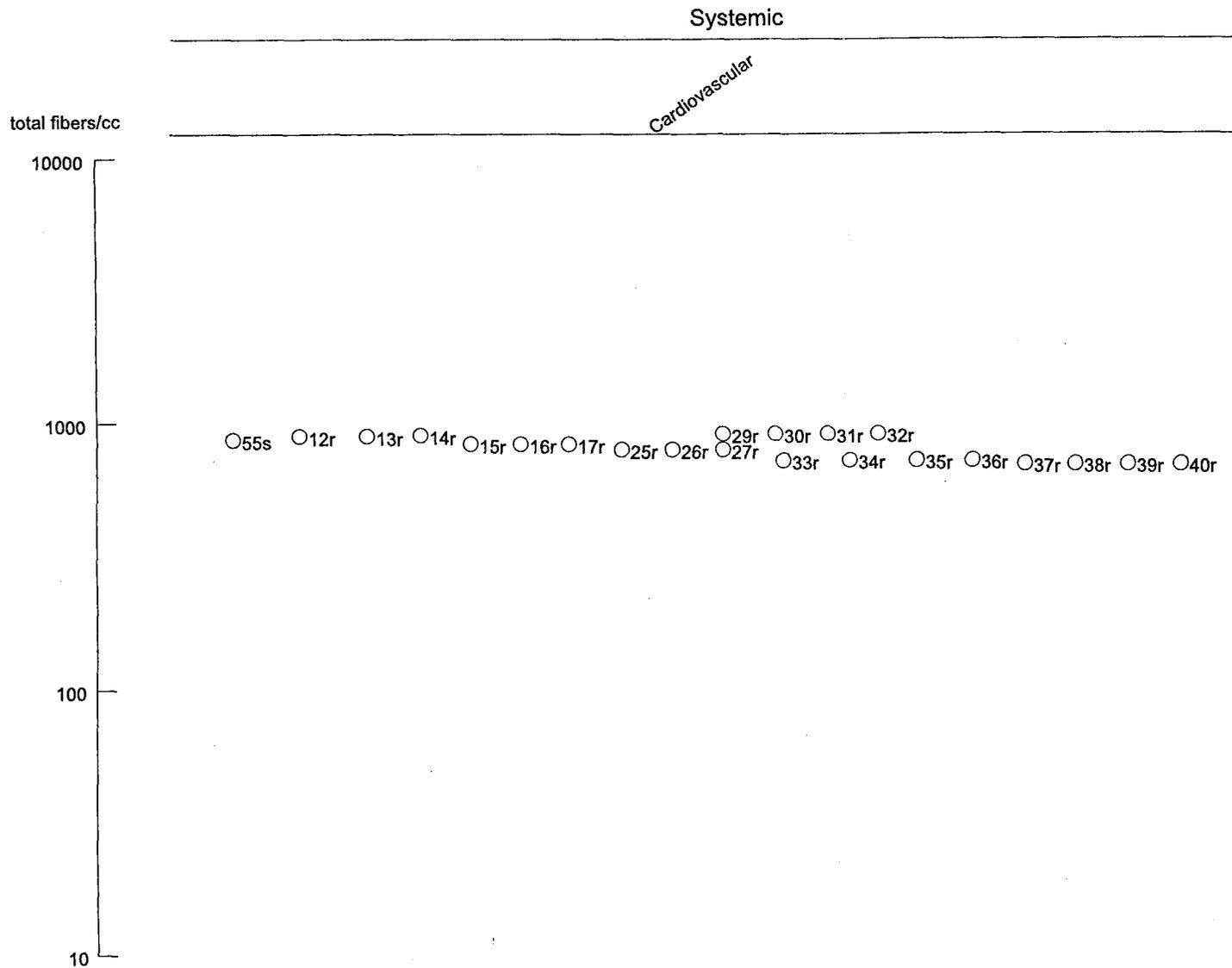


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (Continued)

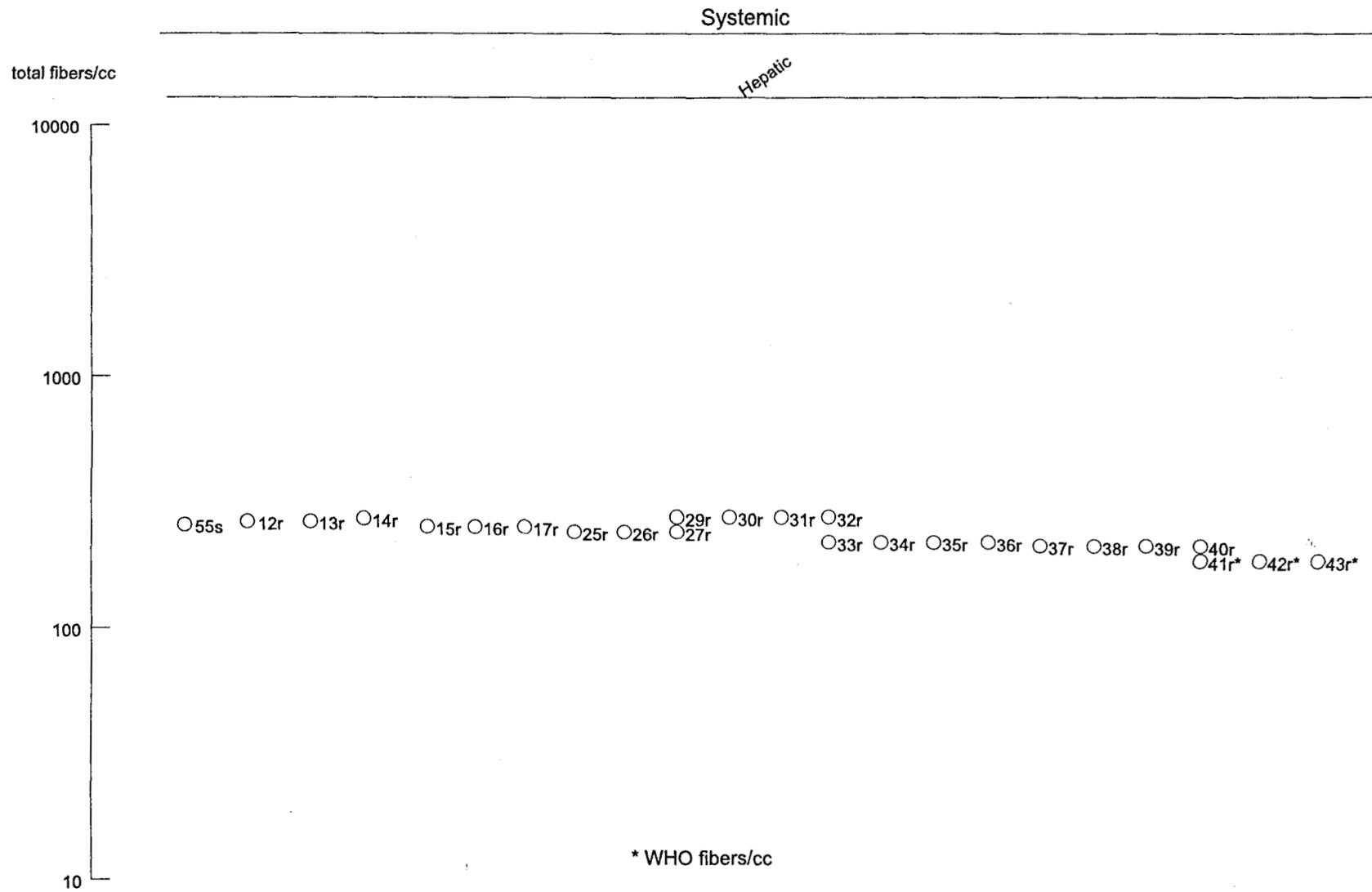
Intermediate (15-364 days)



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

Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (Continued)  
Intermediate (15-364 days)



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

Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (Continued)  
Intermediate (15-364 days)

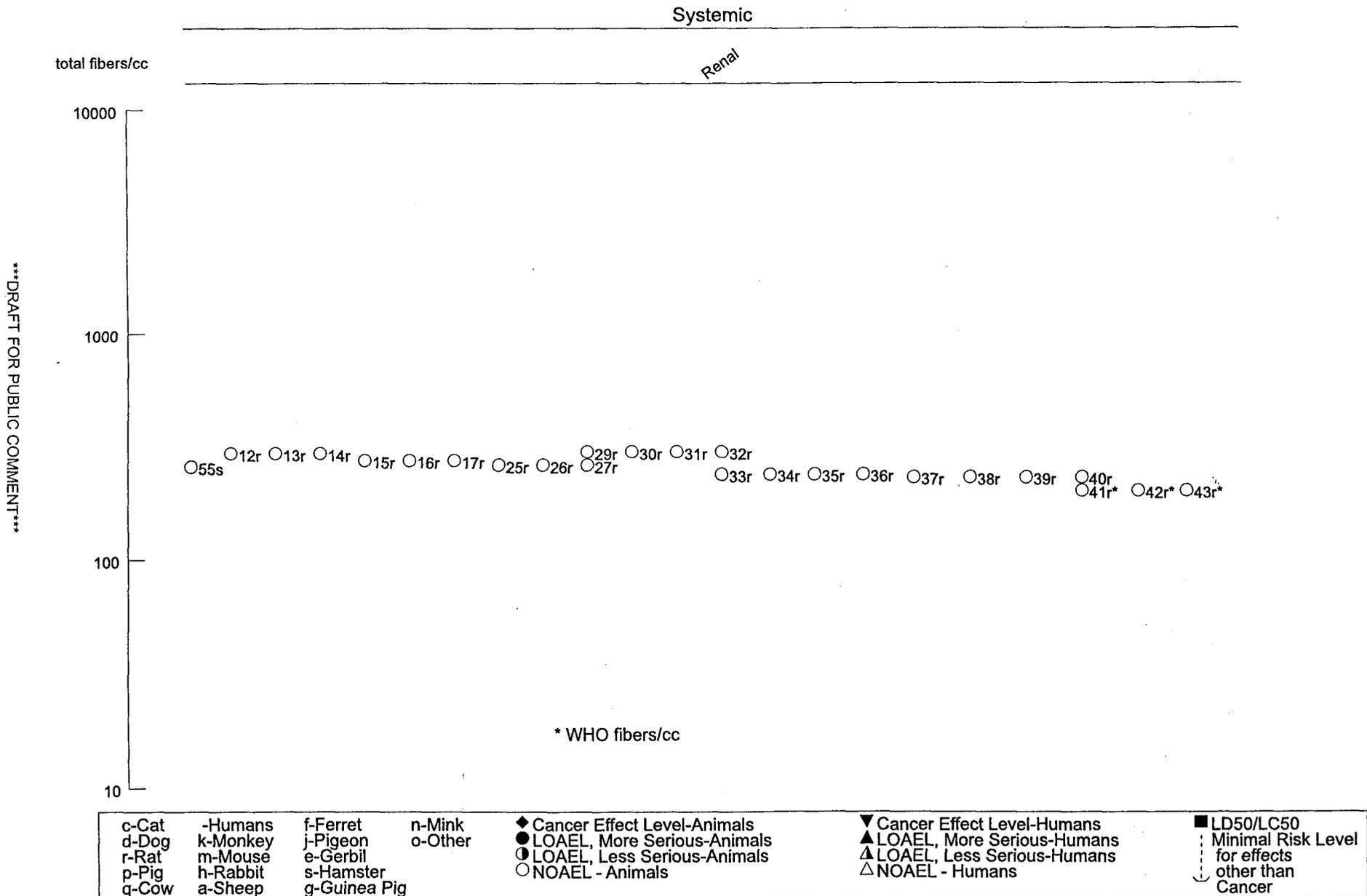
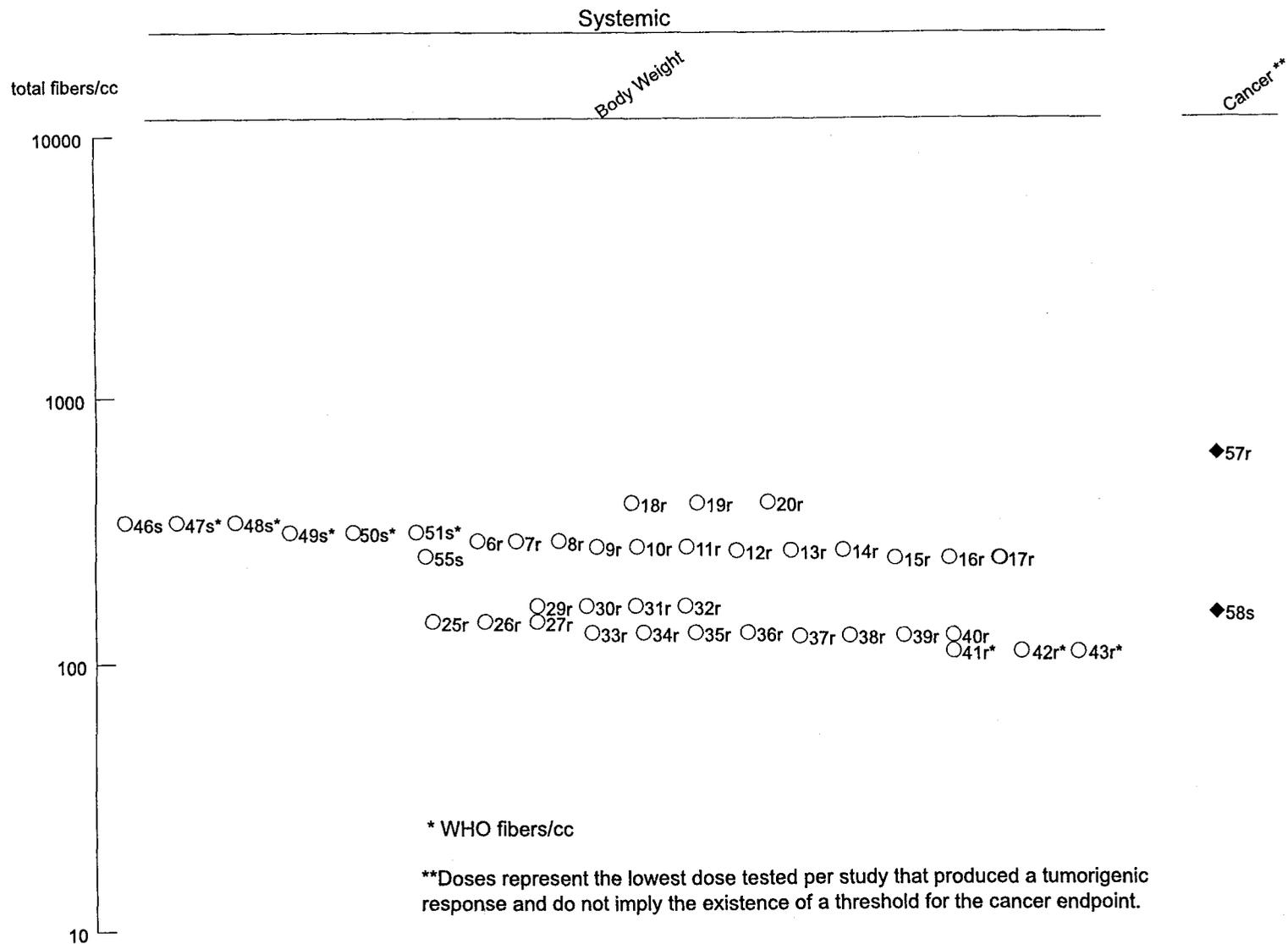


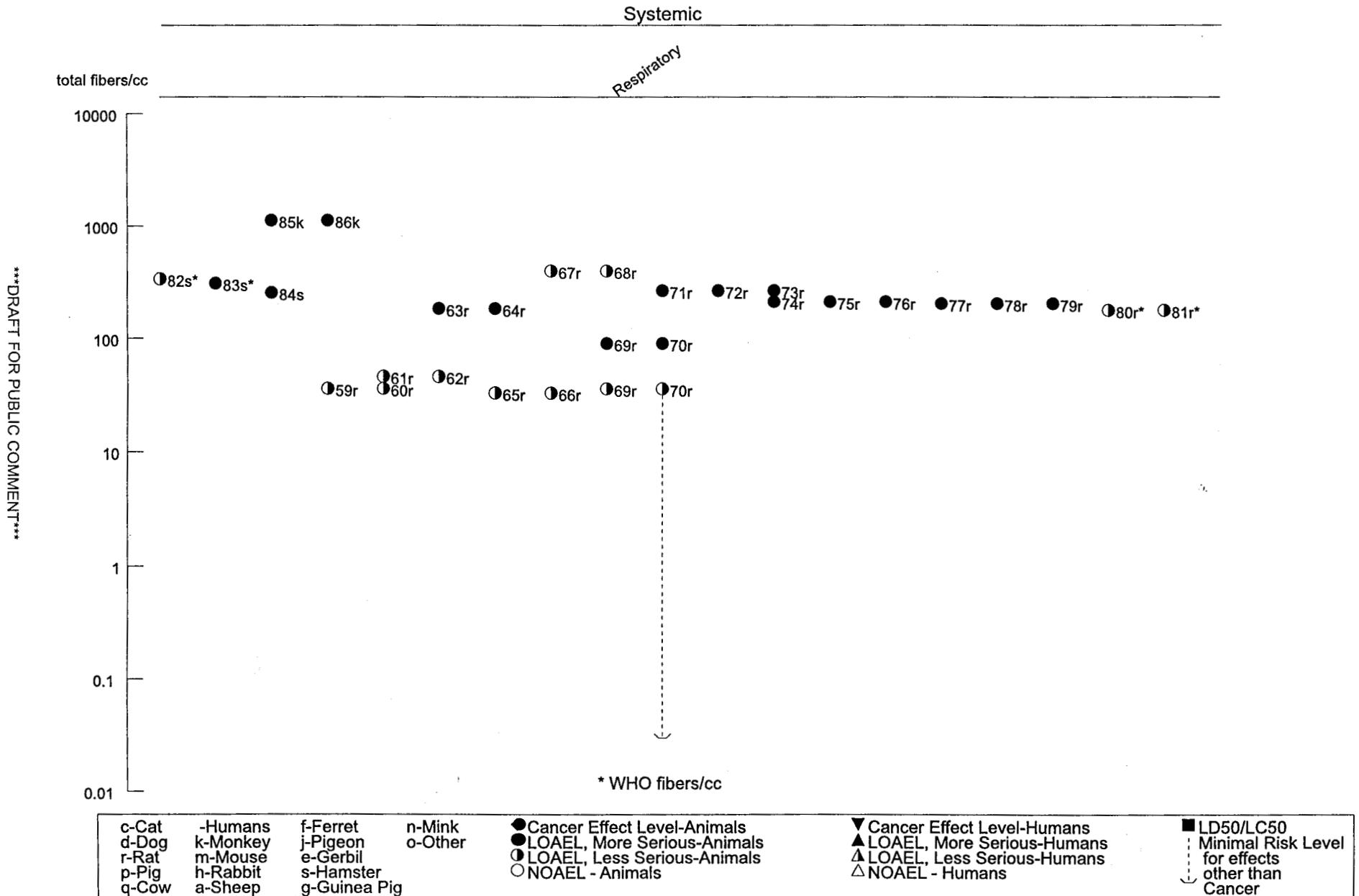
Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (Continued)  
Intermediate (15-364 days)

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

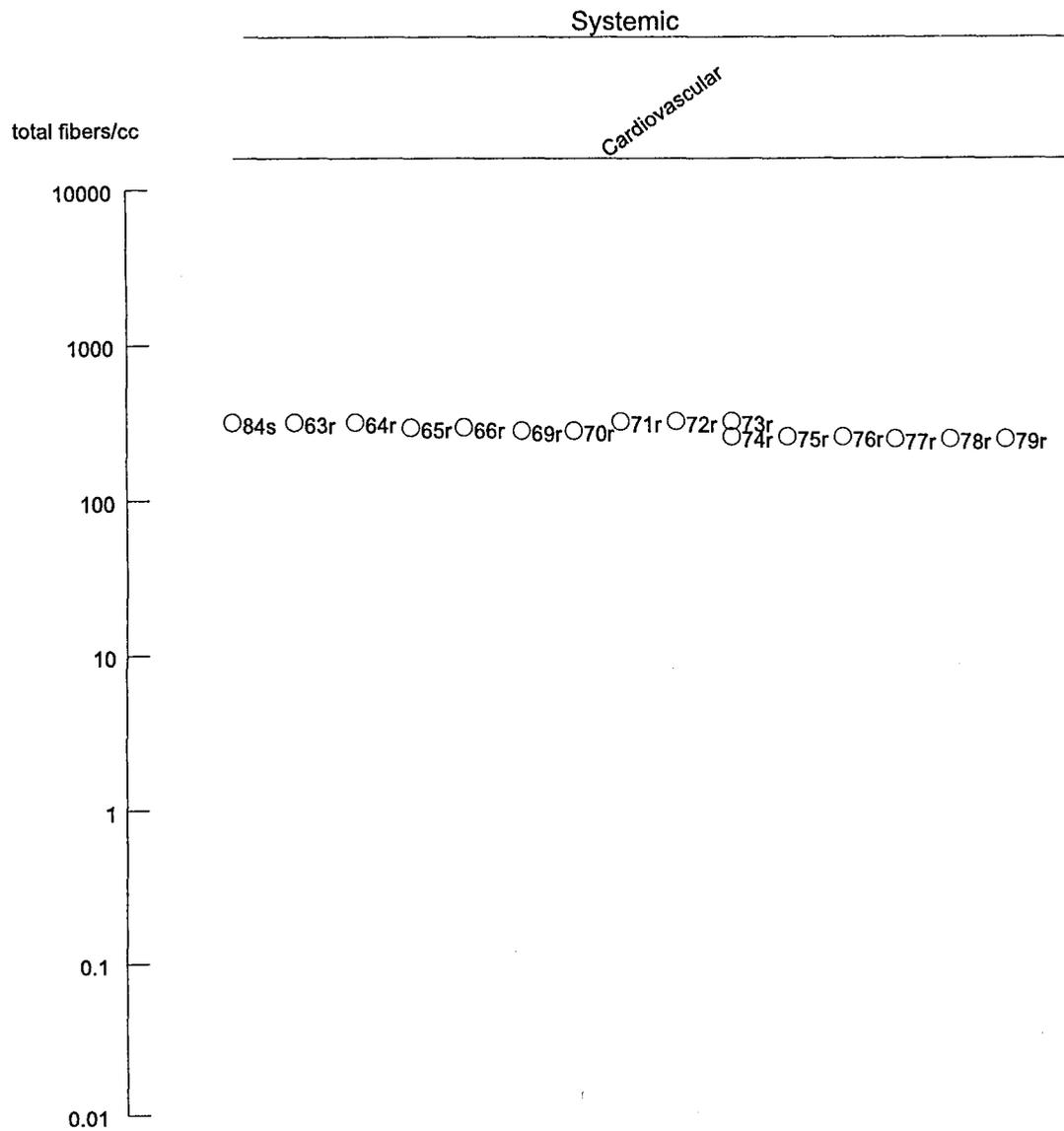
Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (Continued)  
 Chronic ( $\geq 365$  days)



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

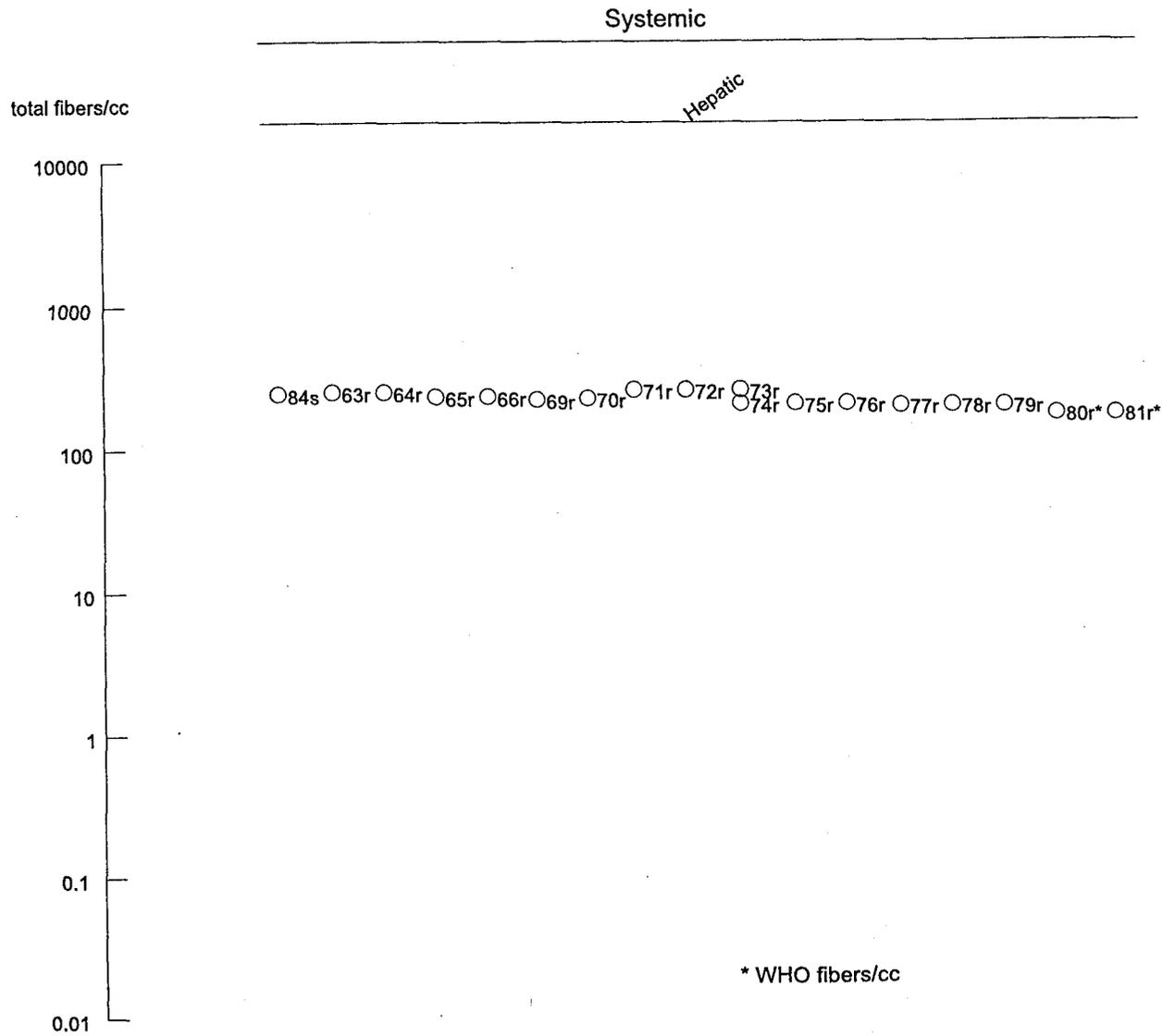
Chronic (≥365 days)



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

Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (Continued)  
 Chronic (≥365 days)

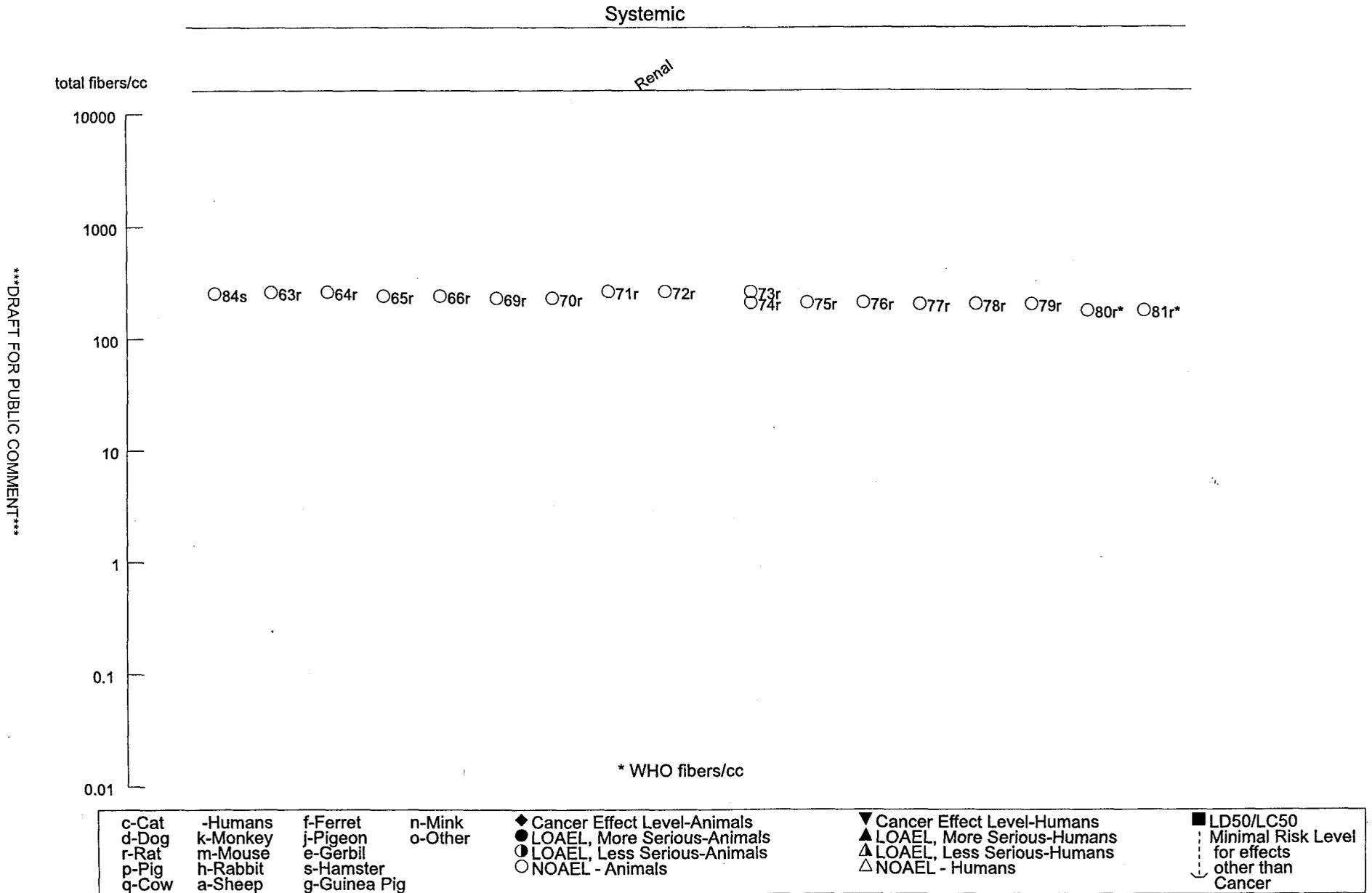


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c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	⋮ Minimal Risk Level
r-Rat	m-Mouse	e-Gerbil		○ LOAEL, Less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

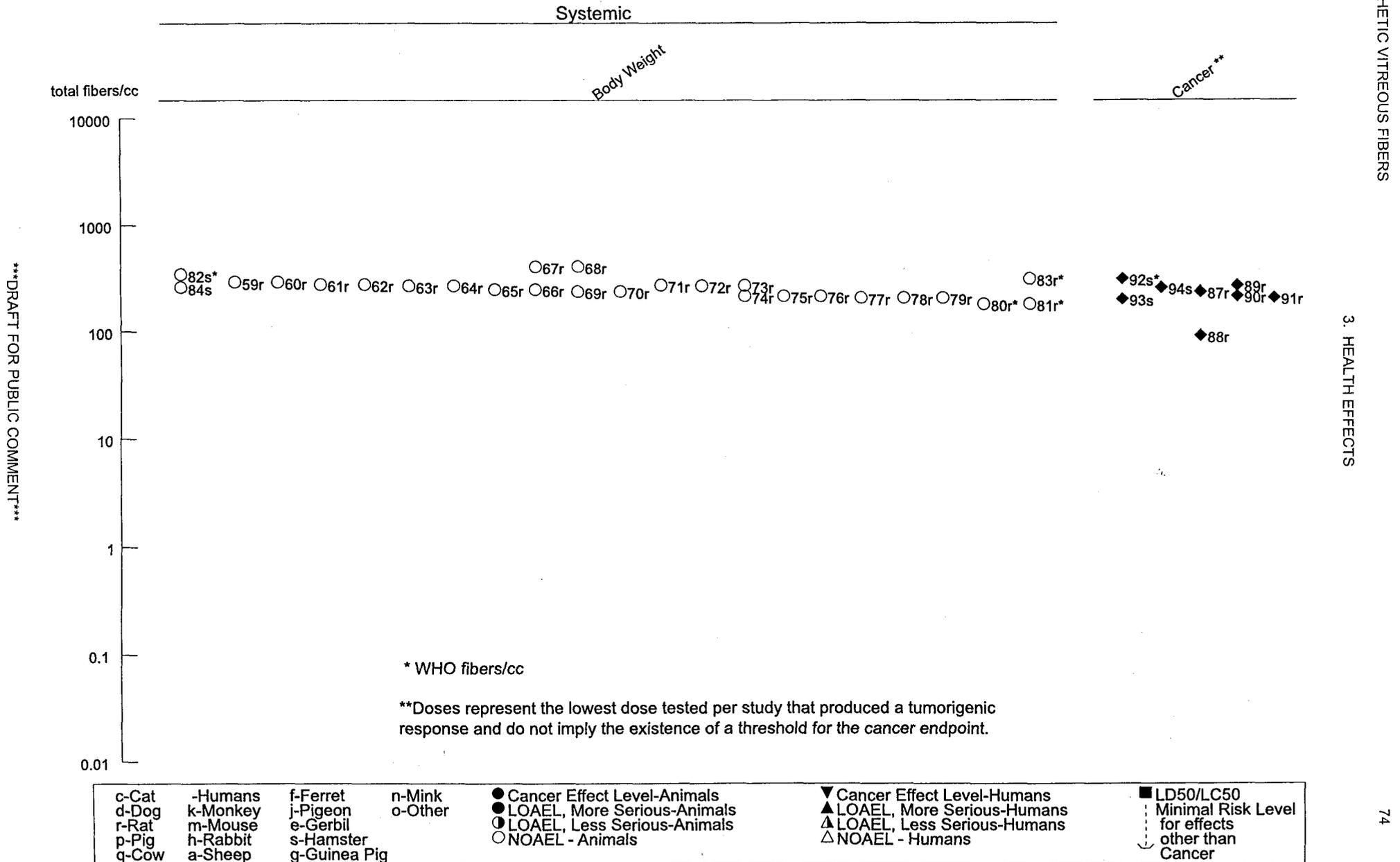
Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (Continued)

Chronic (≥365 days)



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Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (Continued)  
 Chronic (≥365 days)



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SYNTHETIC VITREOUS FIBERS

3. HEALTH EFFECTS

## 3. HEALTH EFFECTS

**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 Sarino, 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).

### 3. HEALTH EFFECTS

**Renal Effects.** Although exposure to crystalline silica may be associated with renal disease (Bernard and Hermans 1997; Goldsmith and Goldsmith 1993; McDonald et al. 2001), 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.

The epidemiological evidence for the potential carcinogenicity of synthetic vitreous fibers in humans is inconclusive (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 glass wool), but not for other fibers that are less biopersistent (see below and Section 3.5).

## 3. HEALTH EFFECTS

Intermediate-duration (1-year) exposure of male Wistar rats to 104E-glass 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 RCF1 and RCF3 have been associated with statistically significant elevations in lung adenoma and carcinoma incidence, whereas RCF2 exposure has been associated with increased lung carcinoma (but not adenoma) incidence (Mast et al. 1995a). In contrast, RCF1 did not induce lung tumor 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 glass wool (Muhle et al. 1987), on GB100R glass wool (Haratake et al. 1995) in rodents or in chronic-duration studies with MMVF10, MMVF11 (Hesterberg et al. 1993c; (McConnell et al. 1999), 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 256 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 fibers/cc of 104E-glass for 1 year (Cullen et al. 2000), rats exposed for 2 years to 91 or 234 (but not 162) fibers/cc of RCF1 as well as RCF2, RCF3, or RCF4 (268, 213, and 206 fibers/cc, respectively) (Mast et al. 1995a, 1995b), and hamsters exposed to 256 fibers/cc of MMVF33 for 18 months (McConnell et al. 1999). Despite the lack of statistical significance, these occurrences of mesothelioma are important because of the rarity of the tumor type.

**Human Studies.**

**Refractory ceramic fibers.** No studies have been published regarding possible increased risks of cancer in humans exposed to refractory ceramic fibers.

**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; Enterline and Henderson 1975; Marsh et al. 1990, 2001a,

## 3. HEALTH EFFECTS

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; 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 to determine whether or not these materials are carcinogenic in humans following inhalation 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; 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

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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 International Agency for Research on Cancer (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 Frenzel-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 (Boffetta et al.

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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.

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 Sarino, Ontario, Canada. In 1978, the mean concentration of glass wool fibers with diameters <3.5  $\mu\text{m}$  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.

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European case-control studies of lung cancer, 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; 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). 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).

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In summary, inhalation exposures to continuous glass filament, glass wool, and rock and slag wool provide inadequate evidence for respiratory 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, 2001; 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 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 256 fibers/cc (215 WHO fibers/cc; 30 mg/m<sup>3</sup>) of RCF1 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 162 fibers/cc (120 WHO fibers/cc; 17 mg/m<sup>3</sup>) for 2 years, although a single mesothelioma was seen at 91 fibers/cc (Mast et al. 1995b). Another 2-year study exposed male Fischer 344 rats nose-only to single concentration levels of RCF1, RCF2, RCF3, or RCF4 (234, 268, 213, and 206 fibers/cc; 30 mg/m<sup>3</sup> for each) (Mast et al. 1995a). The first three concentrations induced statistically significant increases in the incidences of bronchiolar-

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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).

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

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 of X607 (total fiber counts not reported; 30 mg/m<sup>3</sup>) for 2 years (Hesterberg et al. 1998b).

In summary, different types of refractory ceramic fibers induced lung tumors in rats and mesotheliomas in both hamsters and rats. These results have conclusively 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.

**Glass Wool.** Inhaled glass wool has been associated with mesothelioma formation in only one chronic study with MMVF33 (Hesterberg et al. 1999). Studies with MMVF33, MMVF10, MMVF11, and C102/C104 fibrous glass blend did not find 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 576 fibers/cc of glass wool (code 104, Tempstran 475) (252 fibers/cc >5 µm in length; 3 mg/m<sup>3</sup>) 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<sup>3</sup> of a glass wool (fiber counts not reported) for 1 year (Haratake et al. 1995), or rats, hamsters, and guinea pigs exposed to

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70 fibers/cc of a ball-milled fiberglass (7% fiber) for 3 months (Lee et al. 1981b), with postexposure periods up to 1 year.

One pleural mesothelioma (1/83 versus 0/83 for controls) and no lung tumors were observed in male Syrian Golden hamsters exposed to 37 mg/m<sup>3</sup> of MMVF33 durable special applications glass fibers (310 WHO fibers/cc; total fibers/cc not reported) for 18 months (Hesterberg et al. 1999). No lung tumors or mesotheliomas were observed in male Syrian Golden hamsters exposed to 29.6 mg/m<sup>3</sup> (339 WHO fibers/cc; total fibers/cc not reported) 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<sup>3</sup>), 100 fibers/cc of a 3.1 µm diameter glass wool (10 mg/m<sup>3</sup>), 10 or 100 fibers/cc of 5.4 µm diameter glass wool (1.2 or 12 mg/m<sup>3</sup>), 25 fibers/cc of 6.1 µm diameter glass wool (9 mg/m<sup>3</sup>), or 200 fibers/cc of a 2.7 µm diameter slag wool (10 mg/m<sup>3</sup>) (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 36, 179, and 287 fibers/cc (29, 145, and 232 WHO fibers/cc; 3.1, 17.1, and 27.8 mg/m<sup>3</sup>) and MMVF11 was tested at 46, 170, and 273 fibers/cc (41, 153, and 246 WHO fibers/cc; 4.8, 15.8, and 28.3 mg/m<sup>3</sup>).

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

**Slag Wool.** The limited animal 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<sup>3</sup>) (Smith et al. 1987).

In male Fischer 344 rats exposed nose-only for 24 months to 33, 158, or 245 fibers/cc (30, 131, or 213 WHO fibers/cc; 3.1, 16.1, or 29.9 mg/m<sup>3</sup>) of MMVF22, a blast-furnace slag wool, no significant

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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<sup>3</sup> 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 44, 185, or 264 fibers/cc (34, 150, or 243 WHO fiber/cc; 3.1, 16.1, or 30.4 mg/m<sup>3</sup>) of MMVF21, a traditional basalt-based stone/rock 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 400 fibers/cc (291 WHO fibers/cc; 30.1 mg/m<sup>3</sup>; diameter 0.87 µm) of MMVF34/HT, a high-temperature stone 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.** Only one intermediate-duration inhalation study in animals with continuous glass filaments was 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).

In male Wistar rats exposed whole-body to 1,022 fibers/cc of special-purpose 104E-glass microfiber 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). However, exposure of rats to the same concentration of special-purpose glass microfiber type 100/475 using the same protocol did not induce any mesotheliomas or statistically significantly increased incidence of lung tumors (Cullen et al. 2000).

### 3.2.2 Oral Exposure

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#### **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, musculoskeletal, 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.

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**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; 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  $>5 \mu\text{m}$  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; Stockholm 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. 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

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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  $\mu\text{m}$ , lengths  $>10 \mu\text{m}$ ) were very active in transforming Syrian hamster embryo cells, whereas thick glass fibers (diameter about 0.8  $\mu\text{m}$ ) were much less potent (Hesterberg and Barrett 1984). Milling of the thin glass fibers to reduce the length to  $<1 \mu\text{m}$  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 gastrointestinal tract, and the skin is expected to be negligible due to the relatively large physical

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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. 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  $3.5 \times 10^6$  fibers/rat) of a saline suspension of radiolabeled ( $^{24}\text{Na}$ ) glass fibers (Morgan et al. 1993). The fibers were produced as a continuous filament with an approximate uniform diameter of 2  $\mu\text{m}$ . The fibers in the instilled material had a log-normal distribution of lengths, with a median of 16  $\mu\text{m}$  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 gastrointestinal 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.

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 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). In general, relatively thick inhaled fibers are deposited

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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:

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

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  $\beta$ =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  $\mu\text{m}$  are expected to be predominantly deposited in the

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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  $\mu\text{m}$  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 diameters  $>3.5 \mu\text{m}$  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  $\mu\text{m}$ . For example, for exposure to fibers with 30  $\mu\text{m}$  length, 1.5  $\mu\text{m}$  diameter, and 3.26  $\mu\text{m}$  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.

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**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

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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  $\mu\text{m}$  in rats and 14–21  $\mu\text{m}$  in humans (Hesterberg and Hart 2001; Oberdörster 2000). Fibers longer than about 20  $\mu\text{m}$  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  $\mu\text{m}$  and median lengths of 5, 10, 30, or 60  $\mu\text{m}$ .

*Long fibers are poorly cleared by macrophages.* For the 5- and 10- $\mu\text{m}$  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- $\mu\text{m}$  length fibers, respectively, had been cleared. In contrast, the number of fibers in lungs of rats exposed to 30- or 60- $\mu\text{m}$  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- $\mu\text{m}$  length fibers showed evidence of transverse breakage of the fibers. The respective median lengths of recovered fibers at these times were 40 and 25  $\mu\text{m}$ . 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- $\mu\text{m}$  length fibers were decreased by 12, 28, >50, and >50%, respectively, of the original 1.5- $\mu\text{m}$  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).

*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- $\mu\text{m}$  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- $\mu\text{m}$  length fibers. At the same time period, no fibers were detected in the hilar lymph nodes of rats exposed to 60- $\mu\text{m}$  length fibers. The results indicate that only limited numbers of glass fibers were translocated to the lymph nodes under these experimental conditions.

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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  $\mu\text{m}$  and diameter of 0.2  $\mu\text{m}$ ) 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, RCF-1 (Everitt et al. 1997; Gelzleichter et al. 1996a, 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  $>5 \mu\text{m}$ , diameter  $<3 \mu\text{m}$ ) 6 hours/day for 5 days (Gelzleichter et al. 1996a). 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  $<5 \mu\text{m}$  and diameters  $<0.35 \mu\text{m}$ . Fibers detected in the pleural samples had geometric mean lengths of 1.4 and 1.5  $\mu\text{m}$ , and geometric mean diameters of 0.87 and 0.10  $\mu\text{m}$ , 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  $\mu\text{m}$  [range: 0.7–111  $\mu\text{m}$ ] and geometric mean diameter, 0.56  $\mu\text{m}$ ). In subsequent studies in which rats or hamsters were exposed to 650 total fibers/cc of RCF-1, 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  $\mu\text{m}$  accounted for

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approximately 67% of detected fibers, whereas in pleural tissue, fibers longer than 5  $\mu\text{m}$  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  $>20 \mu\text{m}$ , 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  $>20 \mu\text{m}$ . For most fiber types, the two-compartment model provided a better fit than the one-compartment model. From the 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 predicted days required for the fibers with lengths  $>20 \mu\text{m}$  per lung to be decreased to 90% of the predicted value at the end of exposure (T-90). For fiber types for which a two-compartment model did not provide an improved fit over a one-compartment model, clearance half-times ( $T_{1/2}$ 's) were compared with  $WT_{1/2}$ 's 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:

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

where  $\rho$  is the density of the fiber, and  $K_{dis}$  is usually in units of  $\text{ng}/\text{cm}^2\text{-hr}$ . 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  $>500$   $\text{ng}/\text{cm}^2\text{-hour}$ . *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 stone wool) has a moderately low *in vitro* pH 7.4  $K_{dis}$  (59  $\text{ng}/\text{cm}^2\text{-hour}$ ), 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  $\text{ng}/\text{cm}^2\text{-hour}$ ), but displays slow lung clearance ( $WT_{1/2}=37$  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).

Short-term *in vivo* lung clearance tests have been demonstrated to 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  $>20$   $\mu\text{m}$  after 5 days of inhalation exposure of rats to comparable concentrations of rock wools MMVF21 or MMVF 34 (“HT stone wool”) were 92 days and

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**Table 3-2. Lung Clearance of Fibers with Lengths >20  $\mu\text{m}$  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 <sub>1/2</sub> , days)	90% clearance (T-90, days)	<i>In vitro</i> K <sub>dis</sub> , pH 7.4 <sup>a</sup>
amosite	asbestos	418	2,095	<1
crocidolite	asbestos	817 <sup>b</sup>	2,270	<1
MMVF32	special application continuous filament glass	79	371	9
MMVF21	rock (stone) wool	67 (91) <sup>c</sup>	264 (206) <sup>c</sup>	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 <sup>b</sup>	123	300
H	new rock wool	13	49	270
MMVF11	insulation glass wool	9 (13) <sup>c</sup>	38 (40) <sup>c</sup>	100
MMVF22	slag wool	9	37	400
J	experimental	10	18	170
F	new rock wool	9 <sup>b</sup>	28	160
MMVF34	new rock wool (HT fiber, soluble in acid)	6	19	59
O	rock wool	6 <sup>b</sup>	20	>500
P	glass wool	6 <sup>b</sup>	19	>500
M	glass wool	5 <sup>b</sup>	18	>500
G	new rock wool	5 <sup>b</sup>	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

<sup>a</sup>K<sub>dis</sub> is the empirically derived coefficient (in ng/cm<sup>2</sup>-hour) for *in vitro* dissolution in a flowing physiological saline solution at pH 7.4. A larger coefficient indicates faster dissolution.

<sup>b</sup>Values are half-times (T<sub>1/2</sub>) from a one-compartment model; the two-compartment model did not provide an improved fit.

<sup>c</sup>Values in parentheses are from a second experiment.

Source: Hesterberg et al. 1998a

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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  $>20 \mu\text{m}$  of 8, 11, 10, and 11 fibers per mg dry lung  $\times 10^3$  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  $\times 10^3$ .

#### **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

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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 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  $k_{ids}$ , 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

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for long ( $>15\ \mu\text{m}$ ) 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 to 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  $20\ \mu\text{m}$  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 ( $<5\ \mu\text{m}$ ) fibers than of longer ( $>10$  or  $20\ \mu\text{m}$ ) 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

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transverse breakage of long vitreous fibers into shorter fibers. For example, lung clearance half-times in rats for long (>20  $\mu\text{m}$ ) fibers were 44, 6, and 986 days for MMVF10, MMVF11, and crocidolite asbestos, respectively; for short (<5  $\mu\text{m}$ ) 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.

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

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

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

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

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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. 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.

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.

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Model simulations of lung concentrations of fibers of various length classes (lengths <5, 5–10, 10–20, and >20  $\mu\text{m}$ ) 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 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  $\text{mg}/\text{m}^3$  (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).

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**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 <sup>3</sup> )	3,200	6.5
Airway surface area (cm <sup>2</sup> )	627,000	5,500
Number of alveolar macrophages	7x10 <sup>9</sup>	2.6x10 <sup>7</sup>
Alveolar macrophage volume (µm <sup>3</sup> per lung)	2,500	1,000
Total alveolar macrophage volume (mm <sup>3</sup> )	17,500	26
Tidal volume (cm <sup>3</sup> )	500	2.74
Breathing frequency (minute <sup>-1</sup> )	14	98
Minute ventilation (cm <sup>3</sup> /minute)	7,000	268
Life span (years)	70	2

Source: Yu et al. 1997

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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).

### 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,

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strongly influences alveolar deposition (Dai and Yu 1998; Oberdörster 2000). Fibers with aerodynamic diameters  $>3\text{--}4\ \mu\text{m}$  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  $5\ \mu\text{m}$  in rats and  $10\ \mu\text{m}$  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 ( $<5\ \mu\text{m}$ ) and thin ( $<0.35\ \mu\text{m}$ ) 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  $5\ \mu\text{m}$  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 ( $150\ \text{fibers per cm}^2$ ) was about 2–3 times that in the rat, whereas the pleural burden of short ( $<5\ \mu\text{m}$ ) 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  $15\text{--}20\ \mu\text{m}$  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

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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 profibrotic 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 two-times the aluminum-oxide weight percentage.

#### 3.5.2 Mechanisms of Toxicity

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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).

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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 noncytotoxic 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

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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.

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).

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Estimated concentrations in rodents ranged from  $1.7 \times 10^6$  to  $20 \times 10^6$  fibers ( $>20 \mu\text{m}$  long) per g dry lung compared with  $1.6 \times 10^6$  to  $30 \times 10^6$  fibers ( $>20 \mu\text{m}$  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 Environmental Protection Agency (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), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavonoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

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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

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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).

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**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

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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)<sup>1</sup>. 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 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

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<sup>1</sup> 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).

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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 titanium 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, ½); 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

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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).

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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

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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 (GST $\mu$ ), 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.

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.

##### 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

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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.

### **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.

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**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.

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

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

**Human**

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

**Animal**

- Existing Studies

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**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 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; Stockholm et al. 1982). The skin irritation has been associated with fibers of diameter  $>5 \mu\text{m}$  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 intraperitoneal 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.

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**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 stone wool MMVF 34, the high-silica synthetic vitreous fiber X607, the special-purpose 104E-glass, 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 effect in rats from samples of glass wools, stone 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

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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, stone 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.** Longitudinal and cross-sectional health evaluations of workers involved in the manufacture of refractory ceramic fibers, fibrous glass, rock wool, and slag wool have not found increased prevalence of workers with serious health effects (Lemasters et al. 1994; Lockey et al. 1996). Epidemiologic studies (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; Chiazzè et al. 1992, 1993, 1995, 1997; Enterline and Henderson 1975; 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 have not been conducted. In animals, chronic-duration inhalation studies were primarily continuations of intermediate-duration studies, with pulmonary

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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 stone 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, stone wool, and slag wool.

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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.

**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  $\mu\text{m}$ , lengths  $>10 \mu\text{m}$ ) were very active in transforming Syrian hamster embryo cells, whereas thick glass fibers (diameter about 0.8  $\mu\text{m}$ ) were much less potent (Hesterberg and Barrett 1984). Milling of the thin glass fibers to reduce the length to  $<1 \mu\text{m}$  diminished the transforming activity.

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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.

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**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 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 (Lemasters et al. 1994; Lockey et al. 1996).

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; Enterline and Henderson 1975; 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 have not been conducted.

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

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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

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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 stone 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  $>3\text{--}5\ \mu\text{m}$  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

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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).

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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 (Bernstein et al. 2001a, 2001b; Eastes and Hadley 1996; Eastes et al. 2000; Hesterberg et al. 1998a; 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

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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.

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

#### 3.12.3 Ongoing Studies

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Ongoing studies funded 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). 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. In order to compare the chemical properties of certain types of synthetic vitreous fibers, it is useful to classify these fibers into three general groups: fibrous glass, mineral wool (e.g., rock wool and slag wool), and refractory ceramic fibers (Navy Environmental Health Center 1997). Fibrous glass can be further subdivided as either continuous filament (sometimes called textile fibers) or glass wool, depending upon the method in which it is produced. 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 are 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). 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). Other types of glass are used for certain types of specialized purposes, and relatively small changes in the 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

**Table 4-1. Chemical Identity of Some Types of Synthetic Vitreous Fibers<sup>a,b</sup>**

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 <sup>c</sup>
SiO <sub>2</sub>	52–56	65	60.7	55–70	45–48	41–53	38–52	49.5–53.5	47.5–50	57–58
Al <sub>2</sub> O <sub>3</sub>	12–16	25		0–7	12–13.5	6–14	5–15	43.5–47	35–36	5–6
B <sub>2</sub> O <sub>3</sub>	5–10			3–12						10–11
K <sub>2</sub> O	0–2		2	0–2.5	0.8–2	0.5–2	0.3–2	<0.01	<0.01	2–3
Na <sub>2</sub> O	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 <sub>2</sub>	0–1.5			0–0.5	2.5–3	0.9–3.5	0.3–1	2	0.04	0–0.1
Fe <sub>2</sub> O <sub>3</sub>	0–0.8			0.1–0.5				1	<0.05	0–0.1
FeO					11–12	3–8	0–2			
Li <sub>2</sub> O			1.3	0–0.5						
SO <sub>3</sub>				0–0.5						
S					0–0.2	0–0.2	0–2			
F <sub>2</sub>	0–1			0–1.5						
BaO				0–3						5
ZrO <sub>2</sub>			21.5					0.1	15–17	

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SYNTHETIC VITREOUS FIBERS

4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-1. Chemical Identity of Some Types of Synthetic Vitreous Fibers<sup>a,b</sup> (continued)**

Percent composition	E-Glass	S-Glass	AR-Glass	Glass wool	Rock wool from basalt 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 <sup>c</sup>
P <sub>2</sub> O <sub>5</sub>							0–0.5			
Cr <sub>2</sub> O <sub>3</sub>								<0.03	<0.01	
ZnO										4

<sup>a</sup>Navy Environmental Health Center 1997; TIMA 1993

<sup>b</sup>As is standard practice, the chemical composition of the elements are reported as oxides, even though no such individual crystals exist in the fibers.

<sup>c</sup>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)

## 4. CHEMICAL AND PHYSICAL INFORMATION

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 ( $\text{SiO}_2$ ,  $\text{B}_2\text{O}_3$ ), basic oxides ( $\text{CaO}$ ,  $\text{MgO}$ ,  $\text{Na}_2\text{O}$ ,  $\text{K}_2\text{O}$ ), and amphoteric oxides ( $\text{Al}_2\text{O}_3$ ). 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 collectively refers to rock wool and slag wool, although occasionally, glass wool has been 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 ( $\text{MgO}$  and  $\text{CaO}$ ) and lower alkali metal oxide content ( $\text{Na}_2\text{O}$  and  $\text{K}_2\text{O}$ ) than glass wool. Rock wool is derived from igneous rocks such as diabase, basalt, or olivine, while slag wool is derived from the waste of metal smelters (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  $10^7$  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

## 4. CHEMICAL AND PHYSICAL INFORMATION

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  $<3 \mu\text{m}$  are generally considered respirable in humans. There is also a strong correlation between the nominal fiber diameter and the airborne fiber levels found in workplaces (Esmen and Erdal 1990; Esmen et al. 1979a, 1979b). Generally, the greater the nominal 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  $\mu\text{m}$ , depending upon the application, with typical diameters in the range of 6–15  $\mu\text{m}$  (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 diameters in the range of about 3–7  $\mu\text{m}$  for rock wool and slag wool and 3–15  $\mu\text{m}$  for ordinary glass wool (Navy Environmental Health Center 1997). Special purpose glass fibers are produced by a flame attenuation process whereby the hot, molten glass is poured in front of a

**Table 4-2. Physical Properties of Some Types of Synthetic Vitreous Fibers<sup>a</sup>**

Property	E-Glass	S-Glass	AR-Glass	Glass wool	Rock wool	Slag wool	Refractory ceramic fibers	Special purpose glass fiber 475 formulation <sup>b</sup>
Molecular weight	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Density (g/cm <sup>3</sup> )	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 EC	835–860	970	680	650–700	No data	No data	1,740–1,800	650
Dielectric constant at 1 MHz	5.8–6.4 <sup>d</sup>	4.9–5.3 <sup>d</sup>	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 <sup>d</sup>	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 <sup>d</sup>	4,590 <sup>d</sup>	3,700 <sup>d</sup>	No data	482–689 <sup>c</sup>	482–689 <sup>c</sup>	1,000–1,300 <sup>d,e</sup>	No data

<sup>a</sup>All data derived from TIMA 1993 unless otherwise noted

<sup>b</sup>There are several formulations applicable to this category and formulation 475 is generally representative.

<sup>c</sup>Navy Environmental Health Center 1997

<sup>d</sup>Fitzer et al. 1988

<sup>e</sup>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.

## 4. CHEMICAL AND PHYSICAL INFORMATION

high temperature gas flame, resulting in fibers with a mean diameter of  $<3 \mu\text{m}$  and very often  $<1 \mu\text{m}$ . 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  $\mu\text{m}$ .

Christensen et al. (1993) employed light microscopy (LM) and scanning electron microscopy (SEM) to measure the length-weighted nominal 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  $\mu\text{m}$ . The arithmetic mean and standard deviation were reported as 1.05  $\mu\text{m}$  and 0.64  $\mu\text{m}$ , respectively, while the geometric mean and standard deviation were reported as 0.84  $\mu\text{m}$  and 2.05 (the geometric standard deviation is unitless), respectively (Mast et al. 2000a). Fiber lengths ranged from 0.6 to 138  $\mu\text{m}$ , with an arithmetic mean length and standard deviation of 20.6  $\mu\text{m}$  and 19.3  $\mu\text{m}$ , respectively. The geometric mean length and geometric standard deviation were reported as 14.1  $\mu\text{m}$  and 2.48, respectively.

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-3. Measured Nominal Diameters of Glass Wool, Rock Wool, Slag Wool, Refractory Ceramic Fibers, and a Special Purpose Glass Fiber<sup>a</sup>**

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 <sup>b</sup>				
1	Not applicable <sup>b</sup>	Not applicable <sup>b</sup>	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

<sup>a</sup>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.

<sup>b</sup>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

## 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<sup>th</sup> 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 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,

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

**Table 5-1. Production Volumes of Glass Wool, Rock Wool, and Slag Wool Products in the United States<sup>a</sup>**

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) <sup>b</sup>	530.0 (R-19 or more) <sup>b</sup>
	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 <sup>c</sup>		
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

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

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

**Table 5-2. Continuous Filament Glass Fiber Production in the United States<sup>a</sup>**

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

<sup>a</sup>IARC 1988

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

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  $\mu\text{m}$  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. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

**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).

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**Table 5-3. U.S. Import/Export Volume of Glass Fibers (Including Glass Wool), Mineral Wool and Refractory Ceramic Goods<sup>a</sup>**

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

<sup>a</sup> USDOC 2002

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

**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  $>1 \mu\text{m}$ , 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  $\leq 1 \mu\text{m}$ , 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 1,613 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2002). 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, that 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. Because of their amorphous structure, synthetic vitreous fibers undergo dissolution at a rate about 2–4 times that of crystalline fibers such as asbestos. 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  $1 \times 10^{-4}$  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  $1 \times 10^{-4}$  fiber/cc.

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

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



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## 6. POTENTIAL FOR HUMAN EXPOSURE

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  $\mu\text{m}$ , 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  $<3 \mu\text{m}$  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  $\mu\text{m}$  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  $<3 \mu\text{m}$ , length  $\geq 5 \mu\text{m}$ , and an aspect ratio of  $\geq 3:1$  (ACGIH 2001). The term respirable fiber in this chapter refers to fibers possessing diameters of  $<3 \mu\text{m}$ , 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  $\mu\text{m}$ . 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  $\mu\text{m}$  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

## 6. POTENTIAL FOR HUMAN EXPOSURE

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  $>5 \mu\text{m}$  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  $>5 \mu\text{m}$ , their diameters are  $<3 \mu\text{m}$ , 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 (Breyse 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 (TRI99 2002).

## 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 arises 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 2002). Synthetic vitreous fibers were not included in the TRI (TRI99 2002).

### 6.2.2 Water

## 6. POTENTIAL FOR HUMAN EXPOSURE

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 2002). Synthetic vitreous fibers were not included in the TRI (TRI99 2002).

### 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 2002). Synthetic vitreous fibers were not included in the TRI (TRI99 2002).

## 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. POTENTIAL FOR HUMAN EXPOSURE

**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 37EC with simulated extracellular fluid (pH 7.4), the dissolution rates of glass, rock, and slag wools with diameters of 1  $\mu\text{m}$  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).

**6.3.2.4 Other Media****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 level of fibrous glass in ventilation systems and in the ambient air from various locations of California were studied from 1968–1971, 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  $\mu\text{m}$ , with an arithmetic mean of 4.3  $\mu\text{m}$ . The concentration of fibrous glass in 37 ventilation system samples ranged from not detected to  $2.0 \times 10^{-3}$  fiber/cc ( $8.7 \times 10^{-4}$  fiber/cc, arithmetic mean), and the fiber diameters were 0.10–17.7  $\mu\text{m}$  (3.7  $\mu\text{m}$ , arithmetic mean). The mean airborne concentration 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.

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The fibers identified as synthetic vitreous fibers constituted >1–5% of the inorganic fibers, with a concentration range of  $4.0 \times 10^{-5}$ – $1.7 \times 10^{-3}$  fiber/cc (Hohr 1985). The results of these, and several other past monitoring studies have been compiled and summarized in IARC (1988) 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  $1.0 \times 10^{-5}$  fiber/cc to  $1.4 \times 10^{-4}$  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  $1.0 \times 10^{-5}$  fiber/cc to  $1.5 \times 10^{-4}$  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  $1.5 \times 10^{-5}$  fiber/cc, with a mean value of  $2.0 \times 10^{-6}$  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  $1.66 \times 10^{-3}$  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  $2.60 \times 10^{-5}$ – $2.13 \times 10^{-4}$  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.

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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  $6.23 \times 10^{-3}$  fiber/cc with a median value of  $3.0 \times 10^{-6}$  fiber/cc (Gaudichet et al. 1989). The levels of respirable fibers (diameter <3  $\mu\text{m}$  and lengths >5 but <100  $\mu\text{m}$ ) 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  $1.0 \times 10^{-4}$  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 was 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.

#### 6.4.2 Water

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

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**Table 6-1. Airborne Concentrations of Synthetic Vitreous Fibers in Buildings in Denmark<sup>a</sup>**

Type of ceiling board <sup>b</sup>	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	0–1.66x10 <sup>-3</sup> (2.13x10 <sup>-4</sup> )	0–3.3x10 <sup>-4</sup> (5.7x10 <sup>-5</sup> )
Hotaco mineral	14	Yes	0–4.3x10 <sup>-4</sup> (5.6x10 <sup>-5</sup> )	0–1.9x10 <sup>-4</sup> (2.1x10 <sup>-5</sup> )
Ny Hotaco mineral	2	Yes	6–13x10 <sup>-5</sup> (9.5x10 <sup>-5</sup> )	Not detected
Other with water soluble binder	12	Yes	0–3.6x10 <sup>-4</sup> (5.9x10 <sup>-5</sup> )	0–7.0x10 <sup>-5</sup> (1.4x10 <sup>-5</sup> )
Soft mineral wool sealed on three sides	13	No	0–3.4x10 <sup>-4</sup> (2.6x10 <sup>-5</sup> )	0–1.0x10 <sup>-4</sup> (8.0x10 <sup>-6</sup> )
Hard mineral wool sealed on three sides	9	No	0–1.3x10 <sup>-4</sup> (3.1x10 <sup>-5</sup> )	0–7.0x10 <sup>-5</sup> (1.0x10 <sup>-5</sup> )
Unsealed mineral wool	12	No	0–1.03x10 <sup>-3</sup> (1.8x10 <sup>-4</sup> )	0–4.0x10 <sup>-4</sup> (6.7x10 <sup>-5</sup> )
Sealed mineral wool on all six surfaces	9	No	0–6.1x10 <sup>-4</sup> (9.4x10 <sup>-5</sup> )	0–2.4x10 <sup>-4</sup> (4.6x10 <sup>-5</sup> )
Batts on top of perforated panels	11	No	0–1.0x10 <sup>-4</sup> (1.7x10 <sup>-5</sup> )	0–6.0x10 <sup>-5</sup> (9.0x10 <sup>-6</sup> )
No synthetic vitreous fiber (control group)	12	Not applicable	0–6.2x10 <sup>-4</sup> (6.2x10 <sup>-5</sup> )	0–1.3x10 <sup>-4</sup> (1.8x10 <sup>-5</sup> )

<sup>a</sup>Schneider et al. 1990<sup>b</sup>Contains Danish product names

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**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.

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  $\mu\text{m}$  (6.5  $\mu\text{m}$ , 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

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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, however, 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 level 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 level 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 ranged from 0.080 to 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  $<1 \mu\text{m}$ .

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  $>5 \mu\text{m}$  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  $<5 \mu\text{m}$ , rather than the currently accepted value of  $<3 \mu\text{m}$ . 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; 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

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total airborne fibers measured by PCM. The greatest airborne fiber levels 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  $\mu\text{m}$ . 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 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 concentration of respirable (defined in this study as having diameters  $\geq 3 \mu\text{m}$ ) 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 description or job type were compiled (Friar and Phillips 1989). The results of this survey are summarized in Table 6-4. While high levels of exposure were estimated for certain job descriptions, it was noted that >60% of the exposure levels fall within the 0–0.5 fiber/cc range (Friar and Phillips 1989).

**Table 6-2. Concentrations (mg/m<sup>3</sup>) of Total Suspended Airborne Particulate Matter in 16 Facilities in the United States<sup>a</sup>**

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)

<sup>a</sup>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<sup>a</sup>**

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)

<sup>a</sup>Esmen et al. 1979b

ND = nominal diameter; SD = standard deviation

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**Table 6-4. Typical Exposures in the Manufacture and Use of Refractory Ceramic Fibers<sup>a</sup>**

Process description or job	Exposure level (fiber(s)/cc)
<b>Manufacture</b>	
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
<b>Use</b>	
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

<sup>a</sup>Friar and Phillips 1989

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The results of a comprehensive 54-month workplace monitoring study for exposure to refractory ceramic fibers in the United States has 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<sup>3</sup> in about 75% of the samples (Gantner 1986). A study was conducted to determine the level of exposure to 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<sup>3</sup>, with a geometric mean of 0.06 mg/m<sup>3</sup>, which is above the OSHA

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established permissible exposure limit (PEL) of 0.05 mg/m<sup>3</sup> (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 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

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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, and thus, they may also be exposed to synthetic vitreous fibers that have been deposited on these 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

## 6. POTENTIAL FOR HUMAN EXPOSURE

fibers lung concentrations  $>0.2$  fiber/ $\mu\text{g}$  lung tissue (one worker had a concentration of 1 fiber/ $\mu\text{g}$ ), the rest had concentrations below 0.2 fiber/ $\mu\text{g}$  (McDonald et al. 1990). The geometric mean fiber length, fiber diameter, and aspect ratio were 7.5  $\mu\text{m}$ , 1.0  $\mu\text{m}$ , and 8.0, respectively, for those occupationally exposed, while the values for the referents were 6.6  $\mu\text{m}$ , 1.2  $\mu\text{m}$ , and 6.1, respectively.

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).

## 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 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.

### 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.

## 6. POTENTIAL FOR HUMAN EXPOSURE

**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). While production volumes 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; 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 1999, became available in 2001. This database is updated yearly and provides a list of industrial facilities producing, processing, and using friable asbestos and their emissions.

**Environmental Fate.** 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 are largely unknown. It is possible that adsorption of fibers onto other dust particles could influence the location of deposition in the lung, and might even influence the cellular response to the fibers. Research to determine if this occurs and whether this is of biological significance 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.

## 6. POTENTIAL FOR HUMAN EXPOSURE

**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 3.12.2 Identification of Data Needs: Children's Susceptibility.

## 6. POTENTIAL FOR HUMAN EXPOSURE

**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, 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).

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Briefly, when using counting rules B, only fibers  $<3 \mu\text{m}$  in diameter and  $>5 \mu\text{m}$  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  $>3 \mu\text{m}$  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 (Breyse et al. 1999). Fiber concentrations are usually reported as fibers/mL or fibers/cc, although fibers/ $\text{m}^3$  or fibers/L are occasionally employed.

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  $0.25 \mu\text{m}$ . 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.

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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  $\mu\text{m}$  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

## 7. ANALYTICAL METHODS

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 (Nuclpore) 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  $\mu\text{m}$  and an NPF with a pore size of 0.4  $\mu\text{m}$  are capable of collecting fibers in the workplace that are  $>2 \mu\text{m}$  in length (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  $1 \times 10^{-5}$  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  $>0.25 \mu\text{m}$  can be counted by PCM, while fibers with diameters as small as 0.05 and 0.005  $\mu\text{m}$  can be 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

## 7. ANALYTICAL METHODS

**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
Bronchoalveolar 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 $\mu\text{m}$ )	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 $\mu\text{m}$ nuclepore	TEM	0.04 $\mu\text{m}$ (diameter) 0.09 $\mu\text{m}$ (length)	No data	McDonald et al. 1990

PCM = phase contrast microscopy; TEM = transmission electron microscopy

## 7. ANALYTICAL METHODS

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

Sample matrix	Preparation method	Analytical method	Sample detection limit <sup>a</sup>	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 <sup>-5</sup> 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

<sup>a</sup>Sample detection limits are a function of the volume of air collected and thus the sampling time.

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

## 7. ANALYTICAL METHODS

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 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.

#### 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.

**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

## 7. ANALYTICAL METHODS

fibers (Agency for Toxic Substances and Disease Registry 2001).<sup>2</sup> 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, ½); 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

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<sup>2</sup> 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).

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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.

## 8. REGULATIONS AND ADVISORIES

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

Agency	Description	Information	References
<u>INTERNATIONAL</u> Guidelines:			
IARC	Carcinogenicity classification		
	Insulation glass wool, rock (stone) wool, slag wool, and continuous filament glass	Group 3 <sup>a</sup>	IARC 2001
	Refractory ceramic fibers and certain special-purpose glass wools not used as insulating materials	Group 2B <sup>b</sup>	IARC 2001
<u>NATIONAL</u> Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)		
	Synthetic vitreous fibers Continuous filament glass fibers, glass wool fibers, rock wool fibers, slag wool fibers, special purpose glass fibers	1.0 fibers/cc <sup>c</sup>	ACGIH 2001
	Continuous filament glass (inhalable fraction)	5 mg/m <sup>3</sup>	
	Refractory ceramic fibers	0.2 fibers/cc <sup>c</sup>	
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 <sup>3</sup>	
	Refractory ceramic fibers	No data	NIOSH 1992

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Synthetic Vitreous Fibers  
(continued)**

Agency	Description	Information	References
<u>NATIONAL (cont.)</u>			
OSHA	PEL (8-hour TWA)		
	Fiberglass and mineral wool (glass wool, rock wool, and slag wool)	1.0 fiber/cc <i>voluntary</i>	OSHA 1999
	Synthetic vitreous fibers as an inert or nuisance dust		OSHA 2001b
	Respirable fraction	5 mg/m <sup>3</sup>	
	Total dust	15 mg/m <sup>3</sup>	
b. Water	No data		
c. Food	No data		
d. Other			
ACGIH	Carcinogenicity classification		
	Synthetic vitreous fibers Continuous filament glass fibers (respirable fibers and inhalable fraction)	Group A4 <sup>d</sup>	ACGIH 2001
	Glass wool fibers, rock wool fibers, slag wool fibers, and special purpose glass fibers	Group A3 <sup>e</sup>	
	Refractory ceramic fibers	Group A2 <sup>f</sup>	
EPA	Carcinogenicity classification		
	Glass wool, continuous filament glass, rock wool, and slag wool	No data	IRIS 2002
	Refractory ceramic fibers	Group B2 <sup>g</sup>	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 1998
	Continuous filament glass, rock wool, slag wool, and refractory ceramic fibers	No data <sup>h</sup>	NTP 2001

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Synthetic Vitreous Fibers  
(continued)**

Agency	Description	Information	References
STATE Regulations and Guidelines:			
a. Air		No data	
b. Water		No data	
c. Food		No data	
d. Other		No data	

<sup>a</sup>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

<sup>b</sup>Group 2B: possibly carcinogenic to humans, based on limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals

<sup>c</sup>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.

<sup>d</sup>Group A4: not classifiable as a human carcinogen

<sup>e</sup>Group A3: confirmed animal carcinogen with unknown relevance to humans

<sup>f</sup>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

<sup>g</sup>Group B2: probable human carcinogen, based on sufficient evidence of carcinogenicity in animals

<sup>h</sup>Not listed or assessed in the 9<sup>th</sup> 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

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## 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 ( $K_d$ )**—The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

**Asbestos**—A group of highly fibrous minerals with separable, long, thin fibers often arranged in parallel in a column or in matted masses (Veblen and Wylie 1993; Zoltai 1979, 1981). Separated asbestos fibers are generally strong enough and flexible enough to be spun and woven, are heat resistant, and are chemically inert (Veblen and Wylie 1993). (See definitions of *fibrous* and *mineral*.) Currently, U.S. regulatory agencies, such as the EPA and OSHA, recognize six asbestos minerals: the serpentine mineral, chrysotile; and five asbestiform amphibole minerals, actinolite asbestos, tremolite asbestos, anthophyllite asbestos, amosite asbestos (also known as asbestiform cummingtonite-grunerite), and crocidolite asbestos (also known as asbestiform riebeckite) (Agency for Toxic Substances and Disease Registry 2001; OSHA 1992). Proposals have been made to update asbestos regulations to include other asbestiform amphibole minerals such as winchite asbestos and richterite asbestos (Meeker et al. 2001; Wylie and Verkouteren 2000). NOTE: Synthetic vitreous fibers are not minerals because they do not have a crystalline molecular structure and are not asbestos.

**Asbestosis**—Interstitial fibrosis of the pulmonary parenchyma tissue in which asbestos bodies (fibers coated with protein and iron) or uncoated fibers can be detected (American Thoracic Society 1986). Pulmonary fibrosis refers to a scar-like tissue in the lung that does not expand and contract like normal tissue. This makes breathing difficult. Blood flow to the lung may also be decreased, and this causes the heart to enlarge. People with asbestosis have shortness of breath, often accompanied by a persistent cough. Asbestosis is a slow-developing disease that can eventually lead to disability or death in people who have been exposed to high amounts of asbestos over a long period. Asbestosis is not usually of concern to people exposed to low levels of asbestos. For more information, see the *ATSDR Toxicological Profile for Asbestos* (Agency for Toxic Substances and Disease Registry 2001). Asbestosis has not been found in groups of workers involved in the manufacture of synthetic vitreous fibers.

**Benchmark Dose (BMD)**—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a  $BMD_{10}$  would be the dose producing 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.

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**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 which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-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 which 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

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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.

**Fiber**—Any slender, elongated particle or mineral structure. For the purposes of counting fibrous glass fibers or other synthetic vitreous fibers in air samples, the NIOSH (1994a) 7400B counting rule has sometimes been used: length >5  $\mu\text{m}$ , width <3  $\mu\text{m}$ , and length:width ratio 5:1. The ACGIH (2001) TLV-TWAs for synthetic vitreous fibers are for “respirable” fibers with length >5  $\mu\text{m}$ , and length:width ratios 3:1. For the purposes of counting asbestos fibers in air samples, regulatory agencies commonly count particles that have lengths 5  $\mu\text{m}$  and length:width ratios 3:1 as fibers (NIOSH 1994a; counting rule 7400A). For detecting asbestos fibers in bulk building materials, particles with length:width ratios 5:1 are counted as fibers.

**Fiber-year/mL**—Epidemiologic studies of groups of workers exposed to airborne inorganic fibers commonly express exposure in cumulative exposure units of fiber-year/mL or fiber-year/cc. This exposure measure is calculated by multiplying a worker’s duration of exposure (measured in years) by the average air concentration during the period of exposure (measured in number of fibers/mL of air or fiber/cc). The units are sometimes reported as fiber/month-cc or fiber/year-cc.

**Fibrosis, Pulmonary Interstitial**—Scar-like tissue that develops in the lung parenchymal tissue in response to inhalation of dusts of certain types of substances such as asbestos and crystalline silica.

**Fibrous**—Having the slender, elongated shape of a fiber. In mineralogy, fibrous refers to a mineral habit with crystals that look like fibers (Zoltai 1981). A mineral with a fibrous habit is not asbestiform if the fibers are not separable and are not long, thin, strong, and flexible (Veblen and Wylie 1993; Zoltai 1979; 1981).

**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.

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**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<sub>(LO)</sub> (LC<sub>LO</sub>)**—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

**Lethal Concentration<sub>(50)</sub> (LC<sub>50</sub>)**—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

**Lethal Dose<sub>(LO)</sub> (LD<sub>LO</sub>)**—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

**Lethal Dose<sub>(50)</sub> (LD<sub>50</sub>)**—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time<sub>(50)</sub> (LT<sub>50</sub>)**—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

**Lowest-Observed-Adverse-Effect Level (LOAEL)**—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

**Lymphoreticular Effects**—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

**Malformations**—Permanent structural changes that may adversely affect survival, development, or function.

**Mesothelioma**—Cancer of the thin lining surrounding the lung (the pleura) or the abdominal cavity (the peritoneum). Mesotheliomas are rare cancers in general populations. Mesotheliomas annually accounted for an average of 1.75 deaths per million in the U.S. general population for the period 1987–1996 (NIOSH 1999). For U.S. white males (the U.S. group with the highest mortality rate), the rates were 3.61 per million in 1987 and 2.87 per million in 1996 (NIOSH 1999). See the *ATSDR Toxicological Profile for Asbestos* for more information. Increased risk for mesotheliomas has been associated with occupational exposure to asbestos (Agency for Toxic Substance and Disease Registry 2001), but not with employment in the manufacture of fibrous glass, rock wool, or slag wool (Marsh et al. 2001b).

**Mineral**—Any naturally occurring, inorganic substance with a crystal structure. Naturally occurring, inorganic substances without a crystal structure (such as amorphous silica and synthetic vitreous fibers) are called mineraloids (Veblen and Wylie 1993).

**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.

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**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.

**Organophosphate or Organophosphorus Compound**—A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

**Permissible Exposure Limit (PEL)**—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

**Pesticide**—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

**Pharmacokinetics**—The science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

**Pharmacokinetic Model**—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

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**Physiologically Based Pharmacodynamic (PBPD) Model**—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

**Physiologically Based Pharmacokinetic (PBPK) Model**—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

**Pleura**—A thin lining or membrane around the lungs or chest cavity. This lining can become thickened or calcified in asbestos-related disease. Pleural abnormalities associated with exposure to asbestos include pleural plaques (localized thickening), pleural thickening or calcifications (widespread thickening), and pleural effusion (see *ATSDR Toxicological Profile for Asbestos*, Agency for Toxic Substance and Disease Registry 2001). Pleural abnormalities have not been a frequent observation in chest x-ray studies of workers involved in the manufacture of fibrous glass, rock wool, or slag wool (Clausen et al. 1993; Gross 1976; Hill et al. 1973; Hughes et al. 1993; Nasr et al. 1971; Weill et al. 1983; Wright 1968).

**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.

**Pulmonary Clearance of Fibers**—Clearance of particles or fibers deposited in the lower lung (see definition for *respirable fibers or particles*) involves engulfment (i.e., phagocytosis) by cells called alveolar macrophages. Fiber-containing macrophages are transported to the mucociliary escalator where they can be cleared to the larynx. Results from animal studies and studies of lung tissue from fiber-exposed human subjects indicate that fibers with lengths longer than the diameter of macrophage cells (about 12–20  $\mu\text{m}$ ) are not cleared from the lower lung until they dissolve or transversely break, because of the inability of macrophages to fully engulf them (Hesterberg and Hart 2001; Hesterberg et al. 1996; Lippmann 1994). The dissolution and transverse breakage of fibers within cells or interstitial fluids is an important feature of the mechanism by which the lung clears respired fibers (Bernstein et al. 1996; Hesterberg and Hart 2001; Hesterberg et al. 1996; Lippmann 1994). Rates of dissolution of different types of fibers in lung fluid have been correlated with abilities to produce cytotoxicity, lung fibrosis, and cancer (Lippmann 1994).

**$q_1^*$** —The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The  $q_1^*$  can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually  $\mu\text{g/L}$  for water,  $\text{mg/kg/day}$  for food, and  $\mu\text{g/m}^3$  for air).

**Recommended Exposure Limit (REL)**—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) 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.

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The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m<sup>3</sup> 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.

**Respirable Fibers or Particles**—Fibers or particles that can be inhaled into the lower lung where gas exchange occurs. The aerodynamic diameter of a particle is a key determinant of its respirability. The formula for aerodynamic diameter (DA) is  $DA = 1.3 \times p^{1/2} \times d^{5/6} \times L^{1/6}$ , where p=particle density; d=actual diameter; and L=length (Hesterberg and Hart 2001; Stober 1972). The formula shows that length is much less important than actual diameter in determining aerodynamic diameter. Consistent with this are observations that long fibers with very small diameters can be transported into the lower lung. Asbestos fibers longer than 100 µm have been detected in human (Morgan and Holmes 1980; Timbrell 1972) and rat lungs (Morgan et al. 1978). Fibers or particles with aerodynamic diameters >3–5 µm are expected to be predominantly deposited in the upper airways and not transported to the lower lung (Morgan et al. 1980; Oberdörster 1994). Fibers and particles deposited in the upper airways are quickly cleared to the throat by mucociliary action. 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 lower lung: 97, 30, 17, or 1%.

**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.

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**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.

**Synthetic Vitreous Fibers**—Fibers that are manufactured from molten sand, glass, basalt rock, slag (a by-product of certain smelting processes), or clay. The terms *synthetic vitreous fibers*, *man-made vitreous fibers*, or *manufactured vitreous fibers* have replaced the earlier term *man-made mineral fibers*, because these fibers are not naturally occurring and do not have a crystalline structure like naturally-occurring mineral fibers such as asbestos fibers. (See definitions for *asbestos*, *fiber*, *mineral*, and *respirable fibers or particles*.) Glass wool, rock (stone) wool, slag wool, and refractory ceramic fibers are made by spinning or blowing the respective molten starting materials of sand or glass, rock, slag, and clay. Continuous filament glass fibers are made by pulling the molten material through small holes.

**Target Organ Toxicity**—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

**Teratogen**—A chemical that causes structural defects that affect the development of an organism.

**Threshold Limit Value (TLV)**—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

**Time-Weighted Average (TWA)**—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

**Toxic Dose<sub>(50)</sub> (TD<sub>50</sub>)**—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

**Toxicokinetic**—The 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 one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

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**Xenobiotic**—Any chemical that is foreign to the biological system.



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### ATSDR MINIMAL RISK LEVEL 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.

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MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

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**MINIMAL RISK LEVEL WORKSHEET**

Chemical Name: Refractory Ceramic Fibers  
CAS Number: None  
Date: July 17, 2002  
Profile Status: Draft for Public Comment  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Graph Key: 70  
Species: Fischer 344 Rats

Minimal Risk Level: 0.03  mg/kg/day  ppm  fiber/cc

Reference:

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.

Experimental design and effects noted:

In the multiple-dose 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<sup>3</sup> 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<sup>3</sup> RCF1 (from the same lot as the multiple-dose study) via the same protocol.

The RCF1 test material was obtained from Carborundum Company, Niagra Falls, New York and 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  $\geq 5$  µm and length:diameter  $\geq 3$ ), the aerosols contained nonfibrous particles, often referred to as “shot”. The ratio of fibers to nonfibrous particles in the aerosols ranged from 0.9 to 1.5.

Table A-1. RCF1 Aerosol Characteristics in the 2-Year Inhalation Bioassays with F344 Rats (Mast et al. 1995a, 1995b)
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Character [mean ( $\pm$ standard deviation)]	3 mg/m <sup>3</sup>	9 mg/m <sup>3</sup>	16 mg/m <sup>3</sup>	30 mg/m <sup>3</sup>
Gravimetric concentration (mg/m <sup>3</sup> )	3.0 $\pm$ 0.4	8.8 $\pm$ 0.7	16.5 $\pm$ 1.1	29.1 $\pm$ 5.2
Total fibers/cc (L $\geq$ 5 $\mu$ m; L:D $\geq$ 3)	36 $\pm$ 17	91 $\pm$ 34	162 $\pm$ 37	234 $\pm$ 35
WHO fibers/cc (L $\geq$ 5 $\mu$ m; D $<$ 3 $\mu$ m; L:D $\geq$ 3)	26 $\pm$ 12	75 $\pm$ 35	120 $\pm$ 35	187 $\pm$ 53
Diameter (D) range ( $\mu$ m)	0.08-5.32	0.08-5.37	0.07-4.83	0.12-4.53
Length (L) range ( $\mu$ m)	0.77-93.93	1.09-98.25	1.24-97.88	1.30-76.6
Arithmetic mean D ( $\mu$ m)	1.02 $\pm$ 0.73	1.02 $\pm$ 0.71	1.02 $\pm$ 1.70	0.98 $\pm$ 0.61
Geometric mean D ( $\mu$ m)	0.80 $\pm$ 2.06	0.80 $\pm$ 2.03	0.82 $\pm$ 1.99	0.82 $\pm$ 1.89
Arithmetic mean L ( $\mu$ m)	20.2 $\pm$ 18.10	20.3 $\pm$ 17.1	19.6 $\pm$ 16.5	22.3 $\pm$ 17.0
Geometric mean L ( $\mu$ m)	13.5 $\pm$ 2.60	13.9 $\pm$ 2.50	13.8 $\pm$ 2.4	15.9 $\pm$ 2.4

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, 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  $\mu$ m. Concentrations were expressed as total fibers per mg dry lung (length:diameter  $>$ 3) or WHO fibers per mg dry lung (length  $>$ 5  $\mu$ m, diameter  $<$ 3  $\mu$ m, and length:diameter  $\geq$ 3).

Observed nonneoplastic lung lesions were classified with two different grading scales. One 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 “fibrosis” grades increasing in severity from grade 4 (minimal collagen deposition at the bronchoalveolar junction; increased bronchiolization; and associated mucoid debris) to grade 8 (complete obstruction of most airways). The other scale contained five grades (0=normal; 1=minimal; 2=mild; 3=moderate; 4=marked) and was applied to particular 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<sup>3</sup>). At sporadic intervals of exposure, rats exposed to 16 or 30 mg/m<sup>3</sup> 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. As early as 3 months after exposure, absolute and relative lung weights were significantly greater in rats exposed to 16 or 30 mg/m<sup>3</sup>. After 24 months of exposure, absolute lung weights 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<sup>3</sup> groups, 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<sup>3</sup> groups ranged from 2 to 3.2 for macrophage aggregation, from 1.2 to 2.7 for

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bronchiolization, and from 1.5 to 2 for granuloma presence (Table A-2). The mean scores reflect progression of the inflammatory lesions with exposure duration and concentration (Table A-2). Distinct signs of pulmonary fibrosis and pleural fibrosis appeared in rats exposed to concentrations  $9 \text{ mg/m}^3$  and showed progression in severity with exposure duration and concentrations (Table A-2). Signs of fibrosis did not appear until 12 months of exposure. Using the eight-grade 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- $\text{mg/m}^3$  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.

Neoplastic lesions (lung adenomas, lung carcinomas, and mesotheliomas) were found most prominently in rats exposed to  $30 \text{ mg/m}^3$ . 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.

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Table A-2. Severity Scores for Pulmonary Lesions in F344 Rats Exposed to RCF1 (Mast et al. 1995a, 1995b) <sup>a,b</sup>							
<i>Exposure level/ sacrifice month</i>	Number of rats	Macro- phage  (0–4 Scale)	Bronchio- lization  (0–4 Scale)	Granuloma  (0–4 Scale)	Pulmonary fibrosis  (0–4 Scale)	Pleural fibrosis  (0–4 Scale)	8-Grade score for pulmonary cellular change and fibrosis
<i>Control</i>							
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 <sup>b</sup>	32	0.1	0.1	0	0	0	1.0
<i>3 mg/m<sup>3</sup></i>							
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 <sup>b</sup>	23	2.4	1.7	1.5	0.8	0.5	2.9
<i>9 mg/m<sup>3</sup></i>							
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
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 <sup>b</sup>	25	2.7	1.7	1.7	1.7	0.5	3.8
<i>16 mg/m<sup>3</sup></i>							
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 <sup>b</sup>	20	3	2.5	2.1	2	1	4.0
<i>30 mg/m<sup>3</sup></i>							
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 <sup>b</sup>	15	2.8	2.9	1.9	1.9	1.3	4.3
<sup>a</sup> 0–4 Scale for different types of lesion: 0=normal; 1=minimal; 2=mild; 3=moderate; 4=marked. 8-Grade Scale for pulmonary cellular change and fibrosis: 1=normal; 2 or 3=cellular change consistent with inflammation; 4–8=increasing severity of fibrosis from minimal to severe. <sup>b</sup> Exposed for 24 months and sacrificed at 30 months.							

Dose and end point used for MRL derivation:

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Benchmark concentration analysis was conducted for lung weight (absolute weight expressed as percent of control), macrophage aggregation score, and bronchiolization score. Changes in these 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, and therefore, scores for pulmonary or pleural fibrosis were not included in the analysis.

Continuous-variable models available in the EPA Benchmark Dose Software were fit to the lung weight, macrophage, and bronchiolization data shown in Table A-3. Data for group means and standard deviations were obtained from an analysis of the Mast et al. (1995a, 1995b) 24-month-sacrifice data by Dr. C.P. Yu (University of Buffalo, personal communication). The published report by Mast et al. 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 arbitrarily at 10% change in weight; percentage change below this value is assumed to be nonadverse. Benchmark response levels for scores for macrophage aggregation and bronchiolization were set at 1.0 (minimal rating on the 0–4 scale, where 0=normal).

For the benchmark concentration analysis, rat exposure levels were converted to human equivalent exposure levels (shown in Table A-3) using 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). The equations for deposition 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. The calculations were made by Dr. Yu (personal communication). Retained total *fiber surface area* per area of pulmonary surface was the dose metric used in these calculations, although human equivalent concentrations based on retained total fiber number per area of pulmonary surface resulted in very similar values. Human equivalent exposure concentrations of 0, 2.0, 7.0, 8.8, and 12.3 fiber/cc were calculated from the empirical rat exposure levels of 0, 36, 91, 162, and 234 total fibers/cc, respectively (Table A-3; see key assumptions in next paragraph). Human equivalent exposure concentrations based on retained total *fiber number* per area of pulmonary surface were 0, 2.1, 6.8, 9.3, or 11.8 fiber/cc.

Key assumptions made in the dosimetric calculations included the following:

- Rat lung surface area:  $4.3 \times 10^3 \text{ cm}^2$ ; Human lung surface area:  $6.5 \times 10^5 \text{ cm}^2$
- Rat macrophage volume per lung:  $26 \text{ mm}^3$ ; Human macrophage volume per lung:  $1.75 \times 10^4 \text{ mm}^3$
- Rat macrophage diameter:  $10.68 \text{ }\mu\text{m}$ ; Human macrophage diameter:  $16.82 \text{ }\mu\text{m}$
- Dissolution rate (same in rats and humans):  $6.46 \times 10^{-5} \text{ (}\mu\text{m/day)}$
- Breakage rate and scheme: same in rats and humans
- Continuous exposure of humans: 24 hours/day, 7 days/week, 52 weeks/year, 70 years
- Continuous human (nose) breathing at rest (750 mL tidal volume;  $14.5 \text{ minute}^{-1}$  breathing rate)
- Size distribution of refractory ceramic fibers in the human model:
  - Bivariate lognormal distribution (geometric mean $\pm$ standard deviation) similar to workplace RCF size data: fiber diameter:  $0.84 \text{ }\mu\text{m}$  ( $\pm 2.05$ ); fiber length:  $14.1 \text{ }\mu\text{m}$  ( $\pm 2.48$ )
- Rat model: retained volume of nonfibrous plus fibrous particles (lung burden) impacts clearance rate
- Human model: only retained fibrous particle volume impacts clearance rate

<p>Table A-3. Non-neoplastic Lung Responses in F344 Rats Exposed for 24 Months to RCF1 by Inhalation (Mast et al. 1995a, 1995b) and Human Equivalent Exposure Concentrations (HEC) Calculated with Models for RCF1 Developed by Yu et al. (1995a, 1996, 1997, 1998)</p>
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Exposure level (total fibers/cc)		Lung weight	Macrophage aggregation	Bronchiolization	Pulmonary fibrosis
Rat	HEC	(Percent of control)	Mean score±standard deviation (0–4 Scale)		
0	0	100.0±14.0	0±0	0±0	0±0
36	2.0	116.8±12.3	2.0±0	1.2±0.4	0.7±0.8
91	7.0	110.9±8.1	2.5±0.6	1.8±0.4	2.0±0
162	8.8	131.8±15.3	3.0±0	2.7±0.5	2.8±0.4
234	12.3	164.7±44.2	3.2±0.4	2.7±0.5	2.2±0.4

0–4 Scale: 0=normal; 1=minimal; 2=mild; 3=moderate; 4=marked

[ ] NOAEL [ ] LOAEL [X] Benchmark Concentration: Lower 95% confidence limits on benchmark concentrations (lower confidence limit on the estimated human equivalent concentration associated with a mean score of 1.0 for macrophage aggregation or bronchiolization or 10% increase in lung weight) were considered as the basis of the MRL.

*Benchmark Modeling Results.* Available continuous-variable models in the EPA Benchmark Dose Software (linear, polynomial, power, and Hill models) were fit to the data shown in Table A-3.

*Lung Weight.* Adequate fits to the data (as assessed with a chi-square goodness of fit test with a rejection criteria of Chi-square probability <0.05) were obtained with the 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), but models with non-homogeneous variance (i.e., variance as a power function of dose) provided poor fits to the data. Predicted human equivalent benchmark concentrations (i.e., predicted concentrations associated with 10% increase in lung weight, and their lower 95% confidence limits in parentheses) from the power, polynomial, and Hill models (with constant variance) were similar: 6.0 (2.7) fibers/cc; 6.7 (3.6) fibers/cc; and 7.1 (5.1) fibers/cc, respectively. Using 15% increase in lung weight as the benchmark criterion, respective benchmark concentrations from these models were only slightly higher: 7.7 (4.8) fibers/cc; 7.1 (3.8) fibers/cc; and 8.1 (5.3) fibers/cc.

*Macrophage Aggregation Scores.* Statistical tests of fit indicated inadequate fit of the data by each of the available models with constant variance. Models with variance as a power function of dose did not improve the fits to the data. Predicted human equivalent benchmark concentrations (concentrations associated with a mean score of 1.0, and their lower 95% confidence limits) from the linear, polynomial, power, and Hill models (constant variance) were: 2.0 (1.1) fibers/cc; 1.5 (1.1) fibers/cc; 2.0 (1.1) fibers/cc; and 0.6 (0.5) fiber/cc.

*Bronchiolization Scores.* Statistical tests of fit indicated inadequate fit of the data by each of the available models with constant variance. Models with variance as a power function of dose did not improve fit to the data. Predicted human equivalent benchmark concentrations (concentrations associated with a mean score of 1.0, and their lower 95% confidence limits) from the linear, polynomial, power, and Hill models (constant variance) were: 3.3 (2.6) fibers/cc; 2.4 (2.0) fibers/cc; 3.3 (2.6) fibers/cc; and 1.8 (1.3) fibers/cc.

*Selection of MRL Basis.* Macrophage aggregation score is selected as the basis of the chronic inhalation MRL, since it appears to be the most sensitive pulmonary inflammation indicator among the three

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considered from the Mast et al. (1995a, 1995b) data. The statistical inadequacy of the fits of the models to the lesion score data is likely influenced strongly by the small number of rats in each exposure group ( $n=6$ , except for the control where  $n=12$ ). Visual examination of the predicted and observed lesion scores, however, shows a reasonable agreement (for examples, see Figures A-1 and A-2 showing observed and predicted scores for macrophage aggregation and bronchiolization from the polynomial models). Because of this agreement, it appears reasonable to use the models to select the point of departure for MRL derivation.

The benchmark concentration analysis of the macrophage aggregation scores predicted human equivalent concentrations ranging from 0.6 to 2.0 fiber/cc (depending on model) that were associated with a “minimal” score for macrophage aggregation (mean score of 1 on the 0–4 scale). The lower 95% confidence limits on these concentrations ranged from 0.5 to 1.1 fiber/cc. An approximate median value of 1 fiber/cc from this range is selected as the point of departure to which uncertainty factors (noted below) are applied to derive the MRL.

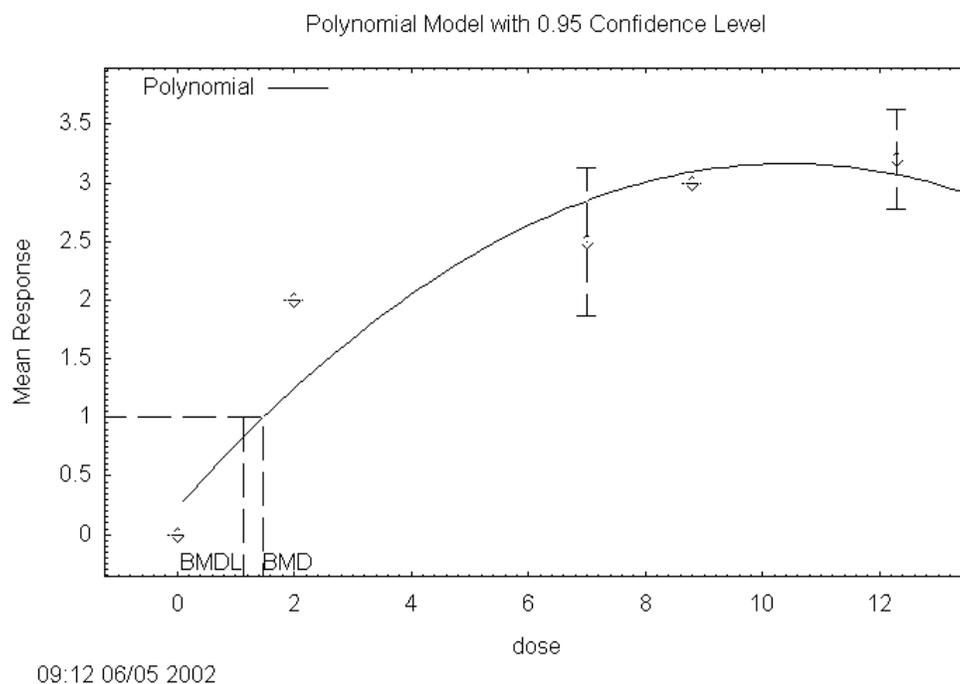


Figure A-1. Predicted (line) and observed (diamonds) mean scores for macrophage aggregation (0–4 scale) plotted against human equivalent concentrations of RCF1 (“dose” = total fibers/cc). BMD refers to the benchmark concentration associated with a score of 1. BMDL is the 95% confidence lower limit on the benchmark concentration.

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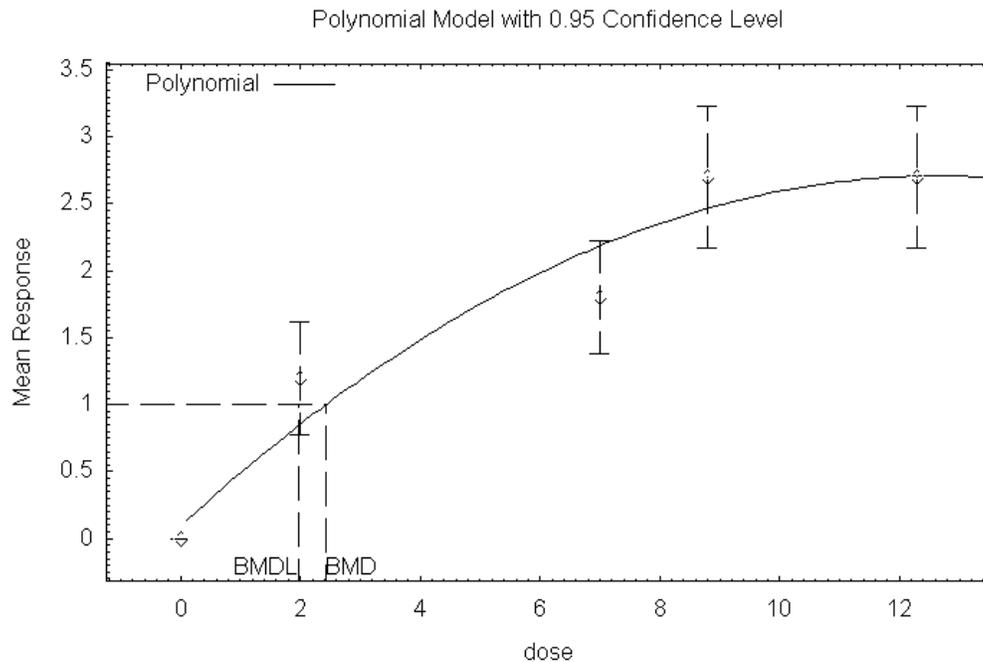


Figure  
Predict  
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A-2.  
ed  
and

observed (diamonds) mean scores for bronchiolization (0–4 scale) plotted against human equivalent concentrations of RCF (“dose” = total fibers/cc). BMD refers to the benchmark concentration associated with a score of 1. BMDL is the 95% confidence lower limit on the benchmark concentration.

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. 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 for the use of a LOAEL is applied. Benchmark concentration analysis predicted surrogate NOAELs for lung weight (95% lower confidence limit on concentration associated with 10% increase in lung weight) and scores for macrophage aggregation and bronchiolization (95% lower confidence limits on concentrations associated with average minimal scores for these lesions).

[ X ] 10 for human variability

Chronic inhalation MRL=1 fiber/cc÷(3x10)=0.03 fiber/cc

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

Was a conversion used from intermittent to continuous exposure? Yes.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: See previous discussion of the calculations made with the rat and human lung deposition and clearance

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models for RCF1 developed by Dr. C.P. Yu and colleagues (Yu et al. 1995a, 1995b, 1996, 1997, 1998a, 1998b).

Other additional studies or pertinent information that lend support to this MRL:

The Mast et al. (1995a, 1995b) study provides the best available data describing dose-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 endpoint 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. These models significantly decrease uncertainty in extrapolating doses from rats to humans.

The MRL derivation assumes that rats and humans are equally sensitive to the inflammatory effects of refractory ceramic fibers. In contrast to the relatively robust understanding of pharmacokinetics of fibers 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. Varying opinions on the relative sensitivity of rodents and humans to deposited fibers have been expressed by Rodelsperger and Weitowitz (1995), Rowe and Springer (1986), and Maxim and McConnell (2001). 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 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. In addition to its relatively high durability, a 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. 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 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 chronic MRL is also 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

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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<sup>3</sup> at 3 months were 1.7, 2, 2, and 2, respectively. At 12 and 24 months, the respective scores were: 2, 2.3, 3, and 3; and 2, 2.5, 3, and 3.2.

Dose-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 dose-response relationships for nonneoplastic pulmonary effects from intermediate- and chronic-duration exposure to these materials. However, lung retention models for these synthetic vitreous fibers 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).

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## APPENDIX B

### USER'S GUIDE

#### Chapter 1

##### Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

#### Chapter 2

##### Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

##### Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These

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MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

## Chapter 3

### Health Effects

#### Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

### LEGEND

See LSE Table 3-1

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- (1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.
- (2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).
- (4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).
- (5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.
- (7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.
- (8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").
- (9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory

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effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

- (10) Reference The complete reference citation is given in Chapter 9 of the profile.
- (11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

**LEGEND****See Figure 3-1**

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

- (13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.
- (14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m<sup>3</sup> or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).
- (17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.
- (18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels ( $q_1^*$ ).
- (19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1

 6

**Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure <sup>a</sup>	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
<b>INTERMEDIATE EXPOSURE</b>							
2		5	6	7	8	9	10
3	Systemic	9	9	9	9		9
4	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3 <sup>b</sup>	10 (hyperplasia)	Nitschke et al. 1981
<b>CHRONIC EXPOSURE</b>							
						11	
	Cancer					9	
38	Rat	18 mo 5 d/wk 7 hr/d				20	(CEL, multiple organs) Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d				10	(CEL, lung tumors, nasal tumors) NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d				10	(CEL, lung tumors, hemangiosarcomas) NTP 1982

<sup>a</sup> The number corresponds to entries in Figure 3-1.

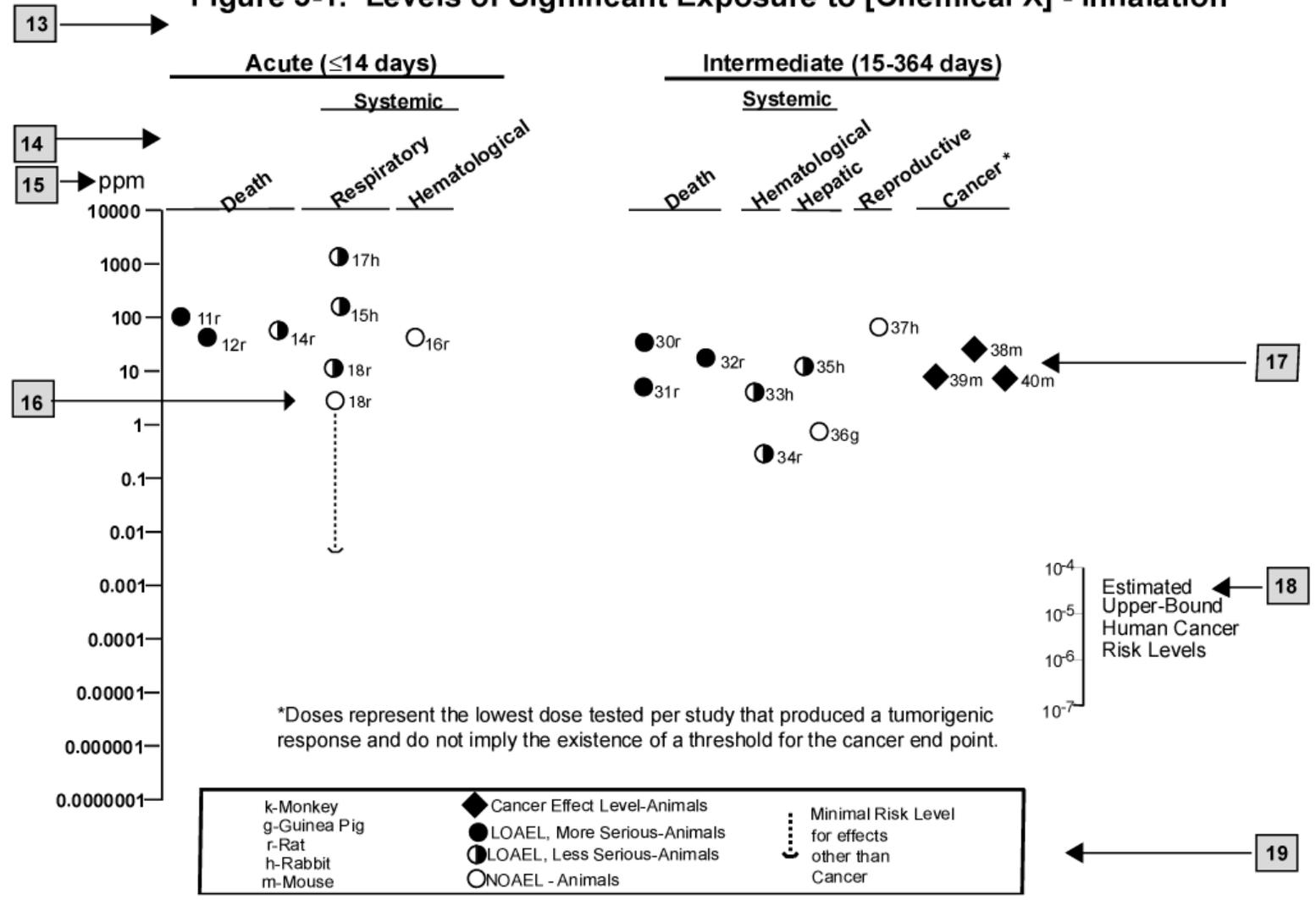
12

 6

<sup>b</sup> Used to derive an intermediate inhalation Minimal Risk Level (MRL) of  $5 \times 10^{-3}$  ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

**SAMPLE**

**Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation**



\*\*\*DRAFT FOR PUBLIC COMMENT\*\*\*

## APPENDIX C

### ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
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
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
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

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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 <sub>1</sub>	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	<i>Federal Register</i>
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
K <sub>d</sub>	adsorption ratio
kg	kilogram
K <sub>oc</sub>	organic carbon partition coefficient
K <sub>ow</sub>	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC <sub>Lo</sub>	lethal concentration, low
LC <sub>50</sub>	lethal concentration, 50% kill
LD <sub>Lo</sub>	lethal dose, low
LD <sub>50</sub>	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	lutinizing hormone
LT <sub>50</sub>	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal

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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
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
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic

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PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	reportable quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD <sub>50</sub>	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization
>	greater than
≥	greater than or equal to

## APPENDIX C

=	equal to
<	less than
#	less than or equal to
%	percent
$\alpha$	alpha
$\beta$	beta
$\gamma$	gamma
$\delta$	delta
$\mu\text{m}$	micrometer
$\mu\text{g}$	microgram
$q_1^*$	cancer slope factor
-	negative
+	positive
(+)	weakly positive result
(-)	weakly negative result



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