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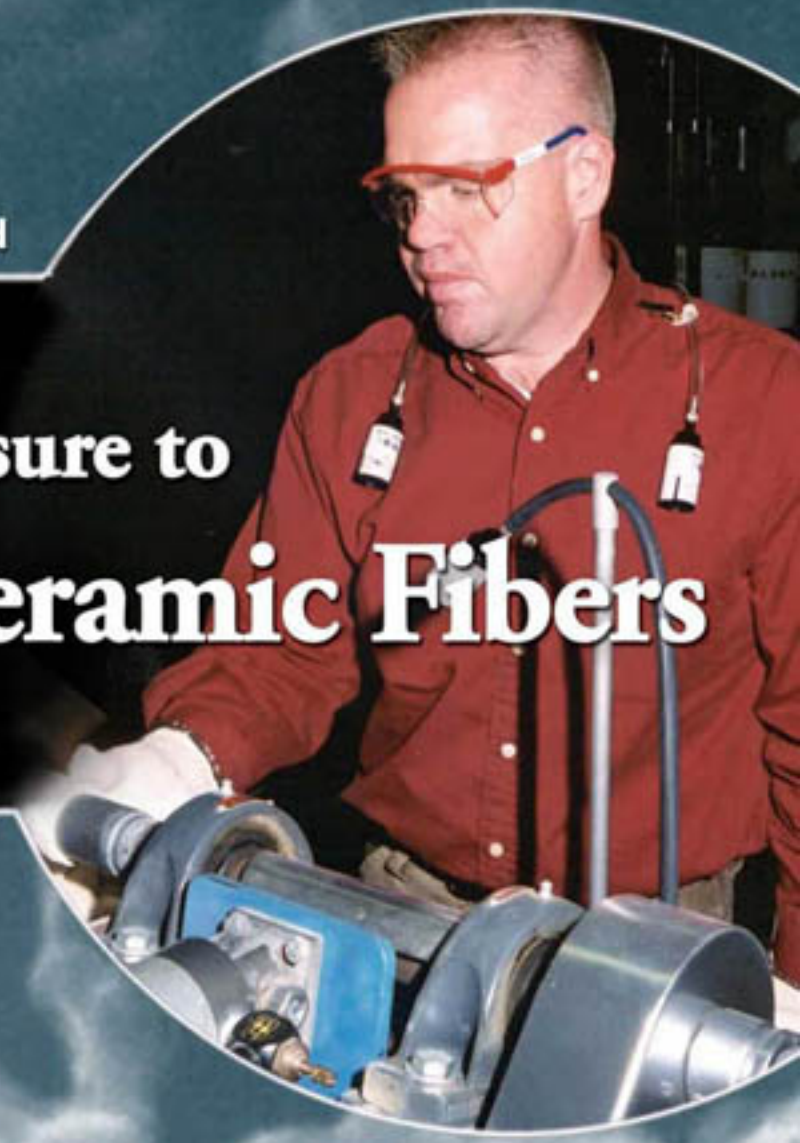
Workplace Safety and Health

Criteria for a Recommended Standard

Occupational Exposure to Refractory Ceramic Fibers



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

NIOSH

Background photo on cover by James Lockey, M.D.: Photomicrograph of a rat lung in inhalation studies with airborne fibers.

Inset photo on cover, courtesy of Kevin H. Dunn: NIOSH industrial hygienist performing air sampling to evaluate engineering controls in simulated work activities using RCF materials.

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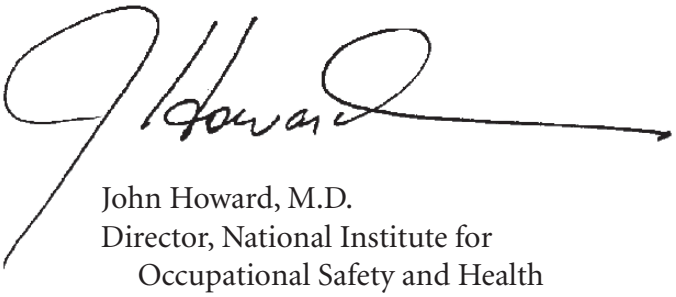
Foreword

When the U.S. Congress passed the Occupational Safety and Health Act of 1970 (Public Law 91–596), it established the National Institute for Occupational Safety and Health (NIOSH). Through the Act, Congress charged NIOSH with recommending occupational safety and health standards and describing exposure limits that are safe for various periods of employment. These limits include but are not limited to the exposures at which no worker will suffer diminished health, functional capacity, or life expectancy as a result of his or her work experience. By means of criteria documents, NIOSH communicates these recommended standards to regulatory agencies (including the Occupational Safety and Health Administration [OSHA]), health professionals in academic institutions, industry, organized labor, public interest groups, and others in the occupational safety and health community. Criteria documents contain a critical review of the scientific and technical information about the prevalence of hazards, the existence of safety and health risks, and the adequacy of control methods.

This criteria document is derived from reviews of information from human and animal studies of the toxicity of refractory ceramic fibers (RCFs) and is intended to describe the potential health effects of occupational exposure to airborne fibers of this material. RCFs are amorphous synthetic fibers produced by the melting and blowing or spinning of calcined kaolin clay or a combination of alumina, silica, and other oxides. RCFs belong to the class of synthetic vitreous fibers (SVFs)—materials that also include fibers of glass wool, rock wool, slag wool, and specialty glass. RCFs are used in commercial applications requiring lightweight, high-heat insulation (e.g., furnace and kiln insulation). Commercial production of RCFs began in the 1950s in the United States, and production increased dramatically in the 1970s. Domestic production of RCFs in 1997 totaled approximately 107.7 million lb. Currently, total U.S. production has been estimated at 80 million lb per year, which constitutes 1% to 2% of SVFs produced worldwide. In the United States, approximately 31,500 workers have the potential for occupational exposure to RCFs during distribution, handling, installation, and removal. More than 800 of these workers are employed directly in the manufacturing of RCFs and RCF products. With increasing production of RCFs, concerns about exposures to airborne fibers prompted animal inhalation studies that have indicated an increased incidence of mesotheliomas in hamsters and lung cancer in rats following exposure to RCFs. Studies of workers who manufacture RCFs have shown a positive association between increased exposure to RCFs and the development of pleural plaques, skin and eye irritation, and respiratory symptoms and conditions (including dyspnea, wheezing, and chronic cough). In addition, current and former RCF production workers have shown decrements in pulmonary function.

After evaluating this evidence, NIOSH proposes a recommended exposure limit (REL) for RCFs of 0.5 fiber per cubic centimeter (f/cm^3) of air as a time-weighted average (TWA) concentration for up to a 10-hr work shift during a 40-hr workweek. Limiting airborne RCF exposures to this concentration will minimize the risk for lung cancer and irritation of the eyes and upper

respiratory system and is achievable based on a review of exposure monitoring data collected from RCF manufacturers and users. However, because a residual risk of cancer (lung cancer and pleural mesothelioma) may still exist at the REL, continued efforts should be made toward reducing exposures to less than 0.2 f/cm^3. Engineering controls, appropriate respiratory protection programs, and other preventive measures should be implemented to minimize worker exposures to RCFs. NIOSH urges employers to disseminate this information to workers and customers. NIOSH also requests that professional and trade associations and labor organizations inform their members about the hazards of exposure to RCFs.



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Executive Summary

The National Institute for Occupational Safety and Health (NIOSH) has reviewed data characterizing occupational exposure to airborne refractory ceramic fibers (RCFs) and information about potential health effects obtained from experimental and epidemiologic studies. From this review, NIOSH determined that occupational exposure to RCFs is associated with adverse respiratory effects as well as skin and eye irritation and may pose a carcinogenic risk based on the results of chronic animal inhalation studies.

In chronic animal inhalation studies, exposure to RCFs produced an increased incidence of mesotheliomas in hamsters [McConnell et al. 1995] and lung cancer in rats [Mast et al. 1995a,b]. The potential role of nonfibrous particulates generated during inhalation exposures in the animal studies complicates the issue of determining the exact mechanisms and doses associated with the toxicity of RCFs in producing carcinogenic effects [Mast et al. 2000]. The induction of mesotheliomas and sarcomas in rats and hamsters following intrapleural and intraperitoneal implantation of RCFs provided additional evidence for the carcinogenic potential of RCFs [Wagner et al. 1973; Davis et al. 1984; Smith et al. 1987; Pott et al. 1987]. Lung tumors have also been observed in rats exposed to RCFs by intratracheal instillation [Manville Corporation 1991].

In contrast to the carcinogenic effects of RCFs observed in experimental animal studies, epidemiologic studies have found no association between occupational exposure to airborne RCFs and an excess rate of pulmonary fibrosis or lung cancer. However, studies of worker populations with occupational exposure to airborne RCFs have shown an association between exposure and the formation of pleural plaques, increased prevalence of respiratory symptoms and conditions (dyspnea, wheezing, chronic cough), decreases in pulmonary function, and skin, eye, and upper respiratory tract irritation [Lemasters et al. 1994, 1998; Lockey et al. 1996]. Increased decrements in pulmonary function among workers exposed to RCFs who are current or former cigarette smokers indicate an apparent synergistic effect between smoking and RCF exposure [Lemasters et al. 1998]. This finding is consistent with studies of other dust-exposed populations. The implementation of improved engineering controls and work practices in RCF manufacturing processes and end uses have led to dramatic declines in airborne fiber exposure concentrations [Rice et al. 1996, 1997; Maxim et al. 2000a], which in turn have lowered the risk of symptoms and health effects for exposed workers.

In 2002, the Refractory Ceramic Fibers Coalition (RCFC) established the Product Stewardship Program (PSP), which was endorsed by the Occupational Safety and Health Administration (OSHA). Contained in the PSP were recommendations for an RCF exposure guideline of 0.5 fiber per cubic centimeter (f/cm^3) of air as a time-weighted average (TWA) based on the contention that exposures at this concentration could be achieved in most industries that manufactured or used RCFs. At this time, the available health data do not provide sufficient evidence for deriving a precise health-based occupational exposure limit to protect

against lung cancer. However, given what is known from the animal and epidemiological data, NIOSH supports the intent of the PSP and concurs that a recommended exposure limit (REL) of 0.5 f/cm^3 as a TWA for up to a 10-hr work shift during a 40-hr workweek will lower the risk for developing lung cancer. Keeping exposures below the REL should reduce the risk of lung cancer to estimates between 0.073/1,000 and 1.2/1,000 (based on extrapolations of risk models from Moolgavkar et al. [1999] and Yu and Oberdörster [2000]). Keeping worker exposures below the REL will also reduce the risk of irritation of the eyes and upper respiratory system.

The risk for mesothelioma at 0.5 f/cm^3 is not known but cannot be discounted. Evidence from epidemiologic studies showed that higher exposures in the past resulted in pleural plaques in workers, indicating that RCFs do reach pleural tissue. Both implantation studies in rats and inhalation studies in hamsters show that RCFs can cause mesothelioma. Because of limitations in the hamster data, the risk of mesothelioma cannot be quantified. However, the fact that no mesothelioma has been found in workers and that pleural plaques appear to be less likely in workers with lower exposures suggests a lower risk for mesothelioma at the REL.

Because residual risks of cancer (lung cancer and pleural mesothelioma) and irritation may still exist at the REL, NIOSH further recommends that all reasonable efforts be made to work toward reducing exposures to less than 0.2 f/cm^3. At this concentration, the risks of lung cancer are estimated to be between 0.03/1,000 and 0.47/1,000 (based on extrapolations of risk models from Moolgavkar et al. [1999] and Yu and Oberdörster [2000]).

Maintaining airborne RCF concentrations below the REL requires a comprehensive safety and health program that includes provisions for the monitoring of worker exposures, installation and routine maintenance of engineering controls, and the training of workers in good work practices. Industry-led efforts have likewise promoted these actions by establishing the PSP. NIOSH believes that maintaining exposures below the REL is achievable at most manufacturing operations and many user applications, and that the incorporation of an action level (AL) of 0.25 f/cm^3 in the exposure monitoring strategy will help employers determine when workplace exposure concentrations are approaching the REL. The AL concept has been an integral element of occupational standards recommended in NIOSH criteria documents and in comprehensive standards promulgated by OSHA and the Mine Safety and Health Administration (MSHA).

NIOSH also recommends that employers implement additional measures under a comprehensive safety and health program, including hazard communication, respiratory protection programs, smoking cessation, and medical monitoring. These elements, in combination with efforts to maintain airborne RCF concentrations below the REL, will further protect the health of workers.

Contents

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ACS	American Cancer Society
Al	aluminum
AL	action level
$A1_2O_3$	alumina
$Al_2Si_2O_5[OH]_4$	siliceous kaolin
AM	arithmetic mean
APF	assigned protection factor
ATSDR	Agency for Toxic Substances Disease Registry
B_2O_3	boron oxide
BAL	bronchoalveolar lavage
°C	degree(s) Celsius
CaO	calcium oxide
CFR	Code of Federal Regulations
CI	confidence interval
DECOS	Dutch Expert Committee on Occupational Standards
dG	2-deoxyguanosine
DNA	deoxyribonucelic acid
EDXA	energy dispersive X-ray analyzer
e.g.	for example
EID	Education and Information Division
EPA	U.S. Environmental Protection Agency
°F	degree(s) Fahrenheit
f/cm^3	fibers per cubic centimeter of air
Fe	iron
$FEF_{25–75}$	forced expiratory flow (liter/second) between 25% and 75% of the forced vital capacity
Fe_2O_3	ferric oxide
FEV_1	forced expiratory volume in one second
FEV_1/FVC	ratio of forced expiratory volume in one second to forced vital capacity
FJC	functional job category
FVC	forced vital capacity
g/cm^3	grams per cubic meter of air
GM	geometric mean

GM_D	geometric mean diameter
GM_L	geometric mean length
GSD	geometric standard deviation
GSH	glutathione
γ-GT	γ-glutamyltransferase
HEPA	high-efficiency particulate air
HHE	Health Hazard Evaluation
hr	hour(s)
HTE	hamster tracheal epithelial
IARC	International Agency for Research on Cancer
i.e.	that is
IgG	immunoglobulin
IJT	industry job title
ILO	International Labor Office
ILs	interleukins
K_2O	potassium oxide
lb	pound(s)
LDH	lactose dehydrogenase
LOAEL	lowest observable adverse effect level
LOD	limit of detection
MAC	maximum achievable concentration
MAN	Manville RCF
mg/m^3	milligrams per cubic meter
MgO	magnesium oxide
min	minute(s)
ml	milliliter(s)
MLE	maximum likelihood estimate
mm	millimeter(s)
MMC	metal matrix composites
MMMF	man-made mineral fiber
MMVF	man-made vitreous fiber
MSDS	material safety data sheet
MSHA	Mine Safety and Health Administration
MTD	maximum tolerated dose
MVK	Moolgavkar-Venzon-Knudson
n	number
Na_2O	sodium oxide
ng	nanogram(s)
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health

nl	nanoliter(s)
NOAEL	no observable adverse effect level
NTP	National Toxicology Program
ODC	ornithine decarboxylase
OM	Osborne Mendel
OR	odds ratio
OSHA	Occupational Safety and Health Administration
P	probability
PA	posteroanterior
PCM	phase contrast optical microscopy
PEL	permissible exposure limit
PFT	pulmonary function test
PG	prostaglandin
PPE	personal protective equipment
PSP	Product Stewardship Program
RCF	refractory ceramic fiber
RCFC	Refractory Ceramic Fibers Coalition
REL	recommended exposure limit
ROM	reactive oxygen metabolite
ROS	reactive oxygen species
RPM	rodent pleural mesothelial
SAED	selected area electron diffraction
SD	standard deviation
SEM	scanning electron microscopy
Si	silicon
SiO_2	silicon dioxide
SMR	standardized mortality ratio
SVF	synthetic vitreous fiber
TEM	transmission electron microscopy
TIMA	Thermal Insulation Manufacturers Association
TiO_2	titanium dioxide
TLV	threshold limit value
TNF	tumor necrosis factor
TWA	time-weighted average
UCL	upper confidence limit
UICC	Union Internationale Contre le Cancer
UJT	uniform job titles
WHO	World Health Organization
ZrO_2	zirconium dioxide
µm	micrometer

Glossary

Action level (AL): A statistically derived concept used to permit an employer to have confidence (e.g., 95%) that if a measured exposure concentration is below the AL, then only a small probability exists that the actual concentration is above the exposure limit. Often established as half of the exposure limit, the AL should be designated for determining when additional controls are needed or administrative actions should be taken to reduce exposures. The purpose of using this reference is to indicate when worker exposures to hazardous substances may be approaching the exposure limit.

After-service refractory ceramic fiber (RCF): RCF that has been subjected to greater than 1,800 °F (~1,000 °C) and has partially converted to the silica polymorph cristobalite. In experimental studies, this fiber is also called RCF4.

Aspect ratio: The length to width ratio of a fiber.

Costophrenic angle: Location on a chest radiograph where the ribs and the diaphragm appear to meet.

Dyspnea grade 1: Shortness of breath on exertion, classified as less severe than grade 2.

Dyspnea grade 2: Shortness of breath on exertion, excluding shortness of breath associated with hurrying on the level or walking up a slight hill, and classified as more severe than dyspnea grade 1.

$FEF_{25–75}$: Forced expiratory flow (liter/second) that is between 25% and 75% of the forced vital capacity.

FEV_1: Forced expiratory volume in one second, or the maximum volume of air that can be forcibly expired during the first second of expiration following a maximal inspiration.

Fiber counting rules: Criteria for identifying and counting fibers during air sampling and exposure assessment. The three main conventions for fiber counting are described below (and in Section 4.2.1 and Appendix A).

- ***NIOSH "A" rules***—any particle >5 µm long with an aspect ratio (length to width) greater than 3:1 is considered a fiber.
- ***NIOSH "B" rules***—any particle >5 µm long with an aspect ratio equal to or greater than 5:1 and a diameter <3 µm is considered a fiber.
- ***World Health Organization (WHO) reference method for man-made mineral fiber***—any particle >5 µm long with an aspect ratio equal to or greater than 3:1 and a diameter <3 µm is considered a fiber.

FVC: Forced vital capacity or the maximum volume of air (in liters) that can be forcibly expired from the lungs following a maximal inspiration.

High-efficiency particulate air (HEPA) filter: A dry-type filter used to remove airborne particles with an efficiency equal to or greater than 99.97% for 0.3-μm particles. The lowest filtering efficiency of 99.97% is associated with 0.3-μm particles, which is approximately the most penetrating particle size for particulate filters.

Inspirable dust: The fraction of airborne particles that would be inspired through the mouth and nose of a worker.

MAN: A refractory ceramic fiber produced by the Johns Manville Company.

Occupational medical monitoring (incorporating medical screening, surveillance): The periodic medical evaluation of workers to identify potential health effects and symptoms related to occupational exposures or environmental conditions in the workplace. An occupational medical monitoring program is a secondary prevention method based on two processes, screening and surveillance. Occupational medical screening focuses on early detection of health outcomes for individual workers. Screening may involve an occupational history assessment, medical examination, and medical tests to detect the presence of toxicants or early pathologic changes before the worker would normally seek clinical care for symptomatic disease. Occupational **medical surveillance** involves the ongoing evaluation of the health status of a group of workers through the collection and analysis of health data for the purpose of disease prevention and for evaluating the effectiveness of intervention programs.

Pleural plaques: Discrete areas of thickening that are generally on the parietal pleura and are most commonly located at the midcostal and posterior costal areas, the dome of the diaphragm, and the mediastinal pleura. Presence of plaques is an indication of exposure to a fibrous silicate, most frequently asbestos.

Radiographic opacity: A shadow on a chest X-ray film generally associated with a fibrogenic response to dust retained in the lungs [Morgan 1995]. Opacities are classified by size, shape, location, and profusion according to guidelines established by the International Labor Office [ILO 2000] www.ilo.org/public/english/support/publ/books.htm).

Refractory ceramic fiber (RCF): An amorphous, synthetic fiber (Chemical Abstracts Services No. 142844–00–6) produced by melting and blowing or spinning calcined kaolin clay or a combination of alumina (Al_2O_3) and silicon dioxide (SiO_2). Oxides may be added such as zirconia, ferric oxide, titanium oxide, magnesium oxide, calcium oxide, and alkalies. The percentage (by weight) of components is as follows: alumina, 20% to 80%; silicon dioxide, 20% to 80%; and other oxides in smaller amounts.

Respirable-sized fiber: Particles >5 μm long with an aspect ratio >3:1 and diameter ≤1.3 μm.

Shot: Nonfibrous particulate that is generated during the production of RCFs from the original melt batch.

Standardized mortality ratio (SMR): The ratio of the observed number of deaths (from a specified cause) to the expected number of deaths (from that same cause) that has been adjusted to account for demographic differences (e.g., age, sex, race) between the study population and the referent population.

Synthetic vitreous fiber (SVF): Any of a number of manufactured fibers produced by the melting and subsequent fiberization of kaolin clay, sand, rock, slag, etc. Fibrous glass, mineral wool, ceramic fibers, and alkaline earth silicate wools are the major types of SVF, also called man-made mineral fiber (MMMF) or man-made vitreous fiber (MMVF).

Thoracic-sized fiber: Particles >5 μm long with aspect ratio >3:1 and a diameter <3 to 3.5 μm. *Thoracic* refers to particles penetrating to the thorax (50% cut at 10-μm aerodynamic diameter). Mineral and vitreous fibers with diameters 3 to 3.5 μm have an aerodynamic diameter of approximately 10 μm.

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1 Recommendations for a Refractory Ceramic Fiber (RCF) Standard

The National Institute for Occupational Safety and Health (NIOSH) recommends that exposure to airborne refractory ceramic fibers (RCFs) be controlled in the workplace by implementing the recommendations presented in this document. These recommendations are designed to protect the safety and health of workers for up to a 10-hr work shift during a 40-hr workweek over a 40-year working lifetime. Observance of these recommendations should prevent or greatly reduce the risks of eye and skin irritation and adverse respiratory health effects (including lung cancer) in workers with exposure to airborne RCFs. Preventive efforts are primarily focused on controlling and minimizing airborne fiber concentrations to which workers are exposed. Exposure monitoring, hazard communication, training, respiratory protection programs, and medical monitoring are also important elements of a comprehensive program to protect the health of workers exposed to RCFs. These elements are described briefly in this chapter and in greater detail in Chapter 9.

1.1 Recommended Exposure Limit (REL)

NIOSH recommends that occupational exposures to airborne RCFs be limited to 0.5 fiber per cubic centimeter (f/cm^3) of air as a time-weighted average (TWA) concentration for up to a 10-hr work shift during a 40-hr workweek, measured according to NIOSH Method 7400 (B rules) [NIOSH 1998].

This recommended exposure limit (REL) is intended to reduce the risk of lung cancer, mesothelioma, and other adverse respiratory health effects (including irritation and compromised pulmonary function) associated with excessive RCF exposure in the workplace. Limiting exposures will also protect workers' eyes and skin from the mechanical irritation associated with exposure to RCFs. In most manufacturing operations, it is currently possible to limit airborne RCF concentrations to 0.5 f/cm^3 or less. Exceptions may occur during RCF finishing operations and during the installation and removal of RCF products, when the nature of job activities presents a challenge to meeting the REL. For these operations, additional protective measures are recommended. Engineering and administrative controls, respirator use, and other preventive measures should be implemented to minimize exposures for workers in RCF industry sectors where airborne RCF concentrations exceed the REL. NIOSH urges employers to disseminate this information to workers and customers, and RCF manufacturers should convey this information to downstream users. NIOSH also requests that professional and trade associations and labor organizations inform their members about the hazards of exposure to RCFs.

1.2 Definitions and Characteristics

1.2.1 Naturally Occurring Mineral Fibers

Many types of mineral fibers occur naturally. Asbestos is the most prominent of these fibers because of its industrial application. The

asbestos minerals include both the serpentine asbestos (chrysotile) and the amphibole mineral fibers, including actinolite, amosite, anthophyllite, crocidolite, and tremolite [Peters and Peters 1980]. Since ancient times, mineral fibers have been mined and processed for use as insulation because of their high tensile strength, resistance to heat, durability in acids and other chemicals, and light weight. The predominant forms of asbestos mined and used today are chrysotile (~95%), crocidolite (<5%), and amosite (<1%).

For the purposes of this document, naturally occurring mineral fibers are distinguishable from synthetic vitreous fibers (SVFs) based on the crystalline structure of the mineral fibers. This property causes the mineral fibers to fracture longitudinally when subjected to mechanical stresses, thereby producing more fibers of decreasing diameter. By contrast, SVFs are amorphous and fracture transversely, resulting in more fibers of decreasing length until the segments are no longer of sufficient length to be considered fibers. Naturally occurring mineral fibers are generally more durable and less soluble than SVFs, a property that accounts for the biopersistence and toxicity of mineral fibers in vivo.

1.2.2 RCFs

RCFs are a type of SVF; they are amorphous synthetic fibers produced from the melting and blowing or spinning of calcined kaolin clay or a combination of alumina (Al_2O_3) and silicon dioxide (SiO_2). Oxides such as zirconia, ferric oxide, titanium oxide, magnesium oxide, calcium oxide, and alkalies may be added. The percentage of components (by weight) is as follows: alumina, 20% to 80%; silicon dioxide, 20% to 80%; and other oxides in smaller amounts. Like the naturally occurring mineral fibers, RCFs possess the desired qualities of heat resistance, tensile strength, durability, and light weight. On a continuum, however, RCFs are less durable (i.e., more soluble) than the least durable asbestos fiber (chrysotile) but more durable than most fibrous glass and other types of SVFs.

1.2.3 SVFs

SVFs include a number of manmade (not naturally occurring) fibers that are produced by the melting and subsequent fiberization of kaolin clay, sand, rock, slag, and other materials. The major types of SVFs are fibrous glass, mineral wool (slag wool, rock wool), and ceramic fibers (including RCFs). SVFs are also frequently referred to as manmade mineral fibers (MMMFs) or manmade vitreous fibers (MMVFs).

1.3 Sampling and Analysis

Employers shall perform air sampling and analysis to determine airborne concentrations of RCFs according to NIOSH Method 7400 (B rules) [NIOSH 1998], provided in Appendix A of this document.

1.4 Exposure Monitoring

Employers shall perform exposure monitoring as follows:

- Establish a workplace exposure monitoring program for worksites where RCFs or RCF products are manufactured, handled, used, installed, or removed.
- Include in this program routine area and personal monitoring of airborne fiber concentrations.
- Design a monitoring strategy that can be used to

— evaluate a worker's exposure to RCFs,

— assess the effectiveness of engineering controls, work practices, and other factors in controlling airborne fiber concentrations, and

— identify work areas or job tasks in which worker exposures are routinely high and thus require additional efforts to reduce them.

1.4.1 Sampling Surveys

Employers shall conduct exposure monitoring surveys to ensure that worker exposures (measured by full-shift samples) do not exceed the REL. Because adverse respiratory health effects may occur at the REL, it is desirable to achieve lower concentrations whenever possible. When workers are potentially exposed to airborne RCFs, employers shall conduct exposure monitoring surveys as follows:

- Collect representative personal samples over the entire work shift [NIOSH 1997a].
- Perform periodic sampling at least annually and whenever any major process change takes place or whenever another reason exists to suspect that exposure concentrations may have changed.
- Collect all routine personal samples in the breathing zones of the workers.
- If workers are exposed to concentrations above the REL, perform more frequent exposure monitoring as engineering changes are implemented and until at least two consecutive samples indicate that exposures no longer exceed the REL [NIOSH 1977a].
- Notify all workers of monitoring results and of any actions taken to reduce their exposures.
- When developing an exposure sampling strategy, consider variations in work and production schedules as well as the inherent variability in most area sampling [NIOSH 1995a].

1.4.1.1 Focused sampling

When sampling to determine whether worker RCF exposures are below the REL, a focused sampling strategy may be more practical than a random sampling approach. A focused sampling strategy targets workers perceived to be exposed to the highest concentrations of a hazardous substance [Leidel and Busch 1994]. This strategy is most efficient for identifying exposures above the REL if maximum-risk workers and time periods are accurately identified. Short tasks involving high concentrations of airborne fibers could result in elevated exposure over full work shifts.

Sampling strategies such as those used by Corn and Esmen [1979], Rice et al. [1997], and Maxim et al. [1997] have been developed and used specifically in RCF manufacturing facilities to monitor airborne fiber concentration. In these strategies, representative workers are selected for sampling and are grouped according to dust zones, uniform job titles, or functional job categories. These approaches are intended to reduce the number of required samples and increase the confidence of identifying workers at similar risk.

1.4.1.2 Area sampling

Area sampling may be useful in exposure monitoring to determine sources of airborne RCFs and to assess the effectiveness of engineering controls.

1.4.2 Action Level

An action level (AL) at half the REL (0.25 f/cm^3) shall be used to determine when additional

controls are needed or when administrative actions should be taken to reduce exposure to RCFs. The purpose of an AL is to indicate when worker exposures to hazardous substances may be approaching the REL. When air samples contain concentrations at or above the AL, the probability is high that worker exposures to the hazardous substance exceed the REL.

The AL is a statistically derived concept permitting the employer to have confidence (e.g., 95%) that if results from personal air samples are below the AL, the probability is small that worker exposures are above the REL. NIOSH has concluded that the use of an AL permits the employer to monitor hazardous workplace exposures without daily sampling. The AL concept has served as the basis for defining the elements of an occupational standard in NIOSH criteria documents and comprehensive standards promulgated by the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA).

1.5 Hazard Communication

Employers shall take the following measures to inform workers about RCF hazards:

- Establish a safety and health training program for all workers who manufacture, use, handle, install, or remove RCF products or perform other activities that bring them into contact with RCFs.
- Inform employees and contract workers about hazardous substances in their work areas.
- Instruct workers about how to get information from material safety data sheets (MSDSs) for RCFs and other chemicals.
- Provide MSDSs onsite and make them easily accessible.
- Inform workers about adverse respiratory health effects associated with RCF exposures.
- In work involving the removal of refractory insulation materials, make workers aware of the potential for exposure to respirable crystalline silica, the health effects related to this exposure, and methods for reducing exposures.
- Make workers who smoke cigarettes or use other tobacco products aware of their increased risk of developing RCF-induced respiratory symptoms and conditions (see Sections 1.12 and 9.6 for recommendations about smoking cessation programs).

1.6 Training

Employers shall provide the following training for workers exposed to RCFs:

- Train workers to detect hazardous situations.
- Inform workers about practices or operations that may generate high airborne fiber concentrations (e.g., cutting and sanding RCF boards and other RCF products).
- Train workers how to protect themselves by using proper work practices, engineering controls, and personal protective equipment (PPE).

1.7 Product Formulation

One factor recognized as contributing to the toxicity of an inhaled fiber is its durability and resistance to degradation in the respiratory tract. Chemical characteristics place RCFs among the most durable SVFs. As a result, an

inhaled RCF that is deposited in the alveolar region of the lung will persist longer in the lungs than a less durable fiber. Therefore, NIOSH recommends substituting a less durable fiber for RCFs or reformulating the chemistry of RCFs toward this end to reduce the hazard for exposed workers. As part of product stewardship efforts, several RCF producers within the Refractory Ceramic Fibers Coalition (RCFC) have developed new and less biopersistent fibers termed alkaline earth silicate wools [Maxim et al. 1999b]. Newly developed fibers should undergo industry-sponsored testing before their selection and commercial use to exclude possible adverse health effects from exposure.

1.8 Engineering Controls and Work Practices

1.8.1 Engineering Controls

Employers shall use and maintain appropriate engineering controls to keep airborne concentrations of RCFs at or below the REL during the manufacture, use, handling, installation, and removal of RCF products. Engineering controls for controlling RCFs include the following:

- Local exhaust ventilation or dust collection systems at or near dust-generating systems
  - Band saws used in RCF manufacturing and finishing operations have been fitted with such engineering controls to capture fibers and dust during cutting operations, thereby reducing exposures for the band saw operator [Venturin 1998].
  - Disc sanders fitted with similar local exhaust ventilation systems effectively reduce airborne RCF concentrations during the sanding of vacuum-formed RCF products [Dunn et al. 2004].
- Enclosed processes used during manufacturing to keep airborne fibers contained and separated from workers
- Water knives, which are high-pressure water jets that effectively cut and trim the edges of RCF blanket while suppressing dust and limiting the generation of airborne fibers

1.8.2 Work Practices

Employers shall implement appropriate work practices to help keep worker exposures at or below the REL for RCFs. The following work practices are recommended to help reduce concentrations of airborne fibers:

- Limit the use of power tools unless they are equipped with local exhaust or dust collection systems.
  - Be aware that manually powered hand tools generate less dust and fewer airborne fibers, but they often require additional physical effort and time and may increase the risk of musculoskeletal disorders.
  - The additional physical effort required by hand tools may also increase the rate and depth of breathing and consequently affect the inhalation rate and deposition of fibers in the lungs.
- Use ergonomically correct tools and proper workstation design to reduce the risk of musculoskeletal disorders.
- Use high-efficiency particulate air-filtered (HEPA-filtered) vacuums.

- Use wet sweeping to suppress airborne fiber and dust concentrations during cleanup.
- When removing after-service RCF products, dampen insulation with a light water spray to prevent fibers and dust from becoming airborne. (However, *use caution when dampening refractory linings during installation*, since water can damage refractory-lined equipment, causing the generation of steam and possible explosion during heating.)
- Clean work areas regularly using a HEPA-filtered vacuum or wet sweeping to minimize accumulation of debris.
- Ensure that workers wear long-sleeved clothing, gloves, and eye protection when performing potentially dusty activities involving RCFs or RCF products. For some activities, disposable clothing or coveralls may be preferred.

1.9 Respiratory Protection

Respirators shall be used while performing any task for which the exposure concentration is unknown or has been documented to be higher than the NIOSH REL of 0.5 f/cm^3 as a TWA. However, respirators shall not be used as the primary means of controlling worker exposures.

When possible, use other methods for minimizing worker exposures to RCFs:

- Product substitution
- Engineering controls
- Changes in work practices

Use respirators when available engineering controls and work practices do not adequately control worker exposures below the REL for RCFs. NIOSH recognizes that controlling exposures to RCFs is a particular challenge during the finishing stages of RCF product manufacturing and during the installation and removal of refractory materials

1.9.1 Respiratory Protection Program

When respiratory protection is needed, employers shall establish a comprehensive respiratory protection program as described in the OSHA respiratory protection standard [29 CFR* 1910.134]. Elements of a respiratory protection program must be established and described in a written plan that is specific to the workplace. The plan must include the following elements:

- Procedures for selecting respirators
- Medical evaluations of workers required to wear respirators
- Fit-testing procedures
- Routine-use procedures and emergency respirator-use procedures
- Procedures and schedules for cleaning, disinfecting, storing, inspecting, repairing, discarding, and maintaining respirators
- Procedures for ensuring adequate air quality for supplied-air respirators
- Training in respiratory hazards
- Training in the proper use and maintenance of respirators
- Program evaluation procedures
- Procedures for ensuring that workers who voluntarily wear respirators (excluding filtering facepieces known as dust masks)

Code of Federal Regulations. See CFR in references.

comply with the medical evaluation and cleaning, storing, and maintenance requirements of the standard

- A designated program administrator who is qualified to administer the respiratory protection program

Employers shall update the written program as necessary to account for changes in the workplace that affect respirator use. In addition, employers are required to provide at no cost to workers all equipment, training, and medical evaluations required under the respiratory protection program.

1.9.2 Respirator Selection

When conditions of exposure to airborne RCFs exceed the REL, proper respiratory protection shall be selected as follows:

- Select, at a minimum, a half-mask, air-purifying respirator equipped with a 100 series particulate filter. This respirator has an assigned protection factor (APF) of 10.
- Provide a higher level of protection and prevent facial or eye irritation from RCF exposure by using a full-facepiece, air-purifying respirator equipped with a 100-series filter; or use any powered, air-purifying respirator equipped with a tight-fitting facepiece (full-facepiece).
- Consider providing a supplied-air respirator with a full facepiece for workers who remove after-service RCF insulation (e.g., furnace insulation) and are therefore exposed to high and unpredictable concentrations of RCFs. These respirators provide a greater level of respiratory protection. Use them whenever the work task involves potentially high concentrations of airborne fibers.
- Always perform a comprehensive assessment of workplace exposures to determine the presence of other possible contaminants (such as silica) and to ensure that proper respiratory protection is used.
- Use only respirators approved by NIOSH and MSHA.

For information and assistance in establishing a respiratory protection program and selecting appropriate respirators, see the OSHA *Respiratory Protection Advisor* on the OSHA Web site at www.osha.gov. Additional information is also available from the *NIOSH Respirator Selection Logic* [NIOSH 2004], the *NIOSH Guide to Industrial Respiratory Protection* [NIOSH 1987b], and the *NIOSH Guide to the Selection and Use of Particulate Respirators Certified under 42 CFR 84* [NIOSH 1996].

1.10 Sanitation and Hygiene

Employers shall take the following measures to protect workers potentially exposed to RCFs:

- Do not permit smoking, eating, or drinking in areas where workers may contact RCFs.
- Provide showering and changing areas free from contamination where workers can store work clothes and change into street clothes before leaving the work site.
- Provide services for laundering work clothes so that workers do not take contaminated clothes home.
- Protect laundry workers handling RCF-contaminated clothes from airborne concentrations that are above the REL.

Workers shall take the following protective measures:

- Do not smoke, eat, or drink in areas potentially contaminated with RCFs.
- If fibers get on the skin, wash with warm water and mild soap.
- Apply skin-moisturizing cream or lotion as needed to avoid irritation caused by frequent washing.
- Wear long-sleeved clothing, gloves, and eye protection when performing potentially dusty activities involving RCFs.
- Vacuum this clothing with a HEPA-filtered vacuum before leaving the work area.
- Do not use compressed air to clean the work area or clothing and do not shake clothing to remove dust. These processes will create a greater respiratory hazard with airborne dust and fibers.
- Do not wear work clothes or protective equipment home. Change into clean clothes before leaving the work site.

1.11 Medical Monitoring

Medical monitoring (in combination with resulting intervention strategies) represents secondary prevention and should not replace primary prevention efforts to control airborne fiber concentrations and worker exposures to RCFs. However, compliance with the REL for RCFs (0.5 f/cm^3) does not guarantee that all workers will be free from the risk of RCF-induced respiratory irritation or respiratory health effects. Therefore, medical monitoring is especially important, and employers shall establish a medical monitoring program as follows:

- Collect baseline data for all employees before they begin work with RCFs.
- Continue periodic medical screening throughout their lifetime.
- Use medical surveillance, which involves the aggregate collection and analysis of medical screening data, to identify occupations, activities, and work processes in need of additional primary prevention efforts.
- Include all workers potentially exposed to RCFs (in both manufacturing and end-use industries) in an occupational medical monitoring program.
- Provide workers with information about the purposes of medical monitoring, the health benefits of the program, and the procedures involved.
- Include the following workers (who could receive the greatest benefits from medical screening) in the medical monitoring program:
  - — Workers exposed to elevated fiber concentrations (e.g., all workers exposed to airborne fiber concentrations above the AL of 0.25 F/cm^3, as described in Section 9.3)
  - — Workers in areas or in specific jobs and activities (regardless of airborne fiber concentration) in which one or more workers have symptoms or respiratory changes apparently related to RCF exposure
  - — Workers who may have been previously exposed to asbestos or other recognized occupational respiratory hazards that place them at an increased risk of respiratory disease

1.11.1 Oversight of the Program

Assign oversight of the medical monitoring program to a qualified physician or other qualified health care provider (as determined by appropriate State laws and regulations) who is informed and knowledgeable about the following:

- Administering and managing a medical monitoring program for occupational hazards
- Establishing a respiratory protection program based on an understanding of requirements of the OSHA respiratory protection standard and types of respiratory protection devices available at the workplace
- Identifying and managing work-related respiratory effects or illnesses
- Identifying and managing work-related skin diseases

1.11.2 Elements of the Medical Monitoring Program

Include the following elements in a medical monitoring program for workers exposed to RCFs: (1) an initial medical examination, (2) periodic medical examinations at regularly scheduled intervals, (3) more frequent and detailed medical examinations as needed on the basis of the findings from these examinations, (4) worker training, (5) written reports of medical findings, (6) quality assurance, and (7) evaluation. These elements are described in the following subsections.

1.11.2.1 Initial (baseline) examination

Perform an initial (baseline) examination as near as possible to the date of beginning employment (within 3 months) and include the following:

- A physical examination of all systems with an emphasis on the respiratory system and the skin
- A spirometric test (note that anyone administering spirometric testing as part of the medical monitoring program should have completed a NIOSH-approved training course in spirometry or other equivalent training)
- A chest X-ray (all chest X-ray films should be interpreted by a certified NIOSH B Reader using the standard *International Classification of Radiographs of Pneumoconioses* [ILO 2000, or the most recent equivalent])
- Other medical tests as deemed appropriate by the responsible health care professional
- A standardized respiratory symptom questionnaire, such as the American Thoracic Society respiratory questionnaire [Ferris 1978, or the most recent equivalent]
- A standardized occupational history questionnaire that gathers information about all past jobs with (1) special emphasis on those with potential exposure to dust and mineral fibers, (2) a description of all duties and potential exposures for each job, and (3) a description of all protective equipment the worker has used

1.11.2.2 Periodic examinations

Administer periodic examinations (including a physical examination of the respiratory system and the skin, spirometric testing, a respiratory symptom update questionnaire, and an occupational history update questionnaire) at regular intervals determined by the medical monitoring program director. Determine the

frequency of the periodic medical examinations according to the following guidelines:

- For workers with fewer than 10 years since first exposure to RCFs, conduct periodic examinations at least once every 5 years.
- For workers with 10 or more years since first exposure to RCFs, conduct periodic examinations at least once every 2 years.

A chest X-ray and spirometric testing are important on initial examination and may also be appropriate medical screening tests during periodic examinations for detecting respiratory system changes, especially in workers with more than 10 years since first exposure to RCFs. A qualified health care provider should consult with the worker to determine whether the benefits of periodic chest X-rays warrant the additional exposure to radiation.

1.11.2.3 More frequent evaluations

Workers may need to undergo more frequent and detailed medical evaluations if the attending physician determines that he or she has any of the following indications:

- New or worsening respiratory symptoms or findings (e.g., chronic cough, difficult breathing, wheezing, reduced lung function, or radiographic indications of pleural plaques or fibrosis)
- History of exposure to other respiratory hazards (e.g., asbestos)
- Recurrent or chronic dermatitis
- Other medically significant reason(s) for more detailed assessment

1.11.2.4 Worker training

Provide workers with sufficient training to recognize symptoms associated with RCF exposures (e.g., chronic cough, difficult breathing, wheezing, skin irritation). Instruct workers to report these symptoms to the designated medical monitoring program director or other qualified health care provider for appropriate diagnosis and treatment.

1.11.2.5 Written reports of medical findings

Following initial and periodic medical examinations, the physician or other qualified health care provider shall give each worker a written report containing

— results of any medical tests performed on the worker,

— a medical opinion in plain language about any medical condition that would increase the worker's risk of impairment from exposure to airborne RCFs,

— recommendations for limiting the worker's exposure to RCFs (which may include the use of appropriate PPE, as warranted), and

— recommendations for further evaluation and treatment of any medical conditions detected.

Following initial and periodic medical examinations, the physician or other qualified health care provider shall also give a written report to the employer containing

— occupationally pertinent results of the medical evaluation,

— a medical opinion about any medical condition that would increase the worker's risk of impairment from exposure to airborne RCFs,

— recommendations for limiting the worker's exposure to RCFs or other

agents in the workplace (which may include the use of appropriate PPE or reassignment to another job), and

— a statement to indicate that the worker has been informed about the results of the medical examination and about any medical condition(s) that should have further evaluation or treatment.

Findings, test results, or diagnoses that have no bearing on the worker's ability to work with RCFs shall not be included in the report to the employer. Safeguards to protect the confidentiality of the worker's medical records shall be enforced in accordance with all applicable regulations and guidelines.

1.11.2.6 Quality assurance

Employers shall do the following to ensure the effective implementation of a medical monitoring program:

- Ensure that workers follow the qualified health care provider's recommended exposure restrictions for RCFs and other workplace hazards.
- Ensure that workers use appropriate PPE if they are exposed to RCF concentrations above the REL.
- Encourage workers to participate in the medical monitoring program and to report any symptoms promptly to the program director.
- Provide any medical evaluations that are part of the medical monitoring program at no cost to the workers.
- When implementing job reassignments recommended by the medical program director, ensure that workers do not lose wages, benefits, or seniority.
- Ensure that the medical monitoring program director communicates regularly with the employer's safety and health personnel (e.g., industrial hygienists) to identify work areas that may require control measures to minimize exposures to workplace hazards.

1.11.2.7 Evaluation

Employers shall evaluate their medical monitoring programs as follows:

- Periodically have standardized medical screening data aggregated and evaluated by an epidemiologist or other knowledgeable person to identify patterns of worker health that may be linked to work activities and practices requiring additional primary preventive efforts.
- Combine routine aggregate assessments of medical screening data with evaluations of exposure monitoring data to identify needed changes in work areas or exposure conditions.

1.12 Labeling and Posting

Employers shall post warning labels and signs as follows:

- Post warning labels and signs describing the health risks associated with RCFs at entrances to work areas and inside work areas where airborne concentrations of RCFs may exceed the REL.
- Depending on work practices and the airborne concentrations of RCFs, state on the signs the need to wear protective clothing and the appropriate respiratory protection for RCF exposures above the REL.

- If respiratory protection is required, post the following statement:

RESPIRATORY PROTECTION REQUIRED IN THIS AREA

- Print all labels and warning signs in both English and the predominant language of workers who do not read English.
- Verbally inform workers about the hazards and instructions printed on the labels and signs if they are unable to read them.

1.13 Smoking Cessation

NIOSH recognizes a synergistic effect between exposure to RCFs and cigarette smoking. This effect increases the risk of adverse respiratory health effects induced by RCFs. In studies of workers exposed to various airborne contaminants, combined exposures to smoking and airborne dust have been shown to contribute to the increased risk of occupational respiratory diseases, including chronic bronchitis, emphysema, and lung cancer [Morgan 1994; Barnhart 1994].

Employers shall encourage smoking cessation among RCF-exposed workers as follows:

- Establish smoking cessation programs to inform workers about the increased hazards of cigarette smoking and exposure to RCFs.
- Provide assistance and encouragement for workers who want to quit smoking.
- Prohibit smoking in the workplace.
- Disseminate information about health promotion and the harmful effects of smoking.
- Offer smoking cessation programs to workers at no cost to participants.
- Encourage activities that promote physical fitness and other healthy lifestyle practices affecting respiratory and cardiovascular health (e.g., through training programs, employee assistance programs, and health education campaigns).

NIOSH recommends that all workers who smoke and are potentially exposed to RCFs participate in smoking cessation programs.

2 Background and Description of RCFs

2.1 Scope

Information about RCFs was collected and reviewed for this document to assess the health hazards associated with occupational exposure to this airborne fiber. Chapter 2 describes the background for studying the health effects of workplace exposures to RCFs. Information is presented about the physical and chemical properties of RCFs, including the morphology, dimensions, and durability of fibers that make up RCF-containing products. Chapter 3 discusses the production and uses of RCFs as a high-temperature insulation material; the chapter also describes the number of workers with potential for exposure to RCFs. Chapter 4 presents a review of the literature on potential workplace exposures to airborne RCFs during manufacturing and end uses of RCF products. Chapter 5 describes the effects of exposure to RCFs—first with reviews of animal studies and then with a description of epidemiologic studies of RCFs, focusing on U.S. and European workers in the RCF manufacturing industry. Recent quantitative risk assessments of RCFs are also summarized in this chapter. Chapter 6 contains a discussion of fiber characteristics and the parameters (dose, dimensions, and durability) that determine fiber toxicity. Chapter 7 summarizes existing standards and guidelines for occupational exposure to RCFs. Chapter 8 provides the basis and rationale for the NIOSH REL. Chapters 1 and 9 provide recommendations and guidelines for minimizing exposures to airborne fibers of RCFs in the workplace. Finally, Chapter 10 discusses future areas for research relating to fiber toxicity and occupational exposures.

2.2 Background

In 1977, NIOSH reviewed health effects data on occupational exposure to fibrous glass and determined the principal adverse health effects to be skin, eye, and upper respiratory tract irritation as well as the potential for nonmalignant respiratory disease. At that time NIOSH recommended the following:

> Occupational exposure to fibrous glass shall be controlled so that no worker is exposed at an airborne concentration greater than 3,000,000 fibers per cubic meter of air (3 fibers per cubic centimeter of air); . . . airborne concentrations determined as total fibrous glass shall be limited to a TWA of 5 milligrams per cubic meter of air [NIOSH 1977].

NIOSH also stated that until more information became available, this recommendation should be applied to other MMMFs, also called SVFs. Since then, additional data have become available from studies in animals and humans exposed to RCFs. The purpose of this report is to review and evaluate these studies and other information about RCFs.

2.3 Chemical and Physical Properties of RCFs

RCFs (Chemical Abstracts Service No. 142844–00–6) are amorphous fibers that belong to the

larger class of SVFs, which also includes fibers of glass wool, mineral wool, slag wool, and specialty glass. SVFs vary according to chemical and physical properties, making them suitable for different uses. Like the naturally occurring mineral fibers defined in Section 1.2, RCFs possess desired qualities of heat resistance, tensile strength, durability, and light weight. The maximum end-use temperature for RCFs ranges from approximately 1,050 to 1,425 °C (1,920 to 2,600 °F), depending on the exact chemistry of the fiber. Unlike naturally occurring mineral fibers, however, SVFs such as RCFs and fibrous glass are noncrystalline in structure and fracture transversely, retaining the same diameter but creating shorter fibers. In contrast, the crystalline structure of mineral fibers such as asbestos causes the fibers to fracture along the longitudinal plane under mechanical stresses, resulting in more fibers with the same length but smaller diameters. These differences in morphology and cleavage patterns suggest that work with SVFs is less likely to generate high concentrations of airborne fibers than work with asbestos for comparable operations, since large-diameter fibers settle out in the air faster than small-diameter fibers [Assuncao and Corn 1975; Cherrie et al. 1986; Lippmann 1990]. During the manufacturing of RCFs, approximately 50% of product (by weight) is generated as fiber, and 50% is a byproduct made up of nonfibrous particulate material called *shot*. Selected physical characteristics of RCFs are presented in Table 2–1.

RCFs are produced by the blowing or spinning of furnace-melted siliceous kaolin ($Al_2Si_2O_5[OH]_4$) clay or blends of kaolin, silica, and zircon. RCFs are also referred to as alumina-based or kaolin-based ceramic fibers because they are produced from a 50:50 mixture of alumina and silica [IARC 1988]. Other oxides (including those of boron, titanium, and zirconium) are added as stabilizers to alter the physical properties of RCFs [RCFC 1996]. The addition of stabilizers and binders alters the properties of durability and heat resistance for RCFs. Generally, three types of RCFs are manufactured, and a fourth *after-service* fiber (often recognized in the literature) is distinguished according to its unique chemistry and morphology. Table 2–2 presents the chemistries of the four fiber types, numbered RCF1 through RCF4. RCF1 is a kaolin fiber; RCF2 is an alumina/silica/zirconia fiber; RCF3 is a high-purity (alumina/silica) fiber; and RCF4 is an *after-service* fiber, characterized by devitrification (i.e., formation of the silica polymorph cristobalite), which occurs during product use over an extended period of time at temperatures exceeding 1,050 to 1,100 °C (>1,900 °F). Another fiber subcategory is RCF1a, prepared from commercial RCFs using a less aggressive method than that used to prepare RCF1 for animal inhalation studies [Brown et al. 2000]. RCF1a is distinguished from RCF1 used in chronic animal inhalation studies, the former having a greater concentration of longer fibers and fewer nonfibrous particles. The lower ratio of respirable nonfibrous particles to fibers in RCF1a compared with RCF1 has been shown to affect lung deposition and clearance in animal inhalation studies [Brown et al. 2000; Bellman et al. 2001]. Chapter 5 presents additional discussion of animal studies and test fiber characteristics.

2.3.1 Fiber Dimensions

Fibers of biological importance are those that become airborne and have dimensions within inhalable, thoracic, and respirable size ranges. Thoracic-sized fibers (<3 to 3.5 μm in diameter) and respirable-sized fibers (<1.3 μm in diameter) with lengths up to 200 μm [Timbrell 1982; Lippmann 1990; Baron 1996] are capable of reaching the portion of the respiratory system below the larynx. Respirable-sized fibers are of biological concern because

Table 2–1. Selected physical characteristics of RCFs

Characteristic	Description
Softening point	1,700 to 1,800 °C
Refractive index	1.55 to 1.57
Specific gravity (density)	2.6 to 2.7 g/cm^3
Shot content (nonfibrous particulate)	20% to 50% by weight
Nominal diameter (bulk)	1.2 to 3 μm
Length (bulk)	2 to 254 μm
Dissolution rate (at pH=7.4)	1 to 10 ng/cm^2/hr

Sources: RCFC [1996], TIMA [1993], and IARC [1988].

Table 2–2. The chemistry of stock RCFs (% oxide)

Oxide component	RCF1	RCF2	RCF3	RCF4
Silicon dioxide (SiO_2)	47.7	50	50.8	47.7
Alumina (Al_2O_3)	48	35	48.5	48
Ferric oxide (Fe_2O_3)	0.97	<0.05	0.16	0.97
Titanium dioxide (TiO_2)	2.05	0.04	0.02	2.05
Zirconium dioxide (ZrO_2)	0.11	15	0.23	0.11
Calcium oxide (CaO)	0.07	0.05	0.04	0.07
Magnesium oxide (MgO)	0.98	0.01	<0.01	0.08
Sodium oxide (Na_2O)	0.54	<0.3	0.19	0.54
Potassium oxide (K_2O)	0.16	<0.01	<0.01	0.16

Adapted from Mast et al. [1995a].

they are capable of reaching the lower airways and gas exchange regions of the lungs when inhaled. Longer or thicker airborne fibers generally settle out of suspension or, if inhaled, are generally filtered out in the nasal passage or deposited in the upper airways. Thoracic-sized fibers that are inhaled and deposited in the upper respiratory tract are generally cleared more readily from the lung, but they have the potential to cause irritation and produce respiratory symptoms. Fiber dimensions are a significant factor in determining their deposition within the lung, biopersistence, and toxicity.

RCFs and other SVFs are manufactured to meet specified nominal diameters according to the fiber type and intended use. RCFs are produced with nominal diameters of 1.2 to 3 μm [Esmen et al. 1979; Vu 1988; TIMA 1993]. Typical diameters for an individual RCF (as measured in

RCF-containing products) range from 0.1 to 20 μm, with lengths ranging from 5 to 200 μm [IARC 1988]. In bulk samples taken from three RCF blanket insulation products, more than 80% of the fibers counted by phase contrast optical microscopy (PCM) were <3 μm in diameter [Brown 1992]. This result is consistent with those from another study of bulk samples of RCF insulation materials [Christensen et al. 1993], which found the fibers to have geometric mean diameters (GM_D) ranging from 1.5 to 2.8 μm (arithmetic mean [AM] diameter range=2.3 to 3.9 μm; median diameter range=1.6 to 3.3 μm).

Studies of airborne fiber size distributions in RCF manufacturing operations indicate that these fibers meet the criteria for thoracic- and respirable-sized fibers. One early study of three domestic RCF production facilities found that approximately 90% of airborne fibers were <3 μm in diameter, and 95% of airborne fibers were <4 μm in diameter and <50 μm long [Esmen et al. 1979]. The study showed that diameter and length distributions of airborne fibers in the facilities were consistent, with a GM_D of 0.7 μm and a geometric mean length (GM_L) of 13 μm. Another study [Lentz et al. 1999] used these data in combination with monitoring data from two additional studies [MacKinnon et al. 2001; Maxim et al. 1997] at RCF manufacturing plants to review characteristics of fibers sized from 118 air samples covering 20 years (1976–1996). Fibers with diameters <1 μm (n=3,711) were measured by transmission electron microscopy (TEM). Of these, 52% had diameters <0.4 μm, 75% had diameters<0.6 μm, and 89% had diameters <0.8 μm. Fiber lengths ranged from <0.6 to >20 μm, with 68% of fibers measuring 2.4 to 20 μm long and 19% of the fibers >20 μm long. On the basis of the results of TEM analysis of 3,357 RCFs observed on 98 air samples collected in RCF manufacturing sites, Allshouse [1995] reported that 99.7% of the fibers had diameters <3 μm and 64% had lengths >10 μm. Measurements of airborne fibers in the European RCF manufacturing industry are comparable: Rood [1988] reported that all fibers observed were in the thoracic and respirable size range (i.e., diameter <3 to 3.5 μm), with median diameters ranging from 0.5 to 1.0 μm and median lengths from 8 to 23 μm.

Cheng et al. [1992] analyzed an air sample for fibers during removal of after-service RCF blanket insulation from a refinery furnace. Fiber diameters ranged from 0.5 to 6 μm, with a median diameter of 1.6 μm. The length of fibers ranged from 5 to 220 μm. Of 100 fibers randomly selected and analyzed from the air sample, 87% were within the thoracic and respirable size range. Another study of exposures to airborne fibers in industrial furnaces during installation and removal of RCF materials found GM_D values of 0.38 and 0.57 μm, respectively [Perrault et al. 1992].

2.3.2 Fiber Durability

Fiber durability can affect the biologic activity of fibers inhaled and deposited in the respiratory system. Durable fibers are more biopersistent, thereby increasing the potential for causing a biological effect. Durability of a fiber is measured by the amount of time it takes for the fiber to fragment mechanically into shorter fibers or dissolve in biological fluids. RCFs tested in vitro with a solution of neutral pH (modified Gamble's solution) had a dissolution rate of 1 to 10 ng/cm^2 per hr [Leineweber 1984]. This test is biologically relevant because of the similarity of the solution to the conditions of the pulmonary interstitial fluid. By comparison, other SVFs (glass and slag wools) are more soluble, with dissolution rates in the 100s of ng/cm^2 per hr [Scholze and Conradt 1987]. Along a continuum of fiber durability

determined in tests using simulated lung fluids at pH 7.4, the asbestos fiber crocidolite has a dissolution rate of <1 ng/cm^2 per hr, RCF1 and MMVF32 (E glass) have dissolution rates of 1 to 10 ng/cm^2 per hr, MMVF21 has a dissolution rate of 15 to 25 ng/cm^2 per hr, other fibrous glass and slag wools have dissolution rates in the range of 50 to 400 ng/cm^2 per hr, and the alkaline earth silicate wools have dissolution rates ranging from approximately 60 to 1,000 ng/cm^2 per hr [Christensen et al. 1994; Maxim et al. 1999b; Moore et al. 2001]. Chrysotile, which is considered the most soluble form of asbestos, has a dissolution rate of <1 to 2 ng/cm^2 per hr.

RCFs dissolve more rapidly than chrysotile, even though RCFs have a thicker diameter (by an order of magnitude) than chrysotile. The rate of dissolution is an important fiber characteristic that affects the clearance time and biopersistence of the fiber in the lung. The significance of fiber dimension, clearance, and dissolution (i.e., breakage, solubility) is discussed in Chapter 6.

3 RCF Production and Potential for Worker Exposure

3.1 Production

RCF production in the United States began in 1942 on an experimental basis, but RCFs were not commercially available until 1953. Sales of RCFs were modest initially, but they began to expand when the material gained acceptance as an economical alternative insulation for high-temperature kilns and furnaces. Commercial production of RCFs first reached significant levels in the 1970s as oil shortages necessitated reductions in energy consumption. The growing demand for RCFs has also been strongly influenced by the recognition of health effects associated with exposure to asbestos-containing materials and the increasingly stringent regulation of these products in the United States and many other countries.

Annual domestic production of RCFs was an estimated 85.7 million lb in 1990; in 1997, production of RCFs in the United States totaled 107.7 million lb annually [RCFC 1998]. Currently, total U.S. production is estimated to be 80 million lb per year, representing about 1% to 2% of the worldwide production of SVFs [RCFC 2004]. RCFs are also produced in Mexico, Canada, Brazil, Venezuela, South Africa, Australia, Japan, China, Korea, Malaysia, Taiwan, and several countries in Europe [RCFC 1996]. In the United States and Puerto Rico, the primary producers of RCFs include A.P. Green Industries (Pryor, OK), Unifrax Corporation (Niagara Falls, NY, formerly Carborundum), Thermal Ceramics (Augusta, GA), and Vesuvius (King of Prussia, PA, formerly Premier Refractories and Chemicals). The latter three producers account for an estimated 90% of domestic production and are members of the RCFC, which has been active in monitoring exposures, developing product stewardship programs, and funding research to study RCF hazards and safe work practices for RCF manufacturing and use.

3.2 Potential for Worker Exposure

Approximately 31,500 workers in the United States are potentially exposed to RCFs during manufacturing, processing, or end use. A similar number of workers are potentially exposed to RCFs in Europe. Of these workers, about 800 (3%) are employed in the actual manufacturing of RCFs and RCF products [Maxim et al. 1997; RCFC 2004].

3.3 RCF Manufacturing Process

The manufacture of RCFs (Figure 3–1) begins by blending raw materials, which may include kaolin clay, alumina, silica, and zirconia in a batch house. The batch mix is then transferred either manually or automatically to a furnace to be melted at temperatures exceeding 1,600 °C. On reaching a specified temperature and viscosity in the furnace, the molten

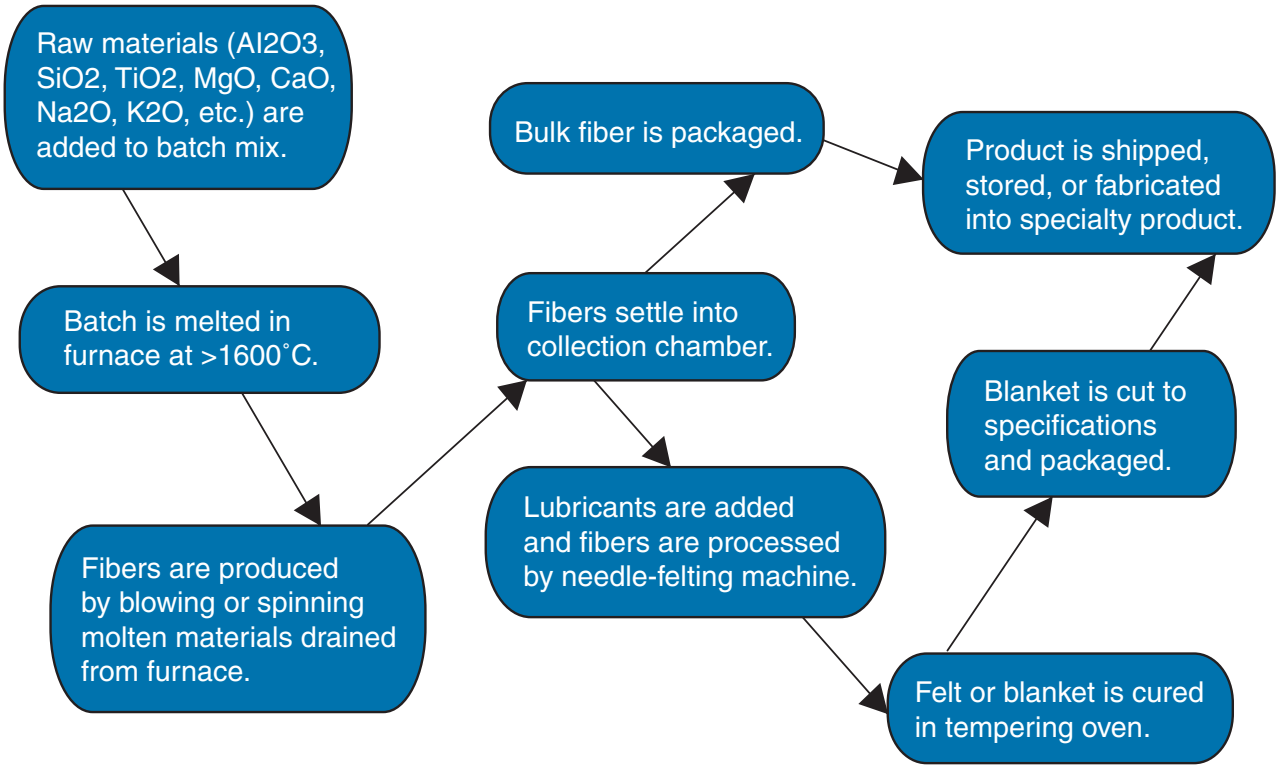

Figure 3–1. Process flow chart for RCF production.

batch mixture drains from the furnace and is fiberized, either through exposure to pressurized air or by flowing through a series of spinning wheels [Hill 1983]. Fans are used to create a partial vacuum that pulls the fibers into a collection or settling chamber. RCFs may then be conveyed pneumatically to a bagging area for packaging as bulk fiber. Some bulk fiber may be used directly in this form, or it may be processed to form textiles, felts, boards, cements, and other specialty items. Other RCFs are formed into blankets as bulk fiber in the collection chamber settles onto a conveyor belt. The blanket passes through a needle felting machine that interlocks the fibers and compresses the blanket to a specified thickness. From the needler, the blanket is conveyed to a tempering oven to remove lubricants that were added in the settling chamber. The lubricants are burned off, and the blanket is cut to desired size and packaged. As with the bulk fiber, the RCF blanket may undergo additional fabrication to create other specialty products. Many of the processes are automated and are monitored by machine operators. Postproduction processes such as cutting, sanding, packaging, handling, and shipping are more labor intensive, but the potential exists for exposure to airborne fibers throughout production.

3.4 RCF Products and Uses

RCFs may be used in bulk fiber form or as one of the RCF specialty products in the form of mats, paper, textiles, felts, and boards [RCFC 1996]. Because of its ability to withstand temperatures exceeding 1,000 °C, RCFs are used predominantly in industrial applications, including insulation, reinforcement, and thermal protection for furnaces and kilns. RCFs can also be found in automobile catalytic converters, in consumer products that operate at high temperatures (e.g., toasters, ovens, woodstoves), and in space shuttle tiles. RCFs have been formed into noise-control blankets [Thornton et al. 1984] and used as a replacement for refractory bricks in industrial kilns and furnaces [RCFC 1996]. RCFs have found increasing application as reinforcements in specialized metal matrix composites (MMC), especially in the automotive and aerospace industries [Stacey 1988]. A summary of RCF products and applications are provided here.

3.4.1 Examples of Products

- **Blankets**—high-temperature insulation produced from spun RCFs in the form of a mat or blanket
- **Boards**—high-temperature insulation produced from bulk fibers in the form of a compressed rigid board (boards have a higher density than blankets and are used as core material or in sandwich assemblies)
- **Bulk RCFs**—fibers with qualities of high-temperature resistance to be used as feedstock in manufacturing processes or other applications for which product consistency is critical—typically in the manufacture of other ceramic-fiber-based products
- **Ropes and braids**—high-temperature insulation produced by textile operations and used for packing, seals, and wicking applications
- **Woven textiles**—high-temperature insulation produced by textile processes in the form of cloth, tape, or sleeves
- **Papers and felts**—flexible high-temperature insulation produced by papermaking processes and used for seals, gaskets, and other automotive and aerospace applications

- **Vacuum cast shapes**—high-temperature insulation produced by forming specialized shapes on prefabricated molds with wet fibers and then drying them by vacuum and heat, thereby transforming bulk fiber into rigid, shaped products
- **Specialties**—forms (i.e., mixes, cements, and caulking compounds) that contain wet, inorganic binder and are used as protective coating putties as well as adhesives and heat and fire barriers in high-temperature applications
- **Modules**—packaged functional assembly of blanket insulation with hardware for attaching to the surfaces of furnaces and kilns

3.4.2 Examples of Applications

- Insulation linings of high-temperature industrial furnaces and related equipment
- Hot spot repair of industrial furnace linings
- Industrial furnace curtains, gaskets, and seals
- Insulation of pipes, ducts, and cables associated with high-temperature industrial furnaces
- Fire protection for industrial process equipment
- Aircraft and aerospace heat shields
- Commercial and consumer appliances consisting of prefabricated chimneys, pizza ovens, self-cleaning ovens, and wood-burning stoves
- Automobile applications consisting of brake pads, clutch facings, catalytic converters, air bags, shoulder belt controls, and passenger compartment heat shields

4 Assessing Occupational Exposure

4.1 Air Sampling and Analytical Methods

The conventional method used to assess the characteristics and concentrations of exposures to airborne fibers is to collect personal and environmental (area) air samples for laboratory analysis.

Personal samples are the preferred method for estimating the exposure characteristics of a worker performing specific tasks. For personal sampling, a worker is equipped with the air sampling equipment, and the collection medium is positioned within the worker's breathing zone. Area sampling is performed to evaluate exposure characteristics associated with an area or process. Sampling equipment for area sampling is stationary, in contrast to personal sampling, which allows for mobility by accompanying the worker throughout the sampling period.

4.2 Sampling for Airborne Fibers

The two NIOSH methods for the sampling and analysis of airborne fibers of asbestos and other fibrous materials are as follows:

- Method 7400 describes air sampling and analysis by PCM
- Method 7402 describes air sampling and analysis by TEM

Both methods (listed in the *NIOSH Manual of Analytical Methods* [NIOSH 1998] and provided in Appendix A) involve using an air sampling pump connected to a cassette. The cassette consists of a conductive cowl equipped with a 25-mm cellulose ester membrane filter (0.45- to 1.2-µm pore size). The pump is used to draw air through the sampling cassette at a constant flow rate between 0.5 and 16 L/min. Airborne fibers and other particulates are trapped on the filter for analysis using microscopic methods. Methods 7400 and 7402 can be used to count the number of fibers (and therefore calculate concentration based on the volume of air sampled) and measure the fiber dimensions. Fiber concentration is reported as the number of fibers per cubic centimeter of air (f/cm^3). Although the two methods differ in preparation of the sampling media for analysis, the major distinction between them is the resolving capabilities of the microscope. With PCM, 0.25 µm is approximately the diameter of the thinnest fibers that can be observed [Dement and Wallingford 1990]. TEM has a lower resolution limit well below the diameter of the smallest RCF (~0.02 to 0.05 µm) [Middleton 1982]. TEM also allows for qualitative analysis of fibers using an energy-dispersive X-ray analyzer (EDXA) to determine elemental composition and selected area electron diffraction (SAED) for comparing diffraction patterns with reference patterns for identification.

4.2.1 NIOSH Fiber-Counting Rules

The appendix to NIOSH Method 7400 specifies two sets of fiber-counting rules that vary

according to the parameters used to define a fiber. Under the *A* rules, any particle >5 µm long with an aspect ratio (length to width) >3:1 is considered a fiber. No upper limit exists on the fiber diameter in the *A* counting rules. In the *B* rules, a fiber is defined as being >5 µm long with an aspect ratio ≥5:1 and a diameter <3 µm. The upper-diameter limit in the *B* rules restricts the measurement to thoracic and respirable fibers. It is important to note which set of fiber-counting criteria is used when reporting analytical results. NIOSH recommends using Method 7400 with the *B* rules for evaluating exposures to airborne RCFs. NIOSH Method 7402 specifies use of the *A* rules, with a lower-diameter limit of 0.25 µm to allow comparison with results obtained from NIOSH Method 7400. Method 7402 can also be used to compare fiber counts obtained from Method 7400 (*B* rules). TEM permits the identification and counting of fibers <0.25 µm in diameter; 0.25 µm is the approximate resolution limit for PCM.

4.2.2 European Fiber-Counting Rules

In Europe, a slightly different fiber-counting convention is used. The World Health Organization (WHO) reference method for MMMFs [WHO/EURO Technical Committee for Monitoring and Evaluating Airborne MMMF 1985] recognizes a fiber as >5 µm long with a diameter <3 µm and an aspect ratio ≥3:1. Several studies comparing fiber counts determined with different counting conventions have found good agreement in air sampling for RCF exposures. Buchta et al. [1998] compared fiber counts of air samples for RCF exposures as analyzed using the NIOSH *A* and *B* rules; both methods produced similar results, with no statistically significant difference in fiber density measurements on sample filters. Maxim et al. [1997] found that fiber counts made using NIOSH Method 7400 *B* rules are equal to approximately 95% of the counts determined using the WHO reference method. In studies with other SVFs, Lees et al. [1993] also found that fiber exposure estimates were slightly higher using the *A* rules but were comparable to the values obtained using *B* rules. Breysse et al. [1999] reported a similar finding when comparing RCF fiber counts determined by both *A* and *B* rules: the ratio of *A* to *B* counts was 1.33. These results suggest that for airborne RCF exposures, most fibers with a >3:1 aspect ratio also meet the ≥5:1 aspect ratio criterion and are <3 µm in diameter.

4.3 Sampling for Total or Respirable Airborne Particulates

Airborne exposures generated during work with RCFs may also be estimated by sampling for general dust concentrations. Sampling for particulates not otherwise regulated is described in NIOSH Method 0500 for total dust concentrations and in NIOSH Method 0600 for the respirable fraction [NIOSH 1998]. Both methods (also included in Appendix A) use a sampling pump to pull air through a filter that traps suspended particulates. NIOSH Method 0600 uses a size-selective sampling apparatus (cyclone) to separate the respirable fraction of airborne material from the nonrespirable fraction. The mass of airborne particulates on the filter is measured using gravimetric analysis, and airborne concentration is determined as the ratio of the particulate mass to the volume of air sampled, reported as mg/m^3 (or $\mu g/m^3$). This method does not distinguish fibers from nonfibrous airborne particles. No NIOSH REL exists for either total or respirable particulates not otherwise regulated. The OSHA permissible exposure limit (PEL) for particulates not otherwise regulated is 15 mg/m^3 for total particulates and 5 mg/m^3 for respirable particulates

as 8-hr TWA concentrations. The American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) for particles (insoluble or poorly soluble) not otherwise specified is 10 mg/m^3 for inhalable particles and 3 mg/m^3 for respirable particles as 8-hr TWA concentrations [ACGIH 2005].

4.4 Sampling for Airborne Silica

Because silica is a major constituent of RCFs, the potential exists for exposure to silica during work with RCFs (e.g., in manufacturing or during removal of after-service RCF furnace insulation). As with sampling for respirable particulates, sampling for respirable silica involves using a pump to draw air through a cyclone before collecting respirable airborne particles on a filter. Qualitative and quantitative analysis of the sample for silica content can be performed using the following analytical methods:

- X-ray powder diffraction (NIOSH Method 7500)
- Visible absorption spectrophotometry (NIOSH Method 7601)
- Infrared absorption spectrophotometry (NIOSH Method 7602)

The NIOSH REL for respirable crystalline silica is 0.05 mg/m^3 as a TWA for up to 10 hr/day during a 40-hr workweek [NIOSH 1974]. The ACGIH TLV for crystalline silica is 0.05 mg/m^3 as an 8-hr TWA [ACGIH 2005].

4.5 Industrial Hygiene Surveys and Exposure Assessments

Assessments of occupational exposures, including quantitative measurement of airborne fiber concentrations associated with manufacturing, handling, and using RCFs, have been performed using industrial hygiene surveys and air sampling techniques at multiple worksites. Sources of monitoring data that characterize occupational exposures to RCFs include the following:

- University of Pittsburgh studies of exposures at RCF manufacturing sites in the 1970s [Corn and Esmen 1979; Esmen et al. 1979]
- An ongoing University of Cincinnati epidemiologic study with exposure assessments that use historical monitoring data and current monitoring strategies [Rice et al. 1994, 1996, 1997]
- A 5-year consent agreement between the RCFC and the U.S. Environmental Protection Agency (EPA) to monitor worker exposures in RCF manufacturing plants and in secondary users of RCFs and RCF products [RCFC 1993; Everest 1998; Maxim et al. 1994, 1997, 2000a]
- Studies of exposure to airborne fibers during the installation and removal of RCF insulation in industrial furnaces [Gantner 1986; Cheng et al. 1992; van den Bergen et al. 1994; Sweeney and Gilgrist 1998; Maxim et al. 1999b]
- International (Canadian, Swedish, Australian) industrial hygiene surveys of occupational exposures to RCFs [Perrault et al. 1992; Krantz et al. 1994; Rogers et al. 1997]
- A study of end-user exposures to RCF insulation products by researchers at Johns Hopkins University [Corn et al. 1992]
- NIOSH Health Hazard Evaluations (HHEs) of occupational exposures to RCFs

4.5.1 University of Pittsburgh Survey of Exposures During RCF Manufacturing

In the mid 1970s, researchers from the University of Pittsburgh conducted environmental monitoring to assess worker exposures to airborne fibers at domestic RCF manufacturing facilities. This research effort was one of the pioneering studies in the use of workplace exposure groupings or *dust zones* for establishing a sampling strategy [Corn and Esmen 1979]. In a series of industrial hygiene surveys, Esmen et al. [1979] collected 215 full-shift air samples at three RCF manufacturing plants. Table 4–1 summarizes the sampling data for the three facilities (A, B, and C) by fiber concentration of total airborne dust. Although a wide range of values for individual samples existed (<0.01 to 16 f/cm^3), average (AM) concentrations ranged from 0.05 to 2.6 f/cm^3. The highest exposure concentrations were measured in manufacturing and finishing operations during which sanding, cutting, sawing, and drilling operations were performed and ventilation was lacking. A large number of these operations were noted in plant A, which is reflected by the elevated fiber and dust concentrations for this plant. When data were compared for similar operations and dust zones, exposure concentrations were consistent across plants. Analyses of air samples also included measurement of fiber dimensions. Approximately 95% of the airborne fibers measured were <4.0 µm in diameter and <50 µm long with a GM_D of 0.7 µm and a GM_L of 13 µm.

4.5.2 University of Cincinnati Study of Exposures During RCF Manufacturing

In 1987, researchers from the University of Cincinnati initiated an industry-wide epidemiologic study of workers who manufacture RCFs. One aim of the study was to characterize current and former exposures to RCFs and silica in U.S. RCF manufacturing facilities. Data from initial surveys conducted at five RCF manufacturing plants indicated airborne RCFs with a GM_D ranging from 0.25 to 0.6 µm and a GM_L ranging from 3.8 to 11.0 µm [Lockey et al. 1990]. The airborne TWA fiber concentrations for these five plants ranged from <0.01 to 1.57 f/cm^3. After the first two rounds of quarterly sampling, Rice et al. [1994] had collected data from 484 fiber count samples (382 samples with values greater than the analytic limit of detection [LOD], 39 overloaded samples, 36 samples with values below the LOD, and 27 samples voided because of tampering or pump failure). They also collected 35 samples from persons working with raw materials that were analyzed quantitatively and qualitatively for respirable mass and for silica polymorphs (quartz, tridymite, and cristobalite). A sampling strategy was developed by identifying more than 100 job

Table 4–1. Industrial hygiene survey data for three RCF* manufacturing plants†

Plant	No. samples	AM total airborne dust		AM fiber concentration	
		mg/m^3	Range	f/cm^3	Range
A	76	6.05	0.37–100.00	2.6	0.02–16.0
B	67	1.6	0.19–9.73	0.63	0.04–6.7
C	72	0.85	0.05–2.34	0.05	<0.01–0.29

Source: Esmen et al. [1997].

*Abbreviations: AM=arithmetic mean; RCF=refractory ceramic fiber.

†Fibers were defined as having an aspect ratio >3:1. Transmission electron microscopy was used to measure fibers ≤1 µm in diameter.

functions across 5 facilities. These job functions were consolidated into industry job titles based on similarities of function, proximity to certain processes, and exposure characteristics within designated dust zones. Table 4–2 presents median TWA exposures to airborne concentrations of RCFs by job title at plants sampled in 1987. TWA fiber concentrations ranged from below the analytical LOD to 1.04 f/cm^3 for workers in 20 different industry job titles. Fiber concentrations obtained by rinsing the walls of the sampling cowl, where a significant number of fibers accumulated during sampling [Cornett et al. 1989; Breysse et al. 1990], ranged from below the analytical LOD to 1.54 f/cm^3. Of the 35 samples analyzed for the silica polymorphs, quantifiable silica was found in 5 samples: 4 of the samples contained cristobalite in concentrations ranging from 20 to 78 µg/m^3, and 1 of the samples contained 70 µg/m^3 quartz. The measurable silica exposures occurred among workers employed as raw material handlers and furnace operators.

As the study progressed, approximately 1,820 work history interviews were conducted and evaluated to refine uniform job titles and to identify dust zones according to the method of Corn and Esmen [1979]. Four years of sampling data (1987–1991) were merged with historic sampling data to construct exposure estimates for 81 job titles in 7 facilities for specified time periods [Rice et al. 1997]. Overall exposures decreased. The maximum exposure estimated was 10 f/cm^3 in the 1950s for carding in a textile operation; subsequent changes in engineering, process, and ventilation reduced exposure estimates for all 20 job titles to near or below 1 f/cm^3 [Rice et al. 1996, 1997]. The study reported that at more recent operations (1987–1991), exposure estimates ranged from below the analytic LOD to 0.66 f/cm^3.

Subsequently, Rice et al. [2005] published the results from an analysis of exposure estimates for 10 years of follow-up sampling (1991–2001) at 5 of 7 facilities (2 facilities had closed before 1991). The researchers found the following estimates for 122 job titles still active in 2001:

Number and % of job titles	*Exposure estimate (f/cm^3)*
97 (79%)	≤0.25
17 (14%)	>0.25 to 0.5
8 (7%)	>0.5

The study shows that exposures decreased for 25% of job titles, remained stable for 53%, and increased for 22%. Of the job titles with increased exposure estimates, 9 estimates were >0.1 f/cm^3 (range = 0.1 to 0.21 f/cm^3), and 19 estimates were <0.1 f/cm^3. The exposure estimates for this study do not include adjustments for respirator use.

4.5.3 RCFC/EPA Consent Agreement Monitoring Data

In 1993, the RCFC and the EPA entered into a negotiated 5-year consent agreement to determine the magnitude of RCF exposures in the primary RCF manufacturing industry and in secondary RCF-use industries [RCFC 1993; Maxim et al. 1994, 1997; Everest 1998]. Another purpose of this consent agreement was to document changes in RCF exposures during the 5 years of the agreement (1993–1998). The Quality Assurance Project Plan in the consent agreement contains the analytical protocols, statistical design, description of the program objectives, and timetables for meeting the objectives [RCFC 1993].

During each year of the consent agreement, a minimum of 720 personal air samples (measured as 8-hr TWAs) were collected according to a stratified random sampling plan. Of these, 320 samples were collected in RCF manufacturing and processing (primary) facilities. The remaining 400 samples were collected in RCF

Table 4–2. Median TWA exposures to airborne concentrations of RCFs[*] by industry job title at plants sampled in 1987[†]

Industry job title	Plant 1			Plant 2			Plant 3			Plant 4			Plant 5		
	No. samples	Median TWA f/cm³	SD	No. samples	Median TWA f/cm³	SD	No. samples	Median TWA f/cm³	SD	No. samples	Median TWA f/cm³	SD	No. samples	Median TWA f/cm³	SD
Blanket line	6	0.03	0.01	21	0.15	0.06	2	0.01	0.01	2	0.02	0.01	9	1.04	0.28
Engineer (nonproduction)	—	—	—	—	—	—	1	0.02		—	—	—	—	—	—
Fabrication (dry)	—	—	—	3	0.14	0.05	4	0.51	0.26	3	0.03	0.18	16	0.61	0.07
Fabrication (wet)	—	—	—	—	—	—	8	0.01	0.02	—	—	—	—	—	—
Fabrication (wet/dry)	12	0.05	0.02	—	—	—	3	0.13	0.04	—	—	—	—	—	—
Fore[‡] (furnace)	5	0.01	0	—	—	—	1	—	0.05	—	—	—	1	—	0.47
Fore (nonfurnace)	3	0.01	0.01	1	—	0.94	—	—	—	—	—	—	3	0.31	0.12
Furnace	5	0.03	0.06	—	—	—	3	0.04	0.03	—	—	—	4	0.41	0.41
Maintenance	7	0.02	0.01	6	0.11	0.03	5	0.08	0.05	3	0.02	0.01	2	0.62	0
Needler	—	—	—	—	—	—	3	0.04	0.01	3	0.02	0.01	1	—	0.25
Office	—	—	—	1	—	0.03	—	—	—	—	—	—	—	—	—
Office plant	—	—	—	1	—	0.04	—	—	—	—	—	—	—	—	—
Plant cleanup	1	—	0.19	—	—	—	—	—	—	—	—	—	—	—	—
Quality control	—	—	—	—	—	—	2	0.16	0.01	—	—	—	—	—	—
Research and development	—	—	—	4	0.13	0.03	—	—	—	—	—	—	—	—	—
Raw materials	—	—	—	—	—	—	—	—	—	1	—	0.02	—	—	—
Ship	6	0.02	0.03	3	0.06	0.02	2	0.25	0.14	1	—	0.01	—	—	—
Supervisor	—	—	—	1	—	0.04	1	—	0.1	—	—	—	—	—	—
Textiles	—	—	—	3	0.16	0.04	—	—	—	—	—	—	—	—	—
Utility	5	0.02	0.01	—	—	—	1	—	0.06	2	0.03	0.01	2	0.56	0.1

Source: Rice et al. [1994].

[*]Abbreviations: RCF=refractory ceramic fiber; SD=standard deviation; TWA=time-weighted average.

[†]Fibers were defined as having an aspect ratio of ≥5:1 and length >0.5 μm if sized using transmission electron micoscopy. For scanning electron microscopy, fibers were defined with the same aspect ratio and length >5 μm.

[‡]Fore is the area of the plant before the furnace.

customer facilities referred to as end-use (secondary) facilities. The researchers collected a total of 4,576 samples. A number of end-use facilities were randomly selected from a list of known purchasers of RCF products. The remainder consisted of facilities that volunteered for sampling once they learned of the consent agreement. The strata from which the 720 samples were collected consist of eight functional job categories derived so that results could be aggregated for comparison across industries, facilities, and similar job functions [RCFC 1993]. This categorization was based on the approach instituted by Corn and Esmen [1979]. Appendix B lists definitions and major work tasks for each functional job category. TWA and task-length average air sampling data were gathered according to NIOSH Method 7400 (*B* rules) and analyzed using PCM and TEM. Data on respirator use (by type) were also collected [Maxim et al. 1998].

As background for the consent agreement monitoring plan, baseline (now referred to as historical) information about airborne fiber concentrations was obtained through personal sampling of workers at RCF manufacturing facilities from January 1989 to May 1993. Exposure monitoring strategies used during the baseline period (1989–1993) provided the framework for the consent agreement (1993–1998) monitoring protocol. Table 4–3 presents AM and geometric mean (GM) concentrations of RCF exposures determined from historical data (1989–1993) by functional job category. Table 4–4 contains these summary statistics for all 5 years of RCF consent agreement monitoring data. Table 4–5 summarizes data from samples collected during the 5th year of the consent agreement only (June 1997 to May 1998). Table 4–6 presents the average airborne fiber concentrations for the baseline (1989–1993) and consent agreement monitoring (1993–1998) periods by manufacturing and end-use sectors.

A comparison of values from Tables 4–4, 4–5, and 4–6 with those in Table 4–3 indicates that average airborne concentrations for 1993–1998 were lower than those for the preceding baseline sampling period (1989–1993). However, a comparison of values in Tables 4–5 and 4–6 shows that average concentrations for the entire 5-year consent agreement monitoring period (1993–1998) are equal to those of year 5 (i.e., no change).

After the first 3 years (1993–1996) of the consent agreement monitoring period, Maxim et al. [1997] performed interim analyses of these data combined with historical data from the baseline monitoring period (1989–1993). The following conclusions about RCF exposures were based on these analyses of data from 1,600 baseline samples and 3,200 consent agreement samples:

- Airborne concentrations of RCFs are generally decreasing in the workplace.
- Ninety percent of airborne concentrations of RCFs in the workplace are below 1 f/cm^3.
- RCF concentrations have an approximately log-normal distribution.
- Significant differences exist in workplace concentrations by facility.
- Workplace concentrations vary with functional job category.
- Respirator usage varies with the worker's functional job category and the associated average fiber concentration.
- Workplace samples have a lower ratio of respirable nonfibrous particles to fibers than samples used in initial animal inhalation studies [Mast et al. 1995a,b; McConnell et al. 1995].

Functional job categories with the highest average TWA fiber concentrations include removal (AM=1.2 f/cm^3), finishing (AM=0.8 f/cm^3), and

Table 4–3. TWA* concentrations of airborne RCFs in personal samples collected during the baseline sampling period (1989–1993),† by functional job category

	Manufacturing (primary production)					End use (secondary processing)				
		AM		GM			AM		GM	
Functional job category	No. samples	f/cm³	SD	f/cm³	GSD	No. samples	f/cm³	SD	f/cm³	SD
Assembly	120	0.5	0.92	0.22	3.94	130	0.29	0.36	0.13	4.08
Auxiliary	119	0.15	0.18	0.07	4.01	26	1.1	2.26	0.2	6.33
Fiber	438	0.52	0.79	0.22	4.17	—	—	—	—	—
Finishing	127	0.76	0.63	0.49	3.11	84	1.57	5.72	0.47	4.18
Installation	—	—	—	—	—	201	0.69	1.09	0.3	4.31
Mixing forming	89	0.27	0.34	0.15	3.23	47	0.41	0.55	0.17	4.71
Other	129	0.33	0.86	0.09	4.25	57	0.38	0.69	0.14	4.88
Removal	—	—	—	—	—	49	1.36	2.97	0.28	6.48
Total	1,022	0.46	0.74	0.19	4.37	594	0.75	2.49	0.23	4.85

*Abbreviations: AM=arithmetic mean; GM=geometric mean; GSD=geometric standard deviation; RCF=refractory ceramic fibers; SD=standard deviation; TWA=time-weighted average.
†Data collected from August 1989 to May 1993 [RCFC 1993].

Table 4–4. TWA* concentrations of airborne RCFs in personal samples collected during the 5-year consent agreement monitoring period, 1993–1998,† by functional job category

	Manufacturing (primary production)					End use (secondary processing)				
		AM		GM			AM		GM	
Functional job category	No. samples	f/cm³	SD	f/cm³	GSD	No. samples	f/cm³	SD	f/cm³	GSD
Assembly	362	0.28	0.27	0.18	2.76	369	0.31	0.4	0.14	4.1
Auxiliary	237	0.12	0.19	0.05	3.87	311	0.19	0.37	0.07	4.68
Fiber	421	0.26	0.47	0.14	3.27	—	—	—	—	—
Finishing	359	0.65	0.56	0.47	2.44	622	0.99	2.09	0.35	4.5
Installation	—	—	—	—	—	456	0.42	0.51	0.2	3.83
Mixing forming	379	0.28	0.27	0.17	2.96	332	0.31	0.47	0.17	3.07
Other	167	0.14	0.21	0.07	3.22	385	0.17	0.46	0.04	4.66
Removal	—	—	—	—	—	176	1.92	2.85	0.82	4.22
Total	1,925	0.31	0.42	0.16	3.65	2,651	0.56	1.39	0.16	5.22

Source: Maxim et al. [1999a].
*Abbreviations: AM=arithmetic mean; GM=geometric mean; GSD=geometric standard deviation; RCF=refractory ceramic fibers; SD=standard deviation; TWA=time-weighted average.
†Data collected from June 1993 to May 1998.

Table 4–5. TWA* concentrations of airborne RCFs in personal samples collected during year 5 of the consent agreement monitoring period, June 1997 to May 1998

	Manufacturing (primary production)					End use (secondary processing)				
	No.	AM		GM		No.	AM		GM	
Functional job category	samples	f/cm³	SD	f/cm³	GSD	samples	f/cm³	SD	f/cm³	GSD
Assembly	78	0.28	0.25	0.19	2.48	92	0.28	0.39	0.1	5.32
Auxiliary	44	0.16	0.21	0.08	4.05	89	0.18	0.36	0.06	4.98
Fiber	85	0.29	0.29	0.18	2.85	—	—	—	—	—
Finishing	77	0.6	0.57	0.44	2.11	126	0.93	1.49	0.37	4.43
Installation	—	—	—	—	—	81	0.34	0.49	0.17	3.54
Mixing forming	75	0.23	0.24	0.14	2.78	69	0.28	0.31	0.18	2.65
Other	39	0.22	0.34	0.12	3	70	0.05	0.12	0.02	3.07
Removal	—	—	—	—	—	39	2.3	3.9	0.58	6.15
Total	398	0.31	0.37	0.18	3.12	566	0.54	0.14	0.13	5.83

Source: Maxim et al. [1999a].

*Abbreviations: AM=arithmetic mean; GM=geometric mean; GSD=geometric standard deviation; RCF=refractory ceramic fibers; SD=standard deviation; TWA=time-weighted average.

installation (AM=0.4 f/cm³). The remainder of the functional job categories had average TWA concentrations near or below 0.3 f/cm³. Although different jobs and activities are associated with the three higher exposure functional job categories, similarities exist that contribute to exposure concentrations. First, removal and installation activities are performed at remote jobsites where implementing fixed engineering controls may be difficult or impractical for reducing airborne fiber concentrations. Removal requires more mechanical energy and may involve fracturing the structure of the RCF product, resulting in fiber release and higher concentrations of airborne fibers. Finishing activities are performed at fixed locations where it is possible to implement engineering controls, but they also involve mechanical energy to shape RCF products by drilling, sanding, and sawing. These processes also result in the dispersal of airborne fibers.

Regarding particle-to-fiber ratio, Maxim et al. [1997] found average workplace values to be much lower (0.53; n=10; range not reported) than the average ratio (9.1; n=7) in the samples used in a series of animal inhalation toxicity studies with RCFs [Mast et al. 1995a,b, 2000; McConnell et al. 1995].

Monitoring performed during the baseline period (August 1989–May 1993) and the 5-year consent agreement period (June 1993–May 1998) provided data from nearly 6,200 air samples in the domestic RCF industry. Table 4–6 presents the summary statistics of workplace RCF exposure concentrations for the baseline (historical) and consent agreement monitoring data. The data suggest that (1) the AMs and GMs of RCF concentrations were higher for workers during the baseline period than during the more recent (consent monitoring data) period, and (2) AM and GM exposure concentrations were lower for workers in manufacturing facilities than at end-use sites.

Table 4–6. TWA* concentrations RCFs in personal samples collected at manufacturing facilities and end-use site during the baseline (1989–1993) monitoring periods

	Baseline data (1989–1993)†					Consent monitoring data (1993–1998)‡				
		AM		GM			AM		GM	
Type of site	No. samples	f/cm³	SD	f/cm³	GSD	No. samples	f/cm³	SD	f/cm³	GSD
Manufacturing (primary production)	1,022	0.46	0.74	0.19	4.37	1,527	0.31	0.42	0.16	3.65
End-use (secondary processing)	594	0.75	2.49	0.23	4.85	2,085	0.56	1.39	0.16	5.22
Total	1,616	0.56	1.63	0.2	4.56	4,576	0.46	1.1	0.16	4.53

Sources: RCFC [1993] and Maxim et al. [1999a].

*Abbreviations: AM=arithmetic mean; GM=geometric mean; GSD=geometric standard deviation; RCFs=refractory ceramic fibers; SD=standard deviation; TWA=time-weighted average.

†Data collected from August 1989 to May 1993 [RCFC 1993].

§Data collected from June 1993 to May 1998 [Maxim et al. 1999a].

4.5.4 Exposures During Installation and Removal of RCF Furnace Insulation

To evaluate exposures to airborne dust associated with removing RCF furnace insulation, Gantner [1986] conducted surveys with air sampling at five sites. The surveys were performed at sites where workers removed modules or blanket-type insulation manually using knives or trowels. During removal activities, workers wore disposable, single-use respirators, disposable protective clothing or their own personal clothing, and (in some cases) goggles or other protective eyewear. Personal sampling was performed for total dust concentration as well as respirable dust concentration using a cyclone. Area samples were collected in the center of work zones (industrial furnaces) at 9 ft above the floor, which was at the breathing zone level of the workers, who were on scaffolding. A total of 24 air samples were collected, including 14 personal samples (9 for respirable dust and 5 for total dust concentrations) and 10 area samples (3 for respirable dust and 7 for total dust concentrations). Bulk samples of the insulation materials were analyzed for cristobalite content, which ranged between 0% and 21%. In area air samples, cristobalite content ranged from 4% to 15%. Personal respirable dust concentrations averaged 4.99 mg/m³ (range=0.12 to 16.9 mg/m³), and personal total dust samples averaged 13.95 mg/m³ (range=0.31 to 35.8 mg/m³). Concentrations in area samples were lower, averaging 1.61 mg/m³ (range=0.1 to 3.4 mg/m³) for respirable dust and 8.98 mg/m³ (range=0.96 to 36.2 mg/m³) for total dust. As expected, the highest cristobalite concentrations in bulk samples were found on the face of insulation materials closest to high temperatures in furnaces (threshold temperature near 1,700 °F). Results of the surveys indicated that concentrations of respirable cristobalite exceeded the ACGIH TLV (then [10 mg/m³]/[% SiO_2 + 2]/2) in 75% of the samples, although all sampling times were short because the removal task lasts only 26 to 183 min. The TLV for cristobalite has since been lowered to 0.05 mg/m³ as an 8-hr TWA [ACGIH 2005].

Cheng et al. [1992] studied exposures to RCFs during the installation and removal of RCF insulation in 13 furnaces at 6 refineries and 2 chemical plants. Air samples were collected and analyzed according to NIOSH Method 7400 (*A* rules); sampling times ranged from 15 to 300 min. Samples collected during minor maintenance and inspection tasks (n=27) showed GM concentrations of 0.08 to 0.39 f/cm^3 (range=0.02 to 17 f/cm^3). Sampling performed during installation of RCF insulation (n=59) revealed GM concentrations of 0.14 to 0.62 f/cm^3 (range=0.02 to 2.6 f/cm^3). The highest exposures were observed in samples collected during removal of RCF insulation (n=32), with GM concentrations of 0.02 to 1.3 f/cm^3 (range=<0.01 to 17 f/cm^3). Workers working outside of enclosed spaces (furnaces) were rarely exposed to more than 0.2 f/cm^3. One sample of after-service RCF insulation was analyzed for fiber diameter and length: median diameter was reported as 1.6 µm (range=0.5 to 6 µm), and length ranged from 5 to 220 µm. Of 100 fibers randomly selected and analyzed from the air sample, 87% were within the respirable size range. Four personal samples were collected during removal of after-service RCF modules and fire bricks and were analyzed for respirable crystalline silica (cristobalite). Samples revealed concentrations ranging from 0.03 mg/m^3 to 0.2 mg/m^3 (GM=0.06 mg/m^3).

At a Dutch oil refinery, van den Bergen et al. [1994] performed personal air monitoring for airborne fibers to assess worker exposures during the removal of RCF insulation from expansion seams in a heat-treating furnace. The 8-hr TWA exposures for 5 workers sampled ranged from 9 to 50 f/cm^3 (GM=16 f/cm^3). Sweeney and Gilgrist [1998] also monitored worker exposures to airborne RCFs and respirable silica during the removal of RCF materials from furnaces. Personal samples from two workers taken during the removal of after-service RCF insulation revealed exposures of 0.15 and 0.16 f/cm^3. Exposures to total particulate (18.3 and 22.4 mg/m^3 as 8-hr TWAs) were above the OSHA PEL of 15 mg/m^3. Exposure concentrations for respirable dust containing crystalline silica (2.4% and 4.3%) were also above the OSHA PEL. The elevated concentrations of respirable and total dust were associated with removal of conventional refractory lining using jackhammers, crowbars, and hammers. A worker performing routing to install new RCF insulation was exposed at 1.29 f/cm^3 (8-hr TWA). Personal samples from another worker using a bandsaw to cut new RCF insulation revealed concentrations of 1.02 f/cm^3 as an 8-hr TWA.

In the RCF industry, worker exposures to respirable crystalline silica (including quartz, cristobalite, and tridymite) may occur during the use of silica in manufacturing, removal of after-service insulation, and waste disposal. Focusing on exposures of workers who install, use, or remove RCF insulation, Maxim et al. [1999a] collected 158 personal air samples analyzed for respirable quartz, cristobalite, and tridymite over the RCFC/EPA 5-year consent agreement monitoring period (1993–1998). A total of 42 removal projects were sampled. For small jobs, all workers engaged in insulation removal were sampled; for larger jobs, workers were selected at random for sampling. Air sampling and analysis were performed according to NIOSH Method 7500 for crystalline silica by X-ray diffraction; sampling times ranged from 37 to 588 min (AM=260 min, standard deviation [SD]=129 min). Short sampling times reflected the short duration of RCF insulation removal tasks (a benefit over time-intensive removal of conventional refractories). Removal of RCF blankets and modules is performed by using knives, pitchforks, rakes, and water lances, or by hand-peeling. The study noted that most (>90%) workers wear respirators (with

protection factors from 10 to 50 or more) when removing insulation. Analysis of 158 samples found the following:

- Fourteen samples had task-time respirable quartz concentrations ranging from 0.01 to 0.44 mg/m^3 (equivalent 8-hr TWA range=0.004 to 0.148 mg/m^3); the remainder of samples were below the LOD.
- Three samples had detectable concentrations of cristobalite that were below the NIOSH REL of 0.05 mg/m^3.
- One sample contained tridymite (0.2 mg/m^3) at a concentration exceeding the NIOSH REL of 0.05 mg/m^3.

4.5.5 International (Canadian, Swedish, and Australian) Surveys of RCF Exposure

Perrault et al. [1992] reported on the characteristics of fiber exposures that occurred during the use of synthetic fiber insulation materials on construction sites in Canada. Fiber dimensions were measured from bulk samples of insulation materials used at five construction sites. Area air samples were also collected during the installation of composite RCF and glass wool insulation, glass wool alone, rock wool (both blown and sprayed on), and RCFs alone.

Respirable fiber concentrations were highest during removal and installation of RCFs (0.39 to 3.51 f/cm^3) compared with concentrations measured during installation of rock wool (0.15 to 0.32 f/cm^3), composite RCF and glass wool (0.04 f/cm^3), and glass wool alone (0.01 f/cm^3). Diameters of fibers in bulk samples differed significantly from diameters in airborne fibers. RCFs had the smallest GM_D of fibers in bulk samples (0.38 to 0.55 µm) compared with glass wool (0.93 µm) and rock wool (1.1 to 3.9 µm). For airborne fibers, rock wool (sprayed on) had a GM_D of 2.0 µm, followed by RCFs (1.1 µm), composite RCFs and glass wool (0.71 µm), glass wool (0.5 µm) and blown rock wool (0.5 µm). Elemental analysis and comparison of bulk samples with air samples revealed a greater concentration of fibers with oxides of silicon and aluminum in air samples. For sites with either glass wool or rock wool insulation, airborne samples contained fewer fibers with silicon oxide as the sole constituent than bulk samples. The authors concluded that airborne fiber concentrations were affected by the type of fiber material used and the confinement of worksites. The authors also concluded that characterization of fibers in bulk samples is not a good representation of physical and chemical parameters of the airborne fibers.

A report by the Swedish National Institute for Occupational Health [Krantz et al. 1994] describes exposure to RCFs in smelters and foundries based on industrial hygiene surveys and sampling at 4 facilities: a specialty steel foundry (2,500 workers), a metal smelting plant (1,500 workers), an aluminum foundry (450 workers), and an iron foundry (450 workers). RCF products were used in these plants in ladles, tapping spouts, holding furnaces, heat treatment furnaces, and spill protection mats. Workers and contractors were placed into three exposure categories, depending on their potential for exposure (as determined by distance from a fiber source). The highest exposures to airborne ceramic fibers (category 1) had median concentrations of 0.26 to 1.2 f/cm^3 and involved about 3% (n=160) of the workers at the plants surveyed. Secondary exposures (categories 2 and 3) involved another 33% (n=1,650) of the workers and had median concentrations of 0.03 to 0.24 f/cm^3. During certain operations such as removal or demolition of RCF materials in enclosed spaces, concentrations of up to 210 f/cm^3 were measured. Total dust

concentrations increased with fiber concentration and were as high as 600 mg/m^3 during demolition and 60 mg/m^3 during reinsulation. Median fiber diameters from bulk samples analyzed by electron microscopy ranged from 0.6 to 1.5 µm, which was comparable to the diameters of airborne fibers. On the basis of air sampling data, *fiber dose* (assuming a working lifetime of 40 years [fiber concentration × exposure time per year × 40 years]) was estimated for 8 occupations with category 1 exposures. Dose estimates ranged from 0.05 fiber-years/cm^3 for a cleaner to 85 fiber-years/cm^3 for a bricklayer or contractor. Dose estimates for the 6 other occupations ranged from 0.6 fiber-years/cm^3 to 3.1 fiber-years/cm^3.

Researchers at the Australian National Occupational Health and Safety Commission established a technical working group to investigate typical exposures in SVF manufacturing and user industries [Rogers et al. 1997]. The RCF manufacturing industry is relatively small in Australia: 2 plants employing roughly 40 workers have been manufacturing RCFs since 1976 and 1977. Since the plants began manufacturing RCFs, 152 persons have been involved with production. Airborne fiber concentrations in both plants decreased over time as a result of (1) the introduction of a national exposure standard of 0.5 f/cm^3 for synthetic fibers and a secondary standard of 2 mg/m^3 for inspirable dust, (2) the use of various controls and handling technologies, and (3) increased awareness of dust suppression by the workforce. GM concentrations of airborne fibers before implementation of the synthetic fiber exposure standard (1983–1990) measured 0.52 f/cm^3 (geometric standard deviation [GSD]=3.9) and 0.29 f/cm^3 (GSD=2.5) for plants 1 and 2, respectively. GM concentrations for the subsequent period (1991–1996) dropped to 0.11 f/cm^3 (GSD=4.1) at plant 1 and 0.27 f/cm^3 (GSD=3.3) at plant 2.

4.5.6 Johns Hopkins University Industrial Hygiene Surveys

A report of RCF end-user exposure data prepared for the Thermal Insulation Manufacturers Association (TIMA) showed that using blanket, bulk, and vacuum-formed RCFs during certain operations resulted in high fiber concentrations [Corn et al. 1992]. For example, 25 personal air samples collected from workers installing RCF blanket modules had an AM, 8-hr TWA concentration of 1.36 f/cm^3 (SD=1.15). The fibers were collected and analyzed using NIOSH Method 7400 (B rules). Seventeen vacuum formers had AM exposure concentrations of 0.71 f/cm^3 (SD=0.83) while using bulk RCF products. Twenty-eight workers with the job title *vacuum-formed RCF cast finisher* had AM exposures of 1.55 f/cm^3 (SD=1.51). Table 4–7 summarizes exposure data collected for the 17 occupations sampled during the study. Scanning electron microscopy (SEM) was used to measure dimensions of approximately 3,500 fibers from selected air samples of the 17 occupations. GM fiber diameters ranged from 0.9 to 1.5 µm, and GM fiber lengths ranged from 20.4 to 36.1 µm. Fiber aspect ratios based on these data ranged between 16:1 and 30:1.

4.5.7 NIOSH HHEs and Additional Sources of RCF Exposure Data

NIOSH has conducted HHEs involving potential exposures to RCFs at the following work places: an RCF manufacturing facility [Lyman 1992], a steel foundry [O'Brien et al. 1990], a power plant [Cantor and Gorman 1987], a foundry [Gorman 1987], and a railroad car wheel and axle production facility [Hewett 1996]. Table 4–8 summarizes data on airborne fiber concentrations and dimensions from these studies.

Table 4–7. Summary of 8-hr TWA* RCF exposures for workers using RCF insulation products

RCF product	Occupation	PCM (f/cm³)			SEM (f/cm³)			Gravimetric (mg/m³)		
		n	AM	SD	n	AM	SD	n	AM	SD
RCF blanket	Module fabricator	5	0.44	0.4	7	0.54	0.8	4	6.26	6.5
	Module installer	25	1.36	1.15	23	1.19	0.8	11	14.2	18.7
	Blanket installer	8	0.37	0.29	9	0.33	0.24	4	1.42	1.2
	Investment caster	20	0.73	0.88	18	0.65	0.57	6	3.59	3.75
	General fabricator	20	0.55	0.55	19	0.46	0.55	7	0.86	0.49
	Fabrication maintenance	—	—	—	—	—	—	—	—	—
RCF bulk	Vacuum former	17	0.71	0.83	13	0.6	0.57	7	1.1	0.7
	Vacuum maintenance	—	—	—	—	—	—	—	—	—
	Vacuum warehouse	—	—	—	—	—	—	—	—	—
	Sprayer	1	1.53	—	1	1.15	—	—	—	—
	Spray feeder	1	0.24	—	1	0.21	—	—	—	—
Vacuum-formed RCFs	General fabricator	2	0.52	0.58	2	0.2	0.05	2	0.57	0.35
	Paper fabricator	—	—	—	—	—	—	—	—	—
	Paper finisher	—	—	—	—	—	—	—	—	—
	Cast finisher	28	1.55	1.51	32	1.17	1.17	8	4.05	5.42
	Finishing maintenance	1	0.12	—	2	0.07	0.01	1	0.75	—
	Board installer	9	0.78	0.84	9	0.66	0.67	1	6.09	—

Source: Corn et al. [1992].

*Abbreviations: AM=arithmetic mean; PCM=phase contrast microscopy; RCF-refractory ceramic fiber; SD=standard deviation; SEM=scanning electron microscopy; TWA=time-weighted average.

Table 4–8. NIOSH Health Hazard Evaluations involving investigation of exposures to RCFs*

Reference	Worksite	Samples		Concentration		Fiber dimension
		No.	Type	f/cm³	SD	
Lyman [1992]	RCF manufacturing	286	Breathing zone	0.69	—	—
		4	Breathing zone	4.02	1.82	—
		126	Breathing zone	0.81	—	AMD=0.6 µm
				—	—	AML=13.8 µm
		24	Breathing zone	1.65	—	—
O'Brien et al. [1990]	Steel foundry	48	Fibers in an insulating blanket	—	—	D=<1.5 µm (81% of fibers)
				—	—	L= 4-64 µm (77% of fibers)
		54	Fibers in settled dust	—	—	D=<0.5 µm (73% of fibers)
				—	—	L=4-64 µm (62% of fibers)
Cantor and Gorman [1987]	Power plant	4	Breathing zone	0.26	0.08	D=0.5-2.0 µm (73% of fibers)
		2	Area	0.08	0.01	L=>20 µm (60% of fibers)
Gorman [1987]	Foundry	7	Breathing zone	0.1	0.06	D=<2 µm (96% of fibers)
		5	Area	0.4	0.26	L=<20 µm (80% of fibers)
Hewett [1996]	Railroad car wheel and axle manufacturer	6	Breathing zone near heat treatment plant	0.024	0.012	—
		14	Breathing zone during RCF removal	1.44	0.84	—
		1	Breathing zone	3.04†	—	—
				1.7‡	—	Mean D=0.71 (SD=0.44)
				—	—	Mean L=11.9 (SD=11.3)

*Abbreviations: AMD=arithmetic mean diameter; AML=arithmetic mean length; D=diameter; L=length; RCFs=refractory ceramic fibers; SD=standard deviation.
†Measured by phrase control optical microscopy (PCM).
‡Measured by transmission electron microscopy (TEM).

4.5.8 Discussion

Recent and historical environmental monitoring data [Esmen et al. 1979; Cantor and Gorman 1987; Gorman 1987; O'Brien et al. 1990; Cheng et al. 1992; Brown 1992; Corn et al. 1992; Lyman 1992; Allshouse 1995; Hewett 1996] indicate that airborne concentrations of RCFs include fibers in the thoracic and respirable size range (<3.5 μm in diameter and <200 μm long [Timbrell 1982; Lippmann 1990; Baron 1996]). Workers are exposed to these concentrations during primary RCF manufacturing, secondary manufacturing or processing, and end-use activities such as RCF installation and removal. Sampling data from studies of domestic primary RCF manufacturing sites indicate that average airborne fiber concentrations have steadily declined by nearly 2 orders of magnitude over the past 2 decades. Rice et al. [1997] report an estimated maximum airborne concentration of 10 f/cm^3 associated with an RCF manufacturing process in the 1950s. Esmen et al. [1979] recognized average exposure concentrations ranging from 0.05 to 2.6 f/cm^3 in RCF manufacturing facilities in the mid- to late-1970s. During the late 1980s, Rice et al. [1994, 1996, 1997] calculated average airborne concentrations in manufacturing facilities that ranged from <LOD to 0.66 f/cm^3. Maxim et al. [1994, 1997, 2000a] report that from the late 1980s through 1997, concentrations ranged from an AM of <0.3 to 0.6 f/cm^3 (GM≅0.2 f/cm^3).

For many RCF manufacturing processes, reductions in exposure concentrations have been realized through improved ventilation, engineering or process changes, and product stewardship programs [Rice et al. 1996; Maxim et al. 1999b]. Several functional job categories continue to be associated with fiber concentrations that exceed the average; these include finishing operations during manufacturing, removal operations, and installation performed by end users. Activities in these three categories require additional mechanical energy in handling RCF products (e.g., sawing, drilling, cutting, sanding), which increases the generation of airborne fibers. Removal and installation activities are performed at remote sites where conventional engineering strategies and fixed controls are more difficult to implement. For certain operations in which airborne fiber concentrations are greater (such as removal of RCF products from furnaces), jobs are performed for short periods and almost universally with the use of respiratory protection [Maxim et al. 1998].

One additional consideration during work involving RCF exposure is the potential for exposure to respirable silica in the forms of quartz, tridymite, and cristobalite. Although the potential for such exposure exists in primary manufacturing (because silica is a major component of RCFs), monitoring data indicate that these exposures are generally low [Rice et al. 1994]. Maxim et al. [1999a] reported that many airborne silica samples collected to assess exposures during installation and removal of RCF products contain concentrations below the LOD, with average concentrations of respirable silica ranging from 0.01 to 0.44 mg/m^3 (equivalent 8-hr TWA range=0.004 to 0.148 mg/m^3). Other studies indicate a greater potential for exposure to respirable silica (especially in the form of cristobalite) during removal of after-service RCF materials [Gantner 1986; Cheng et al. 1992; Perrault et al. 1992; van den Bergen et al. 1994; Sweeney and Gilgrist 1998]. Processes associated with high concentrations of airborne fibers generally generate high concentrations of total and respirable dust as well [Esmen et al. 1979; Krantz et al. 1994].

5 Effects of Exposure

5.1 Health Effects in Animals (In Vivo Studies)

The health effects of RCF exposures have been evaluated in animal studies using intrapleural, intraperitoneal, intratracheal, and inhalation routes of exposure. All of these routes have demonstrated the carcinogenic potential of RCFs. Chronic inhalation studies provide information that is most relevant to the occupational route of exposure and human risk assessment. Mechanistic information about fiber toxicity may also be derived from other types of studies. Studies investigating the cellular effects of RCFs in vitro are reviewed in Section 5.2 and Appendix C.

When comparing the effects of a fiber dose in animal studies, it is possible to compare fibers on a gravimetric basis (effect per unit weight) or a fiber basis (effect per number of fibers). The same gravimetric dose of different fiber types may contain vastly different numbers of fibers because of differences in their dimensions. RCF1 is a relatively thick fiber compared with many types of asbestos, such as chrysotile, a fiber commonly used as a positive control in pulmonary carcinogenesis experiments in animals (see Table 2–2 for descriptions of RCF1, RCF2, RCF3, and RCF4). A gravimetric dose of RCF1 usually contains far fewer fibers than the same gravimetric dose of chrysotile asbestos fibers, making a direct comparison of their effects difficult when the number of fibers per unit weight is not reported. Comparison on a per-fiber basis rather than a weight basis provides information most applicable to occupational risk assessment.

Animal studies report the concentration(s) to which the animals were exposed. The distinction between administered exposure concentration and received dose is important when analyzing these studies. The dose affecting the target tissues is known only when the amount of fiber present in the lung is measured and reported. To analyze the results of RCF studies, the number of fibers per exposure, their dimensions, durabilities, and the delivered dose should be considered for making comparisons and conclusions regarding potential and relative toxicity.

5.1.1 Intrapleural, Intraperitoneal, and Intratracheal Studies

Instillation and implantation studies deliver fibers directly to the trachea, pleural cavity, or peritoneal cavity, bypassing some of the defense and clearance mechanisms that act on inhaled fibers. Implantation of fibers into either the pleural or abdominal cavities delivers fibers directly to the pleural or abdominal mesothelium, bypassing some or all of the normal defense and clearance mechanisms of the respiratory tract. Intratracheal instillation delivers fibers directly to the trachea, bypassing the upper respiratory tract. These exposure methods do not mimic an occupational inhalation exposure of several hours per day for several days per week over an extended period. However, one advantage of these studies is that they allow the administration of a precise dose of fibers that can be replicated between animals. They also permit the administration of higher doses than may be obtainable by inhalation exposure.

Although the results of implantation and instillation studies may not be directly applicable to occupational exposure and human health effects, they provide important information about the potential toxicity of RCFs. Experiments that control fiber dimensions and other variables provide information about the physiological characteristics relevant to fiber toxicity. They provide a less expensive, quicker means to screen the potential toxicity of a fiber than inhalation studies.

Many of the implantation and instillation studies reviewed here report the administered fiber dose on a gravimetric basis rather than on a per-fiber basis. Some studies assess the toxicity of both RCFs and asbestos independently, which allows for the comparison of these fibers on a gravimetric basis but not on a per-fiber basis.

5.1.1.1 Intraperitoneal Implantation Studies

In intraperitoneal studies, fibers are implanted directly into the abdominal cavity, bypassing the respiratory system defense and clearance mechanisms that act on inhaled fibers. Although the implanted fibers act on some of the same target cell types as the fibers of an inhalation exposure (such as the mesothelium), the effects elicited in the abdominal mesothelium cannot be assumed to be identical to the response of the pleural mesothelium. Table 5–1 summarizes the results of three RCF intraperitoneal implantation studies [Davis et al. 1984; Smith et al. 1987; Pott et al. 1987]. A brief description of these studies follows.

Davis et al. [1987] dosed Wistar rats with 25 mg ceramic aluminum silicate dust by intraperitoneal injection. Tumors were induced in 3 of 32 rats: 2 fibrosarcomas and 1 mesothelioma. Smith et al. [1987] dosed Osborne Mendel (OM) rats and Syrian hamsters with 25 mg RCFs by intraperitoneal injection. Abdominal mesothelioma induction rates were 83% (19/23) in OM rats and 13% (2/15) and 24% (5/21) in two groups of male hamsters. Crocidolite asbestos at 25 mg induced abdominal mesotheliomas in 80% (20/25) of OM rats and 32% (8/25) of hamsters. The difference in tumor incidence reported by Davis et al. [1984] and Smith et al. [1987] may be explained in part by differences in fiber length. Eighty-three percent of RCF fibers used by Smith et al. [1987] had a length >10 μm; 86% had a diameter <2.0 μm. Ninety percent of the ceramic aluminum silicate material used by Davis et al. [1984] had a length <3 μm and a diameter <0.3 μm.

Pott et al. [1987] dosed female Wistar rats by intraperitoneal injection with 9 or 15 mg/week for 5 weeks with 2 ceramic (aluminum silicate) wool fibers, Fibrefrax (RCFs), and MAN (Manville RCFs); total doses of 45 and 75 mg were administered, respectively. Fifty percent of Fibrefrax fibers had a length <8.3 μm and diameter <0.91 μm. Exposure to Fibrefrax fibers induced abdominal tumors (sarcomas, mesotheliomas, or carcinomas) in 68% of the rats. Fifty percent of MAN fibers had a length <6.9 μm and diameter <1.1 μm. The number of fibers in different length categories was not reported. Exposure to MAN fibers induced abdominal tumors in 22% of the rats. Chrysotile (UICC/B) injected intraperitoneally at a single dose of 0.05, 0.25, or 1.00 mg induced abdominal tumors in 19%, 62%, or 86% of rats, respectively. Fifty percent of chrysotile fibers had a length <0.9 μm and diameter <0.11 μm. The number of fibers per dose was not reported for the ceramic fibers and asbestos. Saline induced tumors in 2% of rats.

5.1.1.2 Intrapleural Implantation Studies

Intrapleural implantation studies permit the investigation of the effect of RCFs directly on the pleural mesothelium while controlling variables such as inhalation kinetics and translocation.

Table 5–1. Intraperitoneal implantation studies of RCFs* in animals

Reference	Species	Number and sex per group	Fiber dose	Fiber dimensions (μm)	Tumor incidence
Davis et al. [1984]	Wistar rats	32, sex unspecified	25 mg ceramic fibers (aluminum silicate glass)	L=90% <3 D=90% <0.3	1 mesothelioma 2 fibrosarcomas First tumor occurred 850 days postinjection.
Pott et al. [1987]	Wistar rats	47, female	9 mg (×5)=45 mg RCFs (Fibrefrax)	L=50% <8.3 D=50% <0.91	32 mesotheliomas, sarcomas, or adenomas of the abdominal cavity
		54, female	15 mg (×5)=75 mg Manville RCFs (MAN)	L=50% <6.9 D=50% <1.1	12 mesotheliomas, sarcomas, or adenomas of the abdominal cavity
		36, female	1 mg UICC/B chrysotile	L=50% <0.9 D=50% <0.11	31 mesotheliomas, sarcomas, or adenomas of the abdominal cavity
		102, female	2 ml saline (×5)=10 ml	NA	2 mesotheliomas, sarcomas, or adenomas of the abdominal cavity
Smith et al. [1987]	Osborne Mendel rats	23, female	25 mg RCFs (Fibrefrax)	GM_L=25.0 L=83% >10 GM_D=0.9 D=80% <2	20 abdominal mesotheliomas

See footnotes at end of table.

(Continued)

Table 5–1 (Continued). Intraperitoneal implantation studies of RCFs* in animals

Reference	Species	Number and sex per group	Fiber dose	Fiber dimensions (μm)	Tumor incidence
Smith et al. [1987] (continued)		25, female	25 mg UICC crocidolite	Mean L=3.1 (SD, 10.2)	20 abdominal mesotheliomas
		25, female	0.5 ml physiological saline	L=95% ≤5 NA	0 abdominal mesotheliomas
		125, female	Cage controls	NA	0 abdominal mesotheliomas
	Syrian golden hamsters	15, male	25 mg RCF (Fibrefrax)	L=83% >10 GM_L=25.0 D=80% <2 GM_D= 0.9	2 abdominal mesotheliomas
		21,male	25 mg RCFs	GM_L=25.0 L=83% >10 GM_D=0.9 D=80% <2	5 abdominal mesotheliomas
		25, male	25 mg UICC crocidolite	Mean L=3.1 (SD, 10.2) L=95% ≤5	8 abdominal mesotheliomas
		25, male	0.5 ml physiological saline	NA	0 abdominal mesotheliomas
		112, male	Cage controls	NA	0 abdominal mesotheliomas

*Abbreviations: D=diameter; GM_D=geometric mean diameter; GM_L=geometric mean length; L=length; NA=not applicable; RCFs=refractory ceramic fibers; SD=standard deviation; UICC=Union Internationale Contre le Cancer; UICC/B=Union Internationale Contre le Cancer/Type B.

Table 5–2 summarizes the results of the intrapleural study of Wagner et al. [1973]. Intrapleural injection of 20 mg of ceramic fiber (unspecified type) or 20 mg for each of two samples of chrysotile produced mesotheliomas in 10% (3/31), 64% (23/36), and 66% (21/32) of Wistar rats, respectively. The mean ceramic fiber diameter was 0.5 to 1.0 µm. The lengths of the chrysotile fibers were mostly <6 µm. The chrysotile fiber diameter, RCF fiber length, and number of fibers per dose were not reported, making a direct comparison of the samples difficult.

5.1.1.3 Intratracheal Instillation Studies

The technique of intratracheal instillation has the advantage of affecting the same target tissues (other than the upper respiratory tract) as an inhalation exposure. Other advantages, compared with inhalation exposure, include a simpler technique, lower cost, accurate dosing, and the ability to deliver materials (such as long fibers) that may not be respirable to rodents [Driscoll et al. 2000]. The faster dose rate and bolus delivery of tracheal instillation may affect the response of the lung defense mechanisms, resulting in differences in clearance and biopersistence relative to an inhalation exposure. Intratracheal instillation may also produce a clumping of fibers with a resulting effect on fiber distribution and clearance [Davis et al. 1996; Driscoll et al. 2000]. Intratracheal instillation results in a heavier, more centralized distribution pattern; inhalation exposure results in a more evenly and widely distributed pattern [Brain et al. 1976]. Table 5–3 summarizes the results of two RCF intratracheal instillation studies [Smith et al. 1987; Manville 1991]. A brief description of these studies follows.

In the study by Smith et al. [1987], Syrian golden hamsters and OM rats were dosed with 2 mg of RCFs suspended in saline (Fibrefrax) by intratracheal instillation once a week for 5 weeks (10 mg total). The animals were maintained for the rest of their lives. Approximately 50% of the RCFs were <20 µm long with a mean fiber diameter of 1.8 µm. No primary lung tumors developed in RCF-exposed animals. These animals did not have an increased incidence of pulmonary fibrosis or tumor production compared with controls; however, the rats had a statistically significant increase in bronchoalveolar metaplasia. The median lifespan was 479 days for hamsters and 736 days for rats. Hamsters (median lifespan 657 days) and rats (median lifespan 663 days) exposed to the same dosing schedule with 2 mg crocidolite asbestos had a statistically significant increase in bronchoalveolar lung tumors in 20 of 27 (74%) and 2 of 25 (8%) animals, respectively. The fiber numbers per dose were not reported.

Manville [1991] reported a statistically significant increase in lung tumors in Fischer rats exposed intratracheally to 2 mg of RCF1, RCF2, RCF3, and RCF4 in saline [Manville 1991]. Animals were terminally sacrificed at 128 weeks with interim sacrifices at 13, 26, 52, 78, and 104 weeks. RCF1, RCF2, RCF3, and RCF4 exposure resulted in adenomas or adenocarcinomas in 6 of 109 (5.5%), 4 of 107 (3.7%), 4 of 109 (3.7%), and 7 of 108 (6.5%) rats, respectively. One mesothelioma was identified in a rat exposed to RCF2. Exposure to 0.66 mg chrysotile asbestos resulted in 8 primary lung tumors in 8 of 55 rats (14.5%). The fiber dimensions and numbers per dose were not reported.

5.1.2 Chronic Inhalation Studies

In animal bioassays, administering RCFs by chronic inhalation most closely mimics the occupational route of exposure. Exposure to RCFs over a time period that approximates the lifespan of the animal provides the most accurate prediction of the potential pathogenicity and carcinogenicity of these fibers in animals.

Table 5–2. Intrapleural study of RCFs[*] in animals

Reference	Species	Number per group[†]	Fiber dose	Fiber dimensions (µm)	Tumor incidence
Wagner et al. [1973]	Wistar rats	31	20 mg ceramic fibers (aluminum silicate)	D=0.5–1.0	3 mesotheliomas
		35	20 mg aluminum oxide	Area D=<10	1 mesothelioma
		35	20 mg fiberglass	L=60%>20 D=55% 2.5–7	0 mesotheliomas
		35	20 mg glass powder	Area D=<8	1 mesothelioma
		36	20 mg Canadian chrysotile	L=92% <6	23 mesotheliomas
		32	20 mg Canadian chrysotile	L=92% <6	21 mesotheliomas

[*]Abbreviations: D=diameter; L=length; RCFs=refractory ceramic fibers.
[†]The sex ratio for all groups was approximately 2 male rats to 1 female rat.

Table 5–3. Intratracheal studies of RCFs* in animals

Reference	Species	Number and sex per group	Fiber dose	Fiber dimensions (μm)	Tumor incidence
Manville [1991]	Fischer 344 rats	109, male	2 mg RCF1 (0.2 ml of a 10-mg/ml suspension)	NR	6 lung adenomas
		107, male	2 mg RCF2 (0.2 ml of a 10-mg/ml suspension)	NR	4 lung tumors: 3 adenomas 1 carcinoma 1 mesothelioma
		109, male	2 mg RCF3 (0.2 ml of a 10-mg/ml suspension)	NR	4 lung tumors: 2 adenomas 2 carcinomas
		108, male	2 mg RCF4 (0.2 ml of a 10-mg/ml suspension)	NR	7 lung adenomas
		55, male	0.66 mg Canadian chrysotile (0.2 ml of a 3.3-g/ml suspension)	NR	8 lung tumors: 4 adenomas 4 carcinomas
		118, male	0.2 ml (vehicle not specified)	NR	0 lung tumors

(Continued)

See footnotes at end of table.

Table 5–3 (Continued). Intratracheal studies of RCFs* in animals

Reference	Species	Number and sex per group	Fiber dose	Fiber dimensions (μm)	Tumor incidence
Smith et al. [1987]	Osborne Mendel rats	22, female	10 mg RCFs (Fibrefrax) (2 mg/week × 5=10 mg)	GM_L=25.0 GM_D=0.9 L=3% >10 D=80% <2	0 lung tumors
		25, female	10 mg UICC* crocidolite (2 mg/week × 5=10 mg)	L=95% ≤5 mean L=3.1 (SD, 10.2)	2 bronchoalveolar tumors
		25, female	Saline controls	NA	0 lung tumors
		125, female	Cage controls	NA	0 lung tumors
	Syrian golden hamsters	25, male	10 mg RCFs (Fibrefrax) (2 mg/week × 5=10 mg)	GM_L=25.0 GM_D =0.9 L=83% >10 D=80% < 2	0 lung tumors
		27, male	10 mg UICC crocidolite (2 mg/week × 5=10 mg)	mean L=3.1 (SD, 10.2) L=95% ≤ 5	20 bronchoalveolar tumors
		24, male	Saline controls	NA	0 lung tumors
		112, male	Cage controls	NA	0 lung tumors

*Abbreviations: D=diameter; GM_D=geometric mean diameter; GM_L=geometric mean length; L=length; NA=not applicable; NR=not reported; RCFs=refractory ceramic fibers; SD=standard deviation; UICC=Union Internationale Contre le Cancer.

The effects seen in animals may be used to predict the effects of these fibers in humans, although interspecies differences exist in respiratory anatomy, physiology, and tissue sensitivity. Chronic inhalation studies provide the best means to predict the critical disease endpoints of cancer induction and nonmalignant respiratory disease that may occur in humans because of fiber exposure [McConnell 1995; Vu et al. 1996].

Five chronic RCF inhalation studies have been conducted on rats or hamsters [Davis et al. 1984; Smith et al. 1987; Mast et al. 1995a,b; McConnell et al. 1995]. These studies are summarized in Tables 5–4 and 5–5 and are described below.

Davis et al. [1984] exposed Wistar rats by whole-body inhalation to 10 mg/m^3 (95 f/cm^3) ceramic (aluminum silicate glass) dust for 7 hr/day, 5 days/week for 12 months. Ninety percent of the exposure fibers were short (<3 μm) and thin (<0.3 μm). The particle ratio of nonfibrous particulate to fibers was 4:1. Eight of 48 exposed rats (17%) developed pulmonary neoplasms: 1 adenoma, 3 bronchial carcinomas, and 4 histiocytomas. Interstitial fibrosis was observed. No pulmonary tumors were observed in control animals.

Smith et al. [1987] exposed OM rats and Syrian golden hamsters by nose-only inhalation to 10.8±3.4 mg/m^3 (200 f/cm^3) ceramic fiber (Fibrefrax) for 6 hr/day, 5 days/week for 24 months. The ratio of nonfibrous particulate to fibers was 33:1. Exposure to RCFs did not induce pulmonary tumors in rats. One RCF-exposed rat and one chamber control rat developed primary lung tumors. Rats exposed to RCFs had more severe pulmonary lesions than hamsters, and a greater percentage of rats had fibrosis than hamsters (22% versus 1%, respectively). Under similar conditions, exposure to 7 mg/cm^3 (3,000 f/cm^3) crocidolite asbestos produced pulmonary tumors in 3 of 57 rats, including 1 mesothelioma and 2 bronchoalveolar tumors. No pulmonary tumors were observed in crocidolite-exposed hamsters. Exposure to slag wool at 10 mg/m^3 (200 f/cm^3) and several fibrous glasses at similar gravimetric concentrations did not result in pulmonary neoplasms (not shown in Table 5–4).

Mast et al. [1995a] exposed Fischer 344 rats by nose-only inhalation to 30 mg/m^3 (187±53 WHO f/cm^3 RCF1, 220±52 WHO f/cm^3 RCF2, 182±66 WHO f/cm^3 RCF3, 153±49 WHO f/cm^3 RCF4) of one of four types of RCFs for 6 hr/day, 5 days/week for 24 months and held until sacrifice at 30 months. Groups of 3 to 6 animals were sacrificed at 3, 6, 9, 12, 15, 18, and 24 months to examine lesions and determine fiber lung burdens. Other animals were removed from exposure at the same time points and held until sacrifice at 24 months. Positive control rats were exposed to 10 mg/m^3 (1.06±1.14×10^4 WHO f/cm^3) chrysotile under similar exposure conditions. RCF fibers with a mean diameter of 1 μm and mean length of 20 to 30 μm were selected. A particle ratio of nonfibrous particulate to fiber of 1.02–1.88:1 was reported. Interstitial fibrosis was first observed at 6 months with RCF1, RCF2, and RCF3 and at 12 months with RCF4 exposure. Pleural fibrosis was first observed at 9 months with RCF1, RCF2, and RCF3 and at 12 months with RCF4 exposure. A progression in the severity of pleural fibrosis was seen in animals exposed to 30 mg/m^3 for 24 months and examined at 6 months post exposure. The incidence of total lung tumors was significantly increased from controls after exposure to RCF1, RCF2, and RCF3 but not RCF4. Neoplastic disease, including adenomas and carcinomas, was observed in all treatment groups: with RCF1, in 16 of 123 rats (13%); RCF2, 9 of 121 (7.4%); RCF3, 19 of 121(15.7%); RCF4, 4 of 118 (3.4%); and chrysotile, 13 of 69 (18.5%). Mesotheliomas were induced in some rats in all treatment groups: 2 with RCF1; 3 with RCF2; 2 with RCF3; 1 with

Table 5–4. Chronic inhalation studies of RCFs* in animals

Reference	Species	Number and sex per group	Fiber dose	Fiber dimensions (µm)	Tumor incidence
Davis et al. [1984]	Wistar rats	48, sex unspecified	10 mg/m^3 ceramic fibers (aluminum silicate glass) 95 fibers/cm^3	L~90%<3 D~90%<0.3	8 pulmonary tumors: 1 adenoma 3 bronchoalveolar carcinomas 4 histiocytomas 16 nonpulmonary tumors: 8 benign 8 malignant 1 peritoneal mesothelioma
		40, sex unspecified	Control	NA	No pulmonary tumors Nonpulmonary tumors: 11 benign 9 malignant
Mast et al. [1995a]	Fischer 344 rats	123, male	29.1 (SD, 5.2) mg/m^3 RCF1 234 (SD, 35) total f/cm^3 187 (SD, 53) WHO† f/cm^3	mean L=22.3 (SD, 17.0) mean D=0.98 (SD, 0.61)	16 lung tumors: 8 adenomas 8 carcinomas 2 pleural mesotheliomas
		121, male	28.9 (SD, 4.5) mg/m^3 RCF2 268 (SD, 45) total f/cm^3 220 (SD, 52) WHO f/cm^3	mean L=18.7 (SD, 15.5) mean D=1.07 (SD, 0.69)	9 lung tumors: 4 adenomas 5 carcinomas 3 pleural mesotheliomas

See footnotes at end of table.

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Table 5–4 (Continued). Chronic inhalation studies of RCFs* in animals

Reference	Species	Number and sex per group	Fiber dose	Fiber dimensions (μm)	Tumor incidence
		121, male	29.2 (SD, 7.0) mg/m^3 RCF3 213 (SD, 44) total f/cm^3 182 (SD, 66) WHO f/cm^3	mean L=24.2 (SD, 17.9) mean D=1.05 (SD, 0.7)	19 lung tumors: 10 adenomas 9 carcinomas 2 pleural mesotheliomas
		118, male	30.1 (SD, 7.8) mg/m^3 RCF4 206 (SD, 48) total f/cm^3 153 (SD, 49) WHO f/cm^3	mean L=12.7 (SD, 9.9) mean D=1.38 (SD, 0.7)	4 lung tumors: 2 adenomas 2 carcinomas 1 pleural mesothelioma
		130, male	Air only	NA	2 lung adenomas
Mast et al. [1995b]	Fischer 344 rats	131, male	3.0 (SD, 0.4) mg/m^3 RCF1 36 (SD, 17) f/cm^3 26 (SD, 12) WHO f/cm^3	mean L=19.88 (SD, 17.93) mean D=1.03 (SD, 0.73)	2 lung adenomas
		134, male	8.8 (SD, 0.7) mg/m^3 91 (SD, 34) f/cm^3 75 (SD, 35) WHO f/cm^3	mean L=20.54 (SD, 17.08) mean D=1.04 (SD, 0.72)	5 lung tumors: 4 adenoma 1 carcinoma 1 mesothelioma
		132, male	16.5 (SD, 1.1) mg/m^3 RCF 162 (SD, 37) f/cm^3 120 (SD, 35) WHO f/cm^{3†}	mean L=20.11 (SD, 16.87) mean D=1.06 (SD, 0.72)	2 lung tumors: 1 adenoma 1 carcinoma
		132, male	Air only	NA	1 lung adenoma

See footnotes at end of table.

(Continued)

Table 5–4 (Continued). Chronic inhalation studies of RCFs* in animals

Reference	Species	Number and sex per group	Fiber dose	Fiber dimensions (μm)	Tumor incidence
McConnell et al. [1995]	Syrian golden hamsters	102, male	30 mg/m^3 RCF1 256 (SD, 58) f/cm^3 215 (SD, 56) WHO f/cm^3	mean L=22.12 (SD, 6.7) mean D=0.94 (SD, 0.63)	42 pleural mesotheliomas
		49, male	10 mg/m^3 chrysotile, Canadian 8.4 (SD, 9.0)×10^4 f/cm^3 3.0 (SD, 1.4)×10^3 WHO f/cm^3	mean L=1.68 (SD, 2.71) mean D=0.09 (SD, 0.06)	None
		106, male	Negative controls	NA	None
Smith et al. [1987]	Osborne-Mendel rats	55, female	10.8 mg/m^3 RCFs (Fibrefrax), 200 f/cm^3	GM_L=25 GM_D=0.9	None
		57, female	7 mg/m^3 UICC crocidolite, 3,000 f/cm^3	L=95% ≤5	1 mesothelioma 2 bronchoalveolar tumors
		59, female	Chamber controls	NA	None
		125, female	Room controls	NA	None
	Syrian golden hamsters	70, male	10.8 mg/m^3 RCFs (Fibrefrax), 200 f/cm^3	GM_L=25 GM_D=0.9	1 mesothelioma
		58, male	7 mg/m^3 UICC crocidolite, 3,000 f/cm^3	L=91%≤5	None
		58, male	Chamber controls	NA	1 bronchoalveolar tumor
		112, male	Room controls	NA	None

*Abbreviations: D=diameter; GM_D=geometric mean diameter; GM_L=geometric mean length; L=length; NA=not applicable, RCFs=refractory ceramic fibers; UICC=Union Internationale Contre le Cancer; WHO=World Health Organization.

†WHO fibers have diameters <3μm, lengths >5μm, and aspect ratios >3:1 [WHO 1985].

Table 5–5. Nontumor lung effects in animals exposed to RCFs* by inhalation

Reference	Species	Fibrosis	Lung changes	Lung fiber burden
Davis et al. [1984]	Wistar rats	Minimal peribronchiolar fibrosis Interstitial fibrosis at final sacrifice Mean % of lung area (n=6 rats)=5.0% Range=0.2%–14.5%	Large areas of alveolar proteinosis Foamy and aggregated macrophages	Mean=4,130 µg n=4 rats Range=2,800–6,800 µg
Mast et al. [1995a]	Fischer 344 rats	Interstitial fibrosis seen at 3 months (RCFs) 6 months (RCF2, RCF3) 12 months (RCF4) Pleural fibrosis seen at 9 months (RCF1, RCF2, RCF3) 12 months (RCF4)	Alveolar bronchiolization, microgranulomas, collagen deposition, and alveolar macrophage deposition were seen at 6 months (RCF1) 9 months (RCF2, RCF3) 12 months (RCF4)	3.70×10^5 RCF1 fibers/mg dry lung 9.58×10^5 RCF2 fibers/mg dry lung 2.57×10^5 RCF3 fibers/mg dry lung 5.95×10^5 RCF4 fibers/mg dry lung

See footnote at end of table.

(Continued)

Table 5–5 (Continued). Nontumor lung effects in animals exposed to RCFs* by inhalation

Reference	Species	Fibrosis	Lung changes	Lung fiber burden
Mast et al. [1995b]	Fischer 344 rats	Reversible interstitial fibrosis seen at 12 months in 16-mg/m^3 group Pleural fibrosis was minimal Interstitial fibrosis progressed in 16-mg/m^3 group such that it was irreversible Pleural and interstitial fibrosis were irreversible at final sacrifice.	Microgranulomas in 16-mg/m^3 dose group at 3 months Similar but less severe in other dose groups Progression in all 3 groups at 6 months Alveolar bronchiolization in 16-mg/m^3 group	Dose- and time-dependent increases occurred in lung and lung/body weights. RCFs were cleared quickly from lungs of animals with long recovery periods.
McConnell et al. [1995]	Syrian golden hamsters	Pleural fibrosis plateaued after 12 months as diffused thickening to raised nodules. Fibrosis seen between 12 and 18 months showed increased severity.	Alveolar bronchiolization, microgranulomas, and collagen deposition; alveolar macrophage aggregation	RCF burdens leveled off between 9 and 12 months. Recovery animals showed decreased RCF burdens with decreasing lengths and widths.
Smith et al. [1987]	Osborne-Mendel rats	12/55=22%	Bronchoalveolar metaplasia, 1/55=2%	2.18±0.99×10^4 fibers
	Syrian golden hamsters	1/70=1%	Bronchoalveolar metaplasia, 2/69=3%	0.86±0.45×10^4 fibers

*Abbreviation: RCFs=refractory ceramic fibers.

RCF4; and 1 in the chrysotile exposure group. All mesotheliomas were detected at or after 24 months of exposure. Most RCF fibers recovered in the lung were 5 to 10 μm long regardless of exposure time and recovery time. An 80% reduction in fiber lung burden was seen in rats allowed to recover for 21 months following 3 months of RCF exposure.

Mast et al. [1995b] exposed Fischer 344 rats by nose-only inhalation to 0 (air), 3, 9, or 16 mg/m^3 (0, 26±12, 75±35, or 120±35 WHO f/cm^3) RCF1 for 6 hr/day, 5 days/week for 24 months and held them until sacrifice at 30 months. Fibers were selected by size as in Mast et al. [1995a]. A particle ratio of nonfibrous particulate to fibers of 0.9–1.5:1 was reported. Groups of 3 to 6 animals were sacrificed at 3, 6, 9, 12, 18, and 24 months to examine lesions and determine fiber lung burdens. Other animals were removed from exposure at the same time points and held until sacrifice at 24 months. Interstitial fibrosis was observed after 12 months of exposure in the 9- and 16-mg/m^3 exposure groups. Pulmonary fibrosis was first observed after 12 months with 16 mg/m^3 exposure and after 18 months with 9 mg/m^3 exposure. The mean Wagner grades of pulmonary cellular change and fibrosis in rats exposed to 0, 3, 9, 16, and 30 mg/m^3 of RCFs for 24 months were 1.0, 3.2, 4.0, 4.2, and 4.0, respectively. Rats exposed at the same range of doses for 24 months and allowed to recover for 6 months had mean Wagner grades of 1.0, 2.9, 3.8, 4.0, and 4.3. The severity of interstitial and pleural fibrosis was similar between those animals sacrificed at 24 months and those allowed 6 months of recovery following the 24 months of exposure. The incidence of pulmonary neoplasms was not statistically different from the controls in all exposure groups. One pleural mesothelioma was observed in the 9-mg/m^3 exposure group. A dose-related increase occurred in fiber lung burden. Fiber lengths of 5 to 10 μm were most prevalent in the lung fibers recovered after 3 months of exposure followed by 21 months of recovery, after 12 months of exposure, and after 24 months of exposure to all doses of RCFs. Animals exposed for 3 or 6 months and then allowed to recover until sacrifice at 24 months had lung burdens reduced by 96% to 97% compared with animals not allowed recovery time.

McConnell et al. [1995] exposed Syrian golden hamsters by nose-only inhalation to 30 mg/m^3 RCF1 (256±58 WHO f/cm^3) for 6 hr/day, 5 days/week for 18 months and held them until sacrifice at 20 months. Positive control animals were exposed to 10 mg/m^3 (8.4±9.0×10^4 WHO f/cm^3) chrysotile asbestos. Groups of 3 to 6 animals were sacrificed at 3, 6, 9, 12, 15, and 18 months to examine lesions and determine fiber lung burdens. Other animals were removed from exposure at the same time points and held until sacrifice at 20 months. Interstitial and pleural fibrosis were first observed after 6 months of exposure in RCF-exposed hamsters. No pulmonary neoplasms developed. Forty-two of 102 (41.2%) RCF-exposed animals developed pleural mesotheliomas. Most mesotheliomas developed after 18 months of exposure. Animals exposed to chrysotile developed a more severe interstitial fibrosis and pleural fibrosis than those exposed to RCFs. No neoplasms were observed in the lungs or pleura of the chrysotile-exposed or air control animals. The greatest percentage of retained fibers had lengths of 5 to 10 μm and diameters <5 μm in the lungs after 6 months of exposure followed by 12 months of recovery.

McConnell et al. [1999] conducted a multidose chronic study of the effects of amosite inhalation in hamsters. The data can be compared with the effects of RCF1. Syrian golden hamsters were exposed to 0.8 (36±23 WHO f/cm^3), 3.7 (165±61 WHO f/cm^3), or 7 mg/m^3 (263±90 WHO f/cm^3) amosite asbestos. Pleural mesothelioma incidences of 3.6%, 25.9%, and 19.5%, respectively, were reported. The aerosol mean

diameter of the amosite asbestos was 0.60 µm ±0.25; its aerosol mean length was 13.4 µm ±16.7. The dimensions of this asbestos fiber were more similar to those of the RCFs used in the chronic inhalation studies of McConnell et al. [1995] than the chrysotile asbestos used as the positive control in that same study.

NIOSH [Dankovic 2001] analyzed the hamster data from the RCF [McConnell et al. 1995] and amosite studies [McConnell et al. 1999]. A dose-response model was developed for amosite and was used to predict the amosite response at the one and only dose at which RCFs were tested in hamsters. The modeled amosite response was compared with the observed RCF response. These results are presented in Figures 5–1 and 5–2. Log-probit, log-logistic, multistage, and unrestricted Weibull models were analyzed. The transformation for the log-probit and log-logistic models was log (fibers/cm^3 +1). The dose metric of the multistage and Weibull models was fibers/cm^3, as they did not require a log-transformation. Results of the log-probit model analysis of these data indicated RCF/amosite relative potency estimates of 1.85 and 1.19, using WHO fibers and fibers >20 µm as the dose metric, respectively. The model fits were poor when the amosite high-dose group and 20 µm-fiber dose were included. Sensitivity analyses in which the high-dose amosite group was dropped suggest that the relative potency of RCFs to amosite could be as low as 0.66 based on the log-probit model. Results using the log-logistic, multistage, and Weibull models were similar to those using the log-probit model, with an overall range of RCF/amosite relative potency estimates from these models using all four amosite dose groups of 1.03 to 1.89. Although no clear toxicologic basis exists for disregarding the high-dose amosite data, sensitivity analyses based on excluding these data suggest that the potency of RCFs relative to amosite could be as low as 0.47, based on the multistage model. These models indicate that the plausible carcinogenic potency estimates for RCFs relative to amosite, based on hamster mesotheliomas, range from about half to nearly twice the carcinogenicity of amosite.

5.1.3 Discussion of RCF Studies in Animals

The intrapleural, intraperitoneal, and intratracheal RCF studies have demonstrated the carcinogenicity of RCFs. Because of the nonphysiologic delivery of fibers by these methods, it is difficult to compare their results with those of an inhalation exposure. Although tracheal instillation may result in different distribution patterns than an inhalation exposure, this route of exposure is useful as a screening test for relative toxicity and to compare the toxicity of new materials with the toxicity of materials for which data already exist [Driscoll et al. 2000]. Tracheal instillation also is useful when testing fibers respirable by humans but not rodents. Chronic inhalation studies provide the data most relevant to occupational exposure to RCFs.

The RCF chronic animal inhalation studies described above allow for the comparison of health effects of exposure to different doses of RCF1, different types of RCFs, and the interspecies susceptibility of the rat and hamster to RCF exposure.

Results of the multidose chronic inhalation testing of RCF1 in rats indicate the pathogenic potential of RCFs at high doses [Mast et al. 1995a,b]. The incidence of total lung tumors was significantly increased from controls after exposure to 30 mg/m^3 RCF1, RCF2, and RCF3 but not RCF4. A dose-response relationship was demonstrated for nonneoplastic pulmonary changes in rats exposed to 3, 9, and 16 mg/m^3 RCFs. The severity of interstitial and pleural fibrosis was similar between those animals sacrificed at 24 months and those allowed 6 months

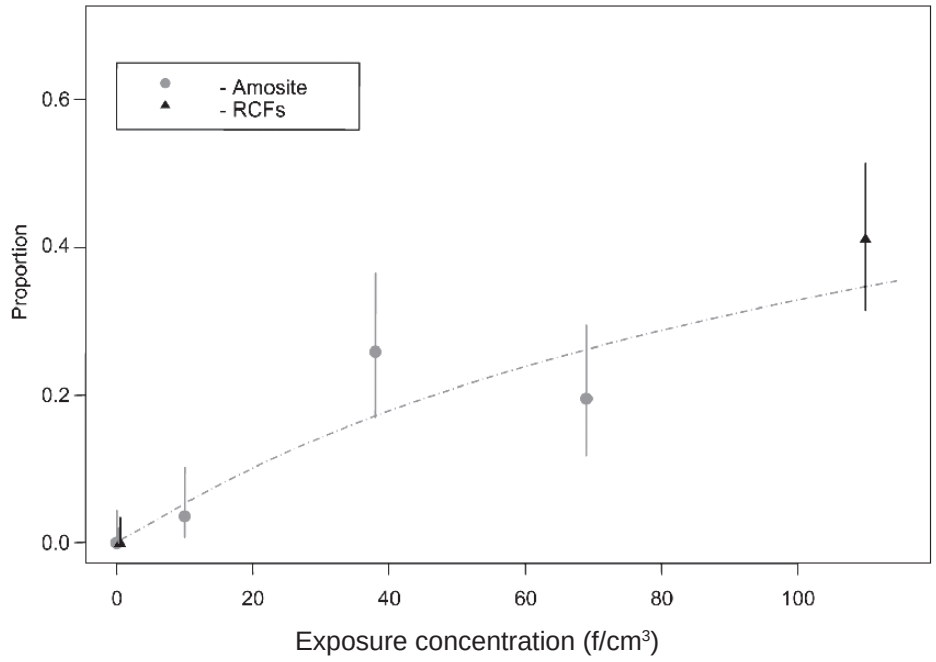

Figure 5–1. Proportion of hamsters with mesotheliomas following exposure to amosite or RCFs. Concentrations are based on fibers >20μm long. The 95% confidence limits are based on assuming a binomial distribution. Dashed lines represent the log-probit model fitted to the amosite data [Dankovic 2001]. (Source: McConnell et al. [1995, 1999].)

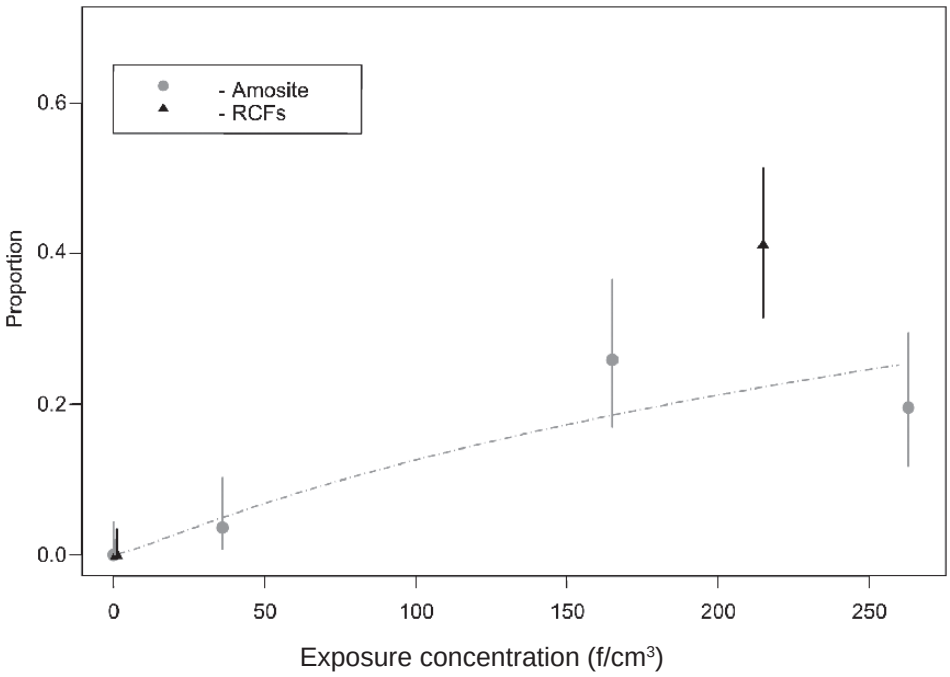

Figure 5–2. Proportion of hamsters with mesotheliomas following exposure to amosite or RCFs. Concentrations are based on WHO fiber dimension criteria. The 95% confidence limits are based on assuming a binomial distribution. Dashed lines represent the log-probit model fitted to the amosite data [Dankovic 2001]. (Source: McConnell et al. [1995, 1999].)

of recovery following the 24-month exposure. Spontaneous primary pulmonary mesotheliomas are rare in rats [Analytical Sciences Incorporated 1999]. Therefore, the presence of any mesothelioma in treated animals is biologically significant and warrants caution.

Comparing the chronic effects of RCF1 with its positive control, chrysotile asbestos, in the hamster is difficult because of the differences in dose, dimensions, and durability of the two fibers tested [McConnell et al. 1995]. More recent dose-response data on amosite asbestos provide a comparison because these amosite fiber dimensions more closely resemble those of RCF1 [McConnell et al. 1999]. The mean lengths of the RCFs and amosite asbestos fibers were 22.1 (±16.7) and 13.4 (±16.7) μm, respectively. Forty-three percent of RCF fibers and ~26% of amosite asbestos fibers were longer than 20 μm. The mean diameters of the RCFs and amosite asbestos fibers were 0.94 (±0.63) and 0.60 (±0.25) μm, respectively. Interstitial and pleural fibrosis were seen much earlier with amosite exposure than with RCF exposure. RCF exposure at 215 (±56) WHO f/cm^3 resulted in mesotheliomas in 42 of 102 (41%) hamsters. Amosite asbestos exposure at 263 (±90) WHO f/cm^3 resulted in mesotheliomas in 17 of 87 (19.5%) hamsters. Modeling of these data indicates that the plausible carcinogenic potency estimates for RCFs relative to amosite, based on hamster mesotheliomas, range from about half to nearly twice the carcinogenicity of amosite [Dankovic 2001]. Differences in the physical characteristics and biopersistence of RCF1 and amosite asbestos must be considered before extrapolating these animal data to human risk.

Hamsters showed a greater susceptibility to mesothelioma induction after RCF1 exposure than did rats under similar exposure conditions [Mast et al. 1995a; McConnell et al. 1995]. Chronic inhalation studies of amosite asbestos in hamsters showed no pulmonary neoplasms, but high incidences of mesothelioma occurred at doses of 125 and 250 f/cm^3 [McConnell et al. 1999]. Many of the mesotheliomas in the more recent hamster studies were identified only on microscopic examination [Mast et al. 1995a; McConnell et al. 1995, 1999]. Previous studies reporting mesotheliomas only by macroscopic identification may have underestimated the mesothelioma incidence. Recent, short-term inhalation studies indicate that hamster mesothelial cells may have a more pronounced inflammatory and proliferative response to RCF1 exposure than those of rats [Everitt 1997; Gelzleichter et al. 1996a,b, 1999]. The reasons for this species difference in response to RCFs have not been explained. The results of these animal studies indicate the need for the inclusion of the hamster as a sensitive test species in those studies in which pleural mesothelioma is an endpoint of concern.

Results from Mast et al. [1995a] indicate that under the conditions studied, exposure to RCF4 may have a less pronounced effect on pulmonary pathology than exposure to RCF1, RCF2, and RCF3. Rats exposed to RCF4 did not have a significant increase in total lung tumors compared with controls; those exposed to RCF1, RCF2, and RCF3 did. Exposure to RCF4 produced a less severe fibrosis than was seen in the other RCF exposure groups. Differences in the dimensions or physical properties of RCF4 may explain its different respiratory effects from RCF1, RCF2, and RCF3. RCF4 was produced by heating RCF1 in a furnace at 2,400 °F for 24 hr. This "after-service" fiber contained approximately 27% free crystalline silica. Silicotic nodules were observed in the RCF4-exposed animals. RCF4 fibers were shorter (~34% between 5 and 10 μm) and thicker (~35% <0.5 μm) than those of RCF1, RCF2, and RCF3.

The particle content of the RCF test material may have been responsible for some of the respiratory pathology observed in these studies.

However, an analysis of the ratio of nonfibrous to fibrous particulates in the reviewed studies does not indicate a correlation between the particulate content and observed effects. Smith et al. [1987] performed testing with the highest particulate to fiber ratio at 33:1 and did not report a high tumor incidence. Comparing studies based on the ratio of nonfibrous particulates to fibers is complicated by differences among the studies in fiber preparation, doses tested, fiber dimensions, and methods of fiber analysis. The techniques used to detect and measure nonfibrous particulates have improved over time so that the comparison of recent and older studies may reflect these inconsistencies.

These chronic RCF inhalation studies indicate the ability of RCFs to induce cancer in two laboratory species—mesotheliomas in hamsters and pulmonary tumors in rats. The late onset of tumors indicates the importance of chronic studies on the effects of RCF exposure. Short-term intraperitoneal, intrapleural, intratracheal, and inhalation studies provide important information about the action of fibers, the fiber characteristics associated with toxicity, and potential toxicity. Currently it is only through lifespan toxicologic testing of animals that the respiratory and other chronic health effects of RCFs can be accurately assessed.

5.1.4 Lung Overload Argument Regarding Inhalation Studies in Animals

Mast et al. [2000] published a review interpreting the results of chronic inhalation studies of RCF1 in rats and hamsters [Mast et al. 1995a,b; McConnell et al. 1995]. In the review, the authors suggest the possibility that the maximum tolerated dose (MTD) may have been exceeded and that lung overload may have compromised the pulmonary clearance mechanisms of test animals. Building on the concept of lung overload (first advanced by Bolton et al. [1983]), Mast et al. [2000] considered particulate coexposure (i.e., nonfibrous particulate or shot) to be a confounding factor that may have had a major effect on the observed chronic adverse effects. The authors propose that the MTD was exceeded at the highest exposure concentration of 30 mg/m^3 for RCF1 in the rat bioassay.

The concept of pulmonary overload in the Fischer 344 rats is based on the recognition that excessive particulate exposures (>1,500 µg/rat, according to Bolton et al. [1983]) eventually reduce the clearance effectiveness of the lungs, causing the normal linear clearance kinetics to follow a nonlinear pattern. On a cellular level, the overload conditions may result in alveolar macrophages becoming engorged with particulate, pulmonary and alveolar inflammation, increased translocation of particles to the interstitium and lymph, granuloma formation, pulmonary fibrosis, and lung tumors, depending on the time and severity of the overload [Mast et al. 2000]. Ambiguity about the definition of MTD for chronic inhalation studies with animals was also a concern expressed by the authors. One reference [Morrow 1986] recognizes the MTD as that which causes "a significant functional impairment of lung clearance." At a National Toxicology Program (NTP) workshop on establishing exposure concentrations for inhalation studies in animals, it was concluded that the highest exposure concentration should produce only minimal changes in lung defense mechanisms as measured by clearance [Lewis et al. 1989]. At a similar workshop convened by the EPA, it was proposed that the MTD for fiber inhalation studies is equivalent to the lung dose produced at the maximum achievable concentration (MAC) [Vu et al. 1996]. The MAC is calculated as the highest fiber concentration based on a 90-day study that results in significant changes in alveolar macrophage clearance rates, lung burden normalized to exposure

concentration, cell proliferation, inflammation, lung weight, and other measures.

The methodology described for the RCF chronic inhalation studies involved procedures (i.e., wet cyclone separation technology) for removing the nonfibrous particulate fraction from the commercial fiber (RCF1) used for the inhalation exposures [Mast et al. 1995a,b 2000; McConnell et al. 1995]. This process resulted in an aerosol with a 9.1:1 particle-to-fiber ratio [Maxim et al. 1997; Mast et al. 2000], compared with a study by Smith et al. [1987], which reported 33 nonfibrous particles per fiber in airborne exposures. Results from Esmen et al. [1979] indicate that despite a poor correlation between mass of total airborne dust and fiber concentration in RCFs measured in manufacturing, fibers generally constitute only a small portion of the total dust. This finding is consistent with other reported measures of occupational exposures to airborne RCFs [Krantz et al. 1994; Trethowan et al. 1995]. However, Maxim et al. [1997] reported an average particle-to-fiber ratio of 0.53:1 (n=10, range not reported), or roughly 1 particle to 2 fibers in RCF manufacturing facilities.

Muhle and Bellmann [1996] conducted a 5-day inhalation study with Fischer 344 rats to measure the biopersistence of RCF1 (with the 9:1 particulate-to-fiber ratio) and RCF1a (RCF1 that is further processed to reduce particulate mass). The study showed a 1.5-fold longer time-weighted half-life for RCF1 ($t_{1/2}$=78 days) compared with RCF1a ($t_{1/2}$=54 days). That study also involved a 3-week inhalation experiment with Fischer 344 rats, in which the clearance of RCF1 ($t_{1/2}$=103 days) was almost twice as long as that of RCF1a ($t_{1/2}$=54 days).

In a follow-up study by Brown et al. [2000], female Wistar rats were exposed to RCF1 and RCF1a by inhalation for 3 weeks and followed for 12 months to evaluate alveolar macrophage clearance and inflammation. The exposure concentrations were 130 fibers/ml >20 μm for RCF1 and 125 fibers/ml >20 μm for RCF1a. The nonfibrous content of RCF1 was approximately 25%, whereas the nonfibrous content of RCF1a was 2%. The mean diameter of the nonfibrous particles was 2 to 3 μm. The aerosol exposure to RCF1 contained twice as many short fibers (<20 μm) as RCF1a and twice the amount of dust (fibers and nonfibrous dust/mg · m^3) as RCF1a (51 versus 25.8 mg/m^3). At the end of the inhalation period, animals exposed to RCF1a had a higher pulmonary concentration of long fibers but lower concentrations of short fibers and nonfibrous particles. The difference in particle content was enhanced in the lungs—15 times more particles were found in the lungs of the RCF1-exposed animals than in those exposed to RCF1a. In the aerosol exposure, only an eightfold difference was found in the number of particles between RCF1 and RCF1a. The RCF1a-exposed animals had a half-time alveolar clearance of 80 days (71–91) compared with 60 days (49–77) for the controls; clearance half-time for exposed RCF1 animals was 1,200 days (573-infinity) compared with 66 (58–88) for the corresponding controls. To evaluate respiratory inflammation, bronchoalveolar lavage (BAL) measurements (lactose dehyrdogenase [LDH], γ-glutamyltransferase [γ –GT], total protein, reduced glutathione [GSH]) were taken at the end of the 3-week study period and at subsequent intervals over the next 12 months. Immediately following the 3-week inhalation study, all BAL measurements were statistically elevated in both RCF1 and RCF1a animals. However, after 91 days of recovery, the BAL measurements for RCF1a animals returned to normal. Indications of inflammation continued for RCF1 through the entire observation period. The greater and more persistent inflammation seen with RCF1 was attributed to the greater mass of material or to increased activity of the nonfibrous particles, although the high concentration of short fibers in RCF1 (twice that of RCF1a) could

have contributed to the observed impedance in alveolar macrophage clearance and inflammation.

Tran et al. [1997] examined how overloading the alveolar macrophage defense system affects the clearance of fibers versus that of nonfibrous particles. Modeling was performed based on data for rats exposed by inhalation to titanium dioxide (TiO_2) at 1, 10, and 50 mg/m^3 or to glass wool (MMVF10) at 3, 16, and 30 mg/m^3. Lung burdens and clearance kinetics during exposure (0 to 100 weeks) were compared with those at 3, 10, and 38 days post-exposure. The models showed that overloading of the lung by fibers or nonfibrous particles are similar when fibers are short (<15 µm). This observation is plausible, as nonfibrous particles and short fibers smaller than the diameter of the alveolar macrophage are most readily engulfed and cleared via the macrophages. When this defense is overwhelmed (lung burden ≥10 mg), these particles are cleared less effectively. For fibers longer than 15 µm, phagocytosis by alveolar macrophage is reduced. As fiber length increases, fibers tend to be cleared by dissolution and disintegration of long fibers into shorter fibers or fragments. Therefore, clearance of long fibers is not affected by the overloading of macrophage-mediated defenses with shorter fibers or nonfibrous particles.

The exposure concentrations for the RCF chronic inhalation bioassays were measured and reported as mass in mg/m^3. Monitoring of exposures as performed by gravimetric analysis does not distinguish fibers from nonfibrous particulate, although fiber concentration and dimensions were also checked by phase contrast and electron microscopy [Mast et al. 1995a,b]. Consequently, the particulate fraction was included in the dose measurements. This fact does complicate efforts to compare the relative toxicity of fibers, nonfibrous particulate, and total combined particulate, especially regarding the lung overload hypothesis. During production of RCFs and RCF products, however, the nonfibrous particulate fraction is associated with the fiber, as shown in Table 2–1 (i.e., 20% to 50% of RCFs by weight is nonfibrous particulate). This suggests that occupational exposures to airborne RCFs necessarily involve coexposures to a fraction of nonfibrous particulate, a suggestion that has been supported by exposure assessment studies [Esmen et al. 1979; Krantz et al. 1994; van den Bergen et al. 1994; Trethowan et al. 1995; Maxim et al. 1997; Mast et al. 2000].

5.2 Cellular and Molecular Effects of RCFs (In Vitro Studies)

The cellular and molecular effects of RCF exposures have been studied with two different objectives. One purpose of these in vitro studies is to provide a quicker, less expensive, and more controlled alternative to animal toxicity testing. These experiments are best interpreted by comparing their results with those of in vivo experiments. The second objective of in vitro studies is to provide data that may help to explain the pathogenesis and mechanisms of action of RCFs at the cellular and molecular levels. These cytotoxicity and genotoxicity studies are best interpreted by comparing the effects of RCFs with those of other SVFs and asbestos fibers. In vitro studies serve as screening tools and provide insights into the molecular mechanisms of fibers. They are an important complement to animal studies. Currently it is not possible to use these data to derive the NIOSH REL for RCFs. For this reason, a discussion of in vitro studies is included here, but the more comprehensive summaries of studies are included in Appendix C.

The toxicity of fibers has been attributed to their dose, dimensions, and durability. Any test

system that is designed to assess the potential toxicity of fibers must address these factors. Durability is difficult to assess using in vitro studies because of their acute time course. However, in vitro studies provide an opportunity to study the effects of varying doses and dimensions of fibers in a quicker, more efficient method than animal testing. They do not currently provide data that can be extrapolated to occupational risk assessment.

The association between fiber dimension and toxicity has been documented and reviewed [Stanton et al. 1977, 1981; Pott et al. 1987; Warheit 1994]. RCFs may have different toxicities, depending on the fiber length relative to macrophage size. Longer fibers are more toxic. Fiber length has been correlated with the cytotoxicity of glass fibers [Blake et al.1998]. Manville code 100 (JM–100) fiber samples with average lengths of 3, 4, 7, 17, and 33 μm were assessed for their effects on LDH activity and rat alveolar macrophage function. The greatest cytotoxicity was reported in the 17- and 33-μm samples, indicating that length is an important factor in the toxicity of this fiber. Multiple macrophages were observed attached along the length of long fibers. Relatively short fibers (<20 μm) were usually phagocytized by one rat alveolar macrophage [Luoto et al. 1994]. Longer fibers were phagocytized by two or more macrophages. Incomplete or frustrated phagocytosis may play a role in the increased toxicity of longer fibers. Long fibers (17 μm average length) were a more potent inducer of tumor necrosis factor (TNF) production and transcription factor activation than shorter fibers (7 μm average length) [Ye et al. 1999]. These studies demonstrate the important role of length in fiber toxicity and suggest that the capacity for macrophage phagocytosis may be a critical factor in determining fiber toxicity.

Several of the in vitro RCF studies (summarized in Appendix C) reported a direct association between a longer fiber length and greater cytotoxicity. Hart et al. [1992] reported the shortest fibers to be the least cytotoxic. Brown et al. [1986] reported an association between length, but not diameter, and cytotoxic activity. Wright et al. [1986] reported that cytotoxicity was correlated with fibers >8 μm long. Yegles et al. [1995] reported that the longest and thickest fibers were the most cytotoxic. The four most cytotoxic fibers had GM lengths ≥13 μm and GM diameters >0.5 μm. The production of abnormal anaphases and telophases was associated with Stanton fibers with a length >8 μm and diameter <0.25 μm. Hart et al. [1994] reported that cytotoxicity increased with increasing average fiber lengths from 1.4 to 22 μm, but did not increase with average lengths from 22 to 31 μm.

Additional studies assessing the cytotoxicity of specific RCF fiber lengths are needed. Such studies will help to describe the association between fiber length and toxicity for RCFs and may allow determination of a threshold length above which toxicity increases significantly. In addition to providing data on the correlation between fiber length and toxicity, in vitro studies have provided data on the relative toxicity of RCFs compared with other fibers, although some uncertainties remain in the interpretation of these studies because of differences in fiber doses, dimensions, and durabilities. RCFs have direct and indirect effects on cells and alter gene function in similar ways. They are capable of inducing enzyme release and cell hemolysis. They may decrease cell viability and inhibit proliferation. RCFs affect the production of TNF and reactive oxygen species (ROS) and affect cell viability and proliferation. They induce necrosis in rat pleural mesothelial cells. They may also induce free radicals, micronuclei, polynuclei, chromosomal breakage, and hyperdiploid cells in vitro.

In vitro studies provide an excellent opportunity for investigating the pathogenesis of RCFs. However, comparisons are difficult to make

between in vitro studies based on differences in fiber doses, dimensions, preparations, and compositions. Important information such as fiber length distribution is not always determined. Even when comparable fibers are studied, the cell line or conditions under which they are tested may vary. Much of the research to date has been done in rodent cell lines and in cells that are not related to the primary target organ. In vitro studies using human pulmonary cell lines should provide pathogenesis data most relevant to human health risk assessment.

Short-term in vitro studies cannot take into account the influence of fiber dissolution and fiber compositional changes that may occur over time. In an in vivo exposure, fibers are continually modified physically, chemically, and structurally by components of the lung environment. This complex set of conditions is difficult to recreate in vitro. Just as it is unlikely that only one factor is an accurate predictor of fiber toxicity, it is unlikely that any one in vitro test is able to predict fiber toxicity.

5.3 Health Effects in Humans

5.3.1 Morbidity and Mortality Studies

Two major research efforts evaluated the morbidity of RCF-exposed workers—one conducted in U.S. plants and one in European plants. Table 5–6 describes the populations analyzed for both studies. The objective of these research efforts was to evaluate the relationship between occupational exposure to RCFs and potential adverse health effects. These studies included standardized respiratory and occupational history questionnaires, chest radiographs, and pulmonary function tests (PFTs) of workers, as well as air sampling to estimate worker exposures. The studies of European plants began in 1986. Study subjects included only current workers at seven RCF manufacturing plants [Rossiter et al. 1994; Trethowan et al. 1995; Burge et al. 1995]. A followup cross-sectional study conducted in 1996 evaluated the same medical endpoints in workers from six of these seven European manufacturing plants (one plant had ceased operation) [Cowie et al. 1999, 2001]. Current and former workers were included as study subjects in the followup study. The studies of U.S. plants began in 1987 and involved evaluations of current workers at five RCF manufacturing plants and former workers at two RCF manufacturing plants [Lemasters et al. 1994, 1998; Lockey et al. 1993, 1996, 1998, 2002].

In the United States, the earliest commercial production of RCFs and RCF products began in 1953; in Europe, RCF production began in 1968. The demographics of the U.S. and European populations were similar at the time they were studied, although the average age of U.S. workers was slightly higher than that of the workforce in the 1986 European studies because of the earlier development of this industry in the United States. The mean age for the European RCF workers was 37.7 in the 1986 study [Trethowan et al. 1995] and 42.0 for males and 39.4 for female workers in the 1996 study [Cowie et al. 1999]. In the U.S. RCF manufacturing industry, the average age is 40 for current workers and 45 for former workers [Lemasters et al. 1994]. The mean duration of employment in the European cohort was 10.2 years (range 7.2 to 13.8 years) in 1986 [Trethowan et al. 1995] and 13.0 years in 1996 [Cowie et al. 1999]. The U.S. study reports the mean duration of employment for 23 workers with pleural plaques as 13.6 years (±9.8); the median is 11.2 years (range 1.4 to 32.7) [Lemasters et al. 1994].

The following text and Table 5–7 summarize findings from the U.S. and European research efforts, organized according to results from radiographic examinations, respiratory symptoms, and PFTs. Discussion of two related

Table 5–6. Cited studies of populations with occupational exposures to RCFs*

Study	Design	Population analyzed				Outcome measures		
		Employment status	Number	% male workers	% female workers	Radiography	PFT	Symptoms
European:								
Burge et al. 1995‡	Cross-sectional	Current§	532	100	0	N	Y	Y
Rossiter et al. 1994‡	Cohort morbidity	Current**	543	100	0	Y	N	N
Trethowanet al. 1995‡	Cross-sectional	Current	628	91	9	Y	Y	Y
Cowie et al. 1999††	Cross-sectional	Current	695	90	10	Y	Y	Y
		Former	79	85	15			
United States:‡‡								
Lemasters et al. 1994	Cross-sectional	Current	627	83	17	Y	N	N
Lemasters et al. 1994	Cross-sectional	Former§§	220	91	9			
Lockey et al. 1993:	Cohort mortality	Current and former	684 (including 46 deceased and 5 lost to followup)***	100	0	N	N	N (Cause of death)
	Cohort morbidity	Current and former	801 (participants; 99% provided respiratory history, 94% provided PFTs, and 90% provided chest X-rays [radiography])	85	15	Y	Y	Y
Lockey et al. 1996	Cohort morbidity	Current	370	NA	NA	Y	N	N
		Former	282†††	NA	NA	NA	NA	NA
	Nested case-control	Both (17 cases with 3 controls each matched on current versus former status)	NA	NA	Y	Y	N	N
Lockey et al. 1998	Cross-sectional and longitudinal	Current	361‡‡‡	100	0	N	Y	N

See footnotes on next page.

*Abbreviations: N=number; NA=not available from published citation; PFT=pulmonary function test; RCFs=refractory ceramic fibers; Y=yes.
†Current versus former (and leaver) worker status at an RCF manufacturing plant as determined at time of survey.
‡Study included current workers at seven ceramic fiber manufacturing plants in three European countries.
§From a possible 708 current workers, 628 eligible participants were identified and 596 had chest X-ray examinations; 51 female workers and 13 unexplained others were excluded from analysis.
**From a possible 708 current workers, 628 eligible participants were identified and 596 had chest X-ray examinations; 2 unreadable films and those of 51 female workers were excluded from the analysis.
††Study included current workers at six ceramic fiber manufacturing plants in three European countries as well as leavers from the first three European studies [Burge et al. 1995; Rossiter et al. 1994; Trethowan et al. 1995] (one of the seven plants included earlier had ceased operation).
‡‡Studies included current and former workers at five RCF manufacturing plants in the United States.
§§From a possible 1,030 eligible current and former workers, 183 were either deceased, not located, or did not agree to chest X-ray examinations.
***From a possible 729 eligible current and former workers at 2 plant sites for whom individual work histories were available, 45 were excluded on the basis of insufficient exposures to fibers or insufficient data regarding fiber exposures.
†††From a possible 868 eligible current and former workers at 2 plant sites, 148 were eliminated for lack of exposure characterization data and loss to followup. Of the remaining 720 workers, 68 did not agree to chest X-ray examinations.
‡‡‡From a possible 963 eligible current workers at five plant sites, 209 female workers were excluded as well as 393 male workers with fewer than 5 PFT sessions.

mortality studies is also presented in Section 5.3.5 [Lockey et al. 1993; Lemasters et al. 2003]. Two HHEs of workplaces involving workers exposed to RCFs are also described in Section 5.3.6 [Kominsky 1978; Lyman 1992].

5.3.2 Radiographic Analyses

In both the European and U.S. studies cited in Table 5–6, the study populations included workers at multiple plants involved in the manufacture of RCFs or RCF products. As part of the investigation of potential effects of exposure to airborne RCFs, chest radiography was performed. In all studies, chest radiographs were read independently by three readers using the International Labour Office (ILO) 1980 *International Classification of the Radiographs of Pneumoconioses* [ILO 1980]. Identifiers on films were masked to ensure a blind review by readers, and quality control measures and tests of agreement were used to check consistency among the readers. For each type of abnormality analyzed, the median of the three readings for each film was used.

5.3.2.1 Pleural abnormalities

In the 1986 study of European RCF workers, results of the chest radiography indicated a prevalence of 2.8% (15/543) for pleural abnormalities among male workers [Rossiter et al. 1994]. Of the 15 cases with pleural abnormalities, 4 had bilateral diffuse thickening (1 with calcification), 1 showed bilateral pleural calcification only, 7 presented with unilateral diffuse thickening, and 3 showed costophrenic angle blunting only. The possibility for confounding effects was recognized because of other exposures: 52% of workers reported previous employment in dusty jobs, including 4.5% with prior asbestos exposures and 7% with prior MMMF exposures. When female workers were included in the same population, Trethowan et al. [1995] reported a prevalence of 2.7% (16/592) for pleural abnormalities. Two cases were known to have previous exposure to asbestos, and the possibility for exposure to other respiratory hazards was acknowledged for other persons with pleural abnormalities. Cowie et al. [1999, 2001] reported pleural abnormalities in 10% (78/774) and

Table 5–7. U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Lemasters et al. 1994 (U.S. study)	**Cross-sectional study:** 1,030 current and former workers at five U.S. RCF production facilities employed 10/87–8/89. Male workers: at least 1 year of employment in fiber division. Female workers: at least 1 year of employment in fiber division and ≥4 hr per week in production.	Posteroanterior chest X-ray examinations were performed for 847 workers. Occupational and respiratory health histories were obtained using standardized questionnaire. Standardized measures of pulmonary function (FEV_1, FVC, and $FEF_{25–75}$) were used.	**Radiographic analyses:** ***Pleural changes*** Pleural changes were seen in 3.4% of production workers (23/686) and in 0% of nonproduction workers (0/161); 91.3% of pleural changes were classified as pleural plaques. No irregular opacities were observed.	Multiple logistic regression found a statistically significant association between pleural plaques and time since first RCF production job (>20 years) after adjustment for known asbestos exposure and a statistically significant association between pleural plaques and duration (>20 years) of RCF exposure.

Pleural changes

Item	Prevelance (%)	OR	95% CI
Years of latency:†			
>0–10	1.3	1.0	—
>10–20	3.6	2.9‡,§	0.8, 9.7
>20	11.4	7.7‡,§	2.0, 29.1
Years of RCF exposure:			
>0–10	1.9	1.0	—
>10–20	4.3	2.5**,††	0.9, 7.0
>20	20.7	8.8**,††	2.6, 30.1

(Continued)

*Abbreviations: CI=confidence interval; $FEF_{25–75}$=forced expiratory flow between 25% and 75% of the FVC; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; OR=odds ratio; RCFs=refractory ceramic fibers.
†Latency: time since first RCF exposure.
‡Compared with >0–10 years of latency.
§Adjusted for years of latency and years of asbestos exposure.
**Compared with >0–10 years of RCF exposure.
††Adjusted (confounding variables not described).

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Lemasters et al. 1998 (U.S. study)	**Cross-sectional study:** 742 of 753 active workers (597 male; 145 female) at five RCF manufacturing sites who participated in occupational history interviews between 1987 and 1989.	**Medical Evaluation:** Modified American Thoracic Society (ATS) questionnaire. Spirometric evaluation (pulmonary function) at time of ATS interview. Measures included FEV_1, FVC, and $FEF_{25\%-75\%}$. **Exposure assessment:** Occupational history interview **Production work:** Defined as spending ≥4 hr/week (10% of work time) in production areas.	**Symptom analysis** **Prevalence (%)** **Symptom** / **Nonproduction workers** / **Production workers** / **OR†** / **95% CI** Male workers: n=80 / n=517 / — / — Dyspnea 1: 2.5 / 15.7 / 7.3‡ / 1.7, 30.5 Dyspnea 2: 0.0 / 4.8 / — / *P*=0.03‡ Wheezing: 3.8 / 10.3 / 2.5 / 0.8, 8.5 Asthma: 2.5 / 2.3 / 1.0 / 0.2, 4.7 Chronic cough: 5.0 / 7.4 / 1.0 / 0.3, 3.0 Chronic phlegm: 3.8 / 5.8 / 1.2 / 0.4, 4.6 Pleuritic pain: 0.0 / 1.6 / — / *P*=0.31 One or more symptoms: 11.3 / 29.6 / 2.9‡ / 1.4, 6.2 Female workers: n=59 / n=86 / — / — Dyspnea 1: 18.6 / 25.6 / 1.3 / 0.6, 3.2 Dyspnea 2: 0.0 / 10.5 / — / *P*=0.001‡ Wheezing: 1.7 / 7.0 / 3.9 / 0.4, 38.8 Asthma: 0.0 / 3.5 / — / *P*=0.21 Chronic cough: 1.7 / 9.3 / 5.4 / 0.6, 46.9 Chronic phlegm: 1.7 / 9.3 / 3.8 / 0.4, 33.5 Pleuritic pain: 0.0 / 3.5 / — / *P*=0.21 One or more symptoms: 20.3 / 40.7 / 2.4‡ / 1.1, 5.3	Prevalence of respiratory symptoms (except for asthma) was approximately 2- to 5-fold higher in production workers than in nonproduction workers.

(Continued)

*Abbreviations: ATS = American Thoracic Society; CI = confidence interval; $FEF_{25\%-75\%}$ = Forced expiratory flow between 25% and 75% of the FVC; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; n = number; OR = odds ratio; *P* = probability; RCFs = refractory ceramic fibers.

†Adjusted for age, smoking (category and pack years), and years of possible asbestos exposure in a logistic regression model.

‡Statistically significant ($P<0.05$).

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods				Results	Comments
Lemasters et al. 1998, continued (U.S. study)	**Multiple regression analysis**† of change in volume (ml) of height-adjusted spirometric measures (95% CI) associated with RCF employment duration. Controlled for smoking status.	**Pulmunary function** **Δ volume in (ml)**				Years of RCF production employment were significantly related to volume decline in (1) FVC for male current and past smokers, (2) FEV_1 in male current smokers, and (3) FVC for female never smokers.	
		Item	**Current smokers**	**Past smokers**	**Never smokers**		
		Male workers	**n=245**	**n=174**	**n=173**		
		[FVC] years of RCF employment	–165.4‡ (–279.8, –51.0)	–155.5‡(–301.9, –9.1)	–40.6 (–175.1,193.8)		
		[FEV_1] years of RCF employment	–134.9‡ (–231.3, –38.5)	–72.5 (–195.9, 50.9)	–20.4 (–133.7, 92.9)		
		Female workers	**n=56**	**n=20**	**n=68**		
		[FVC] years of RCF employment	–110.8 (–411.5, 190.0)	–330.5 (–872.1, 211.1)	–350.3‡ (–692.0, 8.7)		
		[FEV_1] years of RCF employment	13.9 (–218.7, 246.5)	–321.4 (–740.2, 97.4)	–223.5 (–487.7, 40.7)		

(Continued)

*Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; n=number; O=odds ratio; RCFs=refractory ceramic fibers.
†Variables included in model: smoking category, interaction term for duration of RCF production and smoking category, interaction term for pack-years and smoking category, weight, and plant location.
‡Statistically significant ($P \leq 0.05$).

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Lockey et al. 1996 (U.S. study)	**Cohort study:** 652 workers (a) who were employed between 10/87 and 12/91 or who had ≥1 year of employment in the RCF division at one of two plant sites, *and* (b) who completed an occupational history and provided posterior-anterior and two oblique chest X-rays. **Nested case-control study:** 17 cases of pleural plaque matched to 3 controls by sex and employment status (current or former worker; production or nonproduction)	**Health:** Occupational history interview, information about work/home asbestos exposure; chest X-rays. **Exposure:** Estimated concentrations of fiber exposure for each job using historical plant process, design and engineering controls, and sampling data plus worker interviews [Rice et al. 1994, 1996]. **Exposure:** Controls and cases reinterviewed with additional questions regarding asbestos exposure (application, manipulation, and distance from exposure). Asbestos exposure categorized (rating index = high, medium, low) from interview data.	**Radiographic analyses** **Item** / **Plaque prevalence (%)** / **OR†** / **95% CI** Years since first RCF production job: 0‡ — 0.9 — 1.0 — — >0–10 — 1.7 — 1.4 — 0.2, 10.3 >10–20 — 2.8 — 2.2 — 0.4, 11.2 >20 — 12.5 — 9.5 — 1.9, 48.2 Years of RCF employment: 0 — 0.9 — 1.0 — — >0–10 — 1.4 — 1.1 — 0.2, 6.1 >10–20 — 7.4 — 6.1 — 1.2, 29.7 >20 — 26.3 — 22.3 — 3.6, 137.0 Cumulative fiber-months/cm³: >0–15 — 0.3 — 1.0 — — >15–45 — 5.3 — 15.4 — 1.9, 125.4 >45-135 — 6.4 — 21.3 — 2.6, 176.2 >135 — 7.8 — 24.2 — 2.6, 224.9 Case-controls: Years since first RCF production job — — 1.2 — 1.0, 1.5 Cumulative RCF fiber-months/cm³ (log): Adjusted for years since first asbestos exposure — — 2.8 — 1.3, 5.8 Adjusted for asbestos rating index — — 3.8 — 1.5, 9.9	In the cohort study, 20 cases of pleural plaque were identified in the cohort: 18 production workers and 2 nonproduction workers. In three logistic regression models, pleural plaques were associated ($P<0.001$) with years since first RCF production job, duration of RCF production jobs, and cumulative fiber-months/cm³. 18 of 20 cases were reinterviewed; 17 were included in the case-control study. One was deceased, one refused interview, and one with asbestos exposure was excluded.

*Abbreviations: CI=confidence interval; *P*=probability; OR=odds ratio; RFCs=refractory ceramic fibers.

†All but last entry are adjusted for years since first asbestos exposure. Last entry is adjusted for asbestos rating index, as indicated.

‡Nonproduction workers.

(Continued)

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Lockey et al. 1998 (U.S. study)	**Cross-sectional and longitudinal study:** Of a possible 754 male workers, the study included 361 who (1) were hired before 6/30/90, (2) were employed ≥1 month at one of five U.S. RCF manufacturing, facilities, and (3) participated in at least five (of a possible seven) PFT sessions between 6/87 and 6/94.	**Medical evaluation:** Yearly spirometric evaluation (pulmonary function) between 1987 and 1994. Measures included FVC and FEV_1. **Exposure assessment:** Period and job-group-specific exposure concentrations; estimated for each of five RCF manufacturing facilities and assigned to each worker based on job history. Cumulative RCF exposure (fiber-months/cm^3) estimated from date of first PFT (1987) through final PFT date. Pre-1987 data on fiber concentrations from two plants permitted calculation of cumulative fiber concentrations from first date of RCF exposure for workers at these plants only.	**Pulmonary function: cross-sectional analysis of initial pulmonary function test for 522 workers** Regression coefficient RCF production years / FVC†,‡ / FEV_1†,‡ ≤7§ / –65.6 (0.44) / –80.6 (0.25) >7§ / –219.4 (<0.01) / –205.2 (<0.01)	193 male workers were excluded from the analysis because they did not participate in at least five PFT sessions. On average, nonparticipants were older, smoked and weighed more, and had lower height-adjusted and percentages of predicted lung function values.

(Continued)

*Abbreviations: FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; PFT=pulmonary function test; RCFs=refractory ceramic fibers.
†In milliliters.
‡Height-adjusted; variables included in the analysis were age, categorical RCF production years (0, ≤7 years, >7 years [first test]), smoking category, pack years, weight, and plant location.
§Compared with nonproduction workers.

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Lockey et al. 1998 (Continued) (U.S. study)			**Pulmonary function: longitudinal analysis**	

Item	Regression coefficient FVC†,‡	Regression coefficient FEV_1 †,‡
Cumulative exposure:		
Initial RCF production category, ≤7 years‡,§	–55.2	–38.9
Initial RCF production category, >7 years‡,§	–168.3**	–99.6
Followup cumulative RCF exposure (fiber-months/cm^3)‡,§	.0.7	+0.5
Production employment duration:		
Initial RCF production years, ≤7 years‡,§	–66.3	–37.6
Initial RCF production years, >7 years‡,§	–171.0**	–100.3
Followup RCF production years§,††	+5.3	+0.2
Cumulative fiber exposure:		
Initial cumulative RCF exposure, >15–60 fiber-months/cm^3,‡‡	–36.2	–100.2
Initial cumulative RCF exposure, >60 fiber-months/cm^3,‡‡	–156.0	–104.7
Followup cumulative RCF exposure, fiber-months/cm^3,‡‡	+0.8**	+0.2

(Continued)

*Abbreviations: FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; *P*=probability; RCFs=refractory ceramic fibers.

† In milliliters for male workers tested five to seven times.

‡ Height-adjusted; variables included in the analysis were age, categorical RCF production years to initial test, followup cumulative RCF exposure, pack years at initial test, dichotomized smoking at each test, weight at initial test, weight change and plant location.

§Compared with nonproduction workers.

** $P<0.05$.

††Height-adjusted; variables included in the analysis were age, categorical RCF production years to initial test, followup RCF production years, pack years at initial test, dichotomized smoking at the time of each test, weight at initial test, weight change, plant location.

‡‡ Height-adjusted; variables included in the analysis were age, categorical cumulative RCF exposure to initial test, followup cumulative RCF exposure, pack years at initial test, dichotomized smoking at each test, weight at initial test, weight change, plant location.

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Burge et al. 1995 (European study)	**Cross-sectional study:** From a possible 708 current workers, 628 eligible participants were identified, and 596 of these had chest X-ray examinations. After exclusion of 51 female workers and 13 unexplained others, data were available from pulmonary function tests for 532 male workers in seven European RCF primary production plants.	**Health:** Workers were evaluated by a self-administered expanded respiratory questionnaire that included questions regarding specific symptoms. Pulmonary function testing was also performed. **Exposure:** Whole-shift personal air samples were collected from randomly selected workers from representative job categories in each of seven RCF production plants. Samples were collected and analyzed according to a WHO/EURO [1985] reference method for MMMFs to obtain data on inspirable and total mass and respirable fiber concentration. **Statistical analysis:** Odds ratios (with 95% CI) adjusted for plant, sex, smoking, and age were calculated for symptoms (i.e., dry cough, chronic bronchitis, wheeze, dyspnea≥2, stuffy nose, eye and skin irritation) and current exposure categories using multiple logistic regression. Multiple linear regression coefficients for lung function related to cumulative exposures controlled for the effects of respirable fiber and inspirable mass separately and together.	**Symptom analyses** **Exposure** — **Effect** **Current concentrations of inspirable mass:†** <2.5 mg/m³ — Baseline 2.5 to <3 mg/m³ — Eye irritation [2.25 (1.43, 2.23)]‡ 3 mg/m³ — Dry cough [3.42 (1.41, 8.33)]; Dyspnea ≥2 [5.84 (2.25, 15.26)]; Stuffy nose [2.01 (1.13, 3.57)]; Eye irritation [4.78 (2.66, 8.6)]; Skin irritation [3.3 (1.8, 6.05)] **Current concentrations of respirable fibers:†** <0.2 f/cm³ — Baseline 0.2 to <0.6 f/cm³ — Dry cough [2.53 (1.25, 5.11)]; Stuffy nose [2.06 (1.25, 3.39)]; Eye irritation [2.16 (1.32, 3.54)]; Skin irritation [1.25 (0.74, 2.11)] ≥0.6 f/cm³ — Dry cough [2.01 (1.05, 3.84)]; Dyspnea 2 [2.66 (1.31, 5.42)]; Eye irritation [2.63 (1.7, 4.08)]; Skin irritation [3.18 (2.01, 5.03)]	Current exposures to both inspirable dust and respirable fibers were related to dry cough, stuffy nose, eye and skin irritation, and breathlessness. No analysis of cumulative exposures was performed with respect to symptoms. Changes in lung function were more strongly related to cumulative exposure to fibers than to cumulative exposure to inspirable mass. Decrements in lung function were limited to current smokers and former smokers, suggesting that exposure to fibers promotes respiratory effects of smoking.

(Continued)

*Abbreviations: CI=confidence interval; MMMFs=man-made mineral fibers; RCFs=refractory ceramic fibers.
†Separate logistic regression models (adjusted for age, sex, smoking, and plant).
‡Figures in brackets=[OR (95% CI)].

Table 5–7 (Continued). U.S. and European Morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Burge et al. 1995, continued (European study)			**Symptom analyses, continued** **Exposure** — **Effect** **Current concentrations of inspirable mass:**§ 2.5 to <3 mg/m³ — Eye irritation [1.90 (1.15, 3.15)]** ≥3 mg/m³ — Dyspnea ≥2 [4.74 (1.56, 14.4)] Eye irritation [3.31 (1.62, 6.77)] **Current concentrations of respirable fibers:**§ 0.2 to <0.6 f/cm³ — None statistically significant ≥ 0.6 f/cm³ — Skin irritation [2.67 (1.52, 4.70)] **Pulmonary function‡‡** **Cumulative inspirable mass exposure:‡‡** Former smokers — FVC –8.7 ml/mg·m³ per year; FEV_1 –6.4 ml/mg·m³ per year **Cumulative respirable fiber exposure:‡‡** Current smokers — FEV_1 –32 ml/f·cm³ per year; $FEF_{25–75}$ –63 ml/s per f·cm³ per year Former smokers — FEV_1 –37 ml/f·cm³ per year **Cumulative respirable fiber exposure:§§** Current smokers — FEV_1 –36 ml/f·cm³ per year **Exposure** **Mean current inspirable mass:** Primary production — 1.7 to 3.4 mg/m³ Secondary production — 1.8 to 11.2 mg/m³ **Mean current respirable fiber concentration:** Primary production — 0.2 to 0.88 f/cm³ Secondary production — 0.49 to 1.36 f/cm³ **Mean cumulative exposure:** Inspirable mass — 28.24 mg/m³·year Respirable fibers — 3.84 f/cm³·year	(Continued)

§Multiple logistic regression (adjusted for age, sex, smoking, and plant) of symptom prevalence by current respirable fibers and current inspirable mass as independent variables after adjustment for the other.
**Figures in brackets=[OR (95%CI)].
††Only statistically significant associations ($P<0.05$) are shown.
‡‡Linear regression modeling of cumulative exposures to inspirable mass and respirable fibers separately (adjusted for age, height, and smoking).
§§Linear regression modeling with both cumulative exposure variables in the same model (adjusted for age, height, and smoking).

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Rossiter et al. 1994 (European study)	**Cohort morbidity study:** 628 currently working employees in seven European RCF production plants. 543 male workers who had readable chest radiographs were included in the analysis (596 of 628 workers [95%] had chest radiographs; 51 women and 2 unreadable films were excluded).	**Health:** Chest radiographs and questionnaire were administered. Data for 14 descriptive variables were collected for each worker as follows: production plant; age; years since first employment at plant; years since first exposed to RCFs; years of employment in the plant; current respirable fiber exposure; current nonrespirable fiber exposure; current inspirable mass exposure; cumulative respirable fiber exposure; cumulative nonrespirable fiber exposure; cumulative inspirable mass exposure; number of jobs at the plant with asbestos exposure; prior asbestos exposure.	**Radiographic analysis** **Effect** / **Prevalence** Pleural changes: 2.8% (15/543) Large opacities: 0 Small opacities: 7.0% (38/543) Irregular: 5.5% Rounded: 3.5% Mixed: 5.2% **Statistical analysis:** *Prevalence of pleural changes (n=15) associated with age (χ^2 =18.85, P=0.0008).* *Prevalence of cases of small opacity profusion (n=38) related to* production plant (χ^2= 22.10, $P<0.0001$); smoking years since first employment, years of employment, prior asbestos exposure, current nonrespirable fiber exposure (no χ^2 reported, $P\leq0.05$). *Prevalence of cases with mostly rounded opacities (n=23) related to* heavy smoking (χ^2=2.18, P=0.14); asbestos exposure within the RCF plants (χ^2=3.08 with continuity correction, P=0.08); but not age (χ^2=1.25, P=0.87) or production plant (χ^2= 5.13, P=0.53). *Prevalence of cases with mostly irregular opacities (n=15) related to* age (χ^2= 38.9, $P<0.0001$); current nonrespirable fiber levels (χ^2=5.2, P=0.07); years since first RCF employment (χ^2=8.16, P=0.09); years of RCF employment (χ^2=8.70, P=0.07); but not plant (P=0.23).	Pleural changes (n=15) included four cases with bilateral diffuse thickening (one with calcification); one with bilateral pleural calcification only; seven with unilateral diffuse thickening; three with costophrenic angle blunting only. Prevalence of pleural changes was associated with age. Irregular opacities were related to age, current nonrespirable fiber concentrations, and duration and latency of RCF employment. Overall, a slight association was noted for prevalence of small opacities and working in ceramic fiber production (i.e., RCF employment latency and duration). The researchers concluded it was unlikely that fiber exposure was the main cause of radiographic abnormalities. The possibility for confounding effects due to other exposures is recognized: 52% of workers reported previous employment in industries with potential exposure to dusts, including asbestos (5%), stone quarrying (2%), iron/steel foundries (6%), refractory brick work (10%), and man-made mineral fibers (8%).

(Continued)

*Abbreviations. N=number; *P*=probability; RCFs=refractory ceramic fibers.

Table 5–7 (Continued). U.S. and European Morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Trethowan et al. 1995 (European study)	**Cross-sectional respiratory morbidity study:** 628 current workers in seven European RCF manufacturing plants. Mean age = 37.7 years. Mean duration of employment = 10.2 years. 91% were male workers and 9% were female workers. 44% were current smokers.	**Health:** A self-administered questionnaire was used to obtain information about respiratory, nasal, eye, and skin symptoms, plus details of subjects' occupational history. PFT was also performed, and chest X-rays were obtained from 592 subjects. **Exposure assessment:** 140 jobs were identified and classified into seven main groups. Full-shift personal air samples were collected for randomly selected workers in each of the seven main groups. Inspirable dust monitoring was performed according to an ACGIH method. Respirable fiber concentration was measured according to a WHO/EURO [1985] reference method for MMMFs. (Respirable fiber is defined as <5µm long with an aspect ratio >3:1 and a diameter ≤3µm.) **Statistical analysis:** Pulmonary function indices were compared for cumulative exposure groups. Symptoms were investigated by logistic regression, and pulmonary function by linear regression. Models were controlled for effects of age, sex, smoking habits, and previous exposure to respiratory hazards.	**Radiographic analysis** Effect — Prevalence Pleural changes — 2.7% (16/592) Large opacities — 0 Small opacities — 13% Irregular — 5.1% Rounded — 3.2% Mixed — 4.7% **Symptom analyses** Current respirable f/cm³ — Effect — [OR† (95% CI)] <0.2 — Baseline 0.2 to <0.6 — Dry cough — [2.53 (1.25, 5.11)] Stuffy nose — [2.06 (1.25, 3.39)] Eye irritation — [2.16 (1.32, 3.54)] ≥0.6 — Dry cough — [2.01 (1.05, 3.84)] Dyspnea ≥2 — [2.66 (1.31, 5.42)] Eye irritation — [2.63 (1.7, 4.08)] Skin irritation — [3.18 (2.01, 5.03)]	Prevalence of small opacities increased with age, smoking, and previous exposure to asbestos, but not with cumulative exposures to ceramic fibers. No description of this analysis is provided. Symptoms present in the study population were related to exposure to respirable fibers. Statistically significant increases were noted in the prevalence of dyspnea (both grades) with increasing cumulative fiber exposure groups. Lung function tests showed a significant relation between increasing cumulative exposure to respirable fibers and decrements in FEV_1 and FEF_{25-75} in current smokers, and FEV_1 in former smokers. Among never smokers, an increase (not statistically significant) occurred in pulmonary function measures with increasing cumulative fiber exposure. Overall, 19% of the population had worked in dusty occupations outside the production of ceramic fibers. Note: In calculating cumulative exposures, the researchers assume past exposure concentrations were equal to current exposure concentrations.

*Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; CI = confidence interval; MMMFs = man-made mineral fibers; OR = odds ratio; PFT=pulmonary function test; RCFs=refractory ceramic fibers.

†Adjusted for the effects of age, sex, smoking, and previous exposures to respiratory hazards.

(Continued)

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Trethowan et al. 1995, continued (European study)		Logistic regression was used to analyze the trend between symptom prevalence and increasing cumulative respirable fiber exposure. Linear regression was used to analyze the trend between pulmonary function measures and increasing cumulative respirable fiber exposure.	**Symptom Analyses (Continued)** **% workers with various respiratory symptoms by fiber exposure**	

	Cumulative respirable fiber exposure (f/cm³ • year)				
Symptom	<1	1 to <2	2 to <4	4 to <8	>8
Dyspnea ≥2	6	9	13	17	20
Dyspnea ≥3	1	3	5	4	10
Wheeze	15	11	20	20	25
Bronchitis	13	9	12	14	10

Pulmonary function (mean % of predicted values)

	Cumulative respirable fiber exposure (f/cm³ • year)				
Function index	<1	1 to <2	2 to <4	4 to <8	>8
FVC	112.0	110.2	111.5	109.2	110.3
FEV_1†	106.5	105.5	106.0	102.3	102.1
FEF_{25-75}†	89.0	90.1	85.3	79.7	74.4

Pulmonary function (Δml/[f/cm³@ yr]) with cumulative exposure‡

Function index	Never smoker	Former smoker	Current smoker
FVC	+7	-34	-25
FEV_1†	+14	-37†	-32†
FEF_{25-75}†	+28	-51	-63†

Exposures

	Subjects	
Exposure concentrations	Number	%
Current exposure (f/cm³):		
<0.2	294	46.8
0.2 to <0.6	123	19.6
0.6 to <1	200	31.8
≥1	11	1.8
Cumulative exposure§ (f/cm³ • y):		
<1	119	18.9
1 to <2	106	16.9
2 to <4	168	26.8
4 to <8	166	26.4
>8	69	11.0

(Continued)

*Abbreviations: RCFs=refractory ceramic fibers.

†Statistically significant ($P<0.05$).

‡Adjusted for the effects of age, height, sex, smoking, and past exposure to RCFs, asbestos, and refractory work.

§Range=0 to 22.9 f/cm³ · year.

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Cowie et al. 1999, 2001 (European study) Cowie et al. 1999, 2001 Respiratory health assessment Groat et al. 1999 Exposure assessment	**Cross-sectional study:** **774 workers:** 695 current workers (90% response rate) in six European RCF manufacturing plants 79 former workers (37% response rate) who had been included in the first European survey [Burge et al. 1995, Rossiter et al. 1994, Trethowan et al. 1995] but had since left the industry 89% male workers and 11% female workers **Mean age:** Male workers, 42.0 years Female workers, 39.4 years **Smoking history:** **Male workers:** Nonsmokers 35% Current smokers 38% Ex-smokers 27% **Female workers:** Nonsmokers 57% Current smokers 29% Ex-smokers 13% **Mean time worked at the plants:** 13.0 years	**Health evaluation:** Chest radiographs, n=760 (98%) Lung function: Spirometry Single breath gas transfer Alveolar volume Questionnaires: Respiratory symptoms Modified American Thoracic Society questionnaire Occupational history **Exposure assessment:** 464 shift concentrations were sampled (>4 hr) Measurements included (1) respirable† and nonrespirable fiber concentration (phase contrast optical microscopy), (2) respirable dust and crystalline silica concentrations, (3) fiber concentrations and fiber size (scanning electron microscopy), and (4) mass concentrations of total inhalable dust. **Statistical analyses:** Regression analyses were performed: Radiographic data—logistic regression adjusted for age and smoking Lung function data—linear regression adjusted for age, physique, and smoking Respiratory symptoms—logistic regression adjusted for age, sex, smoking, and country.	**Radiographic analysis:** Pleural changes, 11% Pleural plaques, 5% 51/682 male workers had RCF exposure before 1971: 10/51 had category 1/0+ opacities 8/10 were exposed to asbestos 3 were current smokers, 6 ex-smokers **Symptom analyses:** Recurrent chest illness was associated with estimated cumulative exposure to respirable fibers [OR=1.48, 95% CI=1.11,1.96] and respirable dust [OR=1.32, 95% CI=1.00, 1.75]. **Pulmonary function analysis:** Male workers: FEV_1 and FVC decreased with increasing exposure to RCFs in current smokers only; strongest association was with estimated cumulative exposure to respirable fibers. Female workers: FEV_1 decreased with increasing cumulative exposure to fibers and dust; strongest association was with cumulative exposure to total dust. **Exposure assessment:** Current exposure concentrations: Respirable fibers: Production, 0.09–0.39 f/cm^3 *Conversion/finishing, 0.03–1.25* f/cm^3 Respirable dust, 0.08–0.42 mg/m^3	Only 14 female workers had small opacities of profusion 0/1; radiograph statistical analyses were restricted to male workers. Pleural changes were associated with age and exposure to asbestos; unadjusted for age, there is an association between pleural changes and number of years at the plant. Respiratory symptoms analyzed included chronic bronchitis, breathlessness, recurrent chest illness, and pleuritic chest pain. The average estimated decreased FEV_1 and FVC in male smokers was ~100 ml.

*Abbreviations: RCFs=respirable ceramic fibers; FEV=forced expiratory volume in 1 second; FVC=forced vital capacity.

†Respirable fibers included effectively no asbestos fibers via scanning electron microscopy (SEM) characterization. Asbestos exposure was judged not to warrant specific sampling.

pleural plaques in 5% (40/774) of study participants. In the U.S. study, 23 cases with pleural abnormalities (all production workers) were identified from 847 male and female workers (686 production, 161 nonproduction) [Lemasters et al. 1994]. The prevalence of pleural abnormalities among all workers was 2.7% and for production workers only, 3.4%. Of the cases, 21 were classified as having pleural plaques and 2 as having diffuse pleural thickening. One worker reported having previously diagnosed kaolinosis from prior employment in a kaolin mine. Lockey et al. [1996] conducted a followup report based on review of 652 chest films from current and former workers at two of the U.S. plants. They reported a prevalence of pleural changes of 3.1% (n=20), including 19 pleural plaque cases and 1 with diffuse pleural thickening. Pleural plaques were present in 18 (4.1%) production workers and 2 (0.9%) nonproduction workers. The two nonproduction workers with pleural plaques had worked with RCFs as laboratory technicians. From statistical analyses of pleural abnormalities, Rossiter et al. [1994] reported an association with age [χ^2=18.85, P=0.0008]. However, no attempt was made to assess whether an association existed between pleural abnormalities and RCF exposure. Trethowan et al. [1995] also noted that pleural abnormalities were related to age but not independently to ceramic fiber exposures. Cowie et al. [1999, 2001] reported pleural abnormalities to be associated with age, exposure to asbestos, and body mass index (weight divided by height squared). When the data were unadjusted for age, an association existed between pleural changes and years worked at the plant. Lemasters et al. [1994] found that pleural abnormalities were associated with time since first RCF exposure (RCF latency) after adjusting for duration of asbestos exposure and time since first asbestos exposure (odds ratio [OR]=2.9 [95% CI=0.8–9.7] for >10 to 20 years of RCF latency, and 7.7 [95% CI=2.0–29.1] for >20 years of RCF latency, when compared with workers having <10 years of RCF latency). Pleural abnormalities remained statistically significant (P<0.001) with time since first RCF exposure (latency) after adjustment for the effects of smoking, body weight, and latency and duration of asbestos exposure. The positive association persisted after exclusion of workers exposed to asbestos. In multiple logistic regression analyses, an association between duration of RCF exposure and pleural abnormalities remained significant (χ^2=7.75, P=0.005) after adjustment for asbestos latency, asbestos duration, and age [Lemasters et al. 1994]. In subsequent analyses with adjustment for age, researchers found that associations persisted between pleural plaques and latency and duration of RCF exposure [Lockey et al. 1996]. In three separate analyses, Lockey et al. [1996] found that prevalence of pleural plaques related to the following:

- >20 years of RCF latency (OR=9.5 [95% CI=1.9–48.2])
- >20 years RCF exposure duration in production jobs (OR=22.3 [95% CI=3.6–137.0])
- Cumulative RCF exposure in the highest exposure category (>135 fiber-months/cm^3) (OR=24.2 [95% CI=2.6–224.9])

Results of a nested case-control study of the 20 workers with pleural plaques (matched to 3 controls based on sex, RCF employment status, and production/nonproduction category) support the associations of pleural changes with RCF latency, RCF exposure duration, and cumulative RCF exposure [Lockey et al. 1996]. A latency validity review was also conducted, involving analysis of 205 historical chest radiographs available for workers with pleural changes. The purpose of the review was to confirm that for persons with pleural plaques, a biologically plausible latency period (≥5 years) existed between initial RCF exposure and appearance of a pleural plaque. Of 18 pleural plaque cases for which historical chest

radiographs were available, only 1 had a latency period of <5 years from initial RCF production to recognition of a pleural plaque.

A subsequent analysis by Lockey et al. [2002] included chest radiographs for 625 current workers obtained every 3 years at 5 RCF manufacturing sites and 383 former workers at 2 of the 5 sites. Pleural changes were seen in 27 workers (2.7%), of which 19 were bilateral plaques (70%) and 3 were unilateral plaques (11%). Cumulative RCF exposure (>135 fiber-months/cm^3) was significantly associated with pleural changes (OR = 6.0, 95% CI = 1.4, 31.0). The researchers noted an increasing but nonsignificant trend involving interstitial changes and RCF exposure duration in a production job and cumulative RCF exposure.

5.3.2.2 Parenchymal Opacities

In the 1987 European study, Rossiter et al. [1994] found that 7% (38/543) of the current male workers had small parenchymal opacities with median profusion of 1/0 or more. No large parenchymal opacities were observed. Both predominantly rounded (n=23, or 4.2%) and predominantly irregular (n=15, or 2.8%) small parenchymal opacities were identified. Prevalence of rounded, small opacities was not associated with age (P=0.87) or production plant (P=0.53). However, with prevalence of opacities, stronger associations existed with asbestos exposure in RCF production plants (P=0.08) and heavy smoking (P=0.14) [Rossiter et al. 1994]. Predominantly irregular, small opacities were associated with age (P<0.0001) but not with production plant (P=0.23). After allowing for age, associations with current nonrespirable fiber concentrations, years since first RCF employment, and duration of RCF employment approached statistical significance (P=0.07 to 0.09). In a subsequent analysis of small opacities for both male and female workers, Trethowan et al. [1995] noted that the prevalence of small opacities increased with age, smoking, and previous exposure to asbestos but not with cumulative RCF exposure. No description of the analysis was provided. Cowie et al. [1999] reported that 10 of 51 (19.6%) men with RCF exposure before 1971 had small opacities of category 1/0 or greater. Eight of these 10 had been exposed to asbestos, and 9 were either current or ex-smokers. In the U.S. study, no analyses were performed to assess the relationship between small opacities and RCF exposure because of the small number of cases (n=4) identified by Lemasters et al. [1994, 1996].

5.3.3 Respiratory Conditions and Symptom Analyses

Using respiratory health questionnaires, the U.S. and European studies sought to identify respiratory conditions and symptoms that could be associated with exposure to RCFs. Lockey et al. [1993] administered to 717 subjects a standardized respiratory symptoms questionnaire that included questions about the following symptoms and conditions: chronic cough, chronic phlegm, dyspnea grades 1 and 2 (described in the Definitions section of this document), wheezing, asthma, pleurisy, and pleuritic chest pain. Logistic regression analyses were adjusted for age, sex, smoking (pack years), duration of asbestos exposure, duration of production employment, duration of other hazardous occupational respiratory exposure, and time since last RCF employment. With the exception of asthma, for which self-selection out of production jobs may have occurred, adjusted ORs for respiratory symptoms were significantly elevated in production workers compared with nonproduction workers. Results of a subsequent analysis with 742 RCF workers by Lemasters et al. [1998] indicated that the prevalence of respiratory symptoms and conditions (except for asthma) was approximately twofold to fivefold higher in

production than in nonproduction workers. The most frequently reported symptom for male production workers was dyspnea grade 1 (15.7%, compared with 2.5% for nonproduction), followed by wheezing (10.3%, compared with 3.8% for nonproduction). Prevalence of one or more respiratory symptoms and conditions among female production workers was 40.7%, compared with 20.3% for nonproduction workers.

Trethowan et al. [1995] examined the relationship of dry cough, chronic bronchitis, dyspnea (two grades), wheeze, stuffy nose, eye irritation, and skin irritation to current and cumulative RCF exposure estimates among 628 workers. Current exposures were based on air sampling measurements taken in association with the respiratory health survey. The researchers noted eye and skin irritation were frequent in all plants and increased significantly, as did dyspnea and wheeze, with increasing current exposure concentrations (i.e., 0.2 to 0.6 and ≥0.6 f/cm^3) after controlling for age, sex, and smoking habits. The most frequent symptom, nasal stuffiness (in 55% of the group), showed no clear association with increasing current exposure. Chronic bronchitis, with a prevalence of 12% among all workers, also appeared unaffected by increasing current exposure concentration. Dry cough, eye irritation, and skin irritation all seemed to be associated with increasing exposure, especially at the highest exposure concentration (≥0.6 f/cm^3). Analyses of cumulative exposure to respirable fibers showed statistically significant associations with dyspnea but no apparent association with chronic bronchitis and wheeze. In a separate analysis of the same cohort, Burge et al. [1995] investigated the relative importance of respirable RCF exposure versus inspirable dust exposure in predicting respiratory symptoms and conditions. The study found workers' current exposures to both inspirable dust and respirable fibers were related (P<0.05) to dry cough, stuffy nose, eye and skin irritation, and breathlessness (dyspnea) after adjustment for the effects of smoking, sex, age, and plant. Only skin irritation was significantly associated with current RCF exposure after controlling for exposure to inspirable dust. Burge et al. [1995] did not analyze the relationship between symptoms and cumulative exposure indices. Cowie et al. [1999, 2001] reported that recurrent chest illness was associated with estimated cumulative exposure to respirable fibers but was not significantly associated with recent exposure.

5.3.4 Pulmonary Function Testing

Trethowan et al. [1995] analyzed spirometry test results from 600 of 628 current workers who participated at 7 European RCF production plants. In separate multiple linear regression analyses for male workers in each smoking category (current, former, never), the authors controlled for age, height, and past exposures to various respiratory hazards (including previous employment in other ceramic fiber plants). Results associated cumulative RCFs with statistically significant (P<0.05) decrements in FEV_1 in both current and former smokers and with decreases in FEF_{25-75} in current smokers. In never smokers (n=154), all regression coefficients of cumulative RCF exposure in relation to lung function were small, positive, and not statistically significant.

As with the symptoms data, Burge et al. [1995] further analyzed the spirometry data from the European study to discern whether the observed effects were more highly associated with current respirable RCF exposure than with concurrent inspirable dust exposure. In a multiple linear regression model that excluded cumulative inspirable dust exposure, statistically significant (P<0.05) decreases in FEV_1 and FEF_{25-75} among current smokers and FEV_1 among former smokers were associated with

cumulative exposure to respirable RCFs. In a multiple linear regression model that included variables for cumulative dust and cumulative respirable RCFs, the only statistically significant ($P<0.05$) association for these variables was for the decrease in FEV_1 among current smokers associated with cumulative respirable RCF exposure. No cumulative dust-associated coefficients remained statistically significant after adjusting for the effect of cumulative RCF exposure. Thus, the investigators attributed the adverse pulmonary function effect observed in smokers to the fiber component of occupational dust exposures at RCF manufacturing plants.

Cowie et al. [1999, 2001] observed that RCF-exposed male workers (n=692) showed a decrease in FEV_1 and FVC only for current smokers, the strongest association being with estimated cumulative exposure to respirable fibers. The average estimated decrease in FEV_1 and FVC was mild, approximately 100 ml. Female RCF-exposed workers (n=82) had a decreased FEV_1 with increasing cumulative exposure to respirable fibers and respirable and total dust. Among the female workers, cumulative exposure to total dust was most strongly associated with decreased pulmonary function measurements.

Lemasters et al. [1998] anaylzed PFT data for 736 male and female current workers at five U.S. RCF plants. They reported decreases in the percentage of predicted FVC and FEV_1 with every 10 years of RCF production work. Although the decreases were greatest among current male smokers and former male smokers, they were greater than decreases associated with smoking alone. No significant changes were noted in pulmonary function of RCF production workers who never smoked. A separate study by Lockey et al. [1998] involved longitudinal analysis of data from a cohort of 361 current male RCF workers hired before June 30, 1990, who had participated in at least five PFT sessions between 1987 and 1994. By comparison, nonparticipants who were excluded from the analysis according to the criteria above were on average older, smoked, weighed more, and had lower height-adjusted and percent-predicted lung function values. Cross-sectional analysis of the initial pulmonary function session in a regression model included coefficients for age, ≤7 versus >7 RCF production years, smoking status (pack years, current versus former smoker), weight, and plant location (categorical). The analysis found decreases in FVC and FEV_1 for workers employed >7 years in production compared with nonproduction workers. In longitudinal analyses of followup production years (i.e., from initial PFT to final PFT) and followup cumulative exposure (i.e., from initial PFT to final PFT), neither of these variables had an effect on FVC or FEV_1. These results led the authors to conclude that more recent exposure concentrations during 1980–1994 had no adverse effect on the longitudinal trend of pulmonary function [Lockey et al. 1998]. Decrements in FVC and FEV_1 noted in initial cross-sectional analyses of PFT data were believed to be related to earlier higher exposure concentrations.

5.3.5 Mortality Studies

Table 5–8 presents findings from a cohort mortality study of two U.S. RCF production plants reported by Lockey et al. [1993]. The study is based on a cohort of 684 male workers at two RCF production plants who were employed for at least 1 year between January 1, 1950, and June 1, 1988. Five workers were lost to follow-up and 46 were deceased. Because this is a relatively new industry (~40 years at the time of the study) that has experienced recent growth of the workforce at the plants studied, person-years at risk were limited at higher latencies (for example, only 126.37 person-years with >30 years since first RCF job). Using standardized mortality ratios (SMRs), the authors found

Table 5–8. Mortality study with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Lockey et al. 1993 (U.S. study)	*Cohort mortality study:* Current and former male workers at two plant sites employed at least l year in the manfacture of RCFs between 10/1/50 and 6/1/88. Of the 684 workers who met the criteria, 633 (92.5%) were alive, 46 (6.7%) were deceased, and 5 (0.7%) were lost to followup.	Cause-specific SMRs were calculated using the total U.S. male population as the reference population. Person-years were stratified by age, race, calendar time, latency, and cumulative duration.	**Demographics:** 624 Caucasions 60 non-Caucasions **Worker distribution** Years since first RCF job / Person-years at risk 1 to 5: 3,390 >5 to 10: 3,155 >10 to 15: 2,512 >15 to 20: 1,197 >20 to 25: 518 >25 to 30: 277 >30: 126 Total: 11,175 Cause of death / SMR (95% CI) All causes: 40 Caucasions: 97 (69–132) 6 non-Caucasions: 126 (46–274) All cancers: 11 Caucasions: 121 (60–216) 2 non-Caucasions: 263 (32–950) 4 lung cancers†: 114 (31–291) 2 cancers of the urinary organs†: 467 (57–1,687) 6 cancers of the digestive organs†: 259 (94–563) 2 pneumoconioses and other respiratory disease†: 205 (25–740)	Statistically significant increase in deaths from the following: (1) pneumoconioses and other respiratory disease for the category of Caucasian male workers with >30 years of RCF latency (n=2, SMR=2,614 [95% CI=246–7,490]); (2) cancers of the digestive organs and peritoneum for non-Caucasian male workers (n=2, SMR=913 [95% CI=110–3,295]); (3) cancers of the urinary organs for male workers with >15–20 years of RCF latency (n=2, SMR=3,306 [95% CI=311–9,471]). The power to detect a significant increase in mortality for any specific cause was low because of the small number of deaths in the cohort.

*Abbreviations: CI=confidence interval; RCFs=refractory ceramic fibers; SMR=standardized mortality ratio.
†Combined race cohort.

the combined-race cohort to have no significant elevations associated with specific causes of death, including cancers of the lung, digestive organs and peritoneum, urinary organs, and pneumoconioses and other respiratory disease. The authors noted that the power to detect a significant increase in mortality for any specific cause was low because of the small number of deaths in the cohort and generally short latencies. However, a statistically significant increase in deaths from pneumoconioses and other respiratory disease occurred in Caucasian males with >30 years RCF latency (n=2, SMR=2,614 [95% CI=246–7,490]). A statistically significant elevation in deaths from cancers of the digestive organs and peritoneum also occurred for non-Caucasian males (n=2, SMR=913 [95% CI=110–3,295]). In addition, a statistically significant elevation occurred in the number of deaths from cancers of the urinary organs for male workers with >15 to 20 years of RCF latency (n=2, SMR=3,306 [95% CI=311–9,471]).

Lemasters et al. [2003] published a subsequent analysis of current and former male workers employed between 1952 and 2000 at the two RCF manufacturing facilities (942 subjects) investigating a possible excess in mortality. The mortality analytic methods included (1) standardized mortality ratios comparing this cohort with the general and State populations and (2) a proportional hazards model that relates risk of death to the lifetime cumulative fiber-months/cm^3 exposure among the RCF cohort, adjusted for age at hire and for race. The analysis found no excess mortality related to all deaths, all cancers, or malignancies or diseases of the respiratory system (including mesothelioma) but found a statistically significant association with cancers of the urinary organs [SMR=344.8 (95% confidence limits of 111.6, 805.4)]. Based on the small size of the cohort, the young average age (51 years), and a mean latency of 21 years, the researchers concluded that the findings warrant continued surveillance of the cohort mortality registry.

Walker et al. [2002] used the same cohort of male RCF production workers described by Lemasters et al. [2003]. Walker et al. performed a risk analysis comparing the lung cancer and mesothelioma in the cohort's accumulated mortality experience to that which would have been expected if RCFs had a carcinogenic potency approximating various forms of asbestos. The authors reported that deaths from lung cancer in the RCF cohort were statistically significantly below that which would be expected if RCFs had the potency of either crocidolite or amosite. The mortality was also lower than would be expected if RCFs had the potency of chrysotile, but the difference is not statistically significant. For mesothelioma, the authors concluded the anticipated numbers of deaths under hypotheses of asbestos-like potency are too small to be rejected by the zero cases seen in the RCF cohorts [Walker et al. 2002]. NIOSH researchers noted that this analysis by Walker et al. was not based on the most current update of the RCF cohort. In addition, the asbestos risk assessment models used by Walker et al. [2002] were fitted to studies with longer followup periods than the cohort of RCF workers. Because these models do not specify length of followup, it is not possible to adjust for these differences. Consequently, it is likely that the RCF cohort has not been followed for a sufficient length of time to demonstrate the risks that were observed in the asbestos cohorts. NIOSH believes the mortality study by Lemasters et al. [2003] and the risk analysis by Walker et al. [2002] have insufficient power for detecting lung cancer risk based on what would be predicted for asbestos.

5.3.6 NIOSH HHEs

As part of its mission as a public health agency, NIOSH performs HHEs at the request of workers, employers, or labor organizations to investigate occupational hazards associated

with a workplace or work-related activity. One such HHE involved evaluating worker exposures to ceramic fibers at a company manufacturing steel forgings [Kominsky 1978]. At the facility, furnaces for heat-treating steel ingots were lined with RCF felt and batting, and this lining required regular maintenance and replacement. Among the workers interviewed were six bricklayers involved in furnace lining maintenance. Four of the bricklayers reported having experienced irritation of exposed skin areas and of the throat during the handling and installation of the RCF-containing insulation. On the basis of the reported symptoms and their consistency with known effects of RCFs, the symptoms of irritation were attributed to RCF exposure. No attempt was made to measure airborne fiber concentrations. Another NIOSH HHE [Lyman 1992] resulted from an OSHA inspection that identified 18 cases of occupational lung disease recorded in 1 year at a plant manufacturing fire bricks, ceramic fiber products, and other thermal insulation components from kaolin. About 600 workers were potentially exposed to respiratory hazards that included not only RCFs but also kaolin dust, crystalline silica dust, and (for maintenance workers) asbestos. A total of 38 workers had been referred to a pulmonary physician for evaluation based on 2 rounds of chest X-ray screening of the workforce in 1980 and 1986. Diagnoses were related to pleural thickening (n=10), pleural plaques (n=3), diffuse pulmonary fibrosis (n=21), mesothelioma (n=1), and other miscellaneous conditions. At least 20 of these cases were classified as work-related by the pulmonologist who evaluated the cases. The nonoccupational classification of some of the remaining 18 cases was questioned by a NIOSH physician who performed a retrospective record review. The 38 cases were reclassified on the basis of job histories into those who were likely to have been exposed to RCFs (n=19, including 4 with pleural abnormalities and 8 with diffuse fibrosis) and those unlikely to have been exposed to RCFs (n=19, including 9 with pleural abnormalities, 13 with fibrosis, and 1 with mesothelioma). However, no attempt was made to analyze further for an association of the cases with exposure to RCFs. The report implied that occupational exposure to kaolin dust and to asbestos caused many or all of the job-related conditions.

5.3.7 Discussion

The radiographic analyses of the U.S. and 1996 European worker groups suggest an association between pleural abnormalities, including pleural plaques, and RCF exposure [Lemasters et al. 1994; Lockey et al. 1996; Cowie et al. 1999]. From Rossiter et al. [1994] it is less apparent whether such an association was investigated. Trethowan et al. [1995] report that pleural abnormalities were not independently related to RCF exposure. Differences between the findings of the U.S. studies and those of the initial European studies may be related to the long latency before pleural abnormalities are detectable, in particular, pleural plaques following RCF exposure. Workers exposed to asbestos developed asbestos-associated pleural plaques after a latency period of more than 15 years after initial exposure [Hillerdal 1994] and in some cases, after 30 to 57 years [Begin et al. 1996]. The European RCF industry developed more than a decade after the U.S. industry. As a result, workers in the U.S. group are slightly older with a longer average employment duration in RCF manufacturing and time since first exposure to RCFs. Historical air sampling data also indicate that airborne fiber concentrations were much higher in early U.S. RCF manufacturing. These factors might explain the finding of RCF-associated pleural abnormalities in the U.S. workers but not in the European workers. A further possible explanation may involve differences in the radiographic surveillance methodologies. Both the U.S. and the European studies used

the 1980 ILO classification systems for pneumonoconioses to review posteroanterior view chest radiographs for study subjects. However, Lockey et al. [2002] began to supplement these views with left and right 45° oblique view films as a standard practice for radiographic surveillance. This methodology, known as a film triad, was evaluated against the posteroanterior-only view to determine reliability, sensitivity, and specificity of each method [Lawson et al. 2001]. The evaluation, involving 652 subjects in the RCF study, showed the film triad had considerably higher interreader reliability (κ=0.59) than the posteroanterior-only method (κ=0.44). The authors concluded that the film triad method provides an optimum approach.

The U.S. and 1986 European studies yielded little evidence of an association between radiographic parenchymal opacities and RCF exposure. In the U.S. study, small opacities were rare [Lockey et al. 1996]. Small opacities of profusion category 1/0 or greater were more frequent in the 1986 European study [Trethowan et al. 1995], but exposures to silica and other dusts were believed to account for many of these cases. The results of statistical analyses did not implicate RCF exposure [Trethowan et al. 1995] or yielded results only slightly suggestive of an RCF exposure effect [Rossiter et al. 1994]. In the 1996 evaluation of the European cohort, small opacities of category 1/0 or greater were positively associated with RCF exposures that occurred before 1971 [Cowie et al. 1999]. Ten of the 51 (19.6%) male workers exposed before 1971 developed category 1/0 or greater opacities—8 had also been exposed to asbestos and 9 were either current or ex-smokers.

Both the U.S. [Lockey et al. 1993; Lemasters et al. 1998] and the European [Trethowan et al. 1995; Burge et al. 1995; Cowie et al. 1999] studies found that occupational exposure to RCFs is associated with various reported respiratory symptoms and conditions, after adjusting for the effects of age, sex, and smoking. Exposure to RCF concentrations in the range of 0.2 to 0.6 f/cm^3 was associated with statistically significant increases in eye irritation (OR=2.16, 95% CI=1.32–3.54), stuffy nose (OR=2.06, 95% CI=1.25–3.39), and dry cough (OR=2.53, 95% CI=1.25–5.11) compared with exposure concentrations lower than 0.2 f/cm^3 [Trethowan et al. 1995]. Increasing ORs were demonstrated for RCF exposure concentrations greater than 0.6 f/cm^3 compared with exposure concentrations <0.2 f/cm^3 for wheeze (P<0.0001), dyspnea (P<0.05), eye irritation (P<0.0001), skin irritation (P<0.0001), and dry cough (P<0.05) but not stuffy nose or chronic bronchitis [Trethowan et al. 1995]. Lockey et al. [1993] found that dyspnea was significantly associated with exposure to >15 fiber-months/cm^3 (that is, >1.25 fiber-years/cm^3) relative to exposure to ≤15 fiber months/cm^3 (dyspnea grade 1—OR=2.1, 95% CI=1.3–3.3; dyspnea grade 2—OR=3.8, 95% CI=1.6–9.4). Lockey et al. [1993] also found statistically significant associations between cumulative RCF exposure and chronic cough (OR=2.0, 95% CI=1.0–4.0) and pleurisy (OR=5.4, 95% CI=1.4–20.2). Lemasters et al. [1998] also noted associations (P<0.05) between employment in an RCF production job and increased prevalence of dyspnea and the presence of at least one respiratory symptom or condition. Recurrent chest illness in the European cohort was associated with cumulative exposure to respirable fibers and was most strongly associated with cumulative exposure to respirable dust [Cowie et al. 1999].

In cross-sectional analyses involving spirometric testing, both the U.S. [Lockey et al. 1998; Lemasters et al. 1998] and 1986 European [Trethowan et al. 1995; Burge et al. 1995] studies found that cumulative RCF exposure was associated with pulmonary function decrements among current and former smokers. The 1996 European study demonstrated

decrements in current smokers only [Cowie et al. 1999]. The observed decreased pulmonary function in the European workers remained significantly associated with cumulative RCF exposure, even after controlling for cumulative exposure to inspirable dust [Burge et al. 1995]. A longitudinal analysis of data from multiple PFTs by Lockey et al. [1998] led the researchers to conclude that exposures to RCFs between 1987 and 1994 were not associated with decreased pulmonary function. The findings from the U.S. and European studies suggest that decrements in pulmonary function observed in current and former smokers result from an interactive effect between smoking and RCF exposure.

5.4 Carcinogenicity Risk Assessment Analyses

The literature contains three significant independent risk analyses of occupational exposure to RCFs and potential health effects. In each of these analyses, health effects data derived from multidose and MTD studies with rats were used with models to extrapolate risks to human populations. The modeling of effects observed in experimental animal studies was necessitated by the lack of adequate data on adverse health effects in humans with occupational exposures to RCFs. The three studies, described in detail below and in Table 5–9, include the following studies: Dutch Expert Committee on Occupational Standards (DECOS) [1995], Fayerweather et al. [1997], and Moolgavkar et al. [1999].

5.4.1 DECOS [1995]

In 1995, DECOS (a workgroup of the Health Council of the Netherlands) published a report evaluating the health effects of occupational exposure to SVFs. The purpose of the report was to establish health-based recommended occupational exposure limits for specific types of SVFs. As one of the criteria for determining the airborne exposure limits for six distinct types of SVFs, risk assessments were performed for each fiber type, including RCFs. The risk analysis for RCFs was based on the assumption that RCFs are a potential human carcinogen as indicated by the positive results of carcinogenicity testing with animals. A health-based recommended occupational exposure limit was determined using the following rationale:

1. If the carcinogenic potential of RCFs is caused by a nongenotoxic mechanism, an occupational exposure limit of 1 respirable f/cm^3 as an 8-hr TWA should be recommended based on an NOAEL of 25 f/cm^3 and a safety factor of 25.

2. If the carcinogenic potential of RCFs is linked to a genotoxic mechanism, a model assuming a linear relationship between dose and the response (cancer) should be used to establish the occupational exposure limit.

The model indicated that an excess cancer risk of 4×10^{-3} is associated with a TWA exposure to 5.6 respirable f/cm^3 based on 40 years of occupational exposure. A cancer risk of 4×10^{-5} is associated with exposure to 0.056 f/cm^3, and a linear extrapolation indicated that occupational exposure to 1 respirable f/cm^3 as an 8-hr TWA for 40 years is associated with a cancer risk of 7×10^{-4}.

The DECOS analysis relied on the data from a long-term multidose study with rats exposed to kaolin ceramic fibers [Bunn et al. 1993; Mast et al. 1995b]. These data showed that exposure by inhalation to 25 f/cm^3 (3 mg/m^3) for 24 months produced a negligible amount of fibrosis (mean Wagner score of 3.2). Consequently, the Dutch committee viewed 25 f/cm^3 as the NOAEL for fibrosis. The report also notes that at the time of publication, no data

Table 5–9. Risk associated with exposure to RCFs* at 1 f/cm³ (TWA) as determined by three independent analyses

Study	Animal data	Extrapolation model	Occupational exposure scenario	Excess lifetime risk of lung cancer–MLE
DECOS 1995	Long-term multidose and MTD rat studies	Linearized multistage model	8 hr/day, 40 years	7×10^{-4}
Fayerweather et al. 1997	Long-term multidose and maximum tolerated dose rat studies (Mast et al. 1995a,b)	Linearized, nonthreshold model	4 hr/day, 5 days/week, 50 weeks/year, 40 years of a 70-year lifespan	3.8×10^{-5}
Moolgavkar et al. 1999	Long-term multidose and maximum tolerated dose rat studies (Mast et al. 1995a,b)	Two-mutation clonal expansion model	8 hr/day, 5 days/week, 52 weeks/year, 30 years (age 20–50) of a 70-year lifespan	**Exponential:** ACS nonsmoking cohort, 3.7×10^{-5} (95% UCL = 0.9×10^{-5}) Steel industry cohort, 1.5×10^{-4} (95% UCL = 1.8×10^{-4}) **Quadratic:** ACS nonsmoking cohort, 4.1×10^{-6} (95% UCL = 1.2×10^{-5}) Steel industry cohort, 1.5×10^{-4} (95% UCL = 1.8×10^{-4}) **Linear:** ACS nonsmoking cohort, 2.7×10^{-4} (95% UCL = 1.5×10^{-3}) Steel industry cohort, 1.1×10^{-3} (95% UCL = 5.8×10^{-3})

*Abbreviations: ACS=American Cancer Society; MLE=maximum likelihood estimate; MTD=maximum tolerated dose; RCFs=refractory ceramic fibers; TWA=time-weighted average; UCL= 95% upper confidence limit.

existed from retrospective cohort mortality or morbidity and case-control studies of persons with occupational exposures to RCFs. The linear modeling approach in this analysis of the exposure-response relationship using the animal data does not take into consideration possible differences in dosimetry and lung burden between rats and humans.

5.4.2 Fayerweather et al. [1997]

Fayerweather et al. [1997] conducted a study primarily focusing on the risk assessment of occupational exposures for glass fiber insulation installers. They performed risk analyses with several other types of SVFs, including RCFs. Only the analysis with RCFs is presented here. This analysis applied an EPA linearized multistage model (representing a linear nonthreshold dose-response) to data from rat multidose and MTD chronic inhalation bioassays [Mast et al. 1995a,b] to determine exposures at which "no significant risk" occurs; i.e., no more than one additional cancer case per 100,000 exposed persons. Nonlinear models were also used for comparison: the Weibull 1.5-hit nonthreshold model (representing the nonlinear, nonthreshold dose-response curve) and Weibull 2-hit threshold model (representing the nonlinear, threshold dose-response curve). Fiber inhalation by rats was equated to humans by determining the fibers/day·kg of body weight for the animals and using an exposure scenario of 4 hr/day (consistent with insulation installation workers' schedules), for 5 days/week and 50 weeks/year over 40 working years of a 70-year lifespan. RCFC interpreted the results of the analysis with the linearized multistage model to represent a risk of 3.8×10^{-5} for developing lung cancer over the working lifetime at an exposure concentration of 1 f/cm^3 [RCFC 1998]. Using the nonlinear models, estimates of nonsignificant exposures (i.e., a working lifetime exposure associated with no more than 1 additional cancer case/100,000 exposed persons) were 2 and 3 orders of magnitude higher. Conversely, the risk estimates for exposure to 1 f/cm^3 for a working lifetime were lower using the Weibull 1.5-hit nonthreshold and Weibull 2-hit threshold models.

5.4.3 Moolgavkar et al. [1999]

This report describes a quantitative assessment of the risk of lung cancer associated with occupational exposure to RCFs [Moolgavkar et al. 1999]. A major premise underlying the risk assessment is that humans are equally susceptible to RCFs as rats, at the tissue level. The risk analysis was performed using data from two chronic inhalation bioassays of RCFs in male Fischer 344 rats [Mast et al. 1995a,b]. Dosimetry in the risk assessment was based on a fiber deposition and clearance model developed by Yu et al. [1996] that was used to estimate the lung burdens of fibers in humans. The dose-response model used for the risk assessment was the two-mutation clonal expansion model, commonly referred to as the Moolgavkar-Venzon-Knudson (MVK) model. The MVK model was fitted to the rat bioassay data to estimate the proportional increase in the rat lung tumor initiation rate in RCF-exposed rats, relative to the background initiation rate in nonexposed rats. An MVK model for human lung cancer was then created by fitting the model to the age-specific lung cancer incidence for either of two human cohorts. Finally, the human lung cancer rate for a given tissue dose was estimated by increasing the tumor initiation rate in the human model by the same proportional amount that an identical tissue dose would increase the initiation rate in the MVK model for rats. The assumption was made that, for any given tissue dose, the proportional increase in the lung tumor initiation rate (relative to the background rate) is the same in humans as in rats. The two human cohorts used for the human modeling were a nonsmoking American

Cancer Society (ACS) cohort [Peto et al. 1992] and a cohort of workers from the steel industry (not exposed to coke oven emissions) believed to be representative of industrial workers. Because of the difference in the baseline lung cancer risk, risk estimates based on the Steel Industry cohort were approximately 4 times higher than those based on the ACS cohort. Both central estimates (maximum likelihood estimates [MLEs]) and 95% upper confidence limits (UCLs) were developed. Three equations were tested to describe the relationship between initiation rate for lung cancer and lung burden:

I=A exp(Bd)	(exponential)
I=A + Bd2	(quadratic)
I=A + Bd	(linear)

where d = lung burden in fibers per milligram of lung (which can vary with time) and A and B are constants (different for each model). With each equation, calculations were made to determine the excess risk for a worker aged 20 to 50 to develop lung cancer by age 70 when exposed to RCFs at a concentration of 1.0 fiber/cm^3 for 8 hr/day, 5 days/week.

Using the exponential model, the excess risk of lung cancer associated with 1.0 f/cm^3 was estimated to be 3.7×10^{-5} (MLE) and 4.9×10^{-5} (95% UCL), based on the ACS cohort. For the same conditions the risk of lung cancer was 1.5×10^{-4} (MLE) and 1.8×10^{-4} (95% UCL) based on the Steel Industry cohort. Using a quadratic equation, the researchers reported slightly lower estimates of excess risk of 4.1×10^{-6} (MLE) and 1.2×10^{-5} (95% UCL) for the ACS cohort, and 1.4×10^{-5} (MLE) and 4.3×10^{-5} (95% UCL) for the Steel Industry cohort. The highest estimates of excess risk resulted with a linear equation: 2.7×10^{-4} (MLE) and 1.5×10^{-3} (95% UCL) for the ACS cohort, and 1.1×10^{-3} (MLE), and 5.8×10^{-3} (95% UCL) for the Steel Industry cohort. Additional risk estimates were calculated according to the conditions described above (i.e., ACS cohort versus Steel Industry cohort; MLE and 95% UCL for exponential, quadratic, and linear models) but with different exposure concentrations. The excess risk was also calculated for exposure concentrations of 0.75 f/cm^3, 0.5 f/cm^3, and 0.25 f/cm^3. These risk estimates are presented in Table 5–10.

As shown in Table 5–10, the highest risk estimates at each of the three exposure concentrations are associated with the linear model, followed by the exponential model. The lowest risk estimates are associated with the quadratic model. At each exposure concentration, more conservative risk estimates are obtained for the ACS cohort than the Steel Industry cohort.

At the recommended exposure guideline established by the RCFC (0.5 f/cm^3), the highest risk estimate (linear model, Steel Industry cohort) is the MLE of 5.3×10^{-4} or 5.3/10,000 (95% UCL=2.9×10^{-3}). At 0.5 f/cm^3, the risk estimates for the steel industry cohort are roughly 1 order of magnitude (factor of 10) lower with the exponential model (MLE=7.3×10^{-5}, 95% UCL= 9.1×10^{-5}), and 2 orders of magnitude lower using the quadratic model (MLE=3.5×10^{-6}, 95% UCL=1.1×10^{-5}). At the lowest exposure concentration (0.25 f/cm^3), the highest risk estimate (Steel Industry cohort, linear model) was the MLE of 2.7×10^{-4} (95% UCL=1.4×10^{-3}). Again, on average, the risk estimates from the 3 models using the steel industry cohort are 3 to 4 times higher than for corresponding model values with the ACS cohort.

The authors concluded that the risk estimates based on the two cohorts "represent bounds on risks likely to be seen in occupational cohorts." However, an occupational cohort is unlikely to share the nonsmoking status of the ACS cohort. Therefore, of the two human populations used for model fitting in the Moolgavkar et al. [1999] risk assessment, the steel industry cohort may be the preferable cohort to use for estimating the risks from occupational exposures to RCFs.

Table 5–10. Estimates (MLE* and 95% UCL) of excess risk of lung cancer at three exposure concentrations using exponential, quadratic, and linear models for an ACS cohort and a steel industry cohort

	ACS cohort			Steel industry cohort		
Exposure	Exponential	Quadratic	Linear	Exponential	Quadratic	Linear
0.75 f/cm^3:						
MLE	2.8×10^{-5}	2.3×10^{-6}	2.0×10^{-4}	1.1×10^{-4}	7.9×10^{-6}	8.0×10^{-4}
95% UCL	3.7×10^{-5}	6.8×10^{-6}	1.1×10^{-3}	1.4×10^{-4}	2.4×10^{-5}	4.3×10^{-3}
0.5 f/cm^3:						
MLE	1.8×10^{-5}	1.0×10^{-6}	1.3×10^{-4}	7.3×10^{-5}	3.5×10^{-6}	5.3×10^{-4}
95% UCL	2.5×10^{-5}	3.0×10^{-6}	7.3×10^{-4}	9.1×10^{-5}	1.1×10^{-5}	2.9×10^{-3}
0.25 f/cm^3:						
MLE	9.2×10^{-6}	2.5×10^{-7}	6.7×10^{-5}	3.6×10^{-5}	8.8×10^{-7}	2.7×10^{-4}
95% UCL	1.2×10^{-5}	7.5×10^{-7}	3.6×10^{-5}	4.6×10^{-5}	2.7×10^{-6}	1.4×10^{-3}

Adapted from Moolgavkar et al.[1999].
*Abbreviations: ACS=American Cancer Society; MLE=maximum likelihood estimate; UCL= 95% upper confidence limit.

The Moolgavkar et al. [1999] report also indicates airborne fiber concentrations estimated to result in excess lifetime risk for cancer of 10^{-4} (1 in 10,000) based on the approaches used by DECOS [1995] and Fayerweather et al. [1997] and using the MVK model for both the ACS cohort and the steel industry cohort. With the DECOS [1995] linearized, nonthreshold model approach, an excess lifetime cancer risk of 10^{-4} was calculated to result from a fiber concentration of 0.14 f/cm^3. Using the linearized, multistage model approach described in Fayerweather et al. [1997], a fiber concentration of 2.6 f/cm^3 was estimated to correspond to the excess lifetime cancer risk of 10^{-4}. With the MVK exponential model, an excess lifetime cancer risk of 10^{-4} was determined for fiber concentrations of 0.7 f/cm^3 for the Steel Industry cohort and 2.7 f/cm^3 for the ACS cohort [Moolgavkar et al. 1999].

5.4.4 Discussion

The estimated lung fiber burden for dosimetry in the analysis by Moolgavkar et al. [1999] is a methodological improvement over the risk assessment for RCFs by Fayerweather et al. [1997], which was based solely on the inhaled fiber concentration. Modeling lung burden dosimetry should, in theory, compensate for the known differences between rats and humans in fiber deposition and clearance. Similarly, using an MVK model for dose-response estimation could compensate for differences in cell mutation and proliferation rates in rats and humans. However, some key parameter values in the MVK and lung dosimetry models are poorly known. For example, the dosimetry model for humans has been validated with only three human tissue samples taken from workers whose exposures to RCFs were not measured [Yu et al. 1997].

A review and comparison of risk modeling approaches for RCFs by Maxim et al. [2003] describes the three models here as well as additional more sophisticated variations of quantitative risk analyses for RCFs. Using approaches such as benchmark dose modeling, Maxim et al. [2003] produced RCF unit potency values ranging from 1.4×10^{-4} to 7.2×10^{-4}.

A common weakness among all three of the risk analyses stems from uncertainty about possible differences in the sensitivity of human lungs to fibers, as compared with rat lungs. The possibility of such a difference is acknowledged in the report by Moolgavkar et al. [1999], but the effect of this uncertainty on the risk estimates is not explored quantitatively. As an example, Pott et al. [1994] estimated that in the case of asbestos fibers, humans are approximately 200-fold more sensitive than rats, on the basis of fiber concentration in air. Pott et al. [1994] further noted that a crocidolite inhalation study that was negative in the rat resulted in a rat lung fiber concentration that was more than 1,000-fold greater than the fiber concentrations in the lungs of asbestos workers with mesotheliomas. In support of this analysis, results of a study by Rödelsperger and Woitowitz [1995] led the authors to conclude that humans are at least 6,000 times more sensitive than rats to a given tissue concentration of amphibole fibers. Although amphibole asbestos fibers have physicochemical characteristics which differ from those of RCFs, these findings raise questions about using experimental animal data for predicting human health effects and assuming that target tissues in humans and rats are equally sensitive to RCF toxicity.

The lung cancer risk estimates for RCFs derived by Moolgavkar et al. [1999] may also be underestimated for occupationally exposed workers because of several basic assumptions made in the lung tissue dosimetry. Tissue dosimetry modeling in the Moolgavkar et al. [1999] risk assessment is based on the assumption that a worker is exposed to RCFs for 8 hr/day, 5 days/week, 52 weeks/year, from age 20 to 50 [Moolgavkar et al. 1999]. An alternative analysis, in which the assumption was changed to 8 hr/day, 5 days/week, 50 weeks/year from age 20 to 60, was also described but not presented in detail. In both cases, the breathing rate for light work was assumed to be 13.5 liters/minute. Additional information might be gained from assuming an exposure period of 8 hr/day, 5 days/week, 50 weeks/year, from age 20 to 65, with a breathing rate matching the International Commission on Radiological Protection "Reference Man" value for light work, which is 20 liters/minute [ICRP 1994]. In addition, the cumulative excess risk of lung cancer was calculated only through age 70 [Moolgavkar et al. 1999]. This practice may underestimate the lifetime risk of lung cancer in the exposed cohort, since a substantial fraction of the cohort may be expected to survive beyond age 70. The excess risk might also be calculated in a competing-risks framework using actuarial methods until most or all of the cohort is presumed to have died because of competing risks (generally 85 years). Finally, risk estimates derived by Moolgavkar et al. [1999] were based solely on data from studies with rats, ignoring data from studies of hamsters [McConnell et al. 1995]. Because 42% of the hamsters in these studies developed mesotheliomas, using this database for the risk assessment would produce higher estimates of risk than the analysis based on the rat data.

6 Discussion and Summary of Fiber Toxicity

6.1 Significance of Studies with RCFs

Three major sources of data contributing to the literature on RCFs are (1) experimental studies with animals and in vitro bioassays, (2) epidemiologic studies of populations with occupational exposure to RCFs (primarily during manufacturing), and (3) exposure assessment studies that provide quantitative and qualitative measurements of exposures as well as the physical and chemical characteristics of airborne RCFs. Each of these sources of information is considered integral to this criteria document for providing a more comprehensive evaluation of occupational exposure to RCFs and their potential health consequences.

Data from inhalation studies with animals exposed to RCFs have demonstrated statistically significant increases in the induction of lung tumors in rats and mesotheliomas in hamsters [Mast et al. 1995a,b; McConnell et al. 1995]. Other inhalation studies with RCFs have shown pathobiologic inflammatory responses in lung and pleural tissues [Gelzleichter et al. 1996a,b]. Implantation and instillation methods have also been used in animal studies with RCFs to determine the potential effects of these fibers on target tissues. These studies have recognized limitations for interpreting results because the exposure techniques bypass the natural defense and clearance mechanisms associated with the normal route of exposure (i.e., inhalation). However, they are useful for demonstrating mechanisms of toxicity and comparative measures of toxicity for different agents. RCFs implanted into the pleural and abdominal cavities of various strains of rats and hamsters have produced mesotheliomas, sarcomas, and carcinomas at the sites of fiber implantation [Wagner et al. 1973; Davis et al. 1984; Pott et al. 1987]. Similar tumorigenic responses have been observed following intratracheal instillation of RCFs [Manville Corporation 1991]. These data provide additional evidence of the carcinogenic effects of RCFs in exposed laboratory animals.

Epidemiological data have not associated occupational exposure to RCFs under current exposure conditions with increased incidence of pleural mesothelioma or lung cancer [Lockey et al. 1993; Lemasters et al. 1998]. However, in epidemiologic studies of workers in RCF manufacturing facilities [Lemasters et al. 1994; Lockey et al. 1993, 1996; Rossiter et al. 1994; Trethowan et al. 1995; Burge et al. 1995; Cowie et al. 1999], increased exposures to airborne fibers have been linked to pleural plaques, small radiographic parenchymal opacities, decreased pulmonary function, respiratory symptoms and conditions (pleurisy, dyspnea, cough), and skin and eye irritation.

Many of the respiratory effects showed a statistically significant association with RCF exposure after controlling or adjusting for potential confounders, including cigarette smoking and exposure to nonfibrous dust. Yet in PFTs, the interactive effect between smoking and RCF exposure was especially pronounced, based on the finding that RCF-associated decreases

in pulmonary function were limited to current and former smokers [Lockey et al. 1998; Lemasters et al. 1998; Trethowan et al. 1995; Burge et al. 1995]. The interactive effect between exposure to airborne fibers and cigarette smoke has been previously documented (e.g., Selikoff et al. [1968]). However, unlike male workers, nonsmoking female workers did show statistically significant decreases in PFT results associated with RCF exposure [Lemasters et al. 1998]. Analyses of data from multiple PFT sessions [Lockey et al. 1998] have led researchers to conclude that decreases in pulmonary function were more strongly influenced by the higher exposures to airborne RCFs that occurred in the past. This conclusion seems plausible, since historical air-sampling data indicate that airborne fiber concentrations were much higher in the first decades of RCF manufacturing and that former workers had potentially higher exposures.

Multiple studies have been performed to characterize the concentrations and characteristics of airborne exposures to RCFs in the workplace. Current and historical environmental monitoring data [Esmen et al. 1979; Cantor and Gorman 1987; Gorman 1987; O'Brien et al. 1990; Cheng et al. 1992; Brown 1992; Corn et al. 1992; Lyman 1992; Allshouse 1995; Hewett 1996] indicate that airborne exposures to RCFs include fibers in the respirable size range (<3.5 μm in diameter and <200 μm long [Timbrell 1965; Lippmann 1990; Baron 1996]). These exposures occur in primary RCF manufacturing as well as in secondary industries such as RCF installation and removal. Sampling data from studies of domestic, primary RCF manufacturing sites indicate that average airborne fiber concentrations have steadily declined by nearly 2 orders of magnitude over the past 2 decades. For example, Rice et al. [1997] report a maximum exposure estimate of 10 f/cm^3 associated with an RCF manufacturing process in the 1950s, and Esmen et al. [1979] measured average exposure concentrations ranging from 0.05 to 2.6 f/cm^3 in RCF facilities in the middle to late 1970s. Rice et al. [1994, 1996, 1997] suggest average concentrations in manufacturing ranging from <LOD to 0.66 f/cm^3 in the late 1980s, and Maxim et al. [1994, 1997, 2000a] report that concentrations from the late 1980s through 1997 ranged from an AM of <0.3 to 0.6 f/cm^3 (GM≅0.2 f/cm^3). For many manufacturing processes, even greater reductions in exposures have been realized through improved ventilation, engineering or process changes, and product stewardship programs [Rice et al. 1996; Maxim et al. 1999b].

Although the potential exists for exposure to respirable crystalline silica in the forms of quartz, tridymite, and cristobalite during work with RCFs, exposure monitoring data indicate that these exposures are generally low [Rice et al. 1994]. Maxim et al. [1999b] report that many airborne samples of crystalline silica collected during the installation and removal of RCF products contain concentrations below the LOD, with average concentrations of respirable crystalline silica per measurable task ranging from 0.01 to 0.44 mg/m^3 (equivalent 8-hr TWA range=0.004 to 0.148 mg/m^3). Other studies have shown greater potential for exposure to respirable crystalline silica (especially in the form of cristobalite) during the removal of after-service RCF materials [Gantner 1986; Cheng et al. 1992; Perrault et al. 1992; van den Bergen et al. 1994; Sweeney and Gilgrist 1998]. For processes associated with higher concentrations of airborne respirable fibers, there are also generally greater concentrations of total and respirable dusts [Esmen et al. 1979; Krantz et al. 1994].

6.2 Factors Affecting Fiber Toxicity

To accurately interpret the results of experimental and epidemiologic studies with RCFs,

it is important to consider recognized factors that contribute to fiber toxicity for RCFs and other SVFs in general. The major determinants of fiber toxicity have been identified as fiber dose (or its surrogate, airborne fiber exposure), fiber dimensions (length and diameter), and fiber durability (especially as it affects fiber biopersistence in the lungs) [Bignon et al. 1994; Bunn et al. 1992; Bender and Hadley 1994; Christensen et al. 1994; Lockey and Wiese 1992; Moore et al. 2001].

6.2.1 Fiber Dose

The measurement of airborne fiber concentrations is frequently used as a surrogate for assessing dose and health risk to workers. Analyses of historical and current air sampling data indicate that occupational exposure concentrations of airborne RCFs have decreased dramatically in the manufacturing sector [Maxim et al. 1997; Rice et al. 1997]. In chronic inhalation studies of RCFs [Mast et al. 1995a,b; McConnell et al. 1995], both rats and hamsters were exposed to a range of size-separated RCF concentrations in a nose-only inhalation protocol. When airborne RCFs are generated, half or more of the aerosol is composed of respirable particles of unfiberized material that was formerly a component of the fiber [Mast et al. 1995a,b]. Because of the nature of this mixed exposure, it is difficult to determine the relative contributions of the airborne fibers and nonfibrous particulates to the adverse effects observed in humans and animals. It has been postulated that the nonfibrous particulates may have contributed to an overload effect in the Mast et al. [1995a,b] animal studies with RCFs [Yu et al. 1994; Mast et al. 1995a,b; Maxim et al. 1997; Brown et al. 2000]. Burge et al. [1995] have suggested that the health effects seen in RCF-exposed workers are a consequence of combined particulate and fiber exposure, but the decrements in lung function are more related to fiber exposure combined with smoking. Other studies have shown that for processes associated with higher concentrations of airborne respirable fibers, there is also a greater concentration of total and respirable dust [Esmen et al. 1979; Krantz et al. 1994].

6.2.2 Fiber Dimensions

Throughout the literature, studies support the theory that fiber toxicity is related to fiber dimensions [Timbrell 1982, 1989; Harris and Timbrell 1977; Stanton et al. 1977, 1981; Lippmann 1988]. Initially, fiber dimensions (length and diameter) play a significant role in determining the deposition site of a fiber in the lungs. Longer and thicker (>3.5 μm in diameter) fibers are preferentially deposited in the upper airways by the mechanisms of impaction [Yu et al. 1986] or interception. Timbrell [1965] suggested that direct interception plays an important role in the deposition of fibers, as the fiber comes into contact with the airway wall and is deposited. Fibers being deposited in the larger ciliated airways are generally cleared via the mucociliary escalator. Thinner fibers tend to maneuver past airway bifurcations into smaller and smaller airways until their dimensions dictate deposition either by sedimentation or diffusion [Asgharian and Yu 1989]. Another factor that may enhance deposition is the electrostatic charge a fiber can accumulate during dust-generating processes in occupational settings [Vincent 1985]. The fiber charge may affect its attraction to the lung surface, causing the fiber to be deposited by electrostatic precipitation.

Although the dimensional characteristics and geometry of a fiber influence its deposition in the respiratory tract, the fiber's length and chemical properties dictate its clearance and retention once it has been deposited within the alveolar region. For the fiber that traverses the respiratory airways and is deposited in the gas exchange region, possible fates include

dissolution, clearance via phagocytic cells (alveolar macrophages) in the alveoli, or translocation through membranes into interstitial tissues. Both test animals and workers have been exposed to RCFs of similar length and diameter [Allshouse 1995], and these exposures include fibers of respirable dimensions [Esmen et al. 1979; Lockey et al. 1990; Cheng et al. 1992]. Since rats and other rodents are obligate nasal breathers, fibers greater than about 1 μm in diameter are too large for deposition in their alveoli [Jones 1993]. By comparison, humans can inhale and deposit fibers up to 3.5 μm in diameter in the thoracic and gas exchange regions of the lung. This physiological difference prevents the evaluation of fibers with diameters of about 1 to 3.5 μm (which would have human relevance) in rodent inhalation studies.

The role of fiber size in inducing biological effects is well documented and reviewed in the literature [Stanton et al. 1977, 1981; Pott et al. 1987; Warheit 1994]. Stanton et al. [1977] hypothesized that glass fibers longer than 8 μm with diameters thinner than 0.25 μm had high carcinogenic potential. In a review of the significance of fiber size to mesothelioma etiology, Timbrell [1989] concluded that the thinner fibers with an upper diameter limit of 0.1 μm are more potent for producing diseases of the parietal pleura (e.g., mesothelioma and pleural plaques) than thicker fibers. That value for fiber diameter is cited by Lippmann [1988] in his asbestos exposure indices for mesothelioma. Oberdörster [1994] studied the effects of both long (>10–16 μm) and short (<10 μm) fibers on alveolar macrophage functions, concluding that both will lead to inflammatory reactions—although a distinct difference exists in the long-term effects because of differential clearance of fibers of different sizes. Alveolar macrophages constitute the first line of defense against particles deposited in the alveoli; they migrate to sites where fibers are deposited and phagocytize them. The engulfed fibers are then moved by the macrophages toward the mucociliary escalator and removed from the respiratory tract. The ability of the macrophages to clear fibers is size-dependent. Short fibers (<15 μm long) can usually be phagocytized by one rat alveolar macrophage [Luoto et al. 1994; Morgan et al. 1982; Oberdörster et al. 1988, Oberdörster 1994], whereas longer fibers may be engulfed by two or more macrophages. Blake et al. [1998] have suggested that incomplete or frustrated phagocytosis may play a role in the increased toxicity of longer fibers. Fiber length has been correlated with the cytotoxicity of glass fibers [Blake et al. 1998], with greatest cytotoxicity for fibers 17 and 33 μm long compared with shorter fiber samples. Long fibers (17 μm average length) tend to be a more potent inducer of TNF production and transcription factor activation than short fibers (7 μm average length) [Ye et al. 1999].

When comparing the dimensions of airborne fibers with those found in the lungs, it is important to consider the preferential clearance of shorter fibers as well as the effects of fiber dissolution and breakage. Yu et al. [1996] evaluated these factors in a study that led to the development of a clearance model for RCFs in rat lungs. Results of that study confirmed that fibers 10 to 20 μm long are cleared more slowly than those <10 μm long because of the incomplete phagocytosis of long fibers by macrophages. The preferential clearance of shorter fibers has also been documented in studies with chrysotile asbestos and other mineral fibers, in which the average length of retained fibers increased during a discrete period following deposition [Coin et al. 1992; Churg 1994]. This increase might also be explained by the longitudinal cleavage pattern of asbestos fibers, which results in longer fibers of decreasing diameters [Coin et al. 1992]. By contrast, any breakage of RCFs would occur perpendicular to the longitudinal plane, resulting in shorter fibers of the same diameter. For the clearance

model developed by Yu et al. [1996], the effect of fiber breakage was also assessed from experimental data and incorporated into the model. The authors concluded that the simultaneous effect of fiber breakage and differential clearance leads only to a small change in fiber size distribution in the lung. This result suggests that the dimensions of fibers in the lung are closely related to the dimensions of fibers measured in the airborne samples (adjusted for deposition); thus, most short fibers in the lungs originated as short fibers in airborne exposures.

The dimensions of airborne fibers have also been characterized for workers with occupational exposure to RCFs. One study of domestic RCF manufacturing facilities found that approximately 90% of airborne fibers were <3 μm in diameter, and 95% of airborne fibers were <4 μm in diameter and <50 μm long [Esmen et al. 1979]. The study showed that diameter and length distributions of airborne fibers in the facilities were consistent with a GM_D of 0.7 μm and a GM_L of 13 μm. Another air sampling study of domestic RCF manufacturing sites reported that 99.7% of the fibers had diameters of <3 μm and 64% had lengths >10 μm [Allshouse 1995]. Measurements of airborne fibers in the European RCF manufacturing industry are comparable: Rood [1988] reported that all fibers observed were in the thoracic and respirable size range (i.e., diameter <3 μm), with median diameters ranging 0.5 to 1.0 μm and median lengths from 8 to 23 μm. During removal of RCF products, Cheng et al. [1992] found that 87% of airborne fibers were within the respirable size range, with fiber diameters ranging from 0.5 to 6 μm (median diameter=1.6 μm) and fiber lengths ranging from 5 to 220 μm. Another study [Perrault et al. 1992] of airborne fiber dimensions measured during installation and removal of RCF materials in industrial furnaces reported GM_D values of 0.38 and 0.57 μm, respectively.

6.2.3 Fiber Durability

Biopersistence (and specifically the retention time of the fiber in the lungs) is considered to be an important predictor of fiber toxicity. Fiber solubility affects the biopersistence of fibers deposited within the lung and is a key determinant of fiber toxicity. Bender and Hadley [1994] suggest that some of the important considerations of fiber durability include the following:

- Fiber size—particularly length as it relates to the dimensions of the alveolar macrophages
- Fiber dissolution rate
- Mechanical properties of the fibers, including partially dissolved and/or digested fibers
- Overloading of the normal clearance mechanisms of the lung

Bignon et al. [1994] argue that fibers that are biopersistent in vivo and in vitro are more biologically active than less durable fibers.

The durability of RCFs [Hammad et al. 1988; Luoto et al. 1995] provides a basis for suggesting that these fibers might persist long enough to induce biological effects similar to those of asbestos. In vitro durability tests have shown RCFs to be highly resistant to dissolution in biologically relevant mixtures such as Gamble's solution [Scholze and Conradt 1987]. The persistence of RCFs in both the peritoneal cavity [Bellman et al. 1987] and the lung [Hammad et al. 1988] has been recognized in experimental studies. Hammad et al. [1988] sacrificed rats exposed to either slag wool or ceramic fibers via inhalation at 5, 30, 90, 180, or 270 days after exposure. The lungs of the animals were ashed in a low-temperature asher, and the fiber content of the lungs was evaluated by PCM. The researchers found that 24% of the

deposited RCFs persisted in the lungs of rats sacrificed 270 days following exposure. In the same study, the lungs of rats exposed to slag wool contained only 6% of the slag wool fibers 270 days after exposure compared with those sacrificed 5 days following inhalation. From these results, it was concluded that RCFs follow a clearance pattern of relatively durable fibers that persist, translocate, or are removed by some mechanism other than dissolution. Similar results were obtained in the study by Mast et al. [1995b], which shows that RCFs are persistent in the lungs of rats exposed by inhalation. Specifically, compared with the fiber burden in the lungs of animals sacrificed 3 months after exposure (recovery), the lungs of animals sacrificed after 21 months of recovery contained approximately 20% of the deposited fibers. Of the retained fibers (measured with both SEM and TEM techniques) 54% to 75% had diameters <0.5 μm, and more than 90% were 5 to 20 μm long.

Researchers have suggested that fibers deposited in the gas exchange region with lengths less than the diameter of an alveolar macrophage are phagocytized and cleared via the mucociliary system or the lymph channels. Dissolution of fibers within the AlM occurs if the fibers are not resistant to the acidic intracellular conditions or a pH~5 [Nyberg et al. 1989]. Fibers that are not engulfed by alveolar macrophages are subjected to a pH of 7.4 in the extracellular fluid of the lung. A study of SVF durability in rat alveolar macrophages reports that RCFs are much less soluble than glass wool and rock wool fibers based on the amounts of silicon (Si) and iron (Fe) dissolved from the fibers in vitro [Luoto et al. 1995]. RCFs in rat alveolar macrophage culture dissolved less than 10 mg Si/m^2 of fiber surface area and less than 1 mg Fe/m^2 of fiber surface area. Glass wool dissolved more than 50 mg Si/m^2, and rock wool dissolved nearly 2 mg Fe/m^2 when measured over comparable time periods. However, degradation and dissolution of deposited RCFs may still occur, based on the findings of higher dissolution of aluminum (Al) from RCFs (0.8 to 2.4 mg Al/m^2) in alveolar macrophages than from the other SVFs [Luoto et al. 1995]. In another study, SEM analysis of fibers recovered from the lungs of rats 6 months after inhalation of RCFs revealed an eroded appearance, causing the researchers to conclude that dissolution of Si in the fibers is a plausible mechanism for long-term fiber clearance [Yamato et al. 1994].

SVFs in general are less durable than asbestos fibers. RCFs are more durable than many other SVFs, with a dissolution rate somewhat higher than chrysotile asbestos. Under the extracellular conditions in the lung, chrysotile—the most soluble form of asbestos—has a dissolution rate of <1 to 2 ng/cm^2/hr. RCFs have a similar dissolution rate of about 1 to 10 ng/cm^2/hr under conditions experienced in pulmonary interstitial fluid. Other more soluble SVFs can be 10 to 1,000 times less durable [Scholze and Conradt 1987; Christensen et al. 1994; Maxim et al. 1999b; Moore et al. 2001]. At the measured solubility rate, an RCF with a 1-μm diameter would take more than 1,000 days to dissolve completely [Leineweber 1984].

6.3 Summary of RCF Toxicity and Exposure Data

In addition to the main determinants of fiber toxicity (dose, dimension, and durability), other factors such as elemental composition, surface area, and composition can also influence the toxicity of the fiber. Thus, it is difficult to predict a fiber's potential for human toxicity based solely on in vitro or in vivo tests. Based on consideration of these factors, the major findings from the RCF animal and human studies are as follows:

- Toxicologic evidence from experimental inhalation studies indicates that RCFs are capable of producing lung tumors in laboratory rats and mesotheliomas in hamsters [Mast et al. 1995a,b; McConnell et al. 1995]. However, interpreting these studies with regard to RCF potency and its implication for occupationally exposed human populations is complicated by the issue of coexposure to fibers and nonfibrous respirable particulate.
- The durability of RCFs contributes to the biopersistence of these fibers both in vivo and in vitro [Bellmann et al. 1987; Scholze and Conradt 1987; Lockey and Wiese 1992].
- Cytotoxicity and genotoxicity studies indicate that RCFs
  - are capable of inducing enzyme release and cell hemolysis [Wright et al. 1986; Fujino et al. 1995; Leikauf et al. 1995; Luoto et al. 1997],
  - affect mediator release [Morimoto et al. 1993; Ljungman et al.1994; Fujino et al. 1995; Leikauf et al. 1995; Hill et al. 1996; Cullen et al. 1997; Gilmour et al. 1997; Luoto et al. 1997; Wang et al. 1999],
  - may decrease cell viability and inhibit proliferation [Yegles et al. 1995; Okayasu et al. 1999; Hart et al. 1992],
  - affect cell viability and proliferation [Hart et al. 1992], and
  - may induce free radicals, micronuclei, polynuclei, chromosomal breakage, and hyperdiploid cells [Brown et al. 1998; Dopp et al. 1997; Hart et al. 1992].
- Exposure monitoring results indicate that airborne fibers measured in both the manufacturing and end-use sectors of the RCF industry have dimensions that fall within the thoracic and respirable size ranges [Esmen et al. 1979; Lockey et al. 1990; Cheng et al. 1992].
- Epidemiologic studies of workers in the RCF manufacturing industry report an association between increased exposures to airborne fibers and the occurrence of pleural plaques, other radiographic abnormalities, respiratory symptoms, decreased pulmonary function, and eye and skin irritation [Lemasters et al. 1994, 1998; Lockey et al. 1996; Trethowan et al. 1995; Burge et al. 1995]. Current occupational exposures to RCFs have not been linked to decreases in pulmonary function of workers [Lockey et al. 1998].
- Worker exposure to airborne fiber in the RCF industry over the past 20 years or more have decreased substantially, reportedly as the result of increased hazard awareness and the design and implementation of engineering controls [Rice et al. 1997; Maxim et al. 1997].

These observations warrant concern for the continued control and reduction of occupational exposures to airborne RCFs.

7 Existing Standards and Recommendations

Standards and guidelines for controlling worker exposures to RCFs vary in the United States. Other governments and international agencies have also developed recommendations and occupational exposure limits that apply to RCFs. Table 7–1 presents a summary of occupational exposure limit standards and guidelines for RCFs.

Within the United States, the RCFC formally established a recommended exposure guideline of 0.5 f/cm^3 as an element of its product stewardship program known as PSP 2002, which was endorsed by OSHA as a 5-year voluntary program [OSHA 2002]. As part of that program, the RCFC recommends that workers wear respirators whenever the workplace fiber concentration is unknown or when airborne concentrations exceed 0.5 f/cm^3. This exposure guideline was established by the RCFC on October 31, 1997, and replaces the previous exposure guideline of 1 f/cm^3 set by the RCFC in 1991.

Before this agreement, the OSHA General Industry Standard was most applicable to RCFs, requiring that a worker's exposure to airborne dust containing <1% quartz and no asbestos be limited to an 8-hr PEL of 5 mg/m^3 for respirable dust and 15 mg/m^3 for total dust [29 CFR 1910.1000].

NIOSH has not previously commented on occupational exposure to RCFs. However, in addressing health hazards for another SVF (fibrous glass), NIOSH [1977] recommended an exposure limit (REL) of 3 f/cm^3 as a TWA for glass fibers with diameters ≤3.5 µm and lengths ≥10 µm for up to 10 hr/day during a 40-hr workweek. NIOSH also recommended that airborne concentrations determined as total fibrous glass be limited to a 5 mg/m^3 of air as a TWA. At that time, NIOSH concluded that exposure to glass fibers caused eye, skin, and respiratory irritation. NIOSH also stated that until more information became available, this recommendation should be applied to other SVFs.

The Agency for Toxic Substances and Disease Registry (ATSDR) calculated an inhalation minimal risk concentration of 0.03 f/cm^3 for humans based on extrapolation from animal studies [ATSDR 2002]. The Agency used macrophage aggregation, the most sensitive indicator of inflammation from RCFs, as the basis for this value. Calculation of this value is based on exposure assumptions for general public health that differ from those used in models for determining occupational exposure limits.

ACGIH proposed a TLV of 0.1 f/cm^3 as an 8-hr TWA for RCFs under its notice of intended changes to the 1998 TLVs [ACGIH 1998]. On further review, this concentration was revised to 0.2 f/cm^3 [ACGIH 2000]. ACGIH also classifies RCFs as a suspected human carcinogen (A2 designations) [ACGIH 2005]. On the basis of a weight-of-evidence carcinogenic risk assessment, the EPA [1993] classified RCFs as a Group B2 carcinogen (probable human carcinogen based on sufficient animal data).

ACGIH and EPA designations are consistent with that of the International Agency for Research on Cancer (IARC), which classified

Table 7–1. Occupational exposure limits and guidelines pertaining to RCFs*, by country

Country	Regulated substance	Exposure limit†
Australia	Synthetic mineral fibers	0.5 f/cm³
	Inspirable dust	2 mg/m³
Austria	Total dust (lists superfine fibers as suspected carcinogen)	10 mg/m³
Canada	RCFs	0.5 f/cm³
Denmark	Manmade mineral fibers	1 f/cm³
	Total dust (nonstationary work site)	5 mg/m³
Finland	Glass wool and mineral wool	10 mg/m³
France	General dust, mineral wool	10 mg/m³
Germany	Synthetic vitreous fibers	0.5 f/cm³
Netherlands	RCFs	1 f/cm³
New Zealand	Synthetic mineral fibers	1 f/cm³
Norway	Synthetic mineral fibers	1 f/cm³
Poland	Glass wool	2 f/cm³
	Total dust	4 mg/m³
Sweden	Synthetic inorganic fibers	1 f/cm³
United Kingdom [HSE 2004]	Machine-made mineral fibers (except RCFs and special-purpose fibers)	2 f/cm³
	RCFs	1 f/cm³
	Total dust (gravimetric limit)	5 mg/m³
United States:		
ACGIH	RCFs	0.2 f/cm³
ATSDR [2002]‡	RCFs	0.03 f/cm³
NIOSH§	RCFs	0.5 f/cm³
	Glass fibers, other SVFs [NIOSH 1977]	3 f/cm³
	Total fibrous glass	5 mg/m³
OSHA [2002]	RCFs	0.5 f/cm³
	Respirable dust (<1% quartz, no asbestos)	5 mg/m³
	Total dust (<1% quartz, no asbestos)	15 mg/m³

Source: Adapted and updated from U.S. Navy [DOD 1997].

*Abbreviations: ACGIH=American Conference of Governmental Industrial Hygienists; ATSDR=Agency for Toxic Substances Disease Registry; NIOSH=National Institute for Occupational Safety and Health; OSHA=Occupational Safety and Health Administration; RCFs=refractory ceramic fibers; REL=recommended exposure limit; TWA=time-weighted average.

†8-hr TWA unless otherwise specified.

‡Inhalation minimal risk level based on general public health assumptions, not occupational exposure.

§The NIOSH REL is established as a TWA for up to a 10-hr work shift in a 40-hr workweek.

ceramic fibers, including RCF, as "possibly carcinogenic to humans (Group 2B)" [IARC 1988, 2002]. The IARC characterization was based on "sufficient evidence for the carcinogenicity of ceramic fibers in experimental animals" and a lack of data on the carcinogenicity of ceramic fibers to humans [IARC 1988, 2002]. DECOS [1995] determined that "RCFs may pose a carcinogenic risk for humans," and set a health-based recommended occupational exposure limit of 1 f/cm^3.

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area published a review of fibrous dusts [Pott 1997] classifying RCFs as category IIIA2, citing "positive results (for carcinogenicity) from inhalation studies (often supported by the results of other studies with intraperitoneal, intrapleural, or intratracheal administration)."

In the United Kingdom, the Health and Safety Commission of the Health and Safety Executive has established a maximum exposure limit for RCFs of 1.0 f/ml of air, with the additional advisory to reduce exposures to the lowest as reasonably practicable concentration based on the category 2 carcinogen classification for RCFs [HSE 2004].

8 Basis for the Recommended Standard

8.1 Background

In the Occupational Safety and Health Act of 1970 (Public Law 91–96), Congress mandated that NIOSH develop and recommend criteria for identifying and controlling workplace hazards that may result in occupational illness or injury. In fulfilling this mission, NIOSH continues to investigate the potential health effects of exposure to naturally occurring and synthetic airborne fibers. This interest stems from the results of research studies confirming asbestos fibers as human carcinogens. Significant increases in the production of RCFs during the 1970s and concerns about potential health effects led to experimental and epidemiological studies as well as worker exposure monitoring. Chronic animal inhalation studies demonstrated the carcinogenic potential of RCFs, with a statistically significant increase in the incidence of lung cancer or mesothelioma in two laboratory species—rats and hamsters [Bunn et al. 1993; Mast et al. 1995a; McConnell et al. 1995]. Evidence of pleural plaques observed in persons with occupational exposures to airborne RCFs is clinically similar to that observed in asbestos-exposed persons after the initial years of their occupational exposures to asbestos [Hourihane et al. 1966; Becklake et al. 1970; Dement et al. 1986]. NIOSH considers the discovery of pleural plaques in U.S. studies of RCF manufacturing workers to be a significant finding because the plaques were correlated with RCF exposure [Lemasters et al. 1994; Lockey et al. 1996]. In addition, NIOSH considers the respiratory symptoms and conditions (including dyspnea, wheezing, coughing, and pleurisy) observed in RCF workers to be adverse health effects associated with exposure to airborne RCFs [Lemasters et al. 1998; Lockey et al. 1993; Trethowan et al. 1995; Burge et al. 1995; Cowie et al. 1999].

An association between inhaling RCFs and fibrotic or carcinogenic effects has been documented in animals, but no evidence of such effects has been found in workers in the RCF manufacturing industry. The lack of such an association could be influenced by the small population of workers in this industry, the long latency period between initial exposure and development of measurable effects, the limited number of persons with extended exposure to elevated concentrations of airborne fibers, and declining occupational exposure concentrations. However, the evidence from animal studies suggests that RCFs should be considered a potential occupational carcinogen. This classification is consistent with the conclusions of ACGIH, EPA, DECOS, and IARC. (See discussion in Chapter 7.)

Given these considerations, the NIOSH objective in developing an REL for RCFs is to reduce the possible risk of lung cancer and mesothelioma. In addition, maintaining exposures below the REL will also help to prevent other adverse effects, including irritation of the skin, eyes, and respiratory tract in exposed workers. To establish an REL for RCFs, NIOSH took into account not only the animal and human health data but also exposure

information describing the extent to which RCF exposures can be controlled at different workplaces. On the basis of this evaluation, NIOSH considers an REL of 0.5 f/cm^3 (as a TWA for up to 10 hr/day during a 40-hr workweek) to be achievable for most workplaces where RCFs or RCF products are manufactured, used, or handled. Maintaining exposures at the REL will minimize the risk for lung cancer and reduce the risk of irritation of the eyes and upper respiratory system. The residual risks of lung cancer at the REL are estimated to be 0.073 to 1.2 per 1,000 based on extrapolations of risk models from Moolgavkar et al. [1999] and Yu and Oberdörster [2000].

The risk for mesothelioma at the REL of 0.5 f/cm^3 is not known but cannot be discounted. Evidence from epidemiologic studies showed that higher exposures in the past resulted in pleural plaques in workers, indicating that RCFs do reach pleural tissue. Both implantation studies in rats and inhalation studies in hamsters have shown that RCF fibers can cause mesothelioma. Because of limitations in the hamster data, the risk of mesothelioma cannot be quantified. However, the fact that no mesothelioma has been found in workers and that pleural plaques appear to be less likely to occur in workers with lower exposures suggests a lower risk for mesothelioma at the REL.

Because residual risks of cancer (lung cancer and pleural mesothelioma) and irritation may exist at the REL, NIOSH further recommends that all reasonable efforts be made to work toward reducing exposures to less than 0.2 f/cm^3. At this concentration, the risks of lung cancer are estimated to be 0.03 to 0.47 per 1,000 based on extrapolations of risk models from Sciences International [1998], Moolgavkar et al. [1999], and Yu and Oberdörster [2000].

Maintaining airborne RCF concentrations at or below the REL requires the implementation of a comprehensive safety and health program that includes routine monitoring of worker exposures, installation and routine maintenance of engineering controls, and worker training in good work practices. To ensure that worker exposures are routinely maintained below the REL, NIOSH recommends that an AL of 0.25 f/cm^3 be part of the workplace exposure monitoring strategy to ensure that all exposure control efforts (e.g., engineering controls and work practices) are in place and working properly. The purpose of the AL is to indicate when worker exposures to RCFs may be approaching the REL. Exposure measurements at or above the AL indicate a high degree of certainty that concentrations of RCFs exceed the REL. The AL is a statistically derived concept permitting the employer to have confidence (e.g., 95%) that if exposure measurements are below the AL, only a small probability exists that the exposure concentrations are above the REL. When exposures exceed the AL, employers should take immediate action (e.g., determine the source of exposure, identify measures for controlling exposure) to ensure that exposures are maintained below the exposure limit. NIOSH has concluded that an AL allows for the periodic monitoring of worker exposures in the workplace so that resources do not need to be devoted to conducting daily exposure measurements. The AL concept has been an integral element of recommended occupational standards in NIOSH criteria documents and in comprehensive standards promulgated by OSHA and MSHA.

8.2 Rationale for the REL

The recommendation to limit occupational exposures to airborne RCFs to a TWA of 0.5 f/cm^3 is based on data from animal and human studies, risk assessments, and the

availability of methods to control RCF exposures at the REL in many workplaces. Establishing the REL for RCFs is consistent with the mission of NIOSH mandated in the Occupational Safety and Health Act of 1970. This Act states that NIOSH is obligated to "develop criteria dealing with toxic materials and harmful physical agents and substances which will describe exposure levels that are safe for various periods of employment, including but not limited to the exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience." The carcinogenicity findings from the chronic nose-only inhalation assays of RCF1 in rats and hamsters [Mast et al. 1995a,b; McConnell et al. 1995] warrant concern about possible health effects in workers exposed to RCFs. Although no increase in lung cancer or mesothelioma mortality has been observed in worker populations exposed to RCFs, radiographic analyses indicate an association between pleural changes (including pleural plaques) and RCF exposure [Lemasters et al. 1994; Lockey et al. 1996; Cowie et al. 1999, 2001]. Both the U.S. [Lockey et al. 1993; Lemasters et al. 1998] and the European [Trethowan et al. 1995; Burge et al. 1995; Cowie et al. 1999, 2001] studies have found RCF-associated respiratory symptoms, pulmonary function reductions, and pleural abnormalities among RCF production workers.

Several independent evaluations have quantitatively estimated the risk of lung cancer for workers exposed to RCFs at various concentrations [DECOS 1995; Fayerweather et al. 1997; Moolgavkar et al. 1999]. NIOSH evaluated these studies to determine whether an appropriate qualitative or quantitative assessment of lung cancer risk could be achieved. In addition, exposure information was collected during the 5-year monitoring period covered under the consent agreement between RCFC and EPA [Maxim et al. 1994, 1997, 1998]. NIOSH used the exposure information to evaluate the feasibility of controlling workplace exposures at manufacturing and end-use facilities where RCFs and RCF products are handled.

8.2.1 Carcinogenesis in Animal Studies

Chronic inhalation studies with RCFs demonstrate significant increases in the incidence of mesothelioma in hamsters and lung cancer in rats. Tables 8–1 through 8–4 present a synopsis of the major findings of these studies [Mast et al. 1995a,b; McConnell et al. 1995]. Results from chronic animal inhalation studies with chrysotile and amosite are also presented (i.e., results for the positive control groups); these data provide a reference point for determining the relative toxicity of RCFs [Mast et al. 1995a; McConnell et al. 1999].

Chronic inhalation exposure to RCF1 at 30 mg/m^3 (187 WHO f/cm^3) induced a 13% (16/123) incidence of lung tumors in F344 rats [Mast et al. 1995a]. The incidence of lung cancer at lower doses did not show a statistically significant difference from the unexposed control group. Lung fiber burdens in the multi-dose chronic rat study revealed a dose-response relationship [Mast et al. 1995b]. In the rat, 16 mg/m^3 (120 WHO f/cm^3) appeared to be the NOAEL for lung cancer and 3 mg/m^3 (26 WHO f/cm^3) appeared to be the NOAEL for fibrosis. Although it has been suggested that fibrosis in animals is a precursor to carcinogenesis, a definite link has not been shown for RCFs or other fibers. No lung cancers were found in hamsters exposed to RCF1 [McConnell et al. 1995].

Table 8–1. Doses and dimensions of RCFs* in chronic inhalation studies with F344 rats

Reference	Fiber type	Dose (mg/m³)	WHO f/cm³	WHO SD	Total f/cm³	Total SD	% Fibers >20 µm long	Mean fiber diameter† µm	Mean fiber diameter† SD	Mean fiber length† µm	Mean fiber length† SD
Mast et al. 1995a	RCF1	30	187	53	234	35	43	0.98	0.61	22.3	17.0
Mast et al. 1995b	RCF1	6	120	35	162	37	43	0.98	0.61	22.3	17.0
		9	75	35	91	34	—	—	—	—	—
		3	26	12	36	17	—	—	—	—	—
		0	0	—	0	—	—	—	—	—	—
Mast et al. 1995a	Chrysotile asbestos	10	1.06	$+1.14\times10^{4}$	1×10^{5}		NR	0.10	0.15	2.2	3.0

*Abbreviations: NR=not reported; RCFs=refractory ceramic fibers; SD=standard deviation; WHO=World Health Organization.
†Arithmetic mean.

Table 8–2. Results of RCF* chronic inhalation studies with F344 rats

Reference	Fiber type	Dose (mg/m³)	WHO f/cm³	WHO SD	Time of first occurrence (months) Interstitial fibrosis	Time of first occurrence (months) Pleural fibrosis	Lung neoplasms Number	Lung neoplasms %	Pleural mesotheliomas Number	Pleural mesotheliomas %
Mast et al. 1995a	RCF1	30	187	53	6	9	16/123	13	2/123	1.6
Mast et al. 1995b	RCF1	16	120	35	12	12	2/124	1.6	0	—
		9	75	35	12	18	5/127	3.9	1/127	0.8
		3	26	12	None	None	2/123	1.6	0	—
		0	0	—	None	None	1/129	0.8	0	—
Mast et al. 1995a	Chrysotile asbestos	10	1.06	$+1.14\times10^{4}$	3	9	13/69	18.8	1/69	1.4

*Abbreviations: RCF=refractory ceramic fiber; SD=standard deviation; WHO=World Health Organization.

Table 8–3. Doses and dimensions of RCF* in chronic inhalation studies with Syrian golden hamsters

Reference	Fiber type	Dose (mg/m^3)	WHO		Total		% Fibers >20 µm long			Mean fiber diameter†		Mean fiber length†	
			f/cm^3	SD	f/cm^3	SD	%	f/cm^3	SD	µm	SD	µm	SD
McConnell et al. 1995	RCF1	30	215	56	256	58	43	—	—	0.94	0.63	22.1	16.7
McConnell et al. 1995	Chrysotile asbestos	10	3.0×10^3	1.4×10^3	8.4×10^4	9.0×10^4	NR	—	—	0.09	0.06	1.68	2.71
McConnell et al. 1999	Amosite asbestos	7.1	263	90	NR	—	~26	69	24	0.60	0.25	13.4	16.7
		3.7	165	61	—	—	~23	38	14	—	—	—	—
		0.8	36	23	—	—	~28	10	6	—	—	—	—

*Abbreviations: NR=not reported; RCFs=refractory ceramic fibers; SD=standard deviation; WHO=World Health Organization.
†Arithmetic mean.

Table 8–4. Results of RCF* chronic inhalation studies with Syrian golden hamsters

Reference	Fiber type	Dose (mg/m^3)	WHO		Time of first occurrence		Hamsters with pleural mesotheliomas†	
			f/cm^3	SD	Interstitial fibrosis	Pleural fibrosis	Number	%
McConnell et al. 1995	RCF1	30	215	56	6 months	6 months	42/123	41.6
McConnell et al. 1995	Chrysotile asbestos	10	3.0×10^3	1.4×10^3	3 months	6 months	0	—
McConnell et al. 1995	Amosite asbestos	7.1	263	90	13 weeks	13 weeks	17/87	19.5
		3.7	165	61	13 weeks	13 weeks	22/85	25.9
		0.8	36	23	13 weeks	13 weeks	3/83	3.6

*Abbreviations: RCF=refractory ceramic fiber; SD=standard deviation; WHO=World Health Organization.
†No lung neoplasms were detected.

Chronic inhalation exposure to RCF1 at 30 mg/m^3 induced a 41% (42/102) incidence of mesotheliomas in Syrian golden hamsters [McConnell et al. 1995]. Determining a dose-response relationship for inducing mesothelioma is not possible based on currently available data because of the single exposure dose tested in the hamster and because of the low, sporadic occurrence of mesothelioma in the exposed rats [Mast et al. 1995a]. Yet the occurrence of mesotheliomas in the rat and the high incidence in the hamster are biologically significant because the spontaneous incidence of mesotheliomas in rats and hamsters has historically been very low [Analytical Sciences Incorporated 1999].

To assess the significance of the mesothelioma incidence observed in RCF-exposed hamsters, these results were compared with those obtained from hamsters that were exposed to chrysotile asbestos and were used as positive controls for the study [McConnell et al. 1995] (see Tables 8–3 and 8–4). However, the chrysotile-exposed hamsters failed to develop any tumors and therefore could not be considered true positive controls. Based on these results, a potency ranking could not be assigned for RCFs relative to chrysotile, since the carcinogenic response rate for the latter was zero in this study. The two fibers tested also differed with regard to their dose and fiber dimension.

The McConnell et al. [1999] study of hamsters exposed to amosite asbestos provides dose-response data for comparison with the RCF1 data of McConnell et al. [1995] (See Tables 8–3 and 8–4.). These separate studies examined the effects of RCF1 or amosite asbestos in hamsters using relatively similar exposure conditions, experimental conditions, and fiber dimensions [McConnell et al. 1995, 1999]. Exposure to 263 WHO f/cm^3 and 165 WHO f/cm^3 of amosite asbestos induced pleural mesotheliomas in 20% and 26% of the hamsters, respectively [McConnell et al. 1999]. A concentration of 215 RCF1 WHO f/cm^3 induced mesotheliomas in 41% of hamsters [McConnell et al. 1995]. Interstitial and pleural fibrosis were first observed at 13 weeks following amosite asbestos exposure and at 6 months following RCF1 exposure. Although average fiber dimensions for the RCF1 and amosite asbestos samples were similar, the RCF1 sample contained a higher percentage of fibers longer than 20 μm [McConnell et al. 1995, 1999]. Longer fibers have been associated with increased toxicity in experimental animal studies [Davis et al. 1986; Pott et al. 1987; Davis and Jones 1988; Warheit 1994; Blake et al. 1998].

Results from a dose-response analysis using the mesothelioma data from the RCF and amosite asbestos hamster studies [McConnell et al. 1995, 1999] indicated that the carcinogenic potency estimates for RCFs ranged from about half to two times the carcinogenic potency estimates for amosite asbestos [Dankovic 2001] (see Section 5.1.2). This analysis may not predict the mesothelioma risk in humans, since RCF1 contained a greater percentage of fibers longer than 20 μm and because of differences in fiber durability. Amosite asbestos is a more durable fiber with a longer in vivo half-life than RCF1 [Maxim et al. 1999b; Hesterberg et al. 1993] (see Table 8–5). Yet RCFs are more durable and less soluble than many other types of SVFs that have not demonstrated carcinogenicity in experimental studies. This characteristic is significant, as the durability of asbestos and SVFs (including RCFs) may be linked to the risk of lung cancer in animals chronically exposed to these fibers [Bignon et al. 1994; Bender and Hadley 1994; Hammad et al. 1988; Luoto et al. 1995]. Because of the long latency period for the development of mesotheliomas in humans, Berry [1999] hypothesized that fibers of sufficient durability are needed to cause this disease in humans. Extrapolation of the RCF dose-response data for lung cancer and mesothelioma in exposed rodents should take into

Table 8–5. Dissolution constant (K_{dis}) and weighted in vivo half-life ($t_{0.5}$) of amosite asbestos and RCF1

Fiber type	K_{dis} (ng/cm^2 per hr)	$t_{0.5}$(days)
RCF1	7.6	89.6
Amosite asbestos	1.3	418.0

Source: Adapted from Maxim et al. [1999].
*Abbreviation: RCF=refractory ceramic fiber.

account the durability of RCFs in humans. Some evidence indicates that rats are less sensitive than humans to the development of lung cancer and mesothelioma from exposure to asbestos and may therefore represent an inappropriate model for human risk assessment. Pott et al. [1994] hypothesized that in chronic inhalation studies, rats may have a lower sensitivity to inorganic fiber toxicity than humans. The lung cancer risk from inhaling asbestos may be two orders of magnitude lower in rats than in humans, and the mesothelioma risk from inhaling asbestos may be three orders of magnitude lower for rats. Rödelsperger and Woitowitz [1995] measured amphibole fiber concentration in the lung tissues of humans with mesothelioma and compared the results with fiber burdens reported in rats. A significantly increased OR (OR=4.8, 95%; CI=1.05–21.7) for mesothelioma was seen in humans with amphibole concentrations between 0.1 and 0.2 fiber/μg of dried lung tissue. The lowest tissue concentration reported to produce a significant carcinogenic response in rat inhalation studies of amphiboles (specifically crocidolite) was 1,250 fibers/μg of dried lung tissue. By comparing these results, Rödelsperger and Woitowitz [1995] estimated that humans are at least 6,000 times more sensitive than rats to a given tissue concentration of amphibole fibers.

This work is refuted by other scientists who favor the rat as an appropriate model for evaluating the risk evaluation of lung cancer in humans [Maxim and McConnell 2001]. Limitations of the Rödelsperger and Woitowitz [1995] and Pott [1994] analyses (discussed earlier) include the lack of a dose-response analysis, analysis of only one epidemiologic study, inadequate comparisons of exposure duration, lack of accounting for the potentially multiplicative effect of smoking and asbestos exposure, lack of consideration of latency and clearance, and different fiber measurement techniques.

In summary, multiple factors affecting the comparability of different fiber types and animal models reported in the literature make it difficult to determine whether the carcinogenic potency of RCFs in animals is similar to that in humans. Extrapolation of the animal data to humans is further complicated by a limited understanding of the mechanisms of fiber toxicity. Consequently, any extrapolation of the cancer risk found in animals exposed to RCFs must account for differences between humans and rodents with regard to fiber deposition and clearance patterns, uncertainty about the role of RCF durability for potentiating an adverse effect, and possible species differences in sensitivity to fibers.

8.2.2 Health Effects Studies of Workers Exposed to RCFs

Two major research efforts evaluated the morbidity of workers exposed to airborne fibers in the RCF manufacturing industry. One study was conducted in the United States and the other in Europe. The objective of each was to evaluate the relationship between occupational exposure to RCFs and potential adverse health effects. These studies contained multiple components including standardized respiratory and occupational history questionnaires, chest radiographs, pulmonary function tests of workers, and air sampling to estimate worker exposures. The first studies of European plants were conducted in 1986 and included current workers at seven RCF manufacturing plants [Rossiter et al. 1994; Trethowan et al. 1995; Burge et al. 1995]. A followup cross-sectional study conducted in 1996 evaluated the same medical endpoints in workers from six of these seven European manufacturing plants (one plant had ceased operation) [Cowie et al. 1999, 2001]. Current as well as former workers were included as study subjects in the followup study. The studies of U.S. plants began in 1987 and involved evaluations of current workers at five RCF manufacturing plants and former workers at two of the plants [Lemasters et al. 1994, 1998, 2003; Lockey et al. 1993, 1996, 1998, 2002]. In the United States, the earliest commercial production of RCFs and RCF products began in 1953. In Europe, RCF production began in 1968. The demographics of the U.S. and European populations were similar at the time they were studied, but the average age and duration of employment for the U.S. workers were slightly higher than for the workforce in the 1986 European studies because of the earlier development of this industry in the United States.

8.2.2.1 Pleural changes in humans

The radiographic analyses of the U.S. and 1996 European populations in RCF manufacturing detected an association between pleural changes and RCF exposure [Lemasters et al. 1994; Lockey et al. 1996; Cowie et al. 1999, 2001]. In the initial European studies, Trethowan et al. [1995] found pleural abnormalities in a small number of RCF workers who had other confounding exposures that did not include asbestos. Differences observed in pleural abnormalities between the U.S. and European worker populations may be related to the latency of exposure required to cause specific pleural changes [Hillerdal 1994; Begin et al. 1996], especially the formation of pleural plaques, which were first observed in studies of the U.S. RCF manufacturing industry, with its longer latency period. Historical air sampling data also indicate that airborne fiber concentrations were much higher in early U.S. RCF manufacturing. Therefore, in addition to their longer overall latency, RCF manufacturing workers in the United States probably had generally higher exposures in the early years of the industry than did their European counterparts. These factors might explain the appearance of RCF-associated pleural plaques in the U.S. studies before their detection in the European studies. The U.S. and 1986 European studies yielded little evidence of an association between radiographic parenchymal opacities and RCF exposure. In the U.S. study, small opacities were rare, with only three cases noted in one report [Lockey et al. 1996] and only one case (with small rounded opacities of profusion category 3/2 attributable to prior kaolin mine work) noted in the other [Lemasters et al. 1994]. Small opacities of profusion category 1/0 or greater were more frequent in the European study by Trethowan et al. [1995], but confounding exposures were believed to account for many of these cases. The results of statistical analyses indicated either no

association with RCF exposure [Trethowan et al. 1995] or an association slightly suggestive of an RCF exposure effect [Rossiter et al. 1994]. In a more comprehensive evaluation of the European study population, small opacities of category 1/0 or greater were positively associated with RCF exposures that occurred before 1971 [Cowie et al. 1999].

8.2.2.2 Respiratory symptoms, irritation, and other conditions in humans

In both the U.S. [Lockey et al. 1993; Lemasters et al. 1998] and the European [Trethowan et al. 1995; Burge et al. 1995; Cowie et al. 1999, 2001] studies, occupational exposure to RCFs was associated with various reported respiratory conditions or irritation symptoms after adjusting for the effects of smoking. Worker exposure to RCFs at concentrations of 0.2 to 0.6 f/cm^3 was associated with statistically significant increases in eye irritation (OR=2.16, 95% CI=1.32–3.54), stuffy nose (OR=2.06, 95% CI=1.25–3.39), and dry cough (OR=2.53, 95% CI=1.25–5.11) compared with exposure to concentrations lower than 0.2 f/cm^3 [Trethowan et al. 1995]. Between the 0.2 to 0.6 f/cm^3 and >0.6 f/cm^3 RCF exposure groups, a statistically significant increase occurred in ORs for wheezing ($P<0.0001$), grade 2 dyspnea ($P<0.05$), eye irritation ($P<0.0001$), and skin irritation ($P<0.0001$)—but not for stuffy nose [Trethowan et al. 1995]. Lockey et al. [1993] found that dyspnea was significantly associated with cumulative exposure to >15 fiber-months/cm^3 (i.e., >1.25 fiber-year/cm^3) relative to cumulative exposure to ≤15 fiber-months/cm^3 (dyspnea grade 1–OR=2.1, 95% CI 1.3–3.3; dyspnea grade 2–OR=3.8, 95% CI 1.6–9.4) after adjusting for smoking and other potential confounders. Lockey et al. [1993] also found a statistically significant association between cumulative RCF exposure and pleurisy (OR=5.4, 95% CI=1.4–20.2), and an elevated but nonsignificant association between cumulative RCF exposure and chronic cough (OR=2.0, 95% CI=1.0–4.0). Lemasters et al. [1998] also noted associations ($P<0.05$) between employment in an RCF production job and increased prevalence of dyspnea and the presence of at least one respiratory symptom after adjusting the data for confounders. Recurrent chest illness in the European study population was associated with the estimated cumulative exposure to thoracic-sized fibers but was more strongly associated with estimated cumulative exposure to thoracic-sized dust [Cowie et al. 1999, 2001].

In cross-sectional analyses, both the U.S. [Lockey et al. 1998; Lemasters et al. 1998] and the 1986 European [Trethowan et al. 1995; Burge et al. 1995] studies found that cumulative RCF exposure is associated with pulmonary function decrements among current and former smokers. Lemasters et al. [1998] also found statistically significant deficits in pulmonary function measures for nonsmoking female workers. The decreased pulmonary function in the European study population remained significantly associated with cumulative RCF exposure, even after controlling for cumulative dust exposure [Burge et al. 1995]. The 1996 European study found pulmonary function decrements only in current smokers [Cowie et al. 1999, 2001]. In a longitudinal analysis of data from multiple serial pulmonary function tests, Lockey et al. [1998] concluded that the more recent RCF concentrations occurring after 1987 were not associated with decreased pulmonary function; rather, decreases in pulmonary function were more closely related to typically higher concentrations that occurred before this time period. The U.S. and European studies suggest that decrements in pulmonary function observed primarily in current and former smokers are evidence of an interactive effect between smoking and RCF exposure.

8.2.3 Carcinogenic Risk in Humans

Moolgavkar et al. [1999] derived risk estimates for lung cancer in humans on the basis of the

results from the two chronic bioassays of RCFs in male Fischer 344 rats [Mast et al. 1995a,b]. Several models (linear, quadratic, exponential) were used to estimate and compare risks using reference populations comprised of either a nonsmoking ACS cohort or a cohort of steel workers not exposed to coke oven emissions (see Table 5–10 for risk estimates). The exponential model provided the best statistical fit of the data. The linear model provided the highest estimates of human lung cancer risks from exposure to RCFs when used with the referent steel workers cohort (considered to be most representative of workers exposed to RCFs because it includes blue collar workers who smoke). Lung cancer risk estimates were calculated using each model at exposure concentrations of 0.25 f/cm^3, 0.5 f/cm^3, 0.75 f/cm^3, and 1.0 f/cm^3. The RCF-related lung cancer risk determined from the linear model for the lowest concentration (0.25 f/cm^3) was 0.27/1,000 for the cohort of steel workers compared with 0.036/1,000 using the exponential model and 0.00088/1,000 for the quadratic model when using the same referent population.

The risk estimates incorporated multiple assumptions, including a human breathing rate of 13.5 L/min (considered light work) and multiple criteria for defining the length of time a worker could be exposed to RCFs over a working lifetime. Higher risk estimates could be expected if the assumptions more closely represented those used by NIOSH and OSHA: (1) a human breathing rate of 20 L/min and (2) a worker exposure duration of 8 hr/day, 5 days/wk, 50 wk/yr, from age 20 to 65 with the risk calculated beyond age 70 (e.g., to age 85). Furthermore, the calculated risk estimates could be an underestimation of the lung cancer risk to humans because the models assumed that the tissue sensitivity to RCFs in the rat is equal to that in humans. Although the lung cancer risk estimates derived from the rat data are reason for concern, estimates of human risk for mesothelioma from the high incidence (41%) of mesothelioma in hamsters cannot be appropriately modeled since only a single exposure was administered in the study. Primarily on the basis of chronic animal inhalation studies [Mast et al. 1995a,b; McConnell et al. 1995], NIOSH concludes that RCFs are a potential occupational carcinogen. Furthermore, the evidence of pleural plaques [Lemasters et al. 1994; Lockey et al. 1996] observed in persons with occupational exposures to airborne RCFs is clinically similar to that observed in asbestos-exposed persons after the initial years of their occupational asbestos exposures [Hourihane et al. 1966; Becklake et al. 1970; Dement et al. 1986]. NIOSH considers the discovery of pleural plaques in U.S. studies of RCF manufacturing workers to be a significant finding because the plaques were correlated with RCF exposure [Lemasters et al. 1994; Lockey et al. 1996]. In addition, NIOSH considers the respiratory symptoms and conditions (including dyspnea, wheeze, cough, and pleurisy) [Lemasters et al. 1998; Lockey et al. 1993; Trethowan et al. 1995; Burge et al. 1995; Cowie et al. 1999] in RCF workers to be adverse health effects that have been associated with exposure to airborne fibers of RCFs.

Insufficient evidence exists to document an association between fibrotic or carcinogenic effects and the inhalation of RCFs by workers in the RCF manufacturing industry though these effects have been demonstrated in animal studies. The lack of an observed association between RCF exposure and these effects among workers could be affected by one or more factors, including several relating to the study population: the relatively small cohort, the proportion of workers with short tenure relative to what might be expected (on the basis of an asbestos analogy) in terms of disease latency, and workers with limited cumulative exposures to RCFs.

8.2.4 Controlling RCF Exposures in the Workplace

Table 8–6 summarizes exposure monitoring data collected by the RCFC under a consent agreement with the EPA [Everest 1998; Maxim et al. 1997]. These data indicate that exposures to RCFs during 1993–1998 had an AM fiber concentration of about 0.3 f/cm^3 for manufacturing and nearly 0.6 f/cm^3 for end users. Maxim et al. [1997, 1999a] reported results for both manufacturing and end-use sectors in which airborne fiber concentrations through 1997 were reduced to an AM <0.3–0.6 f/cm^3.

The exposure monitoring data collected as part of the RCFC/EPA consent agreement provide assurance that when appropriate engineering controls and work practices are used, airborne exposure to RCFs can be maintained for most functional job categories (FJCs) at the REL of 0.5 f/cm^3. For many manufacturing processes, reductions in exposures have resulted from the improved ventilation, engineering or process changes, and product stewardship programs [Rice et al. 1996; Maxim et al. 1999b]. These data provide the basis for the NIOSH determination that a REL of 0.5 f/cm^3 as a TWA can be achieved.

Although many RCF manufacturing and end-user job tasks have exposures to RCFs at concentrations below 0.5 f/cm^3, exposure monitoring data also indicate that not all FJCs may be able to achieve these RCF concentrations consistently. FJCs that currently experience airborne AM fiber concentrations >0.5 f/cm^3 include finishing (manufacturing and end use) and removal (end use). Typical processing during finishing operations (e.g., sawing, drilling, cutting, sanding) often requires high-energy sources that tend to generate larger quantities of airborne dust and fibers. For RCF insulation removal, activities are performed at remote sites where conventional engineering controls and fixed ventilation systems are more difficult to implement. For some operations, such as removal of RCF insulation tiles from furnaces, the release of high airborne fiber concentrations can occur. However, removal of RCF insulation tiles is not routine and is generally accomplished in a short period of time. Workers almost universally wear PPE and respiratory protection during these job tasks [Maxim et al. 1997, 1998].

NIOSH acknowledges that the frequent use of PPE, including respirators, may be required for some workers handling RCFs or RCF products. The frequent use of PPE may be required during job tasks for which (1) routinely high airborne concentrations of RCF (e.g., finishing, insulation removal) exist, (2) the airborne concentration of RCF is unknown or unpredictable, and (3) job tasks are associated with highly variable airborne concentrations because of environmental conditions or the manner in which the job task is performed. In all work environments where RCFs or RCF products are handled, control of exposure through the engineering controls should be the highest priority.

8.3 Summary

The following summarize the relevant information used as the basis for the NIOSH assessment of occupational exposures to RCFs:

- Airborne concentrations of RCFs have been characterized as containing fibers of dimensions in the thoracic and respirable size ranges. RCFs are among the most durable types of SVFs. In tests of solubility, RCFs are nearly as durable as chrysotile asbestos but significantly less durable than amphibole asbestos fibers such as amosite.
- Chronic, nose-only inhalation studies with RCFs in animals show a statistically

Table 8–6. Airborne fiber concentrations in the RCF* industry during 1993–1998, by functional job category and production status† (f/cm³ as TWA)

Functional job category and production status	Minimum value	First quartile	Median	Geometric mean	Arithmetic mean	Third quartile	Maximum value
Total:							
Manufacturing	0.001	0.070	0.186	0.16	0.313	0.407	7.700
End use	0.002	0.052	0.173	0.16	0.560	0.524	30.000
Assembly:							
Manufacturing	0.001	0.110	0.208	0.18	0.281	0.366	2.154
End use	0.002	0.050	0.159	0.14	0.316	0.402	2.837
Auxiliary:							
Manufacturing	0.001	0.019	0.038	0.05	0.112	0.132	1.347
End use	0.002	0.021	0.066	0.07	0.198	0.198	2.678
Fiber:							
Manufacturing	0.004	0.063	0.145	0.14	0.257	0.299	7.700
End use	—	—	—	—	—	—	—
Finishing:							
Manufacturing	0.004	0.316	0.488	0.47	0.663	0.803	4.044
End use	0.006	0.124	0.383	0.35	0.991	0.986	30.000
Installation:							
Manufacturing	—	—	—	—	—	—	—
End use	0.003	0.084	0.236	0.20	0.434	0.559	3.371
Mixing/forming:							
Manufacturing	0.004	0.090	0.184	0.17	0.292	0.364	1.445
End use	0.010	0.074	0.159	0.17	0.319	0.369	4.109
Other:							
Manufacturing	0.007	0.027	0.070	0.07	0.112	0.177	1.900
End use	0.003	0.013	0.030	0.04	0.194	0.102	6.400
Removal:							
Manufacturing	—	—	—	—	—	—	—
End use	0.010	0.373	1.914	0.82	1.816	2.340	16.000

Source: Adapted from Everest [1998].
*Abbreviations: RCF = refractory ceramic fiber; TWA = time-weighted average.
†Fiber concentrations were determined during monitoring performed over a 5-year period (1993–1998) under the Refractory Ceramic Fibers Coalition/Environmental Protection Agency (RCFC/EPA) consent agreement. Concentrations were determined by NIOSH method 7400 "B" counting rules.

significant increased incidence of lung tumors in rats and pleural mesotheliomas in hamsters. These data support the NIOSH determination that RCFs are a potential occupational carcinogen.

- Epidemiologic studies of workers in the RCF manufacturing industry show an increased incidence of pleural plaques, respiratory symptoms (dyspnea and cough), skin and eye irritation, and decreased pulmonary function related to increasing exposures to airborne fibers. Some of these conditions are documented for exposure concentrations in a range as low as 0.2 to 0.6 f/cm^3. Studies of workers exposed to airborne RCFs show no evidence of excess risk for lung cancer or mesothelioma. However, the inability to detect such an association could be because of (1) the low statistical power for detecting an effect, (2) the short latency period for most workers occupationally exposed, and (3) the historically low and decreasing fiber exposures that have occurred in this industry.

- Risk assessment analyses using data from chronic inhalation studies in rats indicate that the excess risk of developing lung cancer when exposed to RCFs at a TWA of 0.5 f/cm^3 for a working lifetime is 0.073 to 1.2/1,000. However, on the basis of the assumptions used in the risk analyses, NIOSH concludes that this risk estimate is more likely to underestimate than to overestimate the risk to RCF-exposed workers. Reduction of the RCF TWA concentration to 0.2 f/cm^3 would reduce the risk for lung cancer to 0.03 to 0.47/1,000. OSHA attempts to set PELs for carcinogens that reflect an estimated risk of 1/1,000 but is limited by considerations of technologic and economic feasibility.

- RCF exposure data gathered under a consent agreement between RCFC and EPA, which included a 5-year comprehensive air monitoring program (1993–1998), indicate that airborne exposure concentrations to RCFs have been decreasing. Monitoring results show that 75% to >95% of TWA exposure concentration measurements in all FJCs (with one exception) were below 1.0 f/cm^3. In all but two of the eight FJCs, >70% of TWA measurements were below the RCFC recommended exposure guideline of 0.5 f/cm^3. On the basis of the review of these data, NIOSH has concluded that the REL of 0.5 f/cm^3 can be achieved in most work places where RCFs or RCF products are manufactured or used.

- The combined effect of mixed exposures to fibers and nonfibrous particulates may contribute to increased irritation of the respiratory tract, skin, and eyes. Engineering controls and appropriate work practices used to keep airborne RCF concentrations below the REL should help to minimize airborne exposures to nonfibrous particulates as well. Because the ratio of fibers to nonfibrous particulate in airborne exposures may vary among job tasks, exposure monitoring should include efforts to characterize particulate composition and to control and minimize airborne fibers and nonfibrous particulate accordingly.

From the assessment described above and throughout this document, NIOSH concludes that on a continuum of fiber toxicity, RCFs relate more closely to asbestos than to fibrous glass and other SVFs and should be handled accordingly. NIOSH considers all asbestos types to be carcinogens and has established a REL of 0.1 f/cm^3 for airborne asbestos fibers. This value was determined on the basis of extensive human and animal health effects data and the recognized limits of analytical methods.

Recognizing that RCFs are carcinogens in animal studies and given the limitations in deriving an exposure value that reflects no excess risk of lung cancer or mesothelioma for humans, NIOSH recommends that every effort be made to keep exposures below the REL of 0.5 f/cm^3 as a TWA for up to 10 hr/day in a 40-hr workweek. These efforts will further reduce the risk for malignant respiratory disease and protect workers from conditions and symptoms deriving from irritation of the respiratory tract, skin, and eyes.

From the analysis of historical exposure data (see Chapter 4) and the exposure data collected as part of the RCFC/EPA consent agreement monitoring program (Table 8–6), NIOSH has determined that compliance with the REL for RCFs is achievable in most manufacturing and end-use job categories. Although routine attainment of TWA exposures below the REL may not currently occur at all job tasks, it does represent a reasonable objective that can be achieved through modification of the job task or the introduction or improvement of ventilation controls.

9 Guidelines for Protecting Worker Health

The following guidelines for protecting worker health and minimizing worker exposures to RCFs are considered minimum precautions that should be adopted as a part of a site-specific safety and health plan to be developed and overseen by appropriate and qualified personnel.

9.1 Informing Workers about Hazards

9.1.1 Safety and Health Training Program

Employers should establish a safety and health training program for all workers who manufacture, use, handle, install, or remove RCF products or perform other activities that bring them into contact with RCFs. As part of this training program, employers should do the following:

- Inform all potentially exposed workers (including contract workers) about RCF-associated health risks such as skin, eye, and respiratory irritation and lung cancer.
- Provide MSDSs on site:
  - Make MSDSs readily available to workers.
  - Instruct workers how to interpret information from MSDSs.
- Teach workers to recognize and report adverse respiratory effects associated with RCFs.
- Train workers to detect hazardous situations.
- Establish procedures for reporting hazards and giving feedback about actions taken to correct them.
- Instruct workers about using safe work practices and appropriate PPE.
- Inform workers about practices or operations that may generate high concentrations of airborne fibers (such as cutting and sanding of RCF boards and other RCF products).
- Make workers who remove refractory insulation materials aware of the following:
  - Their potential for exposure to respirable crystalline silica
  - Health effects related to this exposure
  - Methods for reducing their exposure
  - Types of PPE that may be required (including respirators)

9.1.2 Labeling and Posting

Although workers should have received training about RCF exposure hazards and methods for protecting themselves, labels and signs serve as important reminders and provide warnings to workers who may not ordinarily work in the area. Employers should do the following:

- Post warning labels and signs about RCF-associated health risks at entrances and inside work areas where airborne concentrations of RCFs may exceed the REL.

- State the need to wear appropriate respiratory protection and protective clothing in areas where airborne RCFs may exceed the REL.
- If respiratory protection is required, post the following statement:

RESPIRATORS REQUIRED IN THIS AREA.

- Print all labels and warning signs in both English and the predominant language of workers who do not read English.
- If workers are unable to read the labels and signs, inform them verbally about the hazards and instructions printed on the labels and signs.

9.2 Hazard Prevention and Control

Proper use and maintenance of engineering controls, work practices, and PPE are essential for controlling concentrations of airborne fibers during the manufacturing, use, and handling of RCF products. Minimizing exposure to RCFs may be accomplished through a combination of the following work practices and controls:

- Engineering controls and ventilation
- Product reformulation
- Worker isolation
- PPE (such as protective clothing and equipment and respirators)
- Proper decontamination and waste disposal

9.2.1 Engineering Controls

Engineering controls should be the principal method for minimizing exposure to RCFs in the workplace.

9.2.1.1 Ventilation

Achieving reduced concentrations of airborne RCFs depends on adequate engineering controls such as local exhaust ventilation systems that are properly constructed and maintained. Local exhaust ventilation systems that employ hoods and ductwork to remove fibers from the workplace atmosphere have been used by RCF manufacturers. One example is a slotted-hood dust collection system placed over a mixing tank so that airborne fibers are captured and collected in a bag house with HEPA filters [RCFC 1996]. Other types of local exhaust ventilation or dust collection systems may be used at or near dust-generating systems to capture airborne fibers. Band saws used in RCF manufacturing and finishing operations have been fitted with such engineering controls to capture fibers and dust during cutting operations and thereby reduce exposures for the band saw operator [Venturin 1998]. Disc sanders fitted with similar local exhaust ventilation systems are effective in reducing airborne RCF concentrations during sanding of vacuum-formed RCF products [Dunn et al. 2004]. For quality control laboratories or laboratories where production samples are prepared for analyses, exhaust ventilation systems should be designed to capture and contain dust. For guidance in designing local exhaust ventilation systems, see *Industrial Ventilation—A Manual of Recommended Practice*, 25th edition [ACGIH 2005], *Recommended Industrial Ventilation Guidelines* [Hagopian and Bastress 1976], and the OSHA ventilation standard [29 CFR 1910.94].

Additional engineering controls have been evaluated by the Bureau of Mines for minimizing airborne dust in underground mining operations and at industrial sand plants. These controls may also have applications for RCF finishing, installation, and removal operations. The use of air showers (also known as a canopy air curtain or an overhead air supply island) involves positioning an air supply over the head of a worker to provide a flow of clean, filtered air to the worker's breathing zone [Volkwein et al. 1982, 1988]. Proper design and evaluation are critical for ensuring that filtration is adequate to remove airborne fibers from the air supply. Also, selection of the air supply flow rate is important to make sure that the velocity delivered to the worker's breathing zone is sufficient to overcome cross drafts and maintain a clean air flow.

9.2.1.2 Tool selection and modification

The RCFC has reported that using hand tools instead of powered tools can significantly reduce airborne concentrations of dust. However, hand tools often require additional physical effort and time, and they may increase the risk of musculoskeletal disorders. Employers should therefore use ergonomically correct tools and proper workstation design to avoid ergonomic hazards.

The additional physical effort required to use hand tools may also increase the rate and depth of breathing and may consequently affect the inhalation and deposition of fibers. For operations such as cutting, sawing, grinding, drilling, and sanding, the high level of mechanical energy applied to RCF products with power tools increases the potential for elevated concentrations of airborne fiber. Examples [Carborundum 1992] of how airborne fiber concentrations are affected by the equipment used to process RCF products include the following:

- A test of hand sawing versus the use of a powered jigsaw showed an 81% reduction in concentrations of airborne dust generated.
- A comparison of hand sanding versus power sanding showed a 90% reduction in concentrations of airborne dust generated.
- When a light water mist is applied to the surface of a vacuum-formed board before sanding, airborne dust concentration is reduced by 89% for hand sanding and 88% for powered sanding.
- The use of a cork bore (core drill) versus an electric drill with a twist bit for cutting holes in RCF product forms reduces airborne dust concentrations by about 85%.

9.2.1.3 Engineering controls for RCF finishing operations

Researchers at NIOSH have been working with industrial hygienists at RCFC member facilities to study the effectiveness of engineering controls designed and applied to RCF finishing operations. Because hand tools are not always a practical solution to manufacturing and end-use facilities requirements, engineering controls are being designed and evaluated for use with powered tools.

A joint project between NIOSH and RCFC was initiated in 1998 and involved investigating engineering controls for use with a pedestal belt/disc sander [Dunn et al. 2000, 2004]. These units are frequently used by the manufacturers as well as the customer facilities to produce vacuum-formed boards sized to the required dimensions. A continuous misting nozzle and simple local exhaust ventilation system were integrated for use on the pedestal sanding unit. The mister consisted of a standard atomization nozzle that was set for a low-water flow rate to

minimize part degradation. The local exhaust ventilation system used two hoods or pickup points with a total airflow of 700 ft^3/min.

During production of vacuum-formed boards, these two controls reduced fiber concentrations in the breathing zone as follows:

% decrease in airborne fibers:

Disc sanding using water mist 88

Disc sanding using local exhaust ventilation 99

Belt sanding using water mist 50

Belt sanding using local exhaust ventilation 99

These studies highlight the potential for significant reductions in worker exposure using well designed and maintained engineering controls, but their effectiveness needs to be validated in the field.

9.2.1.4 Wet methods for dust suppression

Fiber counts are lower in more humid atmospheres. Examples of using water to suppress dust concentrations are described as follows:

- At one RCF textile facility, misters have been added above broad looms and tape looms to decrease fiber concentrations.
- Water knives are high-pressure water jets that are used to cut and trim edges of RCF blanket while suppressing dust and limiting the generation of airborne fibers.
- During the installation of RCF modules in a furnace, a procedure called tamping is typically performed. After modules are put in place on the furnace wall, the modules are compressed by placing a 1-ft length of 2- by 4-ft lumber against the modules and tapping it lightly with a hammer. The process helps ensure that the RCF modules are installed tightly in place. When a light water spray is applied to the surface of the modules before tamping, airborne fiber concentration is reduced by about 75% [Carborundum 1993]. The water is applied with a garden-type sprayer that is set on mist using about 1 gal of water/100 ft^2 of surface area. However, caution is advised regarding the dampening of refractory-linings during installation. The introduction of water can damage refractory-lined equipment during heating with explosive spalling from the generation of steam.
- After-service RCF insulation removed from furnaces may be wetted to reduce the release of fibers.

9.2.1.5 Isolation

Some manufacturing processes may be enclosed to keep airborne fibers contained and separated from workers.

- When possible, isolate workers from direct contact with RCFs by using automated equipment operated from a closed control booth or room.
- Maintain the control room at greater air pressure than that surrounding the process equipment so that air flows out rather than in.
- Make sure workers take special precautions (such as using PPE) when they must enter the general work area to perform process checks, adjustments, maintenance, assembly-line tasks, and related operations.

9.2.2 Product Reformulation

One factor that contributes to the toxicity of an inhaled fiber is the durability of the fiber and its resistance to degradation in the respiratory tract. The chemical characteristics of RCFs make them one of the most durable types of SVFs. As a result, an inhaled RCF of specific dimensions will persist longer in the lungs. Modifying the physical characteristics of RCFs or reformulating their chemistry to produce less durable fibers are recommended options for reducing the hazard for exposed workers. Such an approach has been taken by one RCF manufacturer in developing two more soluble types of SVF [Maxim et al. 1999b]. However, caution is advised for developing and distributing such modified fibers. Possible adverse health effects of newly developed fibers should be evaluated before introducing them into commerce. Appropriate testing of these fibers should be performed to provide information about the fiber toxicology and potential adverse health effects associated with exposure to these fibers.

9.2.3 Work Practices and Hygiene

Use good work practices to help reduce exposure to airborne fibers. These practices include the following:

- Limit the use of power tools unless they are equipped with local exhaust or dust collection systems. When possible, use hand tools, which generate less dust and fewer airborne particles.
- Use HEPA-filtered vacuums, wet sweeping, or a properly enclosed wet vacuum system for cleaning up dust containing RCFs.
- During removal of RCF products, dampen insulation with a light water spray to keep fibers and dust from becoming airborne.
- Clean work areas regularly with HEPA-filtered vacuums or with wet sweeping methods to minimize the accumulation of debris.
- Limit access to areas where workers may be exposed to airborne RCFs: permit only workers who are essential to the process or operation.

Use good hygiene and sanitation to protect workers as well as people outside the workplace who might be contaminated with take-home dust and fibers:

- Do not allow workers to smoke, eat, or drink in work areas where they contact RCFs.
- If RCFs get on the skin, wash with warm water and mild soap.
- Apply skin moisturizing cream as needed to avoid dryness or irritation from repeated washing.
- Vacuum contaminated clothes with a HEPA-filtered vacuum before leaving the work area.
  - — Do not use compressed air to clean the work area or clothing.
  - — Do not shake clothes to remove dust.
- Do not wear contaminated clothes outside the work area. Instead, take the following measures to prevent taking contaminants home:
  - — Change into street clothes before going home.
  - — Leave contaminated clothes at the workplace to be laundered by the employer.

— Store street clothes in separate areas of the workplace to keep from contaminating them.

- Provide workers with showers and have them shower before leaving work.
- Prohibit removal of contaminated clothes or other items from the workplace [NIOSH 1995b].

9.2.4 Personal Protective Equipment

Wear long sleeves, gloves, and eye protection when performing dusty activities involving RCFs.

9.2.5 Respiratory Protection

NIOSH recommends using a respirator for any task involving RCF exposures that are unknown or have been documented to be higher than the NIOSH REL of 0.5 f/cm^3 (TWA). Respirators should not be used as the primary means of controlling worker exposures. Instead, NIOSH recommends using other exposure-reduction methods, such as product substitution, engineering controls, and changes in work practices. However, respirators may be necessary when available engineering controls and work practices do not adequately control worker exposures below the REL for RCFs. NIOSH recognizes this control to be a particular challenge in the finishing stages of RCF product manufacturing as well as during the installation and removal of RCF insulation materials.

If respiratory protection is needed, the employer should establish a comprehensive respiratory protection program as described in the OSHA respiratory protection standard [29 CFR 1910.134]. Elements of a respiratory protection program should be established and described in a written plan that is specific to the workplace. This respirator program must include the following:

- Procedures for selecting respirators
- Medical evaluations of workers required to wear respirators
- Fit testing procedures
- Routine use procedures and emergency respirator use procedures
- Procedures and schedules for cleaning, disinfecting, storing, inspecting, repairing, discarding, and maintaining respirators
- Procedures for ensuring adequate air quality for supplied-air respirators
- Training in respiratory hazards
- Training in the proper use and maintenance of respirators
- Program evaluation procedures
- Procedures for ensuring that workers who voluntarily wear respirators (excluding filtering facepiece respirators known as dust masks) comply with the medical evaluation and cleaning, storing, and maintenance requirements contained in Appendix D of the OSHA respiratory protection standard
- A designated program administrator who is qualified to administer the respiratory protection program

The written respiratory protection program should be updated as necessary to account for changes in the workplace that affect respirator use. All equipment, training, and medical evaluations required under the respiratory protection program should be provided at no cost to workers. Workers should use only respirators that have been certified by NIOSH [2002].

When airborne RCF concentrations exceed the REL, NIOSH recommends the following respiratory protection:

- At a minimum, use a half-mask, air-purifying respirator equipped with a 100 series particulate filter (this respirator has an assigned protection factor (APF) of 10.

- For a higher level of protection and for prevention of facial or eye irritation, use a full-facepiece, air-purifying respirator (equipped with a 100 series filter) or any powered, air-purifying respirator equipped with a tight-fitting full facepiece.

- For greater respiratory protection when the work involves potentially high airborne fiber concentrations (such as removal of after-service RCF insulation such as furnace insulation), use a supplied-air respirator equipped with a full facepiece, since airborne exposure to RCFs can be high and unpredictable.

A comprehensive assessment of workplace exposures should always be performed to determine the presence of other possible contaminants (such as silica) and to ensure that the proper respiratory protection is used. Table 9–1 provides additional guidance for selecting appropriate respiratory protection with regard to airborne fiber concentrations and the NIOSH REL for RCFs.

Workers may voluntarily choose to use respiratory protection even when airborne fiber concentrations are below the NIOSH REL or other applicable Federal or State standards. When respirators are used voluntarily by workers, employers need to establish only those respiratory protection program elements necessary to assure that the respirator itself is not a hazard [29 CFR 1910.134]. The exception is that filtering-facepiece respirators (for example, any 95 or 100 series filter) can be used without a respirator protection program when they are used voluntarily.

For information and assistance in establishing a respiratory protection program and selecting appropriate respirators, see the OSHA Respiratory Protection Advisor on the OSHA Web site at http://www.osha.gov. Additional information is available from the *NIOSH Respirator Selection Logic* [NIOSH 2004] document at http://www.cdc.gov/niosh/docs/2005–100 and the *NIOSH Guide to the Selection and Use of Particulate Respirators Certified under 42 CFR 84* [NIOSH 1996].

9.3 Exposure Monitoring

9.3.1 Workplace Exposure Monitoring Program

The workplace exposure monitoring program for worksites where RCFs or RCF products are manufactured, handled, or used should include routine environmental and personal monitoring of airborne fiber concentrations. The monitoring strategy should be designed to assess the effectiveness of engineering controls, work practices, PPE, training, and other factors in controlling airborne fiber concentrations. The monitoring program should also be used to identify areas or tasks that are associated with higher exposures to RCFs and that therefore require additional efforts to reduce them.

The goal of an RCF exposure monitoring program is to ensure a more healthful work environment where worker exposure (measured by full-shift samples) does not exceed the REL. Because adverse respiratory health effects can occur at the REL for RCFs, achieving lower concentrations is desirable whenever possible. For work involving potential

Table 9–1. Respiratory protection for exposure to RCFs*

Airborne concentration of RCFs or conditions of use	Minimum respiratory protection options
≤5.0 f/cm^3 (10 × REL)	Any air-purifying, elastomeric half-mask respirator equipped with a 100 series (N†, R, or P) filter‡
	Any negative pressure (demand), suppled-air respirator equipped with a half mask
≤12.5 f/cm^3 (25 × REL)	Any powered, air-purifying respirator equipped with a hood or helmet and a high-efficiency particulate air filter (HEPA filter)
	Any continuous-flow, supplied-air respirator equipped with a hood or helmet
≤25 f/cm^3 (50 × REL)	Any air-purifying, full-facepiece respirator equipped with a 100 series (N†, R, or P) filter‡
	Any powered, air-purifying respirator equipped with a tight-fitting facepiece (half or full facepiece) and a HEPA filter
	Any negative pressure (demand), supplied-air respirator equipped with a full facepiece
	Any continuous flow, supplied-air respirator equipped with a tight-fitting facepiece (half or full facepiece)
	Any negative pressure (demand), self-contained respirator equipped with a full facepiece
≤500 f/cm^3 (1,000 × REL)	Any pressure demand, supplied-air respirator equipped with a half-mask

*Abbreviations: APFs=assigned protection factors; HEPA=high-efficiency particulate air; NIOSH=National Institue for Occupational Safety and Health; RCFs=refractory ceramic fibers.
†N-100 series particulate filters should not be used in environments where there is potential for exposure to oil mists.
‡Assigned protection factors (APFs) for other half-mask and full-facepiece particulate respirators certified under 42 CFR Part 84 are being studied by NIOSH. Recommended APFs for these respirators will be revised accordingly.

exposure to airborne RCFs, perform the exposure sampling survey as follows:

- Collect representative personal samples for the entire work shift using NIOSH Method 7400 (B rules) [NIOSH 1977a, 1998].
- Perform periodic sampling at least annually and whenever any major process change takes place or another reason exists to suspect that exposure concentrations may have changed.
- Collect all routine personal samples in the breathing zones of the workers.
- For workers exposed to concentrations above the REL, perform more frequent exposure monitoring until at least two consecutive samples indicate that the worker's exposures no longer exceed the REL.
- Notify all workers about monitoring results and any actions taken to reduce their exposures.
- Make sure that any sampling strategy considers variations in work and production schedules as well as the inherent exposure variability in most workplaces [NIOSH 1995a].

9.3.2 Action Level

NIOSH has recommended an action level (AL) of 0.25 f/cm^3 for determining when additional controls are needed or when administrative actions should be taken to reduce RCF exposures. The purpose of the AL is to indicate when worker exposures to RCFs may be approaching the REL. Measurement of exposure concentrations at or above the AL indicate that there is a high degree of certainty that RCF concentrations exceed the REL. The AL is a statistically derived concept permitting the employer to have confidence (for example, 95%) that if the measured exposure concentration is below the AL, only a small probability exists that the exposure concentration is above the REL. NIOSH has concluded that the use of an AL permits employers to monitor RCF exposures in the workplace without devoting unnecessary resources to conducting daily exposure measurements. The AL concept has served as the basis for defining the elements of an occupational standard in NIOSH criteria documents and in comprehensive standards promulgated by OSHA and MSHA. Employers should determine whether the use of an AL of 0.25 f/cm^3 provides adequate assurance that worker exposures are being maintained below the REL. In some work environments, the high degree of exposure variability for certain job tasks may require a lower AL to assure that exposures are being maintained below the REL. Similar exposure monitoring strategies have been espoused by the American Industrial Hygiene Association, which recommends that if measured exposures are less than 10% of the designated exposure limit (for example, REL or PEL), there is a high degree of certainty that the exposure limit will not be exceeded.

9.3.3 Sampling Strategies

When sampling to determine whether worker exposures are below the REL, a focused sampling strategy may be more practical than random sampling. A focused sampling strategy targets workers perceived to have the highest exposure concentrations [Leidel and Busch 1994]. A focused strategy is most efficient for identifying exposures above the REL if maximum-risk workers and time periods are accurately identified. Focused sampling may help identify short-duration tasks involving high airborne fiber concentrations that could result in elevated exposures over a full work shift.

Sampling strategies such as those used by Corn and Esmen [1979], Rice et al. [1997], and Maxim et al. [1997] have been derived and used in RCF manufacturing facilities to monitor airborne fiber concentrations by selecting representative workers for sampling. The representative workers are grouped according to dust zones, uniform job titles, or functional job categories. These approaches are intended to reduce the number of required samples while increasing the confidence of identifying workers at similar risk.

Area sampling may also be useful in exposure monitoring for determining sources of airborne RCF exposures and assessing the effectiveness of engineering controls.

9.4 Medical Monitoring

NIOSH recommends periodic medical evaluation, or medical monitoring, of RCF-exposed workers to identify potential health effects and symptoms that may be related to contact with airborne fibers. The following sections describe the objectives of medical monitoring and the elements of a medical monitoring program for workers exposed to RCFs.

The primary goals of a workplace medical monitoring program are (1) early identification of adverse health effects that may be related to exposures at work and (2) possible health trends within groups of exposed workers. These goals are based on the premise that early detection, subsequent treatment, and workplace interventions will ensure the continued health of the affected workforce.

9.4.1 Objectives of Medical Monitoring

Medical monitoring and resulting interventions represent secondary prevention and should not replace primary prevention efforts to minimize worker exposures to RCFs. In the case of RCFs, medical monitoring is especially important because achieving compliance with the REL of 0.5 f/cm^3 does not assure that all workers will be free from the risk of respiratory irritation or chronic respiratory disease caused by occupational exposure. Early identification of respiratory system changes and symptoms associated with RCF exposures (such as decreased pulmonary function, irritation, dyspnea, chronic cough, wheezing, and pleural plaques) may signal the need for more intensive medical monitoring and the assessment of existing controls to minimize the risk of long-term adverse health effects. An ongoing medical monitoring program also serves to inform workers of potential health risks and promotes an understanding of the need for and support of exposure control activities.

A medical monitoring program serves as an effective secondary prevention method on two levels—screening and surveillance. Medical screening in the workplace focuses on the early detection of health outcomes for individual workers and may involve an occupational history, medical examination, and application of specific medical tests to detect the presence of toxicants or early pathologic changes before the worker would normally seek clinical care for symptomatic disease. By contrast, medical surveillance (described in Section 9.5) involves the ongoing evaluation of the health status of a group of workers through the collection and aggregate analysis of health data for the purpose of preventing disease and evaluating the effectiveness of intervention programs.

9.4.2 Criteria for Medical Screening

To determine whether tests or procedures for medical screening are appropriate and relevant to a given hazard (in this case, exposure to airborne RCFs), the following factors should be considered:

- Prevalence of an associated disease or symptoms in the population
- Risk of toxicity associated with the exposure
- Consequences of false positive test results
- Sensitivity, specificity, and predictive value of the screening test(s) to be used
- Reliability and validity of the screening test(s)
- Ability of the screening test(s) to identify disease early so that effective treatment or intervention may be used to impede disease progression
- Availability, accessibility, and acceptability of followup, further diagnostic tests, and effective management of the disease
- Benefits of the screening program compared with the costs [Wagner 1996].

On the basis of these criteria, NIOSH recommends a medical screening program for RCF-exposed workers that require initial and periodic medical examinations. The elements of the program should include a physical examination, occupational history, respiratory symptom questionnaire, spirometric testing, and chest radiograph when warranted. If a particular medical screening test indicates the presence of exposure-related disease or the increased probability that disease will develop, further evaluation and diagnostic testing may be needed. Recommended guidelines and schedules for specific medical tests are described in Section 9.4.5 (Recommended Program Elements).

9.4.3 Worker Participation

All workers potentially exposed to RCFs, in both manufacturing and end-use industries, may benefit by being included in an occupational medical monitoring program. Workers should be provided with information about the purposes of medical monitoring, the health benefits of the program, and the procedures involved. The following hierarchy describes workers who should be included in a medical monitoring program and who could receive the greatest benefit from medical screening:

- Workers exposed to elevated fiber concentrations (for example, all workers exposed to airborne RCFs at concentrations above the AL of 0.25 f/cm^3 [described in Section 9.3])
- Workers in areas or in jobs and activities in which, regardless of airborne fiber concentration, one or more workers have recently developed symptoms or respiratory changes apparently related to RCF exposure
- Workers who may have been previously exposed to asbestos or other respiratory hazards that place them at an increased risk of respiratory disease
- Workers with potential exposure to airborne RCFs who also smoke cigarettes or other tobacco products (see Section 9.6, Smoking Cessation).

9.4.4 Medical Monitoring Program Director

Oversight of the medical monitoring program should be assigned by the employer to a qualified physician or other qualified health care provider (as determined by appropriate State laws and regulations) who is informed and knowledgeable about the following:

- The administration and management of a medical monitoring program for occupational hazards

- The establishment of a respiratory protection program based on an understanding of the requirements of the OSHA respiratory protection standard and types of respiratory protection devices available at the workplace
- The identification and management of work-related respiratory effects or illnesses
- The identification and management of work-related skin diseases

9.4.5 Recommended Program Elements

Recommended elements of a medical monitoring program for workers exposed to RCFs include provisions for an initial medical examination and periodic medical examinations at regularly scheduled intervals. Depending on the findings from these examinations, more frequent and detailed medical examinations may be necessary. Worker education should also be included as a component of the medical monitoring program. Specific elements of the examinations and scheduling are described below and illustrated in the flow chart diagram in Figure 9–1.

9.4.5.1 Initial medical examination

An initial (baseline) examination should be performed as near as possible to the date of beginning employment (within 3 months). The initial medical examination should include the following:

- A physical examination of all systems, with emphasis on the respiratory system and the skin
- A spirometric test (Anyone administering spirometric testing as part of the medical monitoring program should have completed a NIOSH-approved training course in spirometry or other equivalent training.)
- A chest X-ray (All chest X-ray films should be interpreted by a NIOSH-certified B reader using the standard International Classification of Radiographs of Pneumoconioses [ILO 2000 or the most recent equivalent].)
- Other medical tests as deemed appropriate by the attending health care professional
- A standardized respiratory symptom questionnaire such as the American Thoracic Society Respiratory Questionnaire [Ferris 1978 or the most recent equivalent] with additional questions to address symptoms of pleuritic chest pain and pleurisy
- A standardized occupational history questionnaire that gathers (1) information about all past jobs (with special emphasis on those with potential exposure to dust), (2) a description of all duties and potential exposures for each job, and (3) a description of all protective equipment the worker has used

9.4.5.2 Periodic medical examinations

Periodic examinations (including a physical examination of the respiratory system and the skin, spirometric testing, a respiratory symptom update questionnaire, and an occupational history update questionnaire) should be administered at regular intervals determined by the medical monitoring program director. The frequency of the periodic medical examinations should be determined according to the following guidelines:

- For workers with fewer than 10 years since first exposure to RCFs, periodic examinations should be conducted at least once every 5 years.

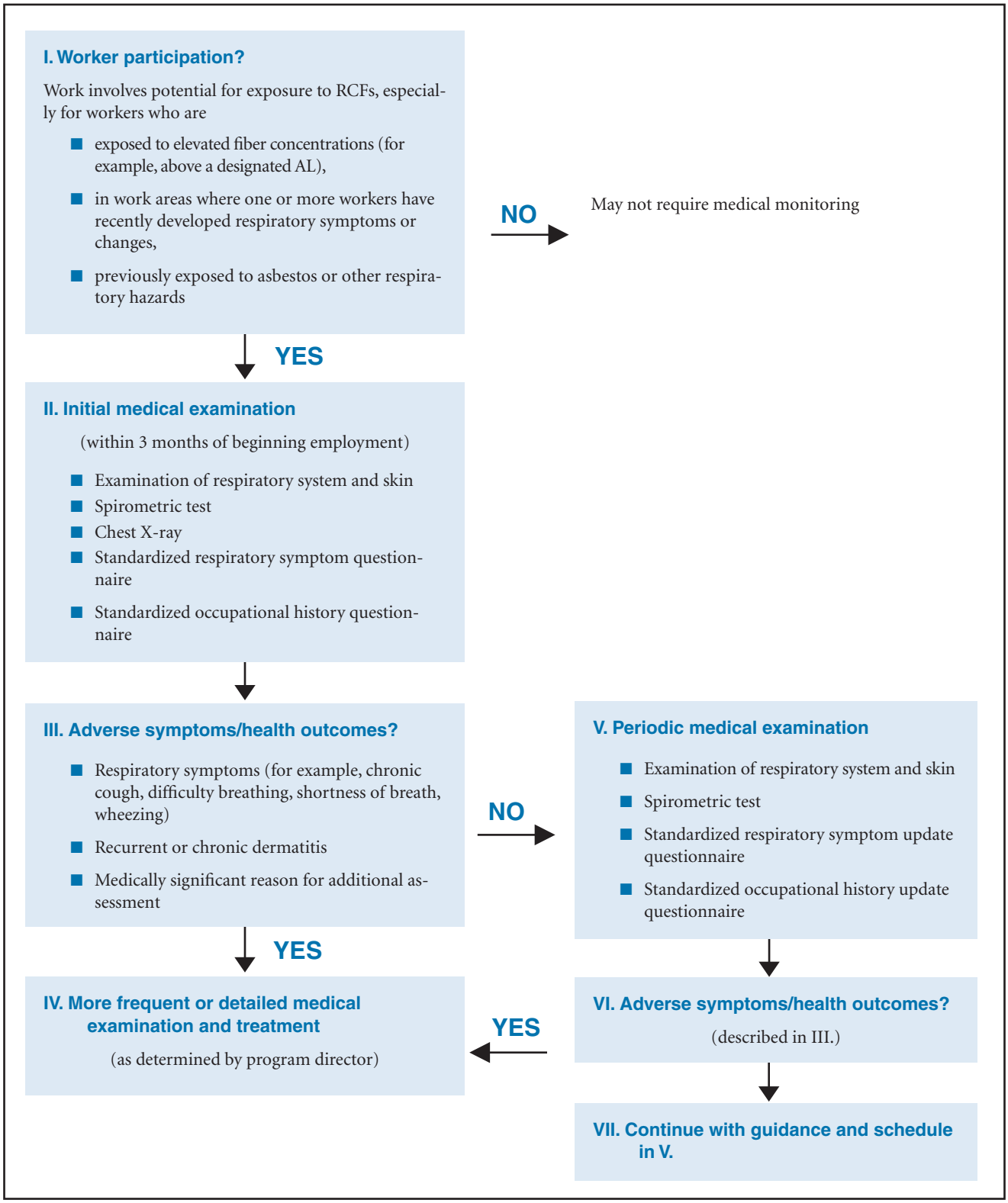

Figure 9–1. Flow chart of medical monitoring guidelines for workers exposed to RCFs. This flow chart is intended as a simplified representation of the minimum requirements of the recommended medical monitoring program guidelines. Administration and management of the program should ultimately rely on the judgment of the medical monitoring program director. Frequency of periodic medical examinations are as follows:

- If time since first RCF exposure is <10 years, examinations should be conducted at least every 5 years.
- If time since first RCF exposure is ≥10 years, then examinations should be conducted at least every 2 years.

- For workers with 10 or more years since first exposure to RCFs, periodic examinations should be conducted at least once every 2 years.

A chest X-ray and spirometric testing are important upon initial examination and may also be appropriate medical screening tests during periodic examinations for detecting respiratory system changes—especially in workers with more than 10 years since first exposure to RCFs. The value of periodic chest X-rays in a medical monitoring program should be evaluated by a qualified health care provider in consultation with the worker to assess whether the benefits of testing warrant the additional exposure to radiation. As with the frequency of periodic examinations, the utility of the chest X-ray as a medical test becomes greater for workers with more than 10 years since first exposure to RCFs (based on the latency period between first exposure and appearance of noticeable respiratory system changes). Because persons with advanced fiber-related pleural changes experience difficulty in breathing as the parietal and visceral surfaces become adherent and lose flexibility, it may prove beneficial to detect fibrotic changes in the early stages so steps may be taken to prevent further lung damage. Similar recommendations have been made for asbestos-exposed workers diagnosed with pleural fibrosis or pleural plaques to prevent more serious types of respiratory disease [Balmes 1990].

9.4.5.3 More frequent medical examinations

Any worker should undergo more frequent and detailed medical evaluation if he or she has any of the following indications:

- New or worsening respiratory symptoms or findings (for example, chronic cough, difficulty breathing, wheezing, reduced lung function, or radiographic evidence of pleural plaques or fibrosis)
- History of exposure to other respiratory hazards (for example, asbestos)
- Recurrent or chronic dermatitis
- Other medically significant reason(s) for more detailed assessment

9.4.5.4 Worker education

Workers should be provided with sufficient training to recognize symptoms associated with RCF exposures (such as chronic cough, difficulty breathing, wheezing, and skin irritation). Workers should also be instructed to report these symptoms to designated safety and health personnel and a physician or other qualified health care provider for appropriate diagnosis and treatment.

9.4.6 Written Reports to the Worker

Following initial and periodic medical examinations, the physician or other qualified health care provider should provide each worker with a written report containing the following:

- Results of any medical tests performed on the worker
- Medical opinion in plain language about any medical condition that would increase the worker's risk of impairment from exposure to airborne RCFs
- Recommendations for limiting the worker's exposure to RCFs, which may include the use of appropriate PPE, as warranted
- Recommendations for further evaluation and treatment of medical conditions detected

9.4.7 Written Reports to the Employer

Following initial and periodic medical examinations, the physician or other qualified health care provider should provide a written report to the employer containing the following:

- Occupationally pertinent results of the medical evaluation
- A medical opinion about any medical condition that would increase the worker's risk of impairment from exposure to airborne RCFs
- Recommendations for limiting the worker's exposure to RCFs (or other agents in the workplace), which may include the use of appropriate PPE or reassignment to another job, as warranted
- A statement to indicate that the worker has been informed about results of the medical examination and about the medical condition(s) that should have further evaluation or treatment

Findings, test results, or diagnoses that have no bearing on the worker's ability to work with RCFs should not be included in the report to the employer. Safeguards to protect the confidentiality of the worker's medical records should be enforced in accordance with all applicable regulations and guidelines.

9.4.8 Employer Actions

The employer should assure that the qualified health care provider's recommended restrictions of a worker's exposure to RCFs or to other workplace hazards are followed and that the REL for RCFs is not exceeded without requiring the use of PPE. Efforts to encourage worker participation in the medical monitoring program and to report symptoms promptly to the program director are essential for the program's success. Medical evaluations performed as part of the medical monitoring program should be provided by the employer at no cost to the participating workers. If the recommended restrictions determined by the medical program director include job reassignment, such reassignment should be implemented with the assurance of economic protection for the worker. When medical removal or job reassignment is indicated, the affected worker should not suffer loss of wages, benefits, or seniority.

The employer should ensure that the medical monitoring program director communicates regularly with the employer's safety and health personnel (such as industrial hygienists), employee representatives, and safety and health committees to identify work areas that may require evaluation and implementation of control measures to minimize the risk from exposure to hazards.

9.5 Surveillance of Health Outcomes

Standardized medical screening data should be periodically aggregated and evaluated by an epidemiologist or other knowledgeable person to identify patterns of worker health that may be linked to work activities and practices that require additional primary prevention efforts. Routine aggregate assessments of medical screening data should be used in combination with evaluations of exposure monitoring data to identify changes needed in work areas or exposure conditions.

One example of surveillance using analyses of medical screening data is the ongoing epidemiologic study of RCF workers described in the RCFC product stewardship plan referred to as PSP 2000 [RCFC 2001]. Elements of this plan may be adapted and modified by other employers to develop medical surveillance programs for workers who are potentially exposed to RCFs.

9.6 Smoking Cessation

NIOSH recognizes a synergistic effect between exposure to RCFs and cigarette smoking that increases the risk of adverse respiratory health effects. The combined effects of smoking and dust exposures have been recognized as contributing to the increased risk of respiratory diseases, including chronic bronchitis, emphysema, and lung cancer. NIOSH urges employers to establish smoking cessation programs that (1) inform workers about the increased hazards of cigarette smoking and exposure to RCFs and (2) provide assistance and encouragement for workers who want to quit smoking. NIOSH recommends that all workers who are potentially exposed to airborne RCF fibers and who also smoke should participate in a smoking cessation program. With regard to smoking in the workplace, NIOSH recommends that employers do the following:

- Prohibit workers from smoking in the workplace.
- Disseminate information about health promotion and the harmful effects of smoking.
- Offer smoking cessation programs to workers at no cost to participants.
- Collect detailed smoking histories as part of the medical monitoring program.
- Use training, employee assistance programs, or health education campaigns to encourage activities promoting physical fitness and other healthy lifestyle practices that affect respiratory and cardiovascular health.

10 Research Needs

NIOSH [1993] has developed a fiber research strategy that proposes the following:

- Research into the mechanisms for human fiber disease
- Epidemiologic studies of fiber-exposed workers for whom limited or no health data exist
- Toxicologic experiments with fibers for which health effects have not been established

The research strategy also considers the usefulness of integrating fiber data from various scientific disciplines (toxicology, epidemiology, industrial hygiene, occupational medicine) to elucidate the characteristics of fibers.

In addition, NIOSH recommends that the following steps be taken with regard to RCF research:

1. Conduct basic scientific investigations, including in vitro and in vivo animal studies, to delineate the mechanism of action for RCF toxicity.
2. Conduct comparable studies for other SVFs and natural fibers so that the mechanistic data can be compared. For instance, Coffin et al. [1992] examined the ability of different synthetic and natural fibers to induce mesotheliomas. They suggested that in addition to fiber length and width, currently undefined intrinsic surface characteristics of the fibers are directly related to their mesothelioma induction potency.
3. Conduct a series of in vitro and in vivo animal studies to ensure that fiber toxicity studies share a consistent, standardized approach. Such studies will ensure comparability of results in a variety of experiments that all use well-characterized, known concentrations of synthetic or natural fibers. A series of controlled, systematic in vitro studies of the factors believed to be involved in RCF pathogenicity should produce valuable data on their mechanism of action. In vitro studies provide an excellent opportunity to investigate fiber toxicity factors such as dose, dimension, surface area, and physicochemical composition. This information is an important supplement to data from chronic inhalation studies.
4. Assure that an independent agency or testing laboratory assembles and keeps a set of reference samples of RCFs (similar to the Union Internationale Contre le Cancer [UICC] asbestos samples). Well-characterized RCF material representative of that found in occupational exposures could serve as an important component of future animal toxicology research into the mechanisms of fiber-induced disease. Additional SVF such as fibrous glass, mineral wool, and other ceramic fibers should also be represented in this repository.
5. Initiate and continue occupational health surveillance for industries that

manufacture, process, install, or remove new fibrous materials. Understanding of this emerging industry is imperative so that exposures to synthetic fibrous materials can be avoided and industry-specific controls can be developed.

6. Continue and expand surveillance of RCF exposure in U.S. manufacturing facilities. Continue monitoring of airborne fiber and total particulate concentrations and analyze them together with the health data using epidemiologic research methods. Extend surveillance efforts to include assessments of worker exposure in secondary facilities.

7. Assess the effects of variable work schedules (such as shifts longer than 8 hr) on RCF exposure concentrations and health effects.

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APPENDIX A

Air Sampling Methods*

*Reprinted from *NIOSH Manual of Analytical Methods (NMAM)*, Fourth Edition, 8/15/94.

PARTICULATES NOT OTHERWISE REGULATED, TOTAL 0500

DEFINITION: total aerosol mass CAS: NONE RTECS: NONE

METHOD: 0500, Issue 2 **EVALUATION:** FULL **Issue 1:** 15 February 1984 **Issue 2:** 15 August 1994

OSHA : 15 mg/m^3
NIOSH: no REL
ACGIH: 10 mg/m^3, total dust less than 1% quartz

PROPERTIES: contains no asbestos and quartz less than 1%

SYNONYMS: nuisance dusts; particulates not otherwise classified

SAMPLING

SAMPLER: FILTER (tared 37-mm, 5-µm PVC filter)

FLOW RATE: 1 to 2 L/min

VOL-MIN: 7 L @ 15 mg/m^3
-MAX: 133 L @ 15 mg/m^3

SHIPMENT: routine

SAMPLE STABILITY: indefinitely

BLANKS: 2 to 10 field blanks per set

BULK SAMPLE: none required

ACCURACY

RANGE STUDIED: 8 to 28 mg/m^3

BIAS: 0.01%

OVERALL PRECISION ($\hat{S}_{rT}$): 0.056 [1]

ACCURACY: ± 11.04%

MEASUREMENT

TECHNIQUE: GRAVIMETRIC (FILTER WEIGHT)

ANALYTE: airborne particulate material

BALANCE: 0.001 mg sensitivity; use same balance before and after sample collection

CALIBRATION: National Institute of Standards and Technology Class S-1.1 weights or ASTM Class 1 weights

RANGE: 0.1 to 2 mg per sample

ESTIMATED LOD: 0.03 mg per sample

PRECISION ($\bar{S}_r$): 0.026 [2]

APPLICABILITY: The working range is 1 to 20 mg/m^3 for a 100-L air sample. This method is nonspecific and determines the total dust concentration to which a worker is exposed. It may be applied, e.g., to gravimetric determination of fibrous glass [3] in addition to the other ACGIH particulates not otherwise regulated [4].

INTERFERENCES: Organic and volatile particulate matter may be removed by dry ashing [3].

OTHER METHODS: This method is similar to the criteria document method for fibrous glass [3] and Method 5000 for carbon black. This method replaces Method S349 [5]. Impingers and direct-reading instruments may be used to collect total dust samples, but these have limitations for personal sampling.

EQUIPMENT:

1. Sampler: 37-mm PVC, 2- to 5-µm pore size membrane or equivalent hydrophobic filter and supporting pad in 37-mm cassette filter holder.
2. Personal sampling pump, 1 to 2 L/min, with flexible connecting tubing.
3. Microbalance, capable of weighing to 0.001 mg.
4. Static neutralizer: e.g., Po-210; replace nine months after the production date.
5. Forceps (preferably nylon).
6. Environmental chamber or room for balance (e.g., 20 °C ± 1 °C and 50% ± 5% RH).

SPECIAL PRECAUTIONS: None.

PREPARATION OF FILTERS BEFORE SAMPLING:

1. Equilibrate the filters in an environmentally controlled weighing area or chamber for at least 2 h.
   NOTE: An environmentally controlled chamber is desirable, but not required.
2. Number the backup pads with a ballpoint pen and place them, numbered side down, in filter cassette bottom sections.
3. Weigh the filters in an environmentally controlled area or chamber. Record the filter tare weight, W_1 (mg).
   a. Zero the balance before each weighing.
   b. Handle the filter with forceps. Pass the filter over an antistatic radiation source. Repeat this step if filter does not release easily from the forceps or if filter attracts balance pan. Static electricity can cause erroneous weight readings.
4. Assemble the filter in the filter cassettes and close firmly so that leakage around the filter will not occur. Place a plug in each opening of the filter cassette. Place a cellulose shrink band around the filter cassette, allow to dry and mark with the same number as the backup pad.

SAMPLING:

5. Calibrate each personal sampling pump with a representative sampler in line.
6. Sample at 1 to 2 L/min for a total sample volume of 7 to 133 L. Do not exceed a total filter loading of approximately 2 mg total dust. Take two to four replicate samples for each batch of field samples for quality assurance on the sampling procedure.

SAMPLE PREPARATION:

7. Wipe dust from the external surface of the filter cassette with a moist paper towel to minimize contamination. Discard the paper towel.
8. Remove the top and bottom plugs from the filter cassette. Equilibrate for at least 2 h in the balance room.
9. Remove the cassette band, pry open the cassette, and remove the filter gently to avoid loss of dust.
   NOTE: If the filter adheres to the underside of the cassette top, very gently lift away by using the dull side of a scalpel blade. This must be done carefully or the filter will tear.

CALIBRATION AND QUALITY CONTROL:

10. Zero the microbalance before all weighings. Use the same microbalance for weighing filters before and after sample collection. Maintain and calibrate the balance with National Institute of Standards and Technology Class S-1.1 or ASTM Class 1 weights.

11. The set of replicate samples should be exposed to the same dust environment, either in a laboratory dust chamber [7] or in the field [8]. The quality control samples must be taken with the same equipment, procedures and personnel used in the routine field samples. The relative standard deviation calculated from these replicates should be recorded on control charts and action taken when the precision is out of control [7].

MEASUREMENT:

12. Weigh each filter, including field blanks. Record the post-sampling weight, W_2 (mg). Record anything remarkable about a filter (e.g., overload, leakage, wet, torn, etc.)

CALCULATIONS:

13. Calculate the concentration of total particulate, C (mg/m^3), in the air volume sampled, V (L):

$$C = \frac{(W_2 - W_1) - (B_2 - B_1) \cdot 10^3}{V}, \ mg/m^3.$$

where: W_1 = tare weight of filter before sampling (mg)
W_2 = post-sampling weight of sample-containing filter (mg)
B_1 = mean tare weight of blank filters (mg)
B_2 = mean post-sampling weight of blank filters (mg)

EVALUATION OF METHOD:

Lab testing with blank filters and generated atmospheres of carbon black was done at 8 to 28 mg/m^3 [2,6]. Precision and accuracy data are given on page 0500-1.

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METHOD REVISED BY:

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PARTICULATES NOT OTHERWISE REGULATED, RESPIRABLE 0600

DEFINITION: aerosol collected by sampler with 4-µm median cut point

CAS: None RTECS: None

METHOD: 0600, Issue 3	EVALUATION: FULL	Issue 1: 15 February 1984 Issue 3: 15 January 1998

OSHA : 5 mg/m³
NIOSH: no REL
ACGIH: 3 mg/m³

PROPERTIES: contains no asbestos and quartz less than 1%; penetrates non-ciliated portions of respiratory system

SYNONYMS: nuisance dusts; particulates not otherwise classified

SAMPLING

SAMPLER: CYCLONE + FILTER (10-mm nylon cyclone, Higgins-Dewell [HD] cyclone, or Aluminum cyclone + tared 5-µm PVC membrane)

FLOW RATE: nylon cyclone: 1.7 L/min
HD cyclone: 2.2 L/min
Al cyclone: 2.5 L/min

VOL-MIN: 20 L @ 5 mg/m³
-MAX: 400 L

SHIPMENT: routine

SAMPLE STABILITY: stable

BLANKS: 2 to 10 field blanks per set

ACCURACY

RANGE STUDIED: 0.5 to 10 mg/m³ (lab and field)

BIAS: dependent on dust size distribution [1]

OVERALL PRECISION ($\hat{S}_{rT}$): dependent on size distribution [1,2]

ACCURACY: dependent on size distribution [1]

MEASUREMENT

TECHNIQUE: GRAVIMETRIC (FILTER WEIGHT)

ANALYTE: mass of respirable dust fraction

BALANCE: 0.001 mg sensitivity; use same balance before and after sample collection

CALIBRATION: National Institute of Standards and Technology Class S-1.1 or ASTM Class 1 weights

RANGE: 0.1 to 2 mg per sample

ESTIMATED LOD: 0.03 mg per sample

PRECISION: <10 µg with 0.001 mg sensitivity balance; <70 µg with 0.01 mg sensitivity balance [3]

APPLICABILITY: The working range is 0.5 to 10 mg/m³ for a 200-L air sample. The method measures the mass concentration of any non-volatile respirable dust. In addition to inert dusts [4], the method has been recommended for respirable coal dust. The method is biased in light of the recently adopted international definition of respirable dust, e.g., ≈ +7% bias for non-diesel, coal mine dust [5].

INTERFERENCES: Larger than respirable particles (over 10 µm) have been found in some cases by microscopic analysis of cyclone filters. Over-sized particles in samples are known to be caused by inverting the cyclone assembly. Heavy dust loadings, fibers, and water-saturated dusts also interfere with the cyclone's size-selective properties. The use of conductive samplers is recommended to minimize particle charge effects.

OTHER METHODS: This method is based on and replaces Sampling Data Sheet #29.02 [6].

EQUIPMENT:

1. Sampler:
   a. Filter: 5.0-µm pore size, polyvinyl chloride filter or equivalent hydrophobic membrane filter supported by a cassette filter holder (preferably conductive).
   b. Cyclone: 10-mm nylon(Mine Safety Appliance Co., Instrument Division, P. O. Box 427, Pittsburgh, PA 15230), Higgins-Dewell(BGI Inc., 58 Guinan St., Waltham, MA 02154)[7], aluminum cyclone (SKC Inc., 863 Valley View Road, Eighty Four, PA 15330), or equivalent.
2. Personal sampling pump, 1.7 L/min ± 5% for nylon cyclone, 2.2 L/min ± 5% for HD cyclone, or 2.5 L/min ± 5% for the Al cyclone with flexible connecting tubing.
   NOTE: Pulsation in the pump flow must be within ± 20% of the mean flow.
3. Balance, analytical, with sensitivity of 0.001 mg.
4. Weights, NIST Class S-1.1, or ASTM Class 1.
5. Static neutralizer, e.g., Po-210; replace nine months after the production date.
6. Forceps (preferably nylon).
7. Environmental chamber or room for balance, e.g., 20 °C ± 1 °C and 50% ± 5% RH.

SPECIAL PRECAUTIONS: None.

PREPARATION OF SAMPLERS BEFORE SAMPLING:

1. Equilibrate the filters in an environmentally controlled weighing area or chamber for at least 2 h.
2. Weigh the filters in an environmentally controlled area or chamber. Record the filter tare weight, W_1 (mg).
   a. Zero the balance before each weighing.
   b. Handle the filter with forceps (nylon forceps if further analyses will be done).
   c. Pass the filter over an anti-static radiation source. Repeat this step if filter does not release easily from the forceps or if filter attracts balance pan. Static electricity can cause erroneous weight readings.
3. Assemble the filters in the filter cassettes and close firmly so that leakage around the filter will not occur. Place a plug in each opening of the filter cassette.
4. Remove the cyclone's grit cap before use and inspect the cyclone interior. If the inside is visibly scored, discard this cyclone since the dust separation characteristics of the cyclone may be altered. Clean the interior of the cyclone to prevent reentrainment of large particles.
5. Assemble the sampler head. Check alignment of filter holder and cyclone in the sampling head to prevent leakage.

SAMPLING:

6. Calibrate each personal sampling pump to the appropriate flow rate with a representative sampler in line.
   NOTE 1: Because of their inlet designs, nylon and aluminum cyclones are calibrated within a large vessel with inlet and outlet ports. The inlet is connected to a calibrator (e.g., a bubble meter). The cyclone outlet is connected to the outlet port within the vessel, and the vessel outlet is attached to the pump. See APPENDIX for alternate calibration procedure. (The calibrator can be connected directly to the HD cyclone.)
   NOTE 2: Even if the flowrate shifts by a known amount between calibration and use, the nominal flowrates are used for concentration calculation because of a self-correction feature of the cyclones.
7. Sample 45 min to 8 h. Do not exceed 2 mg dust loading on the filter. Take 2 to 4 replicate samples for each batch of field samples for quality assurance on the sampling procedure (see Step 10).
   NOTE : Do not allow the sampler assembly to be inverted at any time. Turning the cyclone to anything more than a horizontal orientation may deposit oversized material from the cyclone body onto the filter.

SAMPLE PREPARATION:

8. Remove the top and bottom plugs from the filter cassette. Equilibrate for at least 2 h in an environmentally controlled area or chamber.

CALIBRATION AND QUALITY CONTROL:

9. Zero the microbalance before all weighings. Use the same microbalance for weighing filters before and after sample collection. Calibrate the balance with National Institute of Standards and Technology Class S-1.1 or ASTM Class 1 weights.
10. The set of replicate field samples should be exposed to the same dust environment, either in a laboratory dust chamber [8] or in the field [9]. The quality control samples must be taken with the same equipment, procedures, and personnel used in the routine field samples. Calculate precision from these replicates and record relative standard deviation (S_r) on control charts. Take corrective action when the precision is out of control [8].

MEASUREMENT:

11. Weigh each filter, including field blanks. Record this post-sampling weight, W_2 (mg), beside its corresponding tare weight. Record anything remarkable about a filter (e.g., visible particles, overloading, leakage, wet, torn, etc.).

CALCULATIONS:

12. Calculate the concentration of respirable particulate, C (mg/m^3), in the air volume sampled, V (L):

$$C = \frac{(W_2 - W_1) - (B_2 - B_1)}{V} \cdot 10^3, \; mg/m^3$$

where: W_1 = tare weight of filter before sampling (mg)
W_2 = post-sampling weight of sample-containing filter (mg)
B_1 = mean tare weight of blank filters (mg).
B_2 = mean post-sampling weight of blank filters (mg)
V = volume as sampled at the nominal flowrate (i.e., 1.7 L/min or 2.2 L/min)

EVALUATION OF METHOD:

1. Bias: In respirable dust measurements, the bias in a sample is calculated relative to the appropriate respirable dust convention. The theory for calculating bias was developed by Bartley and Breuer [10]. For this method, the bias, therefore, depends on the international convention for respirable dust, the cyclones' penetration curves, and the size distribution of the ambient dust. Based on measured penetration curves for non-pulsating flow [1], the bias in this method is shown in Figure 1.

   For dust size distributions in the shaded region, the bias in this method lies within the ± 0.10 criterion established by NIOSH for method validation. Bias larger than ± 0.10 would, therefore, be expected for some workplace aerosols. However, bias within ± 0.20 would be expected for dusts with geometric standard deviations greater than 2.0, which is the case in most workplaces.

   Bias can also be caused in a cyclone by the pulsation of the personal sampling pump. Bartley, et al. [12] showed that cyclone samples with pulsating flow can have negative bias as large as -0.22 relative to samples with steady flow. The magnitude of the bias depends on the amplitude of the pulsation at the

cyclone aperture and the dust size distribution. For pumps with instantaneous flow rates within 20% of the mean, the pulsation bias magnitude is less than 0.02 for most dust size distributions encountered in the workplace.

Electric charges on the dust and the cyclone will also cause bias. Briant and Moss [13] have found electrostatic biases as large as -50%, and show that cyclones made with graphite-filled nylon eliminate the problem. Use of conductive samplers and filter cassettes(Omega Specialty Instrument Co., 4 Kidder Road, Chelmsford, MA 01824) is recommended.

2. Precision: The figure 0.068 mg quoted above for the precision is based on a study [3] of weighing procedures employed in the past by the Mine Safety and Health Administration (MSHA) in which filters are pre-weighed by the filter manufacturer and post-weighed by MSHA using balances readable to 0.010 mg. MSHA [14] has recently completed a study using a 0.001 mg balance for the post-weighing, indicating imprecision equal to 0.006 mg.

   Imprecision equal to 0.010 mg was used for estimating the LOD and is based on specific suggestions [8] regarding filter weighing using a single 0.001 mg balance. This value is consistent with another study [15] of repeat filter weighings, although the actual attainable precision may depend strongly on the specific environment to which the filters are exposed between the two weighings.

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METHOD REVISED BY: David L. Bartley, Ph.D., NIOSH/DPSE/ARDB and Ray Feldman, OSHA.

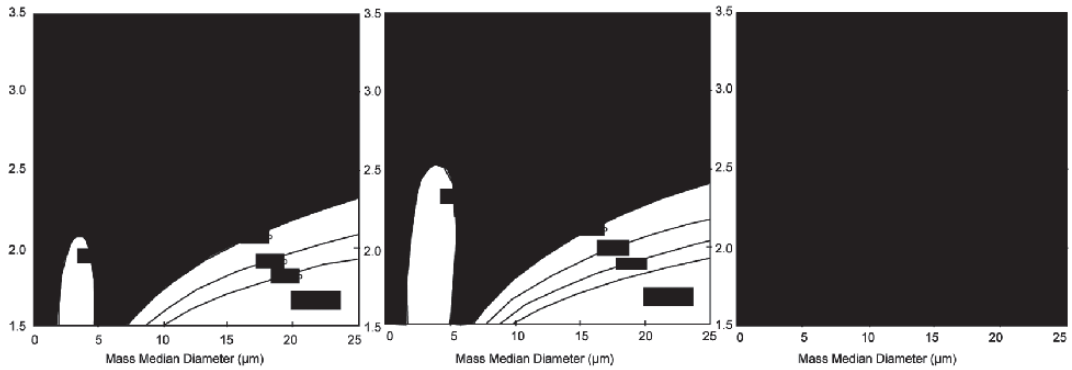

Figure 1. Bias of three cyclone types relative to the international respirable dust sampling convention.

APPENDIX: Jarless Method for Calibration of Cyclone Assemblies

This procedure may be used in the field to calibrate an air sampling pump and a cyclone assembly without using the one-liter "calibration jar".

(1) Connect the pump to a pressure gauge or water manometer and a light load (adjustable valve or 5-µm filter) equal to 2" to 5" H_2O with a "TEE" connector and flexible tubing. Connect other end of valve to an electronic bubble meter or standard bubble tube with flexible tubing (See Fig. 2.1).
NOTE: A light load can be a 5-µm filter and/or an adjustable valve. A heavy load can be several 0.8-µm filters and/or adjustable valve.

(2) Adjust the pump to 1.7 L/min, as indicated on the bubble meter/tube, under the light load conditions (2" to 5" H_2O) as indicated on the pressure gauge or manometer.

(3) Increase the load until the pressure gauge or water manometer indicates between 25" and 35" H_2O. Check the flow rate of the pump again. The flow rate should remain at 1.7 L/min ± 5%.

(4) Replace the pressure gauge or water manometer and the electronic bubble meter or standard bubble tube with the cyclone having a clean filter installed (Fig. 2.2). If the loading caused by the cyclone assembly is between 2" and 5" H_2O, the calibration is complete and the pump and cyclone are ready for sampling.

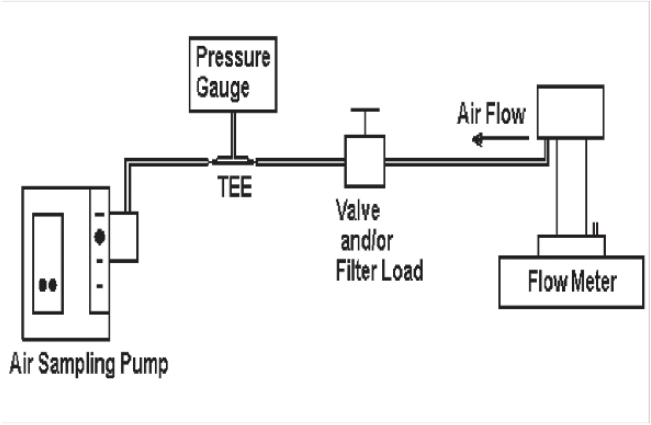

Figure 2.1 Block Diagram of Pump/Load/Flow Meter Set-up.

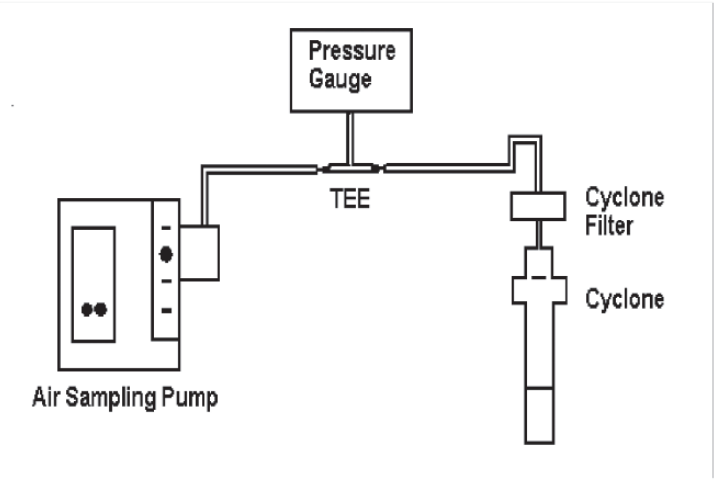

Figure 2.2. Block Diagram with Cyclone as the Test Load.

ASBESTOS and OTHER FIBERS by PCM 7400

Various MW: Various CAS: Various RTECS: Various

METHOD: 7400, Issue 2 **EVALUATION: FULL** **Issue 1: Rev. 3 on 15 May 1989**
Issue 2: 15 August 1994

OSHA : 0.1 asbestos fiber (> 5 µm long)/cc; 1 f/cc/30 min excursion; carcinogen
MSHA: 2 asbestos fibers/cc
NIOSH: 0.1 f/cc (fibers > 5 µm long)/400 L; carcinogen
ACGIH: 0.2 crocidolite; 0.5 amosite; 2 chrysotile and other asbestos, fibers/cc; carcinogen

PROPERTIES: solid, fibrous, crystalline, anisotropic

SYNONYMS [CAS #]: actinolite **[77536-66-4]** or ferroactinolite **[15669-07-5]**; amosite **[12172-73-5]**; anthophyllite **[77536-67-5]**; chrysotile **[12001-29-5]**; serpentine **[18786-24-8]**; crocidolite **[12001-28-4]**; tremolite **[77536-68-6]**; amphibole asbestos **[1332-21-4]**; refractory ceramic fibers **[142844-00-6]**; fibrous glass.

SAMPLING

SAMPLER: FILTER (0.45- to 1.2-µm cellulose ester membrane, 25-mm; conductive cowl on cassette)

FLOW RATE*: 0.5 to 16 L/min

VOL-MIN*: 400 L @ 0.1 fiber/cc
-MAX*: (step 4, sampling)
*Adjust to give 100 to 1300 fiber/mm²

SHIPMENT: routine (pack to reduce shock)

SAMPLE STABILITY: stable

BLANKS: 2 to 10 field blanks per set

ACCURACY

RANGE STUDIED: 80 to 100 fibers counted

BIAS: See EVALUATION OF METHOD

OVERALL PRECISION ($\hat{S}_{rT}$): 0.115 to 0.13 [1]

ACCURACY: See EVALUATION OF METHOD

MEASUREMENT

TECHNIQUE: LIGHT MICROSCOPY, PHASE CONTRAST

ANALYTE: fibers (manual count)

SAMPLE PREPARATION: acetone - collapse/triacetin - immersion

COUNTING RULES: described in previous version of this method as "A" rules [1,3]

EQUIPMENT:
1. positive phase-contrast microscope
2. Walton-Beckett graticule (100-µm field of view) Type G-22
3. phase-shift test slide (HSE/NPL)

CALIBRATION: HSE/NPL test slide

RANGE: 100 to 1300 fibers/mm² filter area

ESTIMATED LOD: 7 fibers/mm² filter area

PRECISION ($\bar{S}_r$): 0.10 to 0.12 [1]; see EVALUATION OF METHOD

APPLICABILITY: The quantitative working range is 0.04 to 0.5 fiber/cc for a 1000-L air sample. The LOD depends on sample volume and quantity of interfering dust, and is <0.01 fiber/cc for atmospheres free of interferences. The method gives an index of airborne fibers. It is primarily used for estimating asbestos concentrations, though PCM does not differentiate between asbestos and other fibers. Use this method in conjunction with electron microscopy (e.g., Method 7402) for assistance in identification of fibers. Fibers < ca. 0.25 µm diameter will not be detected by this method [4]. This method may be used for other materials such as fibrous glass by using alternate counting rules (see Appendix C).

INTERFERENCES: If the method is used to detect a specific type of fiber, any other airborne fiber may interfere since all particles meeting the counting criteria are counted. Chain-like particles may appear fibrous. High levels of non-fibrous dust particles may obscure fibers in the field of view and increase the detection limit.

OTHER METHODS: This revision replaces Method 7400, Revision #3 (date 5/15/89).

NIOSH Manual of Analytical Methods (NMAM), Fourth Edition, 8/15/94

REAGENTS:

1. Acetone,* reagent grade.
2. Triacetin (glycerol triacetate), reagent grade.

* See SPECIAL PRECAUTIONS.

EQUIPMENT:

1. Sampler: field monitor, 25-mm, three-piece cassette with ca. 50-mm electrically conductive extension cowl and cellulose ester filter, 0.45- to 1.2-µm pore size, and backup pad.
   NOTE 1: Analyze representative filters for fiber background before use to check for clarity and background. Discard the filter lot if mean is ≥5 fibers per 100 graticule fields. These are defined as laboratory blanks. Manufacturer-provided quality assurance checks on filter blanks are normally adequate as long as field blanks are analyzed as described below.
   NOTE 2: The electrically conductive extension cowl reduces electrostatic effects. Ground the cowl when possible during sampling.
   NOTE 3: Use 0.8-µm pore size filters for personal sampling. The 0.45-µm filters are recommended for sampling when performing TEM analysis on the same samples. However, their higher pressure drop precludes their use with personal sampling pumps.
   NOTE 4: Other cassettes have been proposed that exhibit improved uniformity of fiber deposit on the filter surface, e.g., bellmouthed sampler (Envirometrics, Charleston, SC). These may be used if shown to give measured concentrations equivalent to sampler indicated above for the application.
2. Personal sampling pump, battery or line-powered vacuum, of sufficient capacity to meet flow-rate requirements (see step 4 for flow rate), with flexible connecting tubing.
3. Wire, multi-stranded, 22-gauge; 1", hose clamp to attach wire to cassette.
4. Tape, shrink- or adhesive-.
5. Slides, glass, frosted-end, pre-cleaned, 25 x 75-mm.
6. Cover slips, 22- x 22-mm, No. 1-1/2, unless otherwise specified by microscope manufacturer.
7. Lacquer or nail polish.
8. Knife, #10 surgical steel, curved blade.
9. Tweezers.

EQUIPMENT:

10. Acetone flash vaporization system for clearing filters on glass slides (see ref. [5] for specifications or see manufacturer's instructions for equivalent devices).
11. Micropipets or syringes, 5-µL and 100- to 500-µL.
12. Microscope, positive phase (dark) contrast, with green or blue filter, adjustable field iris, 8 to 10X eyepiece, and 40 to 45X phase objective (total magnification ca. 400X); numerical aperture = 0.65 to 0.75.
13. Graticule, Walton-Beckett type with 100-µm diameter circular field (area = 0.00785 mm2) at the specimen plane (Type G-22). Available from Optometrics USA, P.O. Box 699, Ayer, MA 01432 [phone (508)-772-1700], and McCrone Accessories and Components, 850 Pasquinelli Drive, Westmont, IL 60559 [phone (312) 887-7100].
    NOTE: The graticule is custom-made for each microscope. (see APPENDIX A for the custom-ordering procedure).
14. HSE/NPL phase contrast test slide, Mark II. Available from Optometrics USA (address above).
15. Telescope, ocular phase-ring centering.
16. Stage micrometer (0.01-mm divisions).

SPECIAL PRECAUTIONS: Acetone is extremely flammable. Take precautions not to ignite it. Heating of acetone in volumes greater than 1 mL must be done in a ventilated laboratory fume hood using a flameless, spark- free heat source.

SAMPLING:

1. Calibrate each personal sampling pump with a representative sampler in line.
2. To reduce contamination and to hold the cassette tightly together, seal the crease between the cassette base and the cowl with a shrink band or light colored adhesive tape. For personal sampling, fasten the (uncapped) open-face cassette to the worker's lapel. The open face should be oriented downward.
    NOTE: The cowl should be electrically grounded during area sampling, especially under conditions of low relative humidity. Use a hose clamp to secure one end of the wire (Equipment, Item 3) to the monitor's cowl. Connect the other end to an earth ground (i.e., cold water pipe).
3. Submit at least two field blanks (or 10% of the total samples, whichever is greater) for each set of samples. Handle field blanks in a manner representative of actual handling of associated samples in the set. Open field blank cassettes at the same time as other cassettes just prior to sampling. Store top covers and cassettes in a clean area (e.g., a closed bag or box) with the top covers from the sampling cassettes during the sampling period.
4. Sample at 0.5 L/min or greater [6]. Adjust sampling flow rate, Q (L/min), and time, t (min), to produce a fiber density, E, of 100 to 1300 fibers/mm^2 ($3.85 \cdot 10^4$ to $5 \cdot 10^5$ fibers per 25-mm filter with effective collection area A_c= 385 mm^2) for optimum accuracy. These variables are related to the action level (one-half the current standard), L (fibers/cc), of the fibrous aerosol being sampled by:

$$t = \frac{A_c \cdot E}{Q \cdot L \cdot 10^3}, \text{ min.}$$

NOTE 1: The purpose of adjusting sampling times is to obtain optimum fiber loading on the filter. The collection efficiency does not appear to be a function of flow rate in the range of 0.5 to 16 L/min for asbestos fibers [7]. Relatively large diameter fibers (>3 µm) may exhibit significant aspiration loss and inlet deposition. A sampling rate of 1 to 4 L/min for 8 h is appropriate in atmospheres containing ca. 0.1 fiber/cc in the absence of significant amounts of non-asbestos dust. Dusty atmospheres require smaller sample volumes (≤400 L) to obtain countable samples. In such cases take short, consecutive samples and average the results over the total collection time. For documenting episodic exposures, use high flow rates (7 to 16 L/min) over shorter sampling times. In relatively clean atmospheres, where targeted fiber concentrations are much less than 0.1 fiber/cc, use larger sample volumes (3000 to 10000 L) to achieve quantifiable loadings. Take care, however, not to overload the filter with background dust. If ≥ 50% of the filter surface is covered with particles, the filter may be too overloaded to count and will bias the measured fiber concentration.

NOTE 2: OSHA regulations specify a minimum sampling volume of 48 L for an excursion measurement, and a maximum sampling rate of 2.5 L/min [3].

5. At the end of sampling, replace top cover and end plugs.
6. Ship samples with conductive cowl attached in a rigid container with packing material to prevent jostling or damage.
   NOTE: Do not use untreated polystyrene foam in shipping container because electrostatic forces may cause fiber loss from sample filter.

SAMPLE PREPARATION:

NOTE 1: The object is to produce samples with a smooth (non-grainy) background in a medium with refractive index ≤1.46. This method collapses the filter for easier focusing and produces permanent (1 - 10 years) mounts which are useful for quality control and interlaboratory comparison. The aluminum "hot block" or similar flash vaporization techniques may be used outside the laboratory [2]. Other mounting techniques meeting the above criteria may also be used (e.g., the laboratory fume hood procedure for generating acetone vapor as described in Method 7400 - revision of 5/15/85, or the non-permanent field mounting technique used in P&CAM 239 [3,7,8,9]). Unless the effective filtration area is known, determine the area and record the information referenced against the sample ID number [1,9,10,11].

NOTE 2: Excessive water in the acetone may slow the clearing of the filter, causing material to be washed off the surface of the filter. Also, filters that have been exposed to high humidities prior to clearing may have a grainy background.

7. Ensure that the glass slides and cover slips are free of dust and fibers.
8. Adjust the rheostat to heat the "hot block" to ca. 70 °C [2].
   NOTE: If the "hot block" is not used in a fume hood, it must rest on a ceramic plate and be isolated from any surface susceptible to heat damage.
9. Mount a wedge cut from the sample filter on a clean glass slide.
   a. Cut wedges of ca. 25% of the filter area with a curved-blade surgical steel knife using a rocking motion to prevent tearing. Place wedge, dust side up, on slide.
      NOTE: Static electricity will usually keep the wedge on the slide.

b. Insert slide with wedge into the receiving slot at base of "hot block". Immediately place tip of a micropipet containing ca. 250 µL acetone (use the minimum volume needed to consistently clear the filter sections) into the inlet port of the PTFE cap on top of the "hot block" and inject the acetone into the vaporization chamber with a slow, steady pressure on the plunger button while holding pipet firmly in place. After waiting 3 to 5 sec for the filter to clear, remove pipet and slide from their ports.
   CAUTION: Although the volume of acetone used is small, use safety precautions. Work in a well-ventilated area (e.g., laboratory fume hood). Take care not to ignite the acetone. Continuous use of this device in an unventilated space may produce explosive acetone vapor concentrations.
c. Using the 5-µL micropipet, immediately place 3.0 to 3.5 µL triacetin on the wedge. Gently lower a clean cover slip onto the wedge at a slight angle to reduce bubble formation. Avoid excess pressure and movement of the cover glass.
   NOTE: If too many bubbles form or the amount of triacetin is insufficient, the cover slip may become detached within a few hours. If excessive triacetin remains at the edge of the filter under the cover slip, fiber migration may occur.
d. Mark the outline of the filter segment with a glass marking pen to aid in microscopic evaluation.
e. Glue the edges of the cover slip to the slide using lacquer or nail polish [12]. Counting may proceed immediately after clearing and mounting are completed.
   NOTE: If clearing is slow, warm the slide on a hotplate (surface temperature 50 °C) for up to 15 min to hasten clearing. Heat carefully to prevent gas bubble formation.

CALIBRATION AND QUALITY CONTROL:

10. Microscope adjustments. Follow the manufacturers instructions. At least once daily use the telescope ocular (or Bertrand lens, for some microscopes) supplied by the manufacturer to ensure that the phase rings (annular diaphragm and phase-shifting elements) are concentric. With each microscope, keep a logbook in which to record the dates of microscope cleanings and major servicing.
    a. Each time a sample is examined, do the following:
       (1) Adjust the light source for even illumination across the field of view at the condenser iris. Use Kohler illumination, if available. With some microscopes, the illumination may have to be set up with bright field optics rather than phase contract optics.
       (2) Focus on the particulate material to be examined.
       (3) Make sure that the field iris is in focus, centered on the sample, and open only enough to fully illuminate the field of view.
    b. Check the phase-shift detection limit of the microscope periodically for each analyst/microscope combination:
       (1) Center the HSE/NPL phase-contrast test slide under the phase objective.
       (2) Bring the blocks of grooved lines into focus in the graticule area.
           NOTE: The slide contains seven blocks of grooves (ca. 20 grooves per block) in descending order of visibility. For asbestos counting the microscope optics must completely resolve the grooved lines in block 3 although they may appear somewhat faint, and the grooved lines in blocks 6 and 7 must be invisible when centered in the graticule area. Blocks 4 and 5 must be at least partially visible but may vary slightly in visibility between microscopes. A microscope which fails to meet these requirements has resolution either too low or too high for fiber counting.
       (3) If image quality deteriorates, clean the microscope optics. If the problem persists, consult the microscope manufacturer.
11. Document the laboratory's precision for each counter for replicate fiber counts.
    a. Maintain as part of the laboratory quality assurance program a set of reference slides to be used on a daily basis [13]. These slides should consist of filter preparations including a range of loadings and background dust levels from a variety of sources including both field and reference samples (e.g., PAT, AAR, commercial samples). The Quality Assurance Officer

should maintain custody of the reference slides and should supply each counter with a minimum of one reference slide per workday. Change the labels on the reference slides periodically so that the counter does not become familiar with the samples.

b. From blind repeat counts on reference slides, estimate the laboratory intra- and intercounter precision. Obtain separate values of relative standard deviation (S_r) for each sample matrix analyzed in each of the following ranges: 5 to 20 fibers in 100 graticule fields, >20 to 50 fibers in 100 graticule fields, and >50 to 100 fibers in 100 graticule fields. Maintain control charts for each of these data files.

NOTE: Certain sample matrices (e.g., asbestos cement) have been shown to give poor precision [9]

12. Prepare and count field blanks along with the field samples. Report counts on each field blank.

NOTE 1: The identity of blank filters should be unknown to the counter until all counts have been completed.

NOTE 2: If a field blank yields greater than 7 fibers per 100 graticule fields, report possible contamination of the samples.

13. Perform blind recounts by the same counter on 10% of filters counted (slides relabeled by a person other than the counter). Use the following test to determine whether a pair of counts by the same counter on the same filter should be rejected because of possible bias: Discard the sample if the absolute value of the difference between the square roots of the two counts (in fiber/mm^2) exceeds 2.77 (X)S_r', where X = average of the square roots of the two fiber counts

(in fiber/mm^2) and $S_r' = \frac{S_r}{2}$, where S_r is the intracounter relative standard deviation for the

appropriate count range (in fibers) determined in step 11. For more complete discussions see reference [13].

NOTE 1: Since fiber counting is the measurement of randomly placed fibers which may be described by a Poisson distribution, a square root transformation of the fiber count data will result in approximately normally distributed data [13].

NOTE 2: If a pair of counts is rejected by this test, recount the remaining samples in the set and test the new counts against the first counts. Discard all rejected paired counts. It is not necessary to use this statistic on blank counts.

14. The analyst is a critical part of this analytical procedure. Care must be taken to provide a non-stressful and comfortable environment for fiber counting. An ergonomically designed chair should be used, with the microscope eyepiece situated at a comfortable height for viewing. External lighting should be set at a level similar to the illumination level in the microscope to reduce eye fatigue. In addition, counters should take 10-to-20 minute breaks from the microscope every one or two hours to limit fatigue [14]. During these breaks, both eye and upper back/neck exercises should be performed to relieve strain.
15. All laboratories engaged in asbestos counting should participate in a proficiency testing program such as the AIHA-NIOSH Proficiency Analytical Testing (PAT) Program for asbestos and routinely exchange field samples with other laboratories to compare performance of counters.

MEASUREMENT:

16. Center the slide on the stage of the calibrated microscope under the objective lens. Focus the microscope on the plane of the filter.
17. Adjust the microscope (Step 10).

NOTE: Calibration with the HSE/NPL test slide determines the minimum detectable fiber diameter (ca. 0.25 µm) [4].

18. Counting rules: (same as P&CAM 239 rules [1,10,11]: see examples in APPENDIX B).
    a. Count any fiber longer than 5 µm which lies entirely within the graticule area.
       (1) Count only fibers longer than 5 µm. Measure length of curved fibers along the curve.
       (2) Count only fibers with a length-to-width ratio equal to or greater than 3:1.
    b. For fibers which cross the boundary of the graticule field:
       (1) Count as 1/2 fiber any fiber with only one end lying within the graticule area, provided that the fiber meets the criteria of rule a above.

(2) Do not count any fiber which crosses the graticule boundary more than once.
(3) Reject and do not count all other fibers.

c. Count bundles of fibers as one fiber unless individual fibers can be identified by observing both ends of a fiber.
d. Count enough graticule fields to yield 100 fibers. Count a minimum of 20 fields. Stop at 100 graticule fields regardless of count.

19. Start counting from the tip of the filter wedge and progress along a radial line to the outer edge. Shift up or down on the filter, and continue in the reverse direction. Select graticule fields randomly by looking away from the eyepiece briefly while advancing the mechanical stage. Ensure that, as a minimum, each analysis covers one radial line from the filter center to the outer edge of the filter. When an agglomerate or bubble covers ca. 1/6 or more of the graticule field, reject the graticule field and select another. Do not report rejected graticule fields in the total number counted.

NOTE 1: When counting a graticule field, continuously scan a range of focal planes by moving the fine focus knob to detect very fine fibers which have become embedded in the filter. The small-diameter fibers will be very faint but are an important contribution to the total count. A minimum counting time of 15 seconds per field is appropriate for accurate counting.

NOTE 2: This method does not allow for differentiation of fibers based on morphology. Although some experienced counters are capable of selectively counting only fibers which appear to be asbestiform, there is presently no accepted method for ensuring uniformity of judgment between laboratories. It is, therefore, incumbent upon all laboratories using this method to report total fiber counts. If serious contamination from non-asbestos fibers occurs in samples, other techniques such as transmission electron microscopy must be used to identify the asbestos fiber fraction present in the sample (see NIOSH Method 7402). In some cases (i.e., for fibers with diameters >1 µm), polarized light microscopy (as in NIOSH Method 7403) may be used to identify and eliminate interfering non-crystalline fibers [15].

NOTE 3: Do not count at edges where filter was cut. Move in at least 1 mm from the edge.

NOTE 4: Under certain conditions, electrostatic charge may affect the sampling of fibers. These electrostatic effects are most likely to occur when the relative humidity is low (below 20%), and when sampling is performed near the source of aerosol. The result is that deposition of fibers on the filter is reduced, especially near the edge of the filter. If such a pattern is noted during fiber counting, choose fields as close to the center of the filter as possible [5].

NOTE 5: Counts are to be recorded on a data sheet that provides, as a minimum, spaces on which to record the counts for each field, filter identification number, analyst's name, date, total fibers counted, total fields counted, average count, fiber density, and commentary. Average count is calculated by dividing the total fiber count by the number of fields observed. Fiber density (fibers/mm^2) is defined as the average count (fibers/field) divided by the field (graticule) area (mm^2/field).

CALCULATIONS AND REPORTING OF RESULTS

20. Calculate and report fiber density on the filter, E (fibers/mm^2), by dividing the average fiber count per graticule field, F/n_f, minus the mean field blank count per graticule field, B/n_b, by the graticule field area, A_f (approx. 0.00785 mm^2):

$$E = \frac{\left(\frac{F}{n_f} - \frac{B}{n_b}\right)}{A_f}, \text{ fibers/mm}^2.$$

NOTE: Fiber counts above 1300 fibers/mm^2 and fiber counts from samples with >50% of filter area covered with particulate should be reported as "uncountable" or "probably biased." Other fiber counts outside the 100-1300 fiber/mm^2 range should be reported as having "greater than optimal variability" and as being "probably biased."

21. Calculate and report the concentration, C (fibers/cc), of fibers in the air volume sampled, V (L), using the effective collection area of the filter, A_c (approx. 385 mm^2 for a 25-mm filter):

$$C = \frac{(E)(A_c)}{V \cdot 10^3}.$$

NOTE: Periodically check and adjust the value of A_c, if necessary.

22. Report intralaboratory and interlaboratory relative standard deviations (from Step 11) with each set of results.
NOTE: Precision depends on the total number of fibers counted [1,16]. Relative standard deviation is documented in references [1,15-17] for fiber counts up to 100 fibers in 100 graticule fields. Comparability of interlaboratory results is discussed below. As a first approximation, use 213% above and 49% below the count as the upper and lower confidence limits for fiber counts greater than 20 (Fig. 1).

EVALUATION OF METHOD:

A. This method is a revision of P&CAM 239 [10]. A summary of the revisions is as follows:
1. Sampling:
The change from a 37-mm to a 25-mm filter improves sensitivity for similar air volumes. The change in flow rates allows for 2-m^3 full-shift samples to be taken, providing that the filter is not overloaded with non-fibrous particulates. The collection efficiency of the sampler is not a function of flow rate in the range 0.5 to 16 L/min [10].
2. Sample Preparation Technique:
The acetone vapor-triacetin preparation technique is a faster, more permanent mounting technique than the dimethyl phthalate/diethyl oxalate method of P&CAM 239 [2,4,10]. The aluminum "hot block" technique minimizes the amount of acetone needed to prepare each sample.
3. Measurement:
a. The Walton-Beckett graticule standardizes the area observed [14,18,19].
b. The HSE/NPL test slide standardizes microscope optics for sensitivity to fiber diameter [4,14].
c. Because of past inaccuracies associated with low fiber counts, the minimum recommended loading has been increased to 100 fibers/mm^2 filter area (a total of 78.5 fibers counted in 100 fields, each with field area = .00785 mm^2.) Lower levels generally result in an overestimate of the fiber count when compared to results in the recommended analytical range [20]. The recommended loadings should yield intracounter S_r in the range of 0.10 to 0.17 [21,22,23].

B. Interlaboratory comparability:
An international collaborative study involved 16 laboratories using prepared slides from the asbestos cement, milling, mining, textile, and friction material industries [9]. The relative standard deviations (S_r) varied with sample type and laboratory. The ranges were:

	Intralaboratory S_r	Interlaboratory S_r	Overall S_r
AIA (NIOSH A Rules)*	0.12 to 0.40	0.27 to 0.85	0.46
Modified CRS (NIOSH B Rules)**	0.11 to 0.29	0.20 to 0.35	0.25

* Under AIA rules, only fibers having a diameter less than 3 µm are counted and fibers attached to particles larger than 3 µm are not counted. NIOSH A Rules are otherwise similar to the AIA rules.
** See Appendix C.

A NIOSH study conducted using field samples of asbestos gave intralaboratory S_r in the range 0.17 to 0.25 and an interlaboratory S_r of 0.45 [21]. This agrees well with other recent studies [9,14,16].

At this time, there is no independent means for assessing the overall accuracy of this method. One measure of reliability is to estimate how well the count for a single sample agrees with the mean count from a large number of laboratories. The following discussion indicates how this estimation can be carried out based on measurements of the interlaboratory variability, as well as showing how the results of this method relate to the theoretically attainable counting precision and to measured intra- and interlaboratory S_r. (NOTE: The following discussion does not include bias estimates and should not be taken to indicated that lightly loaded samples are as accurate as properly loaded ones).

Theoretically, the process of counting randomly (Poisson) distributed fibers on a filter surface will give an S_r that depends on the number, N, of fibers counted:

$$S_r = 1/(N)^{1/2} \qquad (1)$$

Thus S_r is 0.1 for 100 fibers and 0.32 for 10 fibers counted. The actual S_r found in a number of studies is greater than these theoretical numbers [17,19,20,21].

An additional component of variability comes primarily from subjective interlaboratory differences. In a study of ten counters in a continuing sample exchange program, Ogden [15] found this subjective component of intralaboratory S_r to be approximately 0.2 and estimated the overall S_r by the term:

$$\frac{[N + (0.2 \cdot N)^2]^{1/2}}{N} \qquad (2)$$

Ogden found that the 90% confidence interval of the individual intralaboratory counts in relation to the means were +2 S_r and - 1.5 S_r. In this program, one sample out of ten was a quality control sample. For laboratories not engaged in an intensive quality assurance program, the subjective component of variability can be higher.

In a study of field sample results in 46 laboratories, the Asbestos Information Association also found that the variability had both a constant component and one that depended on the fiber count [14]. These results gave a subjective interlaboratory component of S_r (on the same basis as Ogden's) for field samples of ca. 0.45. A similar value was obtained for 12 laboratories analyzing a set of 24 field samples [21]. This value falls slightly above the range of S_r (0.25 to 0.42 for 1984-85) found for 80 reference laboratories in the NIOSH PAT program for laboratory-generated samples [17].

A number of factors influence S_r for a given laboratory, such as that laboratory's actual counting performance and the type of samples being analyzed. In the absence of other information, such as from an interlaboratory quality assurance program using field samples, the value for the subjective component of variability is chosen as 0.45. It is hoped that the laboratories will carry out the recommended interlaboratory quality assurance programs to improve their performance and thus reduce the S_r.

The above relative standard deviations apply when the population mean has been determined. It is more useful, however, for laboratories to estimate the 90% confidence interval on the mean count from a single sample fiber count (Figure 1). These curves assume similar shapes of the count distribution for interlaboratory and intralaboratory results [16].

For example, if a sample yields a count of 24 fibers, Figure 1 indicates that the mean interlaboratory count will fall within the range of 227% above and 52% below that value 90% of the time. We can apply these percentages directly to the air concentrations as well. If, for instance, this sample (24 fibers counted) represented a 500-L volume, then the measured concentration is 0.02 fibers/mL (assuming 100 fields counted, 25-mm filter, 0.00785 mm^2 counting field area). If this same sample were counted by a group of laboratories, there is a 90% probability that the mean would fall between 0.01 and 0.08 fiber/mL. These limits should be reported in any comparison of results between laboratories.

Note that the S_r of 0.45 used to derive Figure 1 is used as an estimate for a random group of laboratories. If several laboratories belonging to a quality assurance group can show that their interlaboratory S_r is smaller, then it is more correct to use that smaller S_r. However, the estimated S_r of 0.45 is to be used in the absence of such information. Note also that it has been found that S_r can be higher for certain types of samples, such as asbestos cement [9].

Quite often the estimated airborne concentration from an asbestos analysis is used to compare to a regulatory standard. For instance, if one is trying to show compliance with an 0.5 fiber/mL standard using a single sample on which 100 fibers have been counted, then Figure 1 indicates that the 0.5 fiber/mL standard must be 213% higher than the measured air concentration. This indicates that if one measures a fiber concentration of 0.16 fiber/mL (100 fibers counted), then the mean fiber count by a group of laboratories (of which the compliance laboratory might be one) has a 95% chance of being less than 0.5 fibers/mL; i.e., 0.16 + 2.13 x 0.16 = 0.5.

It can be seen from Figure 1 that the Poisson component of the variability is not very important unless the number of fibers counted is small. Therefore, a further approximation is to simply use +213% and −49% as the upper and lower confidence values of the mean for a 100-fiber count.

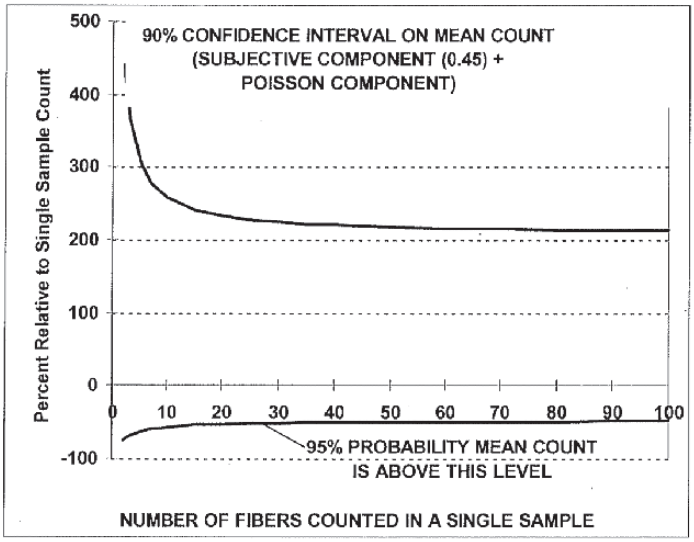

Figure 1. Interlaboratory Precision of Fiber Counts

The curves in Figures 1 are defined by the following equations:

$$UCL = \frac{2X + 2.25 + [(2.25 + 2X)^2 - 4(1 - 2.25 S_r^2) X^2]^{1/2}}{2(1 - 2.25 S_r^2)} \quad (3)$$

$$LCL = \frac{2X + 4 - [(4 + 2X)^2 - 4(1 - 4 S_r^2) X^2]^{1/2}}{2(1 - 4 S_r^2)} \quad (4)$$

where S_r = subjective interlaboratory relative standard deviation, which is close to the total interlaboratory S_r when approximately 100 fibers are counted.
X = total fibers counted on sample
LCL = lower 95% confidence limit.
UCL = upper 95% confidence limit.
Note that the range between these two limits represents 90% of the total range.

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APPENDIX A: CALIBRATION OF THE WALTON-BECKETT GRATICULE:

Before ordering the Walton-Beckett graticule, the following calibration must be done to obtain a counting area (D) 100 µm in diameter at the image plane. The diameter, d_c (mm), of the circular counting area and the disc diameter must be specified when ordering the graticule.

1. Insert any available graticule into the eyepiece and focus so that the graticule lines are sharp and clear.
2. Set the appropriate interpupillary distance and, if applicable, reset the binocular head adjustment so that the magnification remains constant.
3. Install the 40 to 45X phase objective.
4. Place a stage micrometer on the microscope object stage and focus the microscope on the graduated lines.
5. Measure the magnified grid length of the graticule, L_o (µm), using the stage micrometer.
6. Remove the graticule from the microscope and measure its actual grid length, L_a (mm). This can best be accomplished by using a stage fitted with verniers.
7. Calculate the circle diameter, d_c (mm), for the Walton-Beckett graticule:

$$d_c = \frac{L_a}{L_o} \times D. \qquad (5)$$

Example: If L_o = 112 µm, L_a = 4.5 mm and D = 100 µm, then d_c = 4.02 mm.

8. Check the field diameter, D (acceptable range 100 µm ± 2 µm) with a stage micrometer upon receipt of the graticule from the manufacturer. Determine field area (acceptable range 0.00754 mm^2 to 0.00817 mm^2).

APPENDIX B: COMPARISON OF COUNTING RULES:

Figure 2 shows a Walton-Beckett graticule as seen through the microscope. The rules will be discussed as they apply to the labeled objects in the figure.

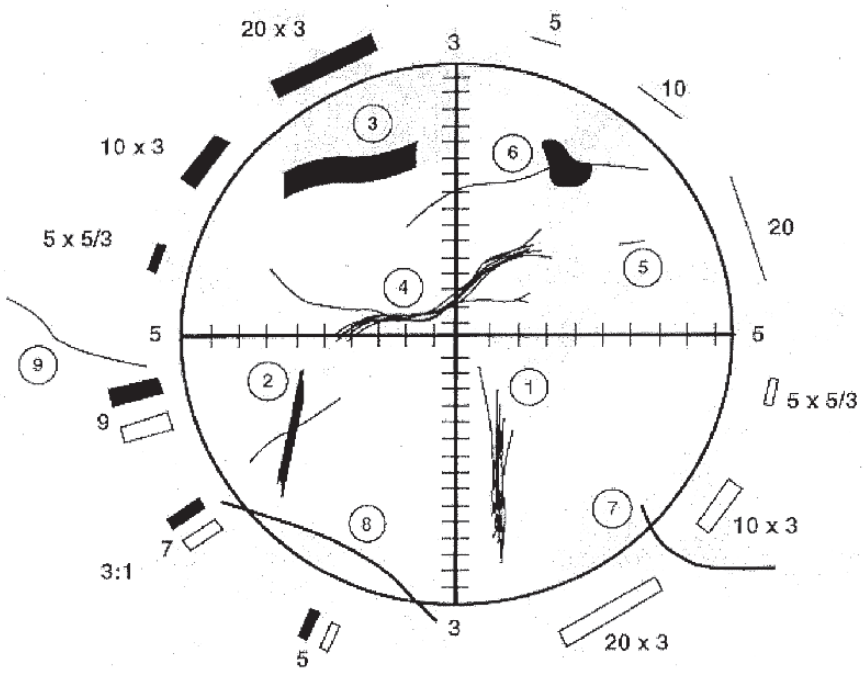

Figure 2. Walton-Beckett graticule with fibers.

These rules are sometimes referred to as the "A" rules.

FIBER COUNT

Object	Count	DISCUSSION
1	1 fiber	Optically observable asbestos fibers are actually bundles of fine fibrils. If the fibrils seem to be from the same bundle the object is counted as a single fiber. Note, however, that all objects meeting length and aspect ratio criteria are counted whether or not they appear to be asbestos.
2	2 fiber	If fibers meeting the length and aspect ratio criteria (length >5 µm and length-to-width ratio >3 to 1) overlap, but do not seem to be part of the same bundle, they are counted as separate fibers.
3	1 fiber	Although the object has a relatively large diameter (>3 µm), it is counted as fiber under the rules. There is no upper limit on the fiber diameter in the counting rules. Note that fiber width is measured at the widest compact section of the object.
4	1 fiber	Although long fine fibrils may extend from the body of a fiber, these fibrils are considered part of the fiber if they seem to have originally been part of the bundle.
5	Do not count	If the object is ≤5 µm long, it is not counted.
6	1 fiber	A fiber partially obscured by a particle is counted as one fiber. If the fiber ends emanating from a particle do not seem to be from the same fiber and each end meets the length and aspect ratio criteria, they are counted as separate fibers.
7	1/2 fiber	A fiber which crosses into the graticule area one time is counted as 1/2 fiber.
8	Do not count	Ignore fibers that cross the graticulate boundary more than once. count
9	Do not count	Ignore fibers that lie outside the graticule boundary.

APPENDIX C. ALTERNATE COUNTING RULES FOR NON-ASBESTOS FIBERS

Other counting rules may be more appropriate for measurement of specific non-asbestos fiber types, such as fibrous glass. These include the "B" rules given below (from NIOSH Method 7400, Revision #2, dated 8/15/87), the World Health Organization reference method for man-made mineral fiber [24], and the NIOSH fibrous glass criteria document method [25]. The upper diameter limit in these methods prevents measurements of non-thoracic fibers. It is important to note that the aspect ratio limits included in these methods vary. NIOSH recommends the use of the 3:1 aspect ratio in counting fibers.

It is emphasized that hybridization of different sets of counting rules is not permitted. Report specifically which set of counting rules are used with the analytical results.

"B" COUNTING RULES:

1. Count only ends of fibers. Each fiber must be longer than 5 µm and less than 3 µm diameter.
2. Count only ends of fibers with a length-to-width ratio equal to or greater than 5:1.
3. Count each fiber end which falls within the graticule area as one end, provided that the fiber meets rules 1 and 2 above. Add split ends to the count as appropriate if the split fiber segment also meets the criteria of rules 1 and 2 above.
4. Count visibly free ends which meet rules 1 and 2 above when the fiber appears to be attached to another particle, regardless of the size of the other particle. Count the end of a fiber obscured by another particle if the particle covering the fiber end is less than 3 µm in diameter.
5. Count free ends of fibers emanating from large clumps and bundles up to a maximum of 10 ends (5 fibers), provided that each segment meets rules 1 and 2 above.
6. Count enough graticule fields to yield 200 ends. Count a minimum of 20 graticule fields. Stop at 100 graticule fields, regardless of count.
7. Divide total end count by 2 to yield fiber count.

APPENDIX D. EQUIVALENT LIMITS OF DETECTION AND QUANTITATION

	fiber density on filter*		fiber concentration in air, f/cc	
	fibers per 100 fields	fibers/mm²	400-L air sample	1000-L air sample
	200	255	0.25	0.10
	100	127	0.125	0.05
LOQ	80	102	0.10	0.04
	50	64	0.0625	0.025
	25	32	0.03	0.0125
	20	25	0.025	0.010
	10	12.7	0.0125	0.005
	8	10.2	0.010	0.004
LOD	5.5	7	0.00675	0.0027

* Assumes 385 mm² effective filter collection area, and field area = 0.00785 mm², for relatively "clean" (little particulate aside from fibers) filters.

ASBESTOS by TEM 7402

FORMULA: Various MW: Various CAS: Various RTECS: Various

METHOD: 7402 **EVALUATION: PARTIAL** **Issue 1: 15 May 1989**
Issue 2: 15 August 1994

OSHA : 0.1 asbestos fibers (>5 µm long)/cc; 1 f/cc/30 min excursion; carcinogen
MSHA: 2 asbestos fibers/cc
NIOSH: 0.1 f/cc (fibers > 5 µm long)/400 L; carcinogen
ACGIH: 0.2 crocidolite; 0.5 amosite; 2 chrysotile and other asbestos, fibers/cc; carcinogen

PROPERTIES: solid, fibrous, crystalline, anistropic

SYNONYMS [CAS#]: actinolite [77536-66-4] or ferroactinolite [15669-07-5]; amosite [12172-73-5]; anthophyllite [77536-67-5]; chrysotile [12001-29-5]; serpentine [18786-24-8]; crocidolite [12001-28-4]; tremolite [77536-68-6]; amphibole asbestos [1332-21-4].

SAMPLING

SAMPLER: FILTER (0.45- to 1.2-µm cellulose ester membrane, 25-mm diameter; conductive cassette)

FLOW RATE: 0.5 to 16 L/min

VOL-MIN*: 400 L @ 0.1 fiber/cc
-MAX*: (step 4, sampling)
*Adjust for 100 to 1300 fibers/mm^2

SHIPMENT: routine (pack to reduce shock)

SAMPLE STABILITY: stable

BLANKS: 2 to 10 field blanks per set

ACCURACY

RANGE STUDIED: 80 to 100 fibers counted

BIAS: not determined

OVERALL PRECISION ($\hat{S}_{rT}$): see EVALUATION OF METHOD

ACCURACY: not determined

MEASUREMENT

TECHNIQUE: MICROSCOPY, TRANSMISSION ELECTRON (TEM)

ANALYTE: asbestos fibers

SAMPLE PREPARATION: modified Jaffe wick

EQUIPMENT: transmission electron microscope; energy dispersive X-ray system (EDX) analyzer

CALIBRATION: qualitative electron diffraction; calibration of TEM magnification and EDX system

RANGE: 100 to 1300 fibers/mm^2 filter area [1]

ESTIMATED LOD: 1 confirmed asbestos fiber above 95% of expected mean blank value

PRECISION ($\hat{S}_r$): 0.28 when 65% of fibers are asbestos; 0.20 when adjusted fiber count is applied to PCM count [2].

APPLICABILITY: The quantitative working range is 0.04 to 0.5 fiber/cc for a 1000-L air sample. The LOD depends on sample volume and quantity of interfering dust, and is <0.01 fiber/cc for atmospheres free of interferences. This method is use d to determine asbestos fibers in the optically visible range and is intended to complement the results obtained by phase con trast microscopy (Method 7400).

INTERFERENCES: Other amphibole particles that have aspect ratios greater than 3:1 and elemental compositions similar to the asbestos minerals may interfere in the TEM analysis. Some non-amphibole minerals may give electron diffraction patterns similar to amphiboles. High concentrations of background dust interfere with fiber identification. Some non-asbestos amphibole m inerals may give electron diffraction patterns similar to asbestos amphiboles.

OTHER METHODS: This method is designed for use with Method 7400 (phase contrast microscopy).

NIOSH Manual of Analytical Methods (NMAM), Fourth Edition, 8/15/94

REAGENTS:

1. Acetone. (See SPECIAL PRECAUTIONS.)

EQUIPMENT:

1. Sampler: field monitor, 25-mm, three-piece cassette with ca. 50-mm electrically-conductive extension cowl, cellulose ester membrane filter, 0.45- to 1.2-µm pore size, and backup pad.
   NOTE 1: Analyze representative filters for fiber background before use. Discard the filter lot if mean count is >5 fibers/100 fields. These are defined as laboratory blanks.
   NOTE 2: Use an electrically-conductive extension cowl to reduce electrostatic effects on fiber sampling and during sample shipment. Ground the cowl when possible during sampling.
   NOTE 3: 0.8-µm pore size filters are recommended for personal sampling. 0.45-µm filters are recommended for sampling when performing TEM analysis on the samples because the particles deposit closer to the filter surface. However, the higher pressure drop through these filters normally preclude their use with personal sampling pumps.
2. Personal sampling pump, 0.5 to 16 L/min, with flexible connecting tubing.
3. Microscope, transmission electron, operated at ca. 100 kV, with electron diffraction and energy-dispersive X-ray capabilities, and having a fluorescent screen with inscribed or overlaid calibrated scale (Step 15).
   NOTE: The scale is most efficient if it consists of a series of lines inscribed on the screen or partial circles every 2 cm distant from the center.
4. Diffraction grating replica with known number of lines/mm.
5. Slides, glass, pre-cleaned, 25- x 75-mm.
6. Knife, surgical steel, curved-blade.
7. Tweezers.
8. Grids, 200-mesh TEM copper, (optional: carbon-coated).
9. Petri dishes, 15-mm depth. The top and bottom of the petri dish must fit snugly together. To assure a tight fit, grind the top and bottom pieces together with an abrasive such as carborundum to produce a ground-glass contact surface.
10. Foam, clean polyurethane, spongy, 12-mm thick.
11. Filters, Whatman No. 1 qualitative paper or equivalent, or lens paper.
12. Vacuum evaporator.
13. Cork borer, (about 8-mm).
14. Pen, waterproof, marking.
15. Reinforcement, page, gummed.
16. Asbestos standard bulk materials for reference; e.g. SRM #1866, available from the National Institute of Standards and Technology.
17. Carbon rods, sharpened to 1 mm x 8 mm.
18. Microscope, light, phase contrast (PCM), with Walton-Beckett graticule (see method 7400).
19. Grounding wire, 22-gauge, multi-strand.
20. Tape, shrink- or adhesive-.

SPECIAL PRECAUTIONS: Acetone is extremely flammable (flash point = 0 °F). Take precautions not to ignite it. Heating of acetone must be done in a fume hood using a flameless, spark-free heat source. Asbestos is a confirmed human carcinogen. Handle only in a well-ventilated fume hood.

SAMPLING:

1. Calibrate each personal sampling pump with a representative sampler in line.
2. For personal sampling, fasten sampler to worker's lapel near worker's mouth. Remove the top cover from cowl extension ("open-face") and orient sampler face down. Wrap joint between extender and monitor body with tape to help hold the cassette together and provide a marking surface to identify the cassette. Where possible, especially at low %RH, attach sampler to electrical ground to reduce electrostatic effects during sampling.
3. Submit at least two field blanks (or 10% of the total samples, whichever is greater) for each set of samples. Remove top covers from the field blank cassettes and store top covers and cassettes in a clean area (e.g., closed bag or box) during sampling. Replace top covers when sampling is completed.
4. Sample at 0.5 to 16 L/min [3]. Adjust sampling rate, Q (L/min), and time, t (min), to produce fiber density, E, of 100 to 1300 fibers/mm ^{2} [3.85 · 10^4 to 5 · 10^5 fibers per 25-mm filter with effective collection area (A_c = 385 mm^2)] for optimum accuracy. Do not exceed ca. 0.5 mg total dust loading on the filter. These variables are related to the action level (one-half the current standard), L (fibers/cc), of the fibrous aerosol being sampled by:

$$t = \frac{A_c \cdot E}{Q \cdot L \cdot 10^3}, \text{ min.}$$

   NOTE: The purpose of adjusting sampling times is to obtain optimum fiber loading on the filter. A sampling rate of 1 to 4 L/min for 8 h (700 to 2800 L) is appropriate in atmospheres containing ca. 0.1 fiber/cc in the absence of significant amounts of non-asbestos dust. Dusty atmospheres require smaller sample volumes (≤400 L) to obtain countable samples. In such cases take short, consecutive samples and average the results over the total collection time. For documenting episodic exposures, use high rates (7 to 16 L/min) over shorter sampling times. In relatively clean atmospheres, where targeted fiber concentrations are much less than 0.1 fiber/cc, use larger sample volumes (3000 to 10000 L) to achieve quantifiable loadings. Take care, however, not to overload the filter with background dust [3].
5. At the end of sampling, replace top cover and small end caps.
6. Ship samples upright with conductive cowl attached in a rigid container with packing material to prevent jostling or damage.
   NOTE: Do not use untreated polystyrene foam in the shipping container because electrostatic forces may cause fiber loss from sample filter.

SAMPLE PREPARATION:

7. Remove circular sections from any of three quadrants of each sample and blank filter using a cork borer [4]. The use of three grid preparations reduces the effect of local variations in dust deposit on the filter.
8. Affix the circular filter sections to a clean glass slide with a gummed page reinforcement. Label the slide with a waterproof marking pen.
   NOTE: Up to eight filter sections may be attached to the same slide.
9. Place the slide in a petri dish which contains several paper filters soaked with 2 to 3 mL acetone. Cover the dish. Wait 2 to 4 min for the sample filter(s) to fuse and clear.
   NOTE: The "hot block" clearing technique [5] of Method 7400 or the DMF clearing technique [6] may be used instead of steps 8 and 9.
10. Transfer the slide to a rotating stage inside the bell jar of a vacuum evaporator. Evaporate a 1-by 5-mm section of a graphite rod onto the cleared filter(s). Remove the slide to a clean, dry, covered petri dish [4].
11. Prepare a second petri dish as a Jaffe wick washer with the wicking substrate prepared from filter or lens paper placed on top of a 12-mm thick disk of clean, spongy polyurethane foam [7].

Cut a V-notch on the edge of the foam and filter paper. Use the V-notch as a reservoir for adding solvent.

NOTE: The wicking substrate should be thin enough to fit into the petri dish without touching the lid.

12. Place the TEM grid on the filter or lens paper. Label the grids by marking with a pencil on the filter paper or by putting registration marks on the petri dish halves and marking with a waterproof marker on the dish lid. In a fume hood, fill the dish with acetone until the wicking substrate is saturated.

NOTE: The level of acetone should be just high enough to saturate the filter paper without creating puddles.

13. Remove about a quarter section of the carbon-coated filter from the glass slide using a surgical knife and tweezers. Carefully place the excised filter, carbon side down, on the appropriately-labeled grid in the acetone-saturated petri dish. When all filter sections have been transferred, slowly add more solvent to the wedge-shaped trough to raise the acetone level as high as possible without disturbing the sample preparations. Cover the petri dish. Elevate one side of the petri dish by placing a slide under it (allowing drops of condensed acetone to form near the edge rather than in the center where they would drip onto the grid preparation).

CALIBRATION AND QUALITY CONTROL:

14. Determine the TEM magnification on the fluorescent screen:
    a. Define a field of view on the fluorescent screen either by markings or physical boundaries.
       NOTE: The field of view must be measurable or previously inscribed with a scale or concentric circles (all scales should be metric) [7].
    b. Insert a diffraction grating replica into the specimen holder and place into the microscope. Orient the replica so that the grating lines fall perpendicular to the scale on the TEM fluorescent screen. Ensure that goniometer stage tilt is zero.
    c. Adjust microscope magnification to 10,000X. Measure the distance (mm) between the same relative positions (e.g., between left edges) of two widely-separated lines on the grating replica. Count the number of spaces between the lines.
       NOTE: On most microscopes the magnification is substantially constant only within the central 8- to 10-cm diameter region of the fluorescent screen.
    d. Calculate the true magnification (M) on the fluorescent screen:

$$m = \frac{X \cdot G}{Y}$$

       where: X = total distance (mm) between the two grating lines;
       G = calibration constant of the grating replica (lines/mm);
       Y = number of grating replica spaces counted
    e. After calibration, note the apparent sizes of 0.25 and 5.0 µm on the fluorescent screen. (These dimensions are the boundary limits for counting asbestos fibers by phase contrast microscopy.)
15. Measure 20 grid openings at random on a 200-mesh copper grid by placing a grid on a glass slide and examining it under the PCM. Use the Walton-Beckett graticule to measure the grid opening dimensions. Calculate an average graticule field dimension from the data and use this number to calculate the graticule field area for an average grid opening.

NOTE: A grid opening is considered as one graticule field.

16. Obtain reference selected area electron diffraction (SAED) or microdiffraction patterns from standard asbestos materials prepared for TEM analysis.

NOTE: This is a visual reference technique. No quantitative SAED analysis is required [7]. Microdiffraction may produce clearer patterns on very small fibers or fibers partially obscured by other material.

    a. Set the specimen holder at zero tilt.

b. Center a fiber, focus, and center the smallest field-limiting aperture on the fiber. Obtain a diffraction pattern. Photograph each distinctive pattern and keep the photo for comparison to unknowns.

NOTE: Not all fibers will present diffraction patterns. The objective lens current may need adjustment to give optimum pattern visibility. There are many more amphiboles which give diffraction patterns similar to the analytes named on p. 7402-1. Some, but not all, of these can be eliminated by chemical separations. Also, some non-amphiboles (e.g., pyroxenes, some talc fibers) may interfere.

17. Acquire energy-dispersive X-ray (EDX) spectra on approximately 5 fibers having diameters between 0.25 and 0.5 µm of each asbestos variety obtained from standard reference materials [7].

NOTE: The sample may require tilting to obtain adequate signal. Use same tilt angle for all spectra.

a. Prepare TEM grids of all asbestos varieties.
b. Use acquisition times (at least 100 sec) sufficient to show a silicon peak at least 75% of the monitor screen height at a vertical scale of ≥500 counts per channel.
c. Estimate the elemental peak heights visually as follows:
   (1) Normalize all peaks to silicon (assigned an arbitrary value of 10).
   (2) Visually interpret all other peaks present and assign values relative to the silicon peak.
   (3) Determine an elemental profile for the fiber using the elements Na, Mg, Si, Ca, and Fe. Example: 0-4-10-3-<1 [7].
      NOTE: In fibers other than asbestos, determination of Al, K, Ti, S, P, and F may also be required for fiber characterization.
   (4) Determine a typical range of profiles for each asbestos variety and record the profiles for comparison to unknowns.

MEASUREMENT:

18. Perform a diffraction pattern inspection on all sample fibers counted under the TEM, using the procedures given in step 17. Assign the diffraction pattern to one of the following structures:
   a. chrysotile;
   b. amphibole;
   c. ambiguous;
   d. none.

   NOTE: There are some crystalline substances which exhibit diffraction patterns similar to those of asbestos fibers. Many of these, (brucite, halloysite, etc.) can be eliminated from consideration by chemistry. There are, however, several minerals (e.g., pyroxenes, massive amphiboles, and talc fibers) which are chemically similar to asbestos and can be considered interferences. The presence of these substances may warrant the use of more powerful diffraction pattern analysis before positive identification can be made. If interferences are suspected, morphology can play an important role in making positive identification.

19. Obtain EDX spectra in either the TEM or STEM modes from fibers on field samples using the procedure of step 18. Using the diffraction pattern and EDX spectrum, classify the fiber:
   a. For a chrysotile structure, obtain EDX spectra on the first five fibers and one out of ten thereafter. Label the range profiles from 0-5-10-0-0 to 0-10-10-0-0 as "chrysotile."
   b. For an amphibole structure, obtain EDX spectra on the first 10 fibers and one out of ten thereafter. Label profiles ca. 0-2-10-0-7 as "possible amosite"; profiles ca. 1-1-10-0-6 as "possible crocidolite"; profiles ca. 0-4-10-3-<1 as "possible tremolite"; and profiles ca. 0-3-10-0-1 as "possible anthophyllite."
      NOTE: The range of profiles for the amphiboles will vary up to ± 1 unit for each of the elements present according to the relative detector efficiency of the spectrometer.
   c. For an ambiguous structure, obtain EDX spectra on all fibers. Label profiles similar to the chrysotile profile as "possible chrysotile." Label profiles similar to the various amphiboles as "possible amphiboles." Label all others as "unknown" or "non-asbestos."

20. Counting and Sizing:
    a. Insert the sample grid into the specimen grid holder and scan the grid at zero tilt at low magnification (ca. 300 to 500X). Ensure that the carbon film is intact and unbroken over ca. 75% of the grid openings.
    b. In order to determine how the grids should be sampled, estimate the number of fibers per grid opening during a low-magnification scan (500 to 1000X). This will allow the analyst to cover most of the area of the grids during the fiber count and analysis. Use the following rules when picking grid openings to count [7,8]:
        (1) Light loading (<5 fibers per grid opening): count total of 40 grid openings.
        (2) Moderate loading (5 to 25 fibers per grid opening): count minimum of 40 grid openings or 100 fibers.
        (3) Heavy loading (>25 fibers per opening): count a minimum of 100 fibers and at least 6 grid openings.

        Note that these grid openings should be selected approximately equally among the three grid preparations and as randomly as possible from each grid.
    c. Count only grid openings that have the carbon film intact. At 500 to 1000X magnification, begin counting at one end of the grid and systematically traverse the grid by rows, reversing direction at row ends. Select the number of fields per traverse based on the loading indicated in the initial scan. Count at least 2 field blanks per sample set to document possible contamination of the samples. Count fibers using the following rules:
        (1) Count all particles with diameter greater than 0.25 µm that meet the definition of a fiber (aspect ratio ≥3:1, longer than 5 µm). Use the guideline of counting all fibers that would have been counted under phase contrast light microscopy (Method 7400). Use higher magnification (10000X) to determine fiber dimensions and countability under the acceptance criteria. Analyze a minimum of 10% of the fibers, and at least 3 asbestos fibers, by EDX and SAED to confirm the presence of asbestos. Fibers of similar morphology under high magnification can be identified as asbestos without SAED. Particles which are of questionable morphology should be analyzed by SAED and EDX to aid in identification.
        (2) Count fibers which are partially obscured by the grid as half fibers.
            NOTE: If a fiber is partially obscured by the grid bar at the edge of the field of view, count it as a half fiber only if more than 2.5 µm of fiber is visible.
        (3) Size each fiber as it is counted and record the diameter and length:
            (a) Move the fiber to the center of the screen. Read the length of the fiber directly from the scale on the screen.
                NOTE 1: Data can be recorded directly off the screen in µm and later converted to µm by computer.
                NOTE 2: For fibers which extend beyond the field of view, the fiber must be moved and superimposed upon the scale until its entire length has been measured.
            (b) When a fiber has been sized, return to the lower magnification and continue the traverse of the grid area to the next fiber.
    d. Record the following fiber counts:
        (1) f_s, f_b = number of asbestos fibers in the grid openings analyzed on the sample filter and corresponding field blank, respectively.
        (2) F_s, F_b = number of fibers, regardless of identification, in the grid openings analyzed on the sample filter and corresponding field blank, respectively.

CALCULATIONS:

21. Calculate and report the fraction of optically visible asbestos fibers on the filter, $(f_s - f_b)/(F_s - F_b)$. Apply this fraction to fiber counts obtained by PCM on the same filter or on other filters for which the TEM sample is representative. The final result is an asbestos fiber count. The type of asbestos present should also be reported.
22. As an integral part of the report, give the model and manufacturer of the TEM as well as the model and manufacturer of the EDX system.

EVALUATION OF METHOD:

The TEM method, using the direct count of asbestos fibers, has been shown to have a precision of 0.275 (s_r) in an evaluation of mixed amosite and wollastonite fibers. The estimate of the asbestos fraction, however, had a precision of 0.11 (s_r). When this fraction was applied to the PCM count, the overall precision of the combined analysis was 0.20 [2].

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Appendix B

Functional Job Categories for RCF Workers

Table B–1. Functional job categories for RCF workers

Functional category	Definition	General examples	Additional comments
Fiber manufacturing	The production or manufacture of RCF bulk or blanket, except in a supervisory capacity. Includes all job functions on the production line, from mixing the raw ingredients to packaging the finished product (bulk or blanket) at the end of the line.	Raw materials, furnace man, furnace operator, or assistant furnace operator Production worker or relief Blanket line Working leader Needler Slit/cut/pack Line utility Utility operator Chopper operator End of line, bagging of bulk RCF End of line trimming, rolling, and packaging of RCF blanket	None to date
Finishing	Cutting or machining RCF materials after fiber manufacture. Hand or power tools may be used in finishing operations.	Operating die stamp on RCF blanket or paper except for automotive applications Sawing, slotting, trimming, or filing casting tips or riser sleeves Cutting blanket for duct wrap	Working in an area where finishing is taking place but not personally working with RCFs unless in a supervisory capacity or in other *auxiliary operations*.

(Continued)

Adapted from Maxim et al. 1997.

Table B–1 (Continued). Functional job categories for RCF workers

Functional category	Definition	General examples	Additional comments
Finishing (Continued)		Cutting or trimming RCF board or other vacuum-formed RCF material capacity Sanding RCF board or other vacuum-formed RCF material Loading sander Off-line cutting and tandem rerolling and/or repackaging of RCF blanket Cutting or trimming RCF modules for use in appliances Milling or routing RCF board or other vacuum-formed RCF material Off-site cutting of batten strips from RCF blanket	EXAMPLE: Unloading dry forms from the drying oven and taking them to the finishing area for final shaping, or packaging shapes immediately after finishing would be considered finishing. However, unloading dry forms from an oven and taking them to be packaged, or packaging shapes that come directly from the drying oven would be considered *auxiliary operations*.
Installation	Building or manufacturing industrial furnaces or boilers, refinery or petrochemical plant equipment, kilns, foundries, electric power generators, and industrial incinerators at end user locations. Includes furnace maintenance. Does not include factory manufacture of industrial furnace components.	Installing hardware or modules On-site cutting (trimming) modules to fit Caulking and filling gaps Wrapping molds with RCF Spraying or pumping RCF castable material inside furnace Cutting and installing laid-in blanket	Working inside furnace during the installation of RCF materials, even though not working directly with that material (e.g., a plumber or electrician working inside a furnace during an installation)
Removal	Removal of after-service RCF material from an industrial furnace, etc., that has completed its economic life. Includes the removal of RCF material during furnace maintenance.	Unwrapping and knocking out molds Furnace disassembly Furnace maintenance Cleanup and disposal of removed material	Working inside furnace during the removal of RCF materials, even though not working directly with that material (e.g., a plumber or electrician working inside a furnace during a removal)
Assembly operations	Combining or assembling RCF material with other material (RCF or other), except automotive applications. Includes factory assembly of industrial furnace components.	Laminating Cutting material for modules Encapsulating RCF blanket Unpacking blanket and loading into module folder	

(Continued)

Table B–1 (Continued). Functional job categories for RCF workers

Functional category	Definition	General examples	Additional comments
Assembly operations (Continued)		Installing bands around modules Packaging modules at end of line Trimming modules and installing hardware Assembling appliances Off-site assembly of industrial furnace components (original equipment manufacture) Changing RCF gaskets, etc. in appliances Cutting and assembling material for sound-proofing exhaust ducts Sewing RCF material Stapling RCF material Ball milling or grinding RCF material Mixing RCF putties, compounds, or castables	
Mixing/forming	Wet end production of vacuum-cast shapes, board, and felt	Forming RCF board or shapes Weighing, batching, or mixing materials to be formed Placing wet parts on conveyor Operating mixing machine Felting	Premixing dry materials before adding to mix tank
Auxiliary operations	Jobs in which workers are *passively* exposed to RCFs while performing their normal duties and whose *exposures are not likely to parallel those of workers working directly with RCF materials*. Includes certain jobs in which RCFs may be handled but with small probability of significant exposures (e.g., warehouse worker or person unloading completed parts for packaging).	Moving RCF-wrapped molds into and out of furnace Warehouse duties, including dock work, loading trucks, moving materials Supervising Driving forklift Making cartons to package RCFs at end of line Quality control inspection Packaging dry parts Maintaining or repairing equipment except furnaces	

(Continued)

Table B–1 (Continued). Functional job categories for RCF workers

Functional category	Definition	General examples	Additional comments
Auxiliary operations (Continued)		Cleaning furnaces or plant areas where RCFs are used Removing vacuum-formed parts from oven and/or packaging them (no finishing)	
Other (not elsewhere classisfied)	All duties performed in the production of RCF paper, textiles, and automotive components or other industry sectors not covered in any of the foregoing categories. Also, exposures that cannot reasonably be included in the categories listed above (i.e., not elsewhere classified). Industrial hygienist personnel should explain tasks and industry sectors as fully as possible for observations in this category.	Diecutting parts for automotive airbag filters, gaskets, mufflers, or catalytic converters Wrapping substrate for catalytic converter Operating former to make roving Operating tape loom Operating carding machine Papermaking	Wrapping RCF blanket around a hot weld so the weld may cool without stress between the hot seam or joint and the cooler surrounding metal (not elsewhere classified)

Appendix C

Cellular and Molecular Effects of RCFs (In Vitro Studies)

The cellular and molecular effects of RCF exposures have been studied with two different objectives. One purpose of these in vitro studies is to provide a quicker, less expensive, and more controlled alternative to animal toxicity testing. These experiments, which strive to act as screening tests or alternatives to animal studies, are best interpreted by comparing their results with those of in vivo experiments. The second objective of in vitro studies is to provide data that may help to explain the pathogenesis and mechanisms of action of RCFs at the cellular and molecular levels. These cytotoxicity and genotoxicity studies are best interpreted by comparing the effects of RCFs with those of other SVFs and asbestos fibers. In vitro studies serve as an important complement to animal studies and provide important tools for studying the molecular mechanisms of fibers. It is not yet possible to use these data in the derivation of an REL.

Drawing strong conclusions relevant to human health based on these in vitro studies is impossible. One point to consider when reviewing these data is the relevance of the cell types studied. Many studies to date have examined the effects of RCFs on rodent cell lines. The cytotoxic effects of RCFs may vary with cell size, volume, and lineage. Effects observed in the cells from organs other than the lung or effects in species other than the human may not be similar to those elicited with human pulmonary cells. The human alveolar macrophage has a volume several times greater than that of the rat alveolar macrophage [Kromback et al. 1997]. Macrophage size and volume may affect (1) the size range of fibers that can be phagocytized, dissolved, and cleared by the lungs and (2) the resulting pathogenicity of the fiber. Even the use of a human lung cell line does not guarantee that in vitro results will be directly applicable to the intact human response. The in vivo integration of stimuli from the nervous, hormonal, and cardiovascular systems cannot be reproduced in vitro.

Another point to consider when reviewing these data is the number and definitions of variables used in different studies. Variables include differences in fiber type, fiber length, fiber dose, cell type, and length of exposure tested, among others. Disparate results between studies make strong conclusions from in vitro studies difficult. At the same time, these studies may provide important data regarding the mechanism of action of RCFs that would not be obtainable in other testing venues.

RCFs may exert their effects on pulmonary target cells via direct or indirect mechanisms. Direct mechanisms are the resultant effects when fibers come in direct physical contact with cells. Direct cytotoxic effects of RCFs include effects on cell viability, responses, and proliferation.

Indirect cellular effects of RCFs involve the interaction of fibers with inflammatory cells that may be activated to produce inflammatory mediators. These mediators may affect target cells directly or may attract other cells that act on target cells. An inflammatory cell type often used in RCF in vitro studies is the pulmonary macrophage. Pulmonary macrophages are the first line of defense against inhaled material that deposits in the alveoli, and among functions, they attempt to phagocytize particles deposited in the lung. Effects of RCF exposure on macrophages and other inflammatory cells are assessed by the measurement of inflammatory mediator release in vitro.

Three important groups of inflammatory mediators are cytokines, ROS, and lipid mediators (prostaglandins and leukotrienes). Some of the cytokines that have been implicated in the inflammatory process include TNF and interleukins (ILs). TNF and many ILs stimulate the deposition of fibroblast collagen, an initial step in fibrosis, and prostaglandins (PG)s inhibit these effects. ROS include hydroxyl radicals, hydrogen peroxide, and superoxide anion radicals. Oxidative stress occurs when the ROS level in a cell exceeds its antioxidant level. Oxidative stress may result in damage to deoxyribo nucelic acid (DNA), lipids, and proteins.

Either direct or indirect effects of RCFs may result in genotoxic effects on pulmonary target cells. Changes in the genetic material may be important in tumor development [Solomon et al. 1991]. Genotoxic effects may be assessed through the analysis of chromosome changes or alterations in gene expression following exposure to RCFs.

The following summary of RCF in vitro studies examines their direct effects on cell proliferation and viability and indirect effects via release of TNF, ROS, and other inflammatory mediators. The genotoxic effects of RCFs are also examined and summarized. Table C–1 describes RCF cytotoxicity studies involving their direct effects on cells. Table C–2 describes RCF cytotoxicity studies involving the release of mediators. Table C–3 summarizes RCF genotoxic studies.

C.1 Direct Cytotoxic Effects of RCFs

RCFs may have a direct cytotoxic effect on target cells. Measurements of cell viability and cell proliferation are both indications of cytotoxic effects. Cell viability can be assessed through the detection of enzymes released by cells or dyes taken up by cells that indicate altered cell membrane integrity or permeability. Measurement of cytoplasmic LDH and trypan blue exclusion are two methods used to assess cell viability. LDH is a cytoplasmic enzyme; its release indicates plasma membrane damage. Trypan blue is a dye that can only penetrate damaged cell membranes. β-glucuronidase is a lysosomal enzyme, it assesses lysosomal permeability and membrane viability. It may also be released when alveolar macrophages are activated by frustrated phagocytosis. The cytotoxic effects of RCFs on rat pleural mesothelial cells, porcine aortic endothelial cells, human-hamster hybrid (A_L) cells, human macrophages, macrophage-like P388D1 cells, and human alveolar epithelial cells are summarized in Table C–1 and C–2 and in the text below.

Luoto et al. [1997] evaluated the effects of RCFs, quartz, and several MMVFs on LDH levels in rat alveolar macrophages and hemolysis in sheep erythrocytes. RCF1, RCF2, RCF3, and RCF4 at 1.0 mg/ml induced a lower release of LDH (less than 20% of control) from rat alveolar macrophages compared with quartz (approximately 40% of control) [Luoto et al. 1997]. RCF1 stimulated the lowest amount of

LDH release (less than 10% of control), lower even than TiO_2 (approximately 15% of control). RCF1, RCF2, RCF3, RCF4, MMVF10, MMVF11, MMVF21, and MMVF22 at 0.5, 2.5, and 5.0 mg/ml induced a dose-dependent increase in sheep erythrocyte hemolysis. RCF1 and RCF3 induced slightly more hemolysis than other MMVFs. The hemolytic activity of MMVFs was similar to that of TiO_2, and much less than that of quartz.

At doses of 100, 300, and 1,000 µg/ml RCFs (unspecified type), an increased release of LDH was induced from rat macrophages [Leikauf et al. 1995]. At equivalent gravimetric doses of 1,000 µg/ml, the effects of RCFs were much less than those of silica. Ceramic fibers (unspecified type) at 50 µg/ml induced no difference in LDH levels compared with negative controls in rat alveolar macrophages [Fujino et al. 1995]. Chrysotile, crocidolite, amosite, and anthophyllite asbestos all induced significant increases in LDH and β-glucuronidase levels. Ceramic fibers also induced a significant increase in β-glucuronidase but much less than that induced by each of the asbestos fiber types.

In the permanent macrophage-like cell line P388D1, an elutriated ceramic fiber (unspecified type) at 10 or 50 µg/ml after 24 or 48 hr had no significant effect on cell viability as measured by the trypan blue assay [Wright et al. 1986]. The elutriation process used for this experiment provided mainly respirable fibers. All other fibers examined, excluding short-fiber amosite, reduced viability. Although the specific data on the effect of exposure to fibers on enzyme release was not presented, an association between decreasing cell viability and increasing loss of intracellular glucosaminidase and LDH was reported under most conditions investigated. Cytotoxicity was correlated with fiber lengths greater than 8 µm when all fiber types were combined.

The effect of several fibers on the viability of rat pleural mesothelial cells was investigated [Yegles et al. 1995]. On a per weight basis, the rank order of cytotoxicity was National Institute for Environmental Health Sciences (NIEHS) chrysotile, RCF3, MMVF10 and RCF1, Calidria chrysotile, RCF4, and all others. Based on the total number of fibers, the rank order of cytotoxicity was RCF3, MMVF10, RCF1, RCF4, MMVF11, NIEHS chrysotile, amosite, and all others. Cytotoxicity was dependent on fiber dimensions as the longest (RCF3, MMVF10, RCF1, MMVF11) or thickest (RCF4, RCF1, MMVF11, RCF3) fibers were the most cytotoxic.

RCF1, RCF2, RCF3, and RCF4 were found to inhibit the proliferation and colony-forming efficiency of Chinese hamster ovary cells in vitro [Hart et al. 1992]. The inhibition was concentration-dependent. RCF4 was least cytotoxic, RCF2 was intermediate, and RCF1 and RCF3 were the most cytotoxic. A correlation existed between average fiber length and toxicity, with the shortest fibers being least cytotoxic. LC_{50}s for the RCF ranged from 10 to 30 µg/cm^2. In each assay, the RCFs were less cytotoxic than those of the positive controls of crocidolite (LC_{50}=5 µg/cm^2) and chrysotile (LC_{50}=1 µg/cm^2) asbestos.

At 0 to 80 µg/cm^2 RCF1, tremolite, and erionite were significantly less cytotoxic to human-hamster hybrid A_L cells than chrysotile as determined by the surviving fraction of colonies after fiber exposure [Okayasu et al. 1999]. RCF1, crocidolite asbestos, and MMVF10 at 25 µg/cm^2 induced focal necrosis in rat pleural mesothelial cells after 24 hr that became a more obvious necrosis by 72 hr [Janssen et al. 1994]. At 72 hr, the qualitative effects of 25 µg/cm^2 RCF1 were comparable to those of 5 µg/cm^2 crocidolite asbestos. In contrast, minimal necrosis was seen at 25 µg/cm^2 crocidolite asbestos, RCF2, and

MMVF10 fibers in hamster tracheal epithelial cells at 24 hr; no necrosis was present at 72 hr.

RCF1, RCF2, RCF3, and RCF4 as well as asbestos and other fibers had a dose-dependent effect on cytotoxicity, as measured by cell detachment, in the human alveolar epithelial cell line A549 [Cullen et al. 1997]. Cell detachment is associated with epithelial damage, an important step in the inflammatory process. These cells are a primary target of inhaled fibers. When equivalent doses (10, 25, 50, and 100 µg/ml) were tested with various fibers, all RCFs had a less significant effect than both crocidolite and amosite asbestos. When the dose data were adjusted for the number of fibers, RCF1, RCF2, and RCF3 were more cytotoxic than RCF4 and crocidolite.

In an assay determining the ability of fibers to induce an increase in the diameter of human A549 cells, an elutriated ceramic fiber (unspecified type) had a midrange of activity when compared with 12 other fibers [Brown et al. 1986]. It was more active than most varieties of amosite tested (but not UICC amosite) but less active than the chrysotile fibers. An association was found between increasing length and assay activity. When these same fiber samples were tested for colony inhibition in V79/4 Chinese hamster lung fibroblasts, the ceramic fiber had even less effect than the TiO_2 control. Analysis of all fibers upheld the association between increasing length and increased activity. In both assays, fiber diameter was not related to activity in most cases.

Chrysotile asbestos at 10 µg/cm^2 and crocidolite asbestos at 5 µg/cm^2 altered porcine aortic endothelial cell morphology and increased neutrophil adherence [Treadwell et al. 1996]. RCF1 fibers at 10 µg/cm^2 did not change cell morphology or increase neutrophil binding.

These studies suggest that RCFs may have some similar direct cytotoxic effects to asbestos. They are capable of inducing enzyme release and cell hemolysis. They may decrease cell viability and inhibit proliferation. In most studies, the effects of RCFs are much less pronounced than the effects of asbestos at similar gravimetric concentrations. Fiber length was demonstrated to be an important factor in determining the cell responses in many studies.

C.2 Indirect Effects of RCFs: Effects on Inflammatory Cells

In addition to direct effects on target cells, RCFs may have indirect mechanisms of action by acting on inflammatory cells. Inflammatory cells, such as pulmonary macrophages, may respond to fiber exposure by releasing inflammatory mediators that initiate the process of pulmonary inflammation and fibrosis. Cytokines and ROS are among the inflammatory mediators released. Many studies, summarized below and in Table C–2, have investigated this link between fiber exposure and mediator release to try to elucidate the mechanism of action of RCFs. Cytokines are a class of proteins that are involved in regulating processes such as cell secretion, proliferation, and differentiation. One of the cytokines most commonly analyzed in RCF cytotoxicity studies is TNF. TNF has been implicated in silica- and asbestos-induced pulmonary fibrosis [Piguet et al. 1990; Lemaire and Ouellet 1996]. TNF and many ILs are associated with collagen deposition (an initial stage of fibrosis), and PGs inhibit these effects. Experiments on the effects of RCF exposure on TNF production in various cell types have had differing results.

TNF secretion has been associated with exposure to asbestos both in vitro and in vivo

[Perkins et al. 1993]. In vitro incubation of human alveolar macrophages from normal volunteers with 25 µg/ml chrysotile asbestos resulted in increased levels of TNF secretion. Alveolar macrophages from 6 human subjects occupationally exposed to asbestos for more than 10 years secreted increased amounts of the cytokines TNF, IL–6, PGE_2, and IL–1ß in vitro. Five human subjects occupationally exposed for less than 10 years did not show increases in these cytokines. The two exposure groups were matched for age, smoking history, and diagnosis. The increased TNF secretion in both in vitro and chronic in vivo asbestos-exposed conditions suggests its importance in the response of the lung to fiber exposure, although the small exposure group sizes warrant caution in drawing strong conclusions.

When equal numbers (8.2×10^6) of various fiber types, including RCF1, RCF2, RCF3, and RCF4, were incubated separately with rat alveolar macrophages, silicon carbide whiskers, amosite, and crocidolite asbestos stimulated the highest TNF release [Cullen et al. 1997]. RCF1, RCF2, RCF3, and RCF4 showed no significant increase in TNF release compared with control.

In contrast, ceramic fibers (unspecified type) at 50 µg/ml (1.72×10^5 f) significantly increased TNF release compared with controls in rat alveolar macrophages [Fujino et al. 1995]. Potassium octatitanate whisker, chrysotile, and crocidolite asbestos induced the greatest TNF release. Alveolar macrophages exposed to either 300 or 1,000 µg/ml RCFs or 1,000 µg/ml asbestos showed a significant increase in TNF production [Leikauf et al. 1995]. At 300 µg/ml RCFs, a significant elevation occurred in leukotriene B_4. At 1,000 µg/ml RCFs, significant elevations occurred in leukotriene B_4 and prostaglandin E_2. Levels induced at lower doses were not different from controls. At equivalent doses, the effect on the levels of all mediators measured was greater after asbestos exposure than after RCF exposure.

Chrysotile A, chrysotile B, crocidolite, MMVF21, RCF1, and silicon carbide at 100 µg/ml caused a significantly increased synthesis of TNF mRNA after 90 minutes of incubation with rat alveolar macrophages [Ljungman et al.1994]. After 4 hr of incubation, chrysotile A still had a significantly increased TNF mRNA production, and all other fibers were at baseline concentrations. None of the fibers studied increased TNF release at 90 minutes. However, an increased TNF bioactivity occurred after 4 hr of incubation with chrysotile A, chrysotile B, crocidolite, or MMVF21. RCF1 at 100 µg/ml did not increase TNF production under these conditions.

Chrysotile asbestos and alumina silicate ceramic fibers increased in vitro alveolar macrophage TNF production in rats exposed to cigarette smoke in vivo and in rats unexposed to smoke [Morimoto et al. 1993]. Asbestos at 50 and 100 µg/ml induced a significantly greater TNF release in rats exposed to cigarette smoke versus unexposed rats. No significant differences were found between groups at all doses of RCF fibers tested (25, 50 and 100 µg/ml). RCF exposure, in contrast to chrysotile, did not have a significant synergistic effect with cigarette smoke exposure.

In addition to the cytokines such as TNF, another group of inflammatory mediators that has been studied in vitro are the ROS. These mediators, also referred to as reactive oxygen metabolites (ROMs) are normally produced during the process of cellular aerobic metabolism and in phagocytic cells in response to particle exposure. One molecular effect of asbestos exposure has been demonstrated to be the induction of ROS [Kamp et al. 1992]. Oxidative stress occurs when the ROS level in a cell exceeds the antioxidant level. ROS may result in

damage to DNA, lipids and proteins and have been implicated in having a role in carcinogenesis [Klaunig et al. 1998; Vallyathan et al. 1998]. This research has suggested that free radical activity may be involved in the pathogenesis of fiber-induced lung disease.

The ability of RCFs to induce the release of free radicals has been studied in rodent alveolar macrophages. RF1 and RF2 (Japanese ceramic fibers) at 200 μg/ml induced a significant production of superoxide anion and a significant increase in intracellular free calcium in guinea pig alveolar macrophages [Wang et al. 1999]. Both superoxide anion and increased intracellular calcium are associated with oxidative stress. Superoxide anions may generate hydrogen peroxide and hydroxyl radical, classified as ROS or free radicals. RF2 exposure resulted in a significant depletion of glutathione. Glutathione is a cellular antioxidant that protects cells against oxidative stress; depletion of glutathione is associated with oxidative stress. The RFs did not affect hydrogen peroxide production. In each test, the effects of chrysotile were significantly greater than those of the RFs.

RCF1, MMVF10, and amosite asbestos at 8.24×10^6 f/ml induced a significant depletion of intracellular glutathione in rat alveolar macrophages [Gilmour et al. 1997]. RCF1 had similar effects to amosite asbestos, whereas MMVF10 caused the greatest depletion of glutathione.

RCF1, RCF2, and RCF3 induced a greater production of ROMs in human polymorphonuclear cell cultures than RCF4 and chrysotile [Luoto et al. 1997]. A dose-dependent production of ROMs was seen in all RCFs and other MMVFs tested from 25 to 500 μg/ml. Quartz had a greater effect on ROM production than all fibers tested.

RCF1 had a high binding capacity for rat immunoglobulin (IgG), a normal component of lung lining fluid [Hill et al. 1996]. At doses >100 μg RCF1, fibers coated with IgG induced a significantly increased superoxide anion release. This supports the premise that lung lining fluid and other substances that fibers are exposed to in vivo may significantly alter the effect of fibers on cells. IgG-coated long fiber amosite asbestos, in spite of a poor binding affinity for IgG, induced a comparable superoxide anion release response to that of coated RCF1.

Brown et al. [1999] investigated the ability of RCF1, amosite asbestos, silicon carbide, MMVF10, Cole 100/475 glass fiber, and RCF4 to cause translocation of the transcription factor NF-κB to the nucleus in A549 lung epithelial cells. RCF1, amosite asbestos, and silicon carbide produced a significant dose-dependent translocation of NF-κB to the nucleus; the other fibers tested did not. Equal fiber numbers were tested.

These cytotoxicity studies indicate that RCFs may share some aspects of their mechanism of action with asbestos. They both affect the production of TNF and ROS as well as cell viability and proliferation. The effects of RCFs have usually been less pronounced than those of asbestos. Results of in vitro studies are difficult to compare, even within studies of different fiber types, because of different study designs, different fiber concentrations and characteristics, and different endpoints.

C.3 Genotoxic Effects of RCFs

In addition to research assessing the cytotoxicity of RCFs, studies have also assessed the genotoxicity of RCFs. Most genotoxicity assays assess changes in or damage to genetic material. Methods that have been used to investigate the genotoxicity of fibers include cell-free or in

vitro cell systems investigating DNA damage, studies of aneuploidy or polyploidy, studies of chromosome damage or mutation, gene mutation assays, and investigations of cell growth regulation [Jaurand 1997]. Several studies, described below and in Table C–3, have examined the ability of RCFs to produce genotoxic changes in comparison with asbestos.

Several fibers, including RCF1 and RCF4, were assayed for free radical generating activity using a DNA assay and a salicylate assay [Brown et al.1998]. The DNA plasmid assay showed only amosite asbestos to have free radical activity. The salicylate assay showed amosite as well as RCF1 to have free radical activity. Coating the fibers with lung surfactant decreased their hydroxyl radical generation. Differences in RCF1 results in the two assays were proposed to be a result of increased iron release from RCF1 in the salicylate assay. An iron chelator inhibited the RCF hydroxylation of salicylate. RCF4 showed no free radical activity.

When equal fiber numbers were compared, RCF1, RCF2, RCF3, and RCF4 had minimal free- radical-generating activity on plasmid DNA compared with crocidolite and amosite asbestos [Gilmour et al. 1995]. RCFs and other MMVF produced a small but insignificant amount of DNA damage. This damage was mediated by hydroxyl radicals. No correlation was found between iron content and free radical generation. At 9.3×10^5 fibers per assay, amosite produced substantial free radical damage to plasmid DNA [Gilmour et al. 1997]. Amosite significantly upregulated the transcription factors AP–1 and NFkB; RCF1 had a much smaller effect on AP–1 upregulation only.

SVFs, including ceramic fibers (unspecified), were reported to form hydroxyl radicals based on the formation of the DNA adduct 8-hydroxydeoxyguanosine (8-OH-dG) from 2-deoxyguanosine (dG) in calf thymus DNA and solution [Leanderson et al. 1989; Leanderson and Tagesson 1989]. Ceramic and glasswool fibers had poor hydroxylating capabilities relative to rockwool and slag wool fibers [Leanderson et al. 1989]. Hydroxyl radical scavengers, such as dimethyl sulfoxide, decreased the hydroxylation. Compounds that increase hydroxyl radical formation, such as hydrogen peroxide, increased hydroxylation. Rockwool in combination with cigarette smoke condensate caused a synergistic increase in 8-OH-dG formation; ceramic and glasswool fibers did not have synergistic effects with cigarette smoke [Leanderson and Tagesson 1989].

RCF1, RCF2, RCF3, and RCF4 induced nuclear abnormalities, including micronuclei and polynuclei, in Chinese hamster ovary cells [Hart et al. 1992]. Micronuclei may form when chromosomes or fragments of chromosomes are separated during mitosis. Polynuclei may arise when cytokinesis fails after mitosis. The incidence of micronuclei and polynuclei after exposure to 20 $\mu g/cm^2$ RCF was from 22% to 33%. At 5 $\mu g/cm^2$, chrysotile and crocidolite induced nuclear abnormalities of 49% and 28%, respectively.

Amosite, chrysotile, and crocidolite asbestos, and ceramic fibers caused a significant increase in micronuclei in human amniotic fluid cells [Dopp et al. 1997]. The response was dose-dependent with asbestos fiber exposure but not with ceramic fiber exposure. Significant increases in chromosomal breakage and hyperdiploid cells were noted after asbestos and ceramic fiber exposure.

RCF1, RCF3, and RCF4 did not induce anaphase aberrations in rat pleural mesothelial cells [Yegles et al. 1995]. Of all fibers tested, UICC chrysotile was the most genotoxic on the basis of weight, number of fibers with a length >4 μm and number of fibers corresponding

to Stanton's and Pott's criteria [Stanton et al. 1981; Pott et al. 1987].

The effect of fibers on the mRNA levels of c-fos and c-jun proto-oncogenes and ornithine decarboxylase (ODC) in hamster tracheal epithelial (HTE) cells and rodent pleural mesothelial (RPM) cells were examined [Janssen et al. 1994]. ODC is a rate-limiting enzyme in the synthesis of compounds involved in cell proliferation and tumor promotion, the polyamines. In HTE cells, crocidolite induced a significant dose-dependent increase in levels of c-jun and ODC mRNA but not c-fos mRNA. RCF1 induced only small nondose-dependent increases in ODC mRNA levels. In RPM cells, crocidolite fibers at 2.5 μg/cm^2 significantly elevated levels of c-fos and c-jun mRNA. RCF1 increased proto-oncogene expression at cytotoxic levels of 25 μg/cm^2; no significant effect was seen at concentrations ≤5 μg/cm^2.

RCF1 fibers were nonmutagenic in the human-hamster hybrid cell line A_L [Okayasu et al. 1999]. Chrysotile was a significant inducer of mutations in the same system.

These studies demonstrate that RCFs may share some similar genotoxic mechanisms with asbestos including induction of free radicals, micronuclei, polynuclei, chromosomal breakage, and hyperdiploid cells. Other studies have demonstrated that, using certain methods and doses, RCFs did not induce anaphase aberrations and induced proto-oncogene expression only at cytotoxic concentrations. RCFs were nonmutagenic in human-hamster hybrid cells.

C.4 Discussion of In Vitro Studies

The toxicity of fibers has been attributable to their dose, dimensions, and durability. Any test system that is designed to assess the potential toxicity of fibers must address these factors. Durability is difficult to assess using in vitro studies because of their acute time course. However, in vitro studies provide an opportunity to study the effects of varying doses and dimensions of fibers in a quicker, more efficient method than animal testing. Although they provide important information about mechanism of action, they do not currently provide data that can be extrapolated to occupational risk assessment.

The association between fiber dimension and toxicity has been documented and reviewed [Stanton et al. 1977, 1981; Pott et al. 1987; Warheit 1994]. Fiber length has been correlated with the cytotoxicity of glass fibers [Blake et al. 1998]. Manville code 100 (JM–100) fiber samples of average lengths of 3, 4, 7, 17, and 33 μm were assessed for their effects on LDH activity and rat alveolar macrophage function. The greatest cytotoxicity was reported in the 17 μm and 33 μm samples, indicating that length is an important factor in the toxicity of this fiber. Multiple macrophages were observed attached along the length of long fibers. Relatively short fibers, <20 μm long, were usually phagocytized by one rat alveolar macrophage [Luoto et al. 1994]. Longer fibers were phagocytized by two or more macrophages. Incomplete, or frustrated, phagocytosis may play a role in the increased toxicity of longer fibers. Long fibers (17 μm average length) were a more potent inducer of TNF production and transcription factor activation than shorter fibers (7 μm average length) [Ye et al. 1999]. These studies demonstrate the important role of length in fiber toxicity and suggest that the capacity for macrophage phagocytosis may be a critical factor in determining fiber toxicity. The toxicity of individual fibers of the same type of RCFs may differ according to their size in relation to alveolar macrophages.

Several RCF in vitro studies reported a direct association between a longer fiber length and greater cytotoxicity. Hart et al. [1992] reported the shortest fibers to be the least cytotoxic. Brown et al. [1986] reported an association between length and cytotoxic activity but not between diameter and activity. Wright et al. [1986] reported that cytotoxicity was correlated with fibers >8 μm length. Yegles et al. [1995] reported that the longest and thickest fibers were the most cytotoxic. The four most cytotoxic fibers had GM lengths ≥13 μm and GM diameters >0.5 μm. The production of abnormal anaphases and telophases was associated with Stanton fibers with a length >8 μm and diameter ≤0.25 μm. Hart et al. [1994] reported that cytotoxicity increased with fiber length up to 20 μm. All of these studies demonstrate the importance of fiber dimensions on cytotoxicity. Other studies have not reported the length distribution of fiber samples used. When studies are done with RCFs for which specific lengths are assessed for cytotoxicity (such as has been done with glass fibers) [Blake et al. 1998], it will be possible to determine the strength of the association between RCF fiber length and toxicity and determine whether a threshold length exists above which toxicity increases steeply.

In addition to providing data on the correlation between fiber length and toxicity, in vitro studies have provided data on the relative toxicity of RCFs compared with asbestos. Uncertainties exist in the interpretation of these studies because of differences in fiber doses, dimensions, and durabilities. RCFs do appear to share some similar mechanisms of action with asbestos. (See references in Tables C–1, C–2, and C–3.) They have similar direct and indirect effects on cells and alter gene function in similar ways. They are capable of inducing enzyme release and cell hemolysis. They may decrease cell viability and inhibit proliferation. They both affect the production of tumor necrosis factor and ROS, and affect cell viability and proliferation. They induce necrosis in rat pleural mesothelial cells. They also may induce free radicals, micronuclei, polynuclei, chromosomal breakage, and hyperdiploid cells in vitro.

In vitro studies also provide an excellent opportunity for investigating the pathogenesis of RCF. However, comparisons are difficult to make between in vitro studies because of differences in fiber doses, dimensions, preparations, and compositions. Important information, such as fiber length distribution, is not always determined. Even when comparable fibers are studied, the cell line or conditions under which they are tested may vary. Much of the research to date has been done in rodent cell lines and in cells that are not related to the primary target organ. In vitro studies using human pulmonary cell lines should provide pathogenesis data most relevant to human health risk assessment.

Short-term in vitro studies cannot take into account the influence of fiber dissolution and fiber compositional changes that may occur over time. In an in vivo exposure, fibers are continually modified physically, chemically, and structurally by components of the lung environment. This complex set of conditions is difficult to recreate in vitro. Just as it is unlikely that only one factor will be an accurate predictor of fiber toxicity, it is much more unlikely that any one in vitro test will be able to predict fiber toxicity. Best results are obtained by toxicity assessment in several in vitro tests and in comparison with in vivo results. In vitro studies provide an excellent opportunity to investigate factors important to fiber toxicity such as dose, dimension, surface area, and physicochemical composition. They provide the ability to obtain information that is an important supplement to the data of chronic inhalation studies. They do not currently provide information that can be directly applied to human health risk assessment and the development of occupational exposure limits.

Table C–1. In vitro cytotoxicity of RCFs:* direct effects on cells

Reference	Cell line and endpoints	Fiber type	Length (μm)	Diameter (μm)	Dose	Results
Brown et al. [1986]	A549 cells Cell diameter V79/4 Chinese hamster lung fibroblasts Colony inhibition	Elutriated (E) ceramic (unspecified) Titanium dioxide Quartz Short fiber amosite UICC crocidolite E factory amosite E UICC crocidolite E brucite UICC amosite Superfine chrysotile E UICC anthophyllite UICC chrysotile A E tremolite E long fiber amosite E UICC chrysotile A	Not reported	Not reported	A549 cells: 25 or 50 μg/ml V79/4 cells: 0, 5, 10, 25, 75, or 100 μg/ml	A549 assay: Chrysotile effect> ceramic effect> most amosites (not UICC amosite). V79/4 assay: Ceramic fiber had no effect. Ceramic fiber had different results in the two assays. Association found between increasing fiber length (all types) and activity in both assays.
Cullen et al. [1997]	Human alveolar epithelial cells Cell detachment	RCF1 RCF2 RCF3 RCF4 Long amosite Crocidolite C100/475 glass 104E glass Silicon carbide 1 Silicon carbide 2 MMVF10 MMVF11 MMVF21 MMVF22	Geometric mean: 10.42 ± 2.66 12.43 ± 2.66 14.99 ± 2.64 6.82 ± 2.00 3.03 ± 2.86 4.96 ± 2.57 2.88 ± 2.62 3.50 ± 2.17 8.73 ± 2.25 Not done 23.91 ± 2.39 14.21 ± 2.64 15.66 ± 2.76 13.67 ± 2.34	Geometric mean: 0.79 ± 2.07 0.84 ± 2.01 0.71 ± 2.12 0.94 ± 1.71 0.26 ± 1.75 0.15 ± 1.53 0.22 ±1.85 0.25 ± 1.6 0.47 ± 1.39 Not done 1.13 ± 1.90 0.57 ± 2.01 0.81 ± 1.76 0.89 ± 1.78	10, 25, 50, or 100 μg/ml	At equivalent doses, all RCFs had less effect than crocidolite and amosite asbestos. When adjusted for equivalent fiber numbers, crocidolite, RCF4, MVF11, and amosite were least cytotoxic; RCF1, RCF2, and RCF3 were more cytotoxic than crocidolite and amosite.

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Table C–1 (Continued). In vitro cytotoxicity of RCFs:* direct effects on cells

Reference	Cell line and endpoints	Fiber type	Length (μm)	Diameter (μm)	Dose	Results
Fujino et al. [1995]	Rat alveolar macrophages LDH β-glucuronidase	Ceramic Glass Potassium octatitanate Magnesium sulfate (long) Magnesium sulfate (short) Chrysotile asbestos Crocidolite asbestos Amosite Anthophyllite Erionite	Geometric mean: 29.5 ± 3.1 12.8 ± 3.0 2.8 ± 2.0 12.0 ± 2.3 4.9 ± 2.1 0.7 ± 1.9 1.3 ± 2.3 2.7 ± 2.5 2.5 ± 3.5 1.4 ± 2.0	Geometric mean: 1.92 ± 2.9 0.54 ± 2.2 0.41 ± 1.5 0.44 ± 1.6 0.31 ± 1.5 0.085 ± 1.4 0.20 ± 1.5 0.32 ± 1.8 0.36 ± 2.3 0.21 ± 1.6	50 μg/ml	LDH: Ceramic fiber, magnesium sulfate whiskers, and erionite were not different from control; all others significantly increased levels. β-glucuronidase: All fibers caused a significant increase compared with control; chrysotile caused the highest release.
Hart et al. [1992]	Chinese hamster ovary cells Cell proliferation Colony formation	RCF1 RCF2 RCF3 RCF4 UICC Crocidolite UICC Chrysotile	Geometric mean: 21.5 ± 16.12 16.7 ± 15.03 24.3 ± 18.82 9.2 ± 7.08 1.8 ± 1.94 1.65 ± 1.83	Geometric mean: 1.03 ± 0.73 1.11 ± 0.82 1.22 ± 0.98 1.43 ± 0.79 0.21 ± 0.12 0.12 ± 0.07	RCF1–4: 0, 5, 10, or 20 μg/ml Crocidolite: 0 or 5 μg/ml Chrysotile: 0, 1, 2, or 5 μg/ml	RCFs induced a concentration-dependent decrease in colony formation and cell proliferation. LC_{50}: RCFs 10–30 μg/cm² Crocidolite 5 μg/cm² Chrysotile 1 μg/cm² RCF cytotoxicity: RCF1 and RCF3 are most cytotoxic; RCF2 is intermediate; RCF4 is least cytotoxic.
Leikauf et al. [1995]	Rat alveolar macrophages LDH	RCF Crocidolite asbestos Silica Titanium dioxide	Median: 4.9 2.5 Not available Not available	Median: 0.59 0.28 0.88 0.18	100, 300, 1,000 μg/ml	RCFs induced moderate increases in LDH levels. % of control: RCFs 100 μg/ml—158% RCFs 300 μg/ml—174% RCFs 1,000 μg/ml—295% Silica 1,000 μg/ml—896%

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(Continued)

Table C–1 (Continued). In vitro cytotoxicity of RCFs:* direct effects on cells

Reference	Cell line and endpoints	Fiber type	Length (μm)	Diameter (μm)	Dose	Results
Luoto et al. [1997]	Sheep erythrocytes Hemolysis Rat alveolar macrophages LDH	RCF1 RCF2 RCF3 RCF4 MMVF10 MMVF11 MMVF21 MMVF22	Mean: 21.29 ± 17.42 20.18 ± 19.63 25.66 ± 25.74 10.34 ± 11.59 23.21 ± 15.57 15.65 ± 13.31 26.02 ± 23.10 20.75 ± 20.52	Mean: 1.30 ± 0.72 1.39 ± 0.98 1.37 ± 0.87 1.33 ± 1.02 1.42 ± 0.78 1.12 ± 0.88 1.18 ± 0.64 0.88 ± 0.45	Hemolysis: 0.5, 2.5, or 5.0 mg/ml LDH: 1.0 mg/ml	Hemolysis: Dose-dependent increase in hemolysis induced by all fibers and dusts. RCF1 and RCF3 were slightly more hemolytic than all other fibers but much less than quartz. LDH: RCF1 induced the least LDH release; MMVF 22 had the greatest fiber-induced LDH release; quartz induced the greatest LDH release overall.
Okayasu et al. [1999]	Human-hamster hybrid A_L cells Surviving colonies	UICC chrysotile Tremolite Erionite RCF1	Geometric mean: 1.78 ± 2.3 1.41 ± 2.7 1.31 ± 2.9 13.5 ± 2.7	Geometric mean: 0.12 ± 0.08 0.13 ± 3.43 0.23 ± 2.74 0.95 ± 2.6	0–400 μg/ml 0–80 μg/cm^2	Chrysotile was more cytotoxic than other fibers. Mean lethal doses: Chrysotile ~4 μg/cm^2 RCF1 35 μg/cm^2 Tremolite 40 μg/cm^2 Erionite 42 μg/cm^2
Wright et al. [1986]	P388D1 Trypan blue assay LDH concentrations Glucosaminidase concentrations	UICC crocidolite UICC amosite UICC chrysotile A E UICC crocidolite E UICC amosite E UICC chrysotile A E UICC anthophyllite E ceramic fiber E long fiber amosite Short fiber amosite E tremolite	Cumulative fiber length distributions reported	Almost all fibers measured had diameters less than 3 μm; details not reported	Fiber number in 10^{-10} g ± SD: 112 ± 10 76 ± 6 185 ± 18 109 ± 10 112 ± 14 144 ± 20 169 ± 15 15 ± 0.4 19 ± 1	Trypan blue assay: Ceramic fibers at both doses had the lowest degree of cytotoxicity; all other fibers, excluding short-fiber amosite, reduced viability. Fibers >8 μm were usually most effective in decreasing viability and increasing LDH and glucosaminidase concentrations; individual fiber effects were not reported.

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Table C–1 (Continued). In vitro cytotoxicity of RCFs:* direct effects on cells

Reference	Cell line and endpoints	Fiber type	Length (μm)	Diameter (μm)	Dose	Results
Wright et al. [1986] (Continued)		E brucite SFA chrysotile Titanium dioxide Quartz			44 ± 2.7 22 ± 1.6 152 ± 14 7.4 ± 0.5 Fiber dose: 10 or 50 μg/ml 80 μg/ml 20 μg/ml	
Yegles et al. [1995]	Rat pleural mesothelial cells Cell viability: Mitochondrial integrity		Mean:	Mean:	12.5, 25, 50, 75, or 100 μg/cm^2	Cytotoxicity per weight basis: Chrys NIEHS > RCF3> MMVF10=RCF1> Chrys, calidria > RCF4 > all others Cytotoxicity per total number of fibers: RCF3 > MMVF10 > RCF1 > RCF4 >MMVF11 > Chrys, NIEHS>amosite >all others Fiber length and diameter correlated with cytotoxicity: longest and thickest fibers were most cytotoxic.
		RCF1	19.2 ± 15.0	1.30 ± 0.80		
		RCF3	31.8 ± 36.0	0.74 ± 0.50		
		RCF4	8.9 ± 7.2	1.30 ± 0.60		
		MMVF10	21.5 ± 16.8	0.55 ± 0.50		
		MMVF11	16.7 ± 12.9	1.10 ± 0.90		
		Chrysotile (chrys), UICC	1.7 ± 2.2	0.05 ± 0.04		
		Chrys 445 (Canadian)	2.3 ± 2.3	0.04 ± 0.03		
		Chrys 443 (Canadian)	1.9 ± 1.9	0.04 ± 0.04		
		Chrys, short Canadian	1.6 ± 1.4	0.06 ± 0.08		
		Chrys, superfine Canadian	2.4 ± 3.1	0.04 ± 0.03		
		Chrys, phosphorylated Canadian	4.7 ± 5.2	0.04 ± 0.03		
		Chrys, phosphorylated, milled Canadian	4.7 ± 5.9	0.07 ± 0.09		
		UICC chrys, leached with oxalic acid	2.3 ± 1.8	0.17 ± 0.11		
		Chrys, Calidria	2.8 ± 3.0	0.05 ± 0.04		
		Chrys, NIEHS	4.2 ± 1.2	0.05 ± 0.05		
		Amosite	2.4 ± 1.8	0.31 ± 0.20		
		Crocidolite	2.1 ± 3.6	0.19 ± 0.12		
		Attapulgite	0.8 ± 0.5	0.04 ± 0.03		

*Abbreviations: E=elutriated; LDH=lactate dehydrogenase; MMVF=man-made vitreous fiber; NIEHS=National Institute of Environmental Health Sciences; RCFs=refractory ceramic fibers; SD=standard deviation; UICC=Union Internationale Contre le Cancer.

Table C–2. In vitro cytotoxicity of RCFs:* effects on mediator release

Reference	Cell line and endpoints	Fiber type	Length (μm)	Diameter (μm)	Dose	Results
			Geometric mean:	Geometric mean:	8.2×10^6 fibers	SiC1, SiC2, crocidolite, and
Cullen et al. [1997]	Human alveolar epithelial cells	RCF1	10.42 ± 2.66	0.79 ± 2.07	(>5 μm long)	long amosite stimulated the highest TNF production.
		RCF2	12.43 ± 2.66	0.84 ± 2.01		
		RCF3	14.99 ± 2.64	0.71 ± 2.12		
	TNF	RCF4	6.82 ± 2.00	0.94 ± 1.71		RCF1–RCF4 did not show more TNF activity than in control cultures.
		Long amosite	3.03 ± 2.86	0.26 ± 1.75		
		Crocidolite	4.96 ± 2.57	0.15 ± 1.53		
		C100/475 glass	2.88 ± 2.62	0.22 ±1.85		
		104E glass	3.50 ± 2.17	0.25 ± 1.6		
		SiC1	8.73 ± 2.25	0.47 ± 1.39		
		SiC2	Not done	Not done		
		MMVF10	23.91 ± 2.39	1.13 ± 1.90		
		MMVF11	14.21 ± 2.64	0.57 ± 2.01		
		MMVF21	15.66 ± 2.76	0.81 ± 1.76		
		MMVF22	13.67 ± 2.34	0.89 ± 1.78		
			Geometric mean:	Geometric mean:	50 μg/ml	All fibers significantly in-
Fujino et al. [1995]	Rat alveolar macrophages	Ceramic	29.5 ± 3.1	1.92 ± 2.9		creased TNF production above no-fiber controls; potassium octatitanate caused the highest TNF production.
		Glass	12.8 ± 3.0	0.54 ± 2.2		
		Potassium octatitanate	2.8 ± 2.0	0.41 ± 1.5		
	TNF	Magnesium sulfate (long)	12.0 ± 2.3	0.44 ± 1.6		
		Magnesium sulfate (short)	4.9 ± 2.1	0.31 ± 1.5		
		Chrysotile asbestos	0.7 ± 1.9	0.085 ± 1.4		
		Crocidolite asbestos	1.3 ± 2.3	0.20 ± 1.5		
		Amosite	2.7 ± 2.5	0.32 ± 1.8		
		Anthophylite	2.5 ± 3.5	0.36 ± 2.3		
		Erionite	1.4 ± 2.0	0.21 ± 1.6		

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Table C–2 (Continued). In vitro cytotoxicity of RCFs:* effects on mediator release

Reference	Cell line and endpoints	Fiber type	Length (µm)	Diameter (µm)	Dose	Results
Gilmour et al. [1997]	Rat alveolar macrophages Glutathione	RCF1 Amosite asbestos MMVF10	Not reported	Not reported	8.24×10^6/ml	All fibers significantly lowered intracellular glutathione. MMVF10 caused the greatest decrease. RCF1 and amosite had similar effects.
Hill et al. [1996]	Rat alveolar macrophages Superoxide anion release after coating with rat immunoglobulin (IgG), a normal component of lung lining fluid.	MMVF21 RCF1 LFA asbestos SiC Johns Manville Code 100/475 (glass)	WHO f/µg 5,462 9,015 164,705 70,550 21,742 Percentage length distribution also reported.	Not reported	RCF1, MMVF21: 125 µg–20 mg/ml Code 100/475, SiC:125 µg–1 mg/ml LFA asbestos: 15.6 µg–5 mg/ml	IgG-coated RCF1 fibers and IgG-coated LFA asbestos fibers induced a significantly increased superoxide anion release. Coating of RCF1 fibers at doses >100 µg greatly increased their superoxide production. RCF1 fibers had a high binding affinity for IgG; LFA asbestos did not.
Leikauf et al. [1995]	Rat macrophages TNF LTB_4 PGE_2	RCF (unspecified) Crocidolite asbestos Silica TiO_2	Median: 4.9 2.5 NA NA	Median: 0.59 0.28 0.88 0.18	100, 300, 1,000 µg/ml	TNF production was increased after exposure to 300 and 1,000 µg/ml RCFs. LTB_4 levels were elevated after exposure to 300 or 1,000 µg/ml RCFs; PGE_2 concentrations were elevated after exposure to 1,000 µg/ml RCFs; effects at lower doses were not significant. At equivalent doses, asbestos induced a greater response than RCFs in TNF, LTB_4, or PGE_2 concentrations.

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Table C–2 (Continued). In vitro cytotoxicity of RCFs:* effects on mediator release

Reference	Cell line and endpoints	Fiber type	Length (µm)	Diameter (µm)	Dose	Results
Ljungman et al. [1994]	Rat alveolar macrophages TNF		Mean:	Mean:	100 µg/ml	Chrysotile A, chrysotile B, crocidolite, MMVF21, RCF1, and SiCwh increased TNF mRNA concentrations after 90 minutes; concentrations had returned to baseline after 4 hours in all but chrysotile A. Chrysotile A, chrysotile B, crocidolite, and MMVF21 induced an increase in TNF bioactivity after 4 hours of incubation; RCF1 did not induce a significant increase.
		Crocidolite	9.9 ± 7.8	0.3 ± 0.2		
		Chrysotile A	Not reported	Not reported		
		Chrysotile B	Not reported	Not reported		
		MMVF21	24.6 ± 19.9	1.3 ± 0.8		
		MMVF22	21.4 ± 17.6	1.2 ± 0.7		
		RCF1	22.4 ± 19.0	1.1 ± 0.8		
		SiCwh	Not reported	Not reported		
Luoto et al. [1997]	Rat alveolar macrophages ROM	RCF1	Mean:	Mean:	25, 50, 100, 200, 400, or 500 µg/ml	All fibers showed a dose-dependent response to ROM production. RCF1, RCF2, or RCF3 exposure resulted in higher ROM production than RCF4 or chrysotile exposure. Quartz had the greatest effect on ROM production.
		RCF2	21.29 ± 17.42	1.30 ± 0.72		
		RCF3	20.18 ± 19.63	1.39 ± 0.98		
		RCF4	25.66 ± 25.74	1.37 ± 0.87		
		MMVF10	10.34 ± 11.59	1.33 ± 1.02		
		MMVF11	23.21 ± 15.57	1.42 ± 0.78		
		MMVF21	15.65 ± 13.31	1.12 ± 0.88		
		MMVF22	26.02 ± 23.10	1.18 ± 0.64		
			20.75 ± 20.52	0.88 ± 0.45		

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Table C–2 (Continued). In vitro cytotoxicity of RCFs:* effects on mediator release

Reference	Cell line and endpoints	Fiber type	Length (μm)	Diameter (μm)	Dose	Results
Morimoto et al. [1993]	Rat alveolar macrophages TNF	Canadian chrysotile Alumina silicate ceramic (Japan)	Not reported	Mass median aerodynamic diameter = 3.1 μm	25, 50, or 100 μg/ml	Both fibers stimulated a dose-dependent TNF production by alveolar macrophages. Chrysotile stimulated greater TNF production than ceramic fibers in cells from rats exposed to cigarette smoke and cells from rats not exposed to smoke. Chrysotile induced higher TNF production in smoke-exposed rats than in controls; ceramic fiber exposure resulted in no significant difference between TNF production in smoke-exposed rats and controls.
Wang et al. [1999]	Guinea pig alveolar macrophages Superoxide anion Hydrogen peroxide GSH Intracellular free calcium	Japan fibrous material : GW1 = glass wool RW1 = rock wool MG1 = micro glass RF1 = refractory ceramic RF2 = refractory ceramic RF3 = refractory mullite PT1 = potassium titanate SC1 = silicon carbide TO1 = titanium oxide WO1 = wollastonite Chrysotile	 20.2 ± 2.58 16.5 ± 2.51 3.0 ± 2.22 12.0 ± 2.36 11.0 ± 1.96 11.0 ± 1.75 6.0 ± 2.04 6.4 ± 2.45 2.1 ± 2.00 10.5 ± 2.03 Not reported	 0.88 ± 3.10 1.80 ± 2.32 0.24 ± 2.35 0.77 ± 2.53 1.10 ± 2.00 2.40 ± 1.37 0.35 ± 1.51 0.30 ± 1.58 0.14 ± 1.53 1.00 ± 1.72 Not reported	200 μg/ml	Chrysotile and all fibers other than WO1 significantly increased superoxide anion production. Chrysotile significantly increased hydrogen peroxide production; RF did not. Chrysotile, RF2, PT1, TO1, SC1, WO1, and MG1 significantly decreased GSH concentration. Chrysotile, RF1, RF2, SC1, TO1, PT1, MG1, and RW1 significantly increased intracellular free calcium. In all tests, chrysotile had greater effects than those of the RCFs.

*Abbreviations: GSH=glutathione; GW1=glass wool; IgG=immunoglobulin; LFA=long fiber amosite; LTB_4=leukotriene B4; MG1=micro glass; MMVF=man-made vitreous fiber; PGE_2=prostaglandin E_2; PT1=potassium titanate; RCFs=refractory ceramic fibers; RF1=refractory ceramic; RF2=refractory ceramic; RF3=refractory mullite; ROM=reactive oxygen metabolites; RW1=rock wool; SC1=silicon carbide in Wang et al. [1999]; SiC=silicon carbide; TNF=tumor necrosis factor; TiO_2=titanium dioxide; TO1=titanium oxide in Wang et al. [1999]; wh=whiskers; WO1=wollastonite.

Table C–3. In vitro genotoxic effects of RCFs*

Reference	Test system and endpoints	Fiber type	Length (μm)	Diameter (μm)	Dose	Results
Brown et al. [1998]	Plasmid oX174RF1 DNA DNA scission Salicylate assay Hydroxyl radical generation		Size distribution >10 >20	Not reported	Plasmid assay: 9.249×10^5 f/20 μl Salicylate assay: 8.24×10^7 f/ml	Plasmid assay: Only amosite had free radical activity. Salicylate assay: Amosite and RCF1 had free radical activity. Coating the fibers with lung surfactant decreased hydroxyl radical activity. An iron chelator inhibited hydroxylation by RCF1.
		Long fiber amosite asbestos	64.75 35.25			
		SiC	60.86 27.6			
		RCF1	77.36 45.27			
		RCF4	59.35 17.96			
		MMVF10	85.24 67.17			
		Code 100/475 glass	50.00 19.32			
Dopp et al. [1997]	Human amniotic fluid cells Micronuclei Hyperdiploidy Chromosomal breakage		Average:	Average:	0.5, 1.0, 5.0, or 10.0 μg/cm²	All fibers caused a significant increase in micronuclei. Dose-dependent response was seen with asbestos but not with ceramic fiber exposure. Asbestos and ceramic fibers induced chromosomal breakage and hyperdiploid cells.
		Amosite asbestos	2.05	0.24		
		Crocidolite asbestos-	1.71	0.25		
		Rhodesian chrysotile asbestos	2.24	0.10		
		Ceramic (unspecified)	12.03	0.90		
		Gypsum				
Gilmour et al. [1995]	Plasmid oX174RF1 DNA Depletion of supercoiled DNA	Short fiber amosite Long fiber amosite Crocidolite asbestos RCF1 RCF2 RCF3 RCF4 MMVF10 MMVF11 MMVF21 MMVF22	Not reported	Not reported	Tested at equal fiber numbers: 6.166×10^5 or 9.249×10^5 or 1.2332×10^6	RCF1, RCF2, RCF3, and RCF4 had a minimal free radical effect compared with asbestos fibers. RCF DNA damage was mediated by hydroxyl radicals but was not associated with iron content.

See footnote at end of table.

(Continued)

Table C–3 (Continued). In vitro genotoxic effects of RCFs*

Reference	Test system and endpoints	Fiber type	Length (µm)	Diameter (µm)	Dose	Results
Gilmour et al. [1997]	Plasmid oX174RF1 DNA Depletion of supercoiled DNA Rat alveolar macrophages Activation of transcription factors	Amosite asbestos MMVF10 RCF1	Not reported	Not reported	Equal fiber numbers per assay. DNA assay: 9.3×10^5 Iron assay: 8.24×10^7/ml	RCF1 and MMVF10 induced significantly less DNA free radical damage than amosite asbestos. Amosite significantly upregulated transcription factors AP–1 and NFkB; RCF1 had a much smaller effect on AP–1 only.
Hart et al. [1992]	Chinese hamster ovary cells Micronuclei induction Polynuclei induction	RCF1 RCF2 RCF3 RCF4 UICC Crocidolite UICC Chrysotile	Mean: 21.5 ± 16.12 16.7 ± 15.03 24.3 ± 18.82 9.2 ± 7.08 1.8 ± 1.94 1.65 ± 1.83	Mean: 1.03 ± 0.73 1.11 ± 0.82 1.22 ± 0.98 1.43 ± 0.79 0.21 ± 0.12 0.12 ± 0.07	RCFs 1–4: 0, 5, 10, or 20 µg/ml Crocidolite: 0 or 5 µg/ml Chrysotile: 0, 1, 2, or 5 µg/ml	Nuclear abnormality incidence: At 20 µg/cm², RCF was 20% to 33%. At 5 µg/cm², crocidolite was 28%. At 5 µg/cm², chrysotile was 49%.
Janssen et al. [1994]	Hamster tracheal epithelial (HTE) cells mRNA concentrations of c-fos, c-jun, and ODC RPM cells mRNA concentrations of c-fos, c-jun, and ODC	Crocidolite Chrysotile MMVF10 RCF1 Polystyrene beads Riebeckite Erionite	Mean: 11.4 1.1 19.8 24.0 — — 6.0	Mean: 0.27 0.08 1.36 1.07 1.05 0.8 0.8	Asbestos: ≤5 µg/cm² All other fibers: 1.25–25 µg/cm²	HTE cells: Crocidolite induced significant dose-dependent concentrations of c-jun and ODC mRNA. RCF1 induced small non-dose-dependent increases in ODC mRNA concentrations only. RPM cells: Crocidolite at 2.5 µg/cm² induced elevated c-fos and c-jun mRNA concentrations. RCF1 at 25 µg/cm² increased c-fos and c-jun mRNA concentrations.

See footnote at end of table.

(Continued)

Table C–3 (Continued). In vitro genotoxic effects of RCFs*

Reference	Test system and endpoints	Fiber type	Length (μm)	Diameter (μm)	Dose	Results
Leanderson et al. [1989]	Calf thymus DNA Hydroxylation of 2-dG to 8–OH–dG dG solution Hydroxylation of dG to 8–OH–dG	European source: Fiber 1 = ceramic Fiber 2 = glass wool Fiber 3 = ceramic Fiber 4 = rock wool Fiber 5 = rock wool Fiber 6 = rock wool Fiber 7 = rock wool Fiber 8 = rock wool Fiber 9 = rock wool Fiber 10 = rock wool Fiber 11 = rock wool Fiber 12 = slag wool Fiber 13 = rock wool Fiber 14 = rock wool Fiber 15 = slag wool Fiber 16 = rock wool	Surface area (m^2/g): 0.95 0.91 1.10 1.30 0.36 0.60 0.73 1.01 1.28 1.16 1.18 1.14 1.30 1.06 0.90 0.62	Not reported	10 mg fiber and 1.0 ml PBS with 0.5 mg DNA or 0.5 mM dG	All fibers caused significant hydroxylation of dG. Glass wool and ceramic fibers had poor hydroxylating capacity relative to rock wools and slag wools.
Leanderson et al. [1989]	Calf thymus DNA Hydroxylation of dG to 8–OH–dG	European source: Rock wool Glass wool Ceramic	Not reported	Not reported	10 mg fiber and/or 300 μl smoke-PBS or 100 μM H_2O_2 in 1.0 ml PBS with 0.5 mg DNA	Ceramic and glass wool fibers caused less DNA hydroxylation than rock wool. Rock wool and cigarette smoke condensate had a synergistic effect on hydroxylation. Ceramic or glass wool fibers and cigarette smoke condensate did not have a synergistic effect on hydroxylation.
Okayasu et al. [1999]	Human-hamster hybrid A_L cells Mutation assay	UICC chrysotile Tremolite Erionite RCF1	Geometric mean: 1.78 ± 2.3 1.41 ± 2.7 1.31 ± 2.9 13.5 ± 2.7	Geometric mean: 0.12 ± 0.08 0.13 ± 3.43 0.23 ± 2.74 0.95 ± 2.6	0–80 μg/cm^2	RCF1 was determined to be nonmutagenic. Chrysotile was the most mutagenic of fibers examined based on fiber concentration.

See footnote at end of table.

(Continued)

Table C–3 (Continued). In vitro genotoxic effects of RCFs*

Reference	Test system and endpoints	Fiber type	Length (μm)	Diameter (μm)	Dose	Results
Yegles et al. [1995]	Rat pleural mesothelial cells Anaphase/telophase aberrations	RCF1	19.2 ± 15.0	1.30 ± 0.80	12.5, 25, 50, 75, or 100 μg/cm^2	UICC chrysotile was the most genotoxic on the basis of weight, number of fibers >4 μm long, and number of fibers corresponding to Stanton's and Pott's criteria. Ceramic and glass fibers did not induce anaphase aberrations.
		RCF3	31.8 ± 36.0	0.74 ± 0.50		
		RCF4	8.9 ± 7.2	1.30 ± 0.60		
		MMVF10	21.5 ± 16.8	0.55 ± 0.50		
		MMVF11	16.7 ± 12.9	1.10 ± 0.90		
		UICC chrysotile	1.7 ± 2.2	0.05 ± 0.04		
		Chrys 445 (Canadian)	2.3 ± 2.3	0.04 ± 0.03		
		Chrys 443 (Canadian)	1.9 ± 1.9	0.04 ± 0.04		
		Chrys, short Canadian	1.6 ± 1.4	0.06 ± 0.08		
		Chrys, superfine Canadian	2.4 ± 3.1	0.04 ± 0.03		
		Chrys, phosphorylated Canadian	4.7 ± 5.2	0.04 ± 0.03		
		Chrys,phosphorylated milled Canadian	4.7 ± 5.9	0.07 ± 0.09		
		UICC chrys, leached with oxalic acid	2.3 ± 1.8	0.17 ± 0.11		
		Chrys, Calidria	2.8 ± 3.0	0.05 ± 0.04		
		Chrys, NIEHS	4.2 ± 1.2	0.05 ± 0.05		
		Amosite	2.4 ± 1.8	0.31 ± 0.20		
		Crocidolite	2.1 ± 3.6	0.19 ± 0.12		
		Attapulgite	0.8 ± 0.5	0.04 ± 0.03		

*Abbreviations: dG=deoxyguanosine; f=fibers; HTE=hamster tracheal epithelial; OH–dG=hydroxydeoxy-guanosine; mRNA=messenger RNA; MMVF=man-made vitreous fiber; NIEHS=National Institute for Environmental Health Sciences; ODC=ornithine decarboxylase; PBS=phosphate-buffered saline; RCFs=refractory ceramic fibers; RPM=rat pleural mesothelial; UICC=Union Internationale Contre le Cancer.

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