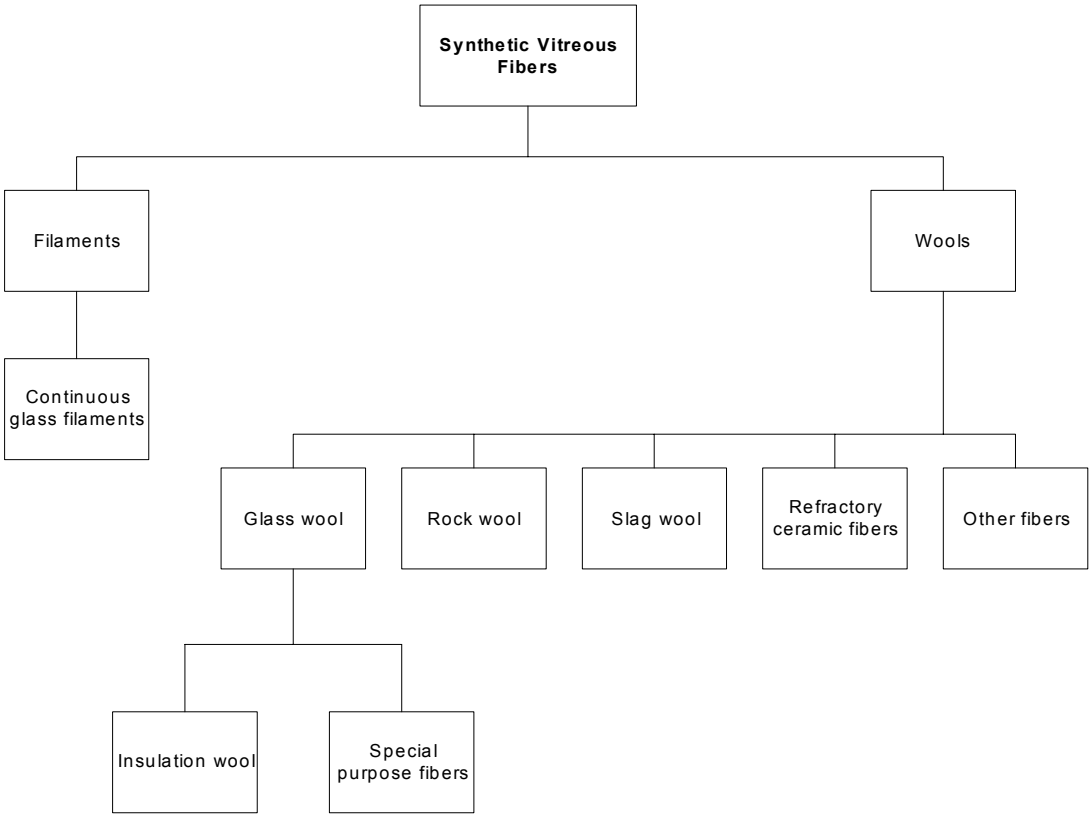
2. RELEVANCE TO PUBLIC HEALTH

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

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

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

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



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

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

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

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

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

2.2 SUMMARY OF HEALTH EFFECTS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Exposure level (total fibers/cc)	Fiber concentrations in lungs at 24 months (mean total fibers per mg lung x10^4)	Lung weight (Percent of control)	Mean score±standard deviation (0–5 Scale)		
			Macrophage aggregation	Bronchio-lization	Collagen deposition at the broncho-alveolar junction
0 (n=12)	NR	100.0±14.0	0±0	0±0	0±0
36 (n=6)	5.55±1.71	116.8±12.3	2.0±0	1.2±0.4	0.7±0.82
91 (n=6)	18.80±3.59	110.9±8.1	2.5±0.6	1.8±0.4	2±0
162 (n=6)	27.80±6.06	131.8±15.3	3.0±0	2.7±0.5	2.8±0.4
234 (n=6)	37.00±8.01	164.7±44.2	3.2±0.4	2.7±0.5	2.2±0.4

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

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

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

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

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

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

Oral MRLs

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

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