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Potential Pulmonary Effects of Man-Made Organic Fiber (MMOF) Dusts

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ABSTRACT: In the first half of the twentieth century epidemiologic evidence linked elevated incidences of pulmonary fibrosis and cancer with inhalation of chrysotile and crocidolite asbestos, a family of naturally occurring inorganic fibrous materials. As the serpentine and amphibole forms of asbestos were phased out, synthetic vitreous fibers (SVFs; fiber glass, mineral wool, and refractory fiber) became increasingly utilized, and concerns were raised that they too might cause adverse health effects. Extensive toxicological research on SVFs has demonstrated that their pulmonary effects are directly related to fiber dose in the lung over time. This is the result of deposition (thin fibers deposit in the lower lung more efficiently than thick fibers) and lung-persistence ("biopersistence" is directly related to fiber length and inversely related to dissolution and fragmentation rates). In rat inhalation studies, asbestos was determined to be 7- to 10-fold more biopersistent in the lung than SVFs. Other than its effect on biopersistence, fiber composition did not appear to play a direct role in the biological activity of SVFs. Recently, the utilization of man-made organic fibers (MMOFs) (also referred to by some as synthetic organic fibers) has increased rapidly for a variety of applications. In contrast to SVFs, research on the potential pulmonary effects of MMOFs is relatively limited, because traditionally MMOFs were manufactured in diameters too thick to be respirable (inhalable into the lower lung). However, new developments in the MMOF industry have resulted in the production of increasingly fine-diameter fibers for special applications, and certain post-manufacturing processes (e.g., chopping) generate respirable-sized MMOF dust. Until the mid-1990s, there was no consistent evidence of human health affects attributed to occupational exposure to MMOFs. Very recently, however, a unique form of interstitial lung disease has been reported in nylon flock workers in three different plants, and respirable-sized nylon shreds (including fibers) were identified in workplace air samples. Whether nylon dust or other occupational exposures are responsible for the development of lung disease in these workers remains to be determined. It is also unknown whether the biological mechanisms that determine the respirability and toxicity of SVFs apply to MMOFs. Thus, it is appropriate and timely to review the current data regarding MMOF workplace exposure and pulmonary health effects, including the database on epidemiological, exposure assessment, and toxicology studies.

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I. INTRODUCTION

Man-made organic fibers (MMOFs) have been produced for over 50 years. Although some chemicals used in the production of these fiber types have been investigated for adverse health effects in occupationally exposed people (ECETOC, 1996), there is a limited toxicological database regarding the pulmonary effects of inhaled MMOF dust. This stems, in large part, from two perceptions: (1) occupational exposures to airborne MMOFs are generally very low (see "Human Exposures" below). (2) MMOF dust in the workplace was assumed to be nonrespirable (i.e., not small enough to deposit in the distal (gas exchange) regions of the lung). Generally, MMOFs are manufactured as continuous filaments and in diameters that exceed the respirable range (i.e., $\geq$ 3 μm diameter). Thus, it was assumed that airborne MMOFs would be too large to penetrate to the distal lung; if inhaled, they would be trapped in the upper airways, wherein clearance is relatively rapid. In recent years, however, the MMOF industry has developed new applications and production methods (i.e., microfibers and flocking material) that have resulted in reduced fiber dimensions. Thus, there has arisen a concern that, in certain occupational settings, people may be exposed to airborne respirable MMOFs. Therefore, it is now timely and necessary to review the existing inhalation toxicology database on MMOFs with regard to occupational exposure, epidemiology, and laboratory experimentation.

The potential for inhaled fibers to cause human health effects was originally recognized nearly a century ago in asbestos-exposed workers. Murray described the first case of asbestosis in 1907 when he reported that a carding machine operator died of diffuse pulmonary fibrosis. Subsequently, Merewether and Price (1924) confirmed the relationship between asbestos exposure and pulmonary fibrosis in British workers. The association between occupational exposure to asbestos and lung cancer or mesothelioma was established during the 1950s, and Gilson (1966) estimated that the average latency interval for the development of lung cancer was 20 years, and 25 to 50 years for mesothelioma. As a result of the asbestos legacy, there seems to be a general impression that all fibrous particulates small enough to reach the distal lung pose a health threat to exposed humans, unless proven otherwise.

As asbestos fibers have been phased out of commercial use in the industrialized nations, synthetic vitreous fibers (SVFs, including fiber glass, mineral wool, slag wool, and refractory ceramic fiber), became increasingly popular as asbestos replacements and for a wide variety of new applications. Concerns were raised that these fibers, when inhaled, might also cause adverse pulmonary effects. After several decades of extensive toxicological research on SVFs, a considerable body of information has emerged (reviewed in Hesterberg and Hart, 2000). A review of these studies indicates that the toxicity of SVFs as well as asbestos is essentially determined by general factors, known as the three "D's": (a) **Dose**: A correlation exists between the number of fibers depositing in the distal regions of the lung over time and the development of adverse health effects. (b) **Dimension**: Thinner fibers are more respirable (i.e., better able to deposit in the gas exchange regions of the lung); longer fibers are more toxic to pulmonary cells and generally more persistent in the lung (fibers longer than about 15 to 20 μm cannot be efficiently cleared from the lung by alveolar macrophages and the mucociliary escalator). (c) **Durability**: The severity of pulmonary effects in animals inhaling inorganic fibers is directly proportional to the biopersistence of the retained fiber in the lung; biopersistence is determined by fiber length (longer = more biopersistent) and chemical durability (resistance to degradation in lung fluids or pulmonary cells). For SVFs and asbestos, the relevance of chemical composition to pulmonary toxicology appears to be limited to its effect on durability in the lung—no evidence has been found that composition of inorganic fibers plays a major role in pulmonary injury.

Twelve different inorganic fiber types (SVFs and asbestos) have been evaluated extensively in a series of rodent inhalation studies conducted during the 1990s, and a correlation between biopersistence and adverse pulmonary effects has been demonstrated (Hesterberg and Hart, 2001). Inhaled fibers that were determined to be the most biopersistent produced the most serious adverse pulmonary effects. The initial pulmonary responses to each of the inhaled inorganic fibrous

dusts were macrophage activation and lung inflammation. In the rats and hamsters exposed to several biosoluble SVFs (which cleared quickly from the lung) these were the only observed effects, and were transient. In contrast, fiber types that demonstrated greater biopersistence produced chronic pulmonary inflammation and interstitial fibrosis (characterized by the accumulation of collagenous scar tissue). For the very biopersistent fiber types, fibrosis was typically followed by lung cancer and/or pleural mesothelioma.

In contrast to the numerous toxicity studies reported for inorganic fiber types (asbestos and SVFs), relatively little research has been conducted on the MMOFs. The paucity of data on occupational exposures and potential effects of MMOFs is due, in large part, to the perception that inhaled MMOFs were not a health hazard because their dimensions were too large to be respirable. Thus, it was assumed that occupational exposures to respirable MMOFs were not of concern. However, as MMOFs are being adapted for an increasing variety of applications, thinner fibers are being produced, and newer processing techniques (such as chopping or flocking) could result in respirable airborne dust.

Because much is known about the determinants of biological activity of SVFs, and relatively little is known about the activity of MMOFs, it is tempting to assume that what has been learned about the former also applies to the latter. However, it is important to recognize that the following questions remain unanswered for MMOFs: Do the three D's apply to MMOFs? Are other factors that are not relevant to SVF toxicology important in determining the biological activity of MMOFs—such as surface area, chemical composition, surface activity, and adsorbed finishes, dyes, and other additives? Are the pulmonary responses to MMOFs similar to inorganic fiber types (i.e., release of intracellular messengers and cytotoxic factors after cell contact with fibers, macrophage responses, and lung inflammation; in some cases fibrosis and cancer)? Are the cellular and molecular responses to MMOFs qualitatively different from those of SVFs? Finally, are the definitions of fiber respirability and the air-sampling methods that were derived from the study of asbestos and SVFs relevant for MMOFs? Respirability of fibers is primarily determined by aerodynamic diameter, which is in turn determined by size, shape, and density. MMOFs are less dense and tend to be more curly than SVFs. Furthermore, MMOFs tend to have charged surfaces. This creates challenges for air sample collection, as the charged fibers tend to adhere to the sides of air sample collection devices.

The purpose of this article is to provide a review of the current literature regarding (1) exposure to airborne dust in man-made organic fiber manufacturing and processing workplaces, and (2) the potential of this exposure to cause adverse respiratory health effects. The present review provides an update to an earlier, comprehensive review of the literature (ECETOC, 1996) and is limited to the pulmonary health effects associated with the inhalation of MMOF-associated particulates. The focus here is on fibrous dusts; however, studies involving nonfibrous man-made organic particulates, natural organic fiber-types such as cellulose, or related fibers (e.g., composed of semisynthetics or carbon) are discussed if they are determined to be relevant to MMOF toxicology. Information on human exposures is dealt with first in recognition of the fact that exposure assessment is the first step in a tiered approach to risk assessment. Other tiers include epidemiology and laboratory experimentation; the latter includes animal studies, *in vitro* cellular effects, and *in vitro* degradation studies in simulated lung fluid. Several animal models have been used to study the biological effects of dusts—exposure by various routes of artificial implantation as well as exposure by inhalation. However, the most relevant animal model for dust inhalation toxicology is the inhalation model; thus, studies employing this model are given greater emphasis in this review.

II. MAN-MADE ORGANIC FIBER TYPES

Polymeric MMOFs are synthesized from organic polymers that are manufactured from petroleum-derived chemicals. Some common examples are polyamides (nylon, aramid), polyester, polyolefins (polyethylene, polypropylene), and polyvinyls (Table 1). The petroleum-based polymeric MMOFs have been used to make textiles for bedding, carpets, clothing, curtains, draperies,

TABLE 1
Examples of Semisynthetic and Man-Made Organic Fibers

Semi-Synthetic Fibers

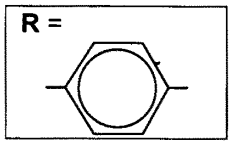
(Derived from Natural Plant Fiber, Cellulose)

Regenerated cellulose derivatives
- Viscose rayon
- Cuprocellulose
- Cellulose acetate
- Cellulose triacetate

Solubilized cellulose derivative
- Lyocel

Man-Made Polymeric Fibers

Polymer	Monomer
Polyamides	
Aliphatic (nylon)	-NH-CO-$(CH_2)_4$-CO-NH-$(CH_2)_5$-
Aromatic (aramid, meta- & para)	-NH-**R**-NH-CO-**R**-CO-
Polyester	
Polyethyleneterephthalate	-O-CO-**R**-CO-O$(CH_2)_n$-
Polyolefins	
Polyethylene	-CH_2-CH_2-
Polypropylene	-$CH(CH_3)$-CH_2-
Polyvinyls	
Polyacrylonitrile (orlon)	-CH(CN)-CH_2-
Polyvinylchloride	-CH(Cl)-CH_2-
Polyurethane (Elastane)	HO**R**-OCO-NH-**R**-NH-COO-



Carbonized Fibers

Carbon fibers: Organic fibers pyrolyzed to ~1500°C; mostly amorphous carbon composition.
- PAN-based. Derived from polyacrylonitrile fibers. Generally too thick to be human-respirable. Most common carbon fiber.
- Regenerated cellulose-based. From rayon.
- Pitch-based. Derived from pitch (coal tar or petroleum). Smaller diameters than PAN-based; more likely to be human-respirable.

Graphite fibers: carbon fibers subjected to further heat-treatment; crystalline carbon composition.

and upholstery. The uses of MMOF microfibers in various products are expanding. The sports clothing industry has greatly increased the use of fine-diameter (1 to 5 μm) polypropylene for moisture-resistant, insulating clothing and bedding (ILO, 1990). Para-aramid fibers are used for tire cords, protective clothing, industrial fabrics, ropes and cables, and friction materials (brake pads).

Also included in Table 1 are two close relatives of the MMOFs—semisynthetic and carbonized fibers, which are discussed briefly in the present review. Semisynthetic organic fibers are derived from cellulose, a natural plant fiber; examples are fibers made from regenerated cellulose (e.g., viscose rayon and cellulose acetate) or solubilized cellulose (lyocell). Carbonized fibers are derived from either semisynthetic or man-made organic fibers by subjecting them to high temperatures that drive off the noncarbon components. Carbonized fibers are used as reinforcements in structural composites and as insulation in applications that require high-temperature resistance combined with light weight. Carbonized fibers include carbon (amorphous) and graphite (crystalline; made by further heating amorphous carbon fibers). Carbon fibers are further subdivided into PAN based (derived from polyacrylonitrile fiber), pitch based (derived from coal tar or petroleum), or rayon based. PAN-based carbon fibers are generally too thick to be human respirable, while pitch-based carbon fibers are made in smaller diameters that are more likely to be respirable. The former are used for reinforcements while the latter are used for ultralight insulation (e.g., in airplanes).

Generally, MMOFs have been manufactured as continuous filaments and in relatively large diameters (>10 μm), and thus have been considered to be nonrespirable (unable to be inhaled into the human lower lung) (ECETOC, 1996). However, during certain manufacturing processes, especially those involving chopping or grinding, aerosols of respirable MMOFs can be formed (Burkhart et al., 1999). Fibers made from para-aramid can have respirable fibrils attached to the fiber surface, which can be shed during processing (Warheit et al., 1992). Additionally, within the last decade several new MMOFs have been developed for increased strength and chemical resistance and are manufactured in fine-diameter microfibers for use in insulation, filtration, and oil-absorbent applications. MMOFs that have dimensions in the respirable range (respirability as defined by the World Health Organization, WHO, 1985 for asbestos: length > 5 μm, diameter < 3 μm, and length/diameter > 3) have been defined as "respirable-sized, fiber-shaped particulates" or RFPs (ECETOC, 1996). This terminology will henceforth be used to describe organic fiber types whose dimensions fall in the respirable size range.

III. HUMAN EXPOSURES

A. Occupational Exposure Limits for MMOFs

There are no occupational exposure standards in the U.S. specifically for MMOFs. The only U.S. standard that is applicable to MMOFs is the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for "particulates not otherwise regulated," which is 15 mg/m^3 for total dust and 5 mg/m^3 for respirable dust, calculated as an 8-h time-weighted average (TWA). Until recently, this OSHA PEL was also the only U.S. exposure standard that applied to SVFs. In May 1999, a voluntary PEL 8-h TWA of 1 respirable fiber/ml for fiber glass and mineral wools was adopted by OSHA and the U.S. insulation industries as part of the voluntary Health and Safety Partnership Program, HSPP. The OSHA PEL for asbestos is 0.1 respirable fiber/ml (8-h TWA).

The corresponding Threshold Limit Values (TLVs) of the American Conference of Governmental Industrial Hygienists (ACGIH) are 10 mg/m^3 total dust and 3 mg/m^3 respirable dust for "particulates not otherwise classified" (including MMOFs), 1.0 respirable fiber/ml for fiber glass, 5 mg/m^3 for inhalable dust of continuous filament fiber glass, and 0.1 fiber/ml for asbestos (ACGIH, 1999). The World Health Organization has defined respirability for asbestos or SVF as fibers having a diameter ≤3 μm, length ≥5 μm, and length/width ratio ≥3 (referred to as "WHO" fibers; WHO, 1985).

B. Methods for Analyzing Airborne MMOFs

Methods for collecting and analyzing airborne dust composed of SVFs or asbestos have been

established and validated, and procedures for accrediting laboratories in analyzing these samples also have been established (NIOSH, 1987; WHO, 1985). In contrast, methods for collecting and analyzing MMOF dusts have not been standardized by national or international regulatory bodies. Methods for MMOFs generally have been based on those established for asbestos and other inorganic fibers. The WHO criteria for defining respirable inorganic fibers have also been used to define respirable MMOFs. However, respirability could be quite different for the two classes of fibers. Respirability is based on aerodynamic behavior, which, in turn, is affected not only by dimensions but also by density and shape (Stoeber, 1972), and MMOFs are generally less dense and have greater irregularity in shape than inorganic fibers (Hart et al., 2000a and b).

Prior to the late 1980s, measurements of MMOF occupational dust consisted of gravimetric determinations of total dust or "respirable" dust (i.e., "respirable" dust particles are those particles that deposit in the alveolar regions of the lung). In a search for a more accurate evaluation of the respirability of para-aramid fibrils, Merriman (1989) counted respirable para-aramid fibrils by adapting NIOSH Analytical Method 7400 (NIOSH, 1987) for counting asbestos fibers by phase contrast optical microscopy (PCOM). In 1990, Verwijst reported on a similar adaptation of European asbestos counting methods. Bahners et al. (1994) reported the first field trials of German research efforts to measure respirable MMOFs. They collected samples of several different types of fibers at fiber processing operations using a Gravikon VC25 dust collector and evaluated the fibers using VDI Guideline 3492 for asbestos. Light microscopy techniques were used to evaluate most samples although a few samples were examined using scanning electron microscopy (SEM). Results were reported as total particle counts (length >0.8 μm) and in counts of "critical particles", that is, those with a length to width ratio ≥3:1 that could be considered "fibers".

Cherrie et al. (1995) developed methods for measuring fiber exposure in the para-aramid industry in the UK. They used PCOM to determine the numbers of WHO fibers in occupational air samples. Because para-aramid, SVFs, and asbestos may all be used in reinforcement applications within the same facility, and PCOM techniques cannot distinguish between different fiber compositions, they used scanning electron microscopy in concert with energy-dispersive X-ray analysis (SEM/EDX) to classify fibers as organic (including para-aramid), chrysotile asbestos, or nonasbestos mineral fibers (including SVFs). They also investigated fluorescent microscopy techniques for identifying fiber composition. In order to overcome the sample collection problems created by MMOF electrostatic charge, Cherrie et al. treated their air filters to remove electrostatic charge activity, used conductive filter holders, and measured fiber deposition on the filter holder cowl (cowl deposition averaged 3% of sample).

More recently, Hengstberger et al. (1998a, 1998b) investigated methods for collecting airborne MMOF dust and issued the following recommendations: (1) to minimize static electricity problems, samples should be collected using grounded metal cassettes; (2) air samples should be collected using an airflow rate that does not cause static buildup (an airflow rate of 2.5 L/min for a 25-mm-diameter filter was optimal); and because of the substantial physical differences between inorganic and organic fibers, (3) microscopists should be specifically trained in methods for counting MMOFs.

Hengstberger et al. (1998a, 1998b) have also done extensive work on developing a variety of microscopy methods for measuring, counting, and identifying the types of particulates in synthetic organic dust and have provided the following information. Fluorescence microscopy is useful for counting polyvinyl chloride (PVC) fibers, which have relatively high intrinsic fluorescence. Light field/dark field microscopy coupled with a highly sensitive video analysis system can be used to measure particles that are only lightly fluorescent such as polyacrylonitrile (Hengstberger et al., 1998a). SEM coupled with energy-dispersive X-ray microanalysis (EDX) can be used to identify different fiber types within one sample. Because the MMOFs are typically quite irregular in shape and diameter, complex video analytical methods are used to measure the length and diameter of particles and to permit optimization of conditions for SEM and EDX analyses. In the latter method, fibers are first counted and measured using SEM and their position within the

sample is stored; conditions are then adjusted for optimal EDX analysis, which is conducted at the previously determined positions.

Hengstberger et al. (1998b) summarized the following problems in identifying the composition of MMOFs in airborne dust samples and provided a number of methods for overcoming them. The limited number of light elements (carbon, oxygen, and nitrogen) used in common synthetic polymers makes it difficult to identify different fiber types within a sample using EDX. The small size of the MMOF respirable fibrous particulates (RFPs; "respirable" according to the WHO criteria for respirability of SVFs) further decreases the precision of the identification compared to what can be achieved with large particles. Furthermore, cellulose-derived RFPs are subject to radiation damage from EDX, which can lead to incorrect identification. Polypropylene fibers can be distinguished by their high carbon content. Nitrogen-containing polymers such as nylon (polyamide) and para-aramid can be separated from those not containing nitrogen such as polyester and cellulose-derived fibers. However, it is not possible to reliably distinguish RFPs within a specific class (e.g., nitrogen containing) with EDX alone. By also using distinctive morphology and/or selective counting with fluorescence microscopy, one may be able to improve on the precision of particle identification. No single, universal analytical process can be used for fiber identification; a suitable strategy must be developed for each analytical task based on the types of fiber sources being evaluated. In addition, one must always be cognizant that some of the fibers being sampled may be from clothing or building sources such as carpet (Hengstberger et al., 1998a, 1998b).

Warheit and colleagues (1999) compared the results of airborne organic fiber measurements using different collection modes and counting techniques. Atmospheres of p-aramid or cellulose RFP were generated in an inhalation chamber. For each experiment, 30 filters (10 gold-coated polycarbonate filters, 10 methyl cellulose filters, and 10 methyl cellulose filters and corresponding cowls) were exposed to fibrous aerosols at concentrations ranging from 25 to 50 f/cc. Subsequently, attempts were made to quantify and compare fiber counts on each of the filters by three optical techniques, including light microscopy (LM) (PCOM-NIOSH 7400), scanning electron microscopy (SEM), and transmission electron microscopy (TEM-NIOSH 7402 method). It was immediately determined that the gold-coated polycarbonate filters were not appropriate for counting by LM and TEM. Moreover, the data indicated that washing the cowl onto the same filter did not contribute greater numbers of fiber counts and seemed to produce a greater amount of fiber clumping. When comparisons were made between LM, SEM, and TEM counts on the same filters, the fiber numbers were not significantly different when evaluated via the different analytical techniques. The investigators concluded that their findings were in contrast to the data of other investigators who have reported a 2 to 5 $\times$ increase in the numbers of organic fibers when counted by SEM vs. PCOM (Hengstberger, unpublished results).

Additional methodological studies (Warheit et al., 2000a) were conducted in an attempt to develop standardized methods for quantifying workplace exposure to respirable organic fibers. The first study evaluated the influence of electrostatic potential of respirable-sized organic fibers on the fiber counts of aerosolized RFP samples. It was hypothesized that counts derived from highly electrostatic RFP such as p-Aramid would result in an underestimate of the actual respirable fiber count, while less electrostatic RFP, such as cellulose, would not affect the fiber count. Thus, studies were conducted to compare the RFP counts from the filters directly exposed to p-Aramid or cellulose RFP with other filters directly exposed and supplemented with any RFP that may have deposited on the supporting cowl. The data demonstrated no significant differences between the two sets of samples for either the highly electrostatic p-Aramid RFP or the low electrostatic cellulose RFP samples.

The specific aim of the second study was to compare the results of aerosolized organic RFP counts from three different laboratories and from four different individual counters, using phase contrast optical microscopy (PCOM) methods. Atmospheres of p-Aramid RFP were generated in an inhalation chamber. Fifteen methylcellulose filters were exposed to a p-Aramid aerosol for 5 min at estimated concentrations of 20 to 30 f/cc. Subsequently, filters were prepared for counting

by standard techniques. The prepared slides containing a portion of the fiber-exposed filters were first counted at DuPont Haskell Lab., and then the same slides were sent to the Denkendorf Institute and finally to the IOM. For quantification of fibers, the NIOSH 7400 method was used at DuPont Haskell Lab., while a WHO/EURO MMF fiber counting method was utilized in the European laboratories.

The results demonstrated that one laboratory had consistently lower counts when compared with a second (mean values for the 15 filters = 18.4 $\pm$ 4.3 f/cc vs. 27.7 $\pm$ 4.3 f/cc). The third laboratory, with two different counters, was frequently intermediate between the counts of Laboratory A and B (24.2 $\pm$ 1.1 f/cc and 22.1 $\pm$ 2.2 f/cc). The differences in fiber counts could be accounted for by (1) variability among counters (i.e., mean values of counts), or (2) to the slight differences in counting rules between the U.S. and European methods.

C. Background Exposures

Schneider et al. (1996) measured background exposure to "respirable" (diameter <3 μm) organic fibers in four groups of people (suburban schoolchildren, rural retired people, office workers, and taxi drivers); each group was selected from a limited geographical area. The researchers collected one 24-h personal sample during each of the four seasons for each of 20 people (five persons per group). One outdoor air sample was also collected in summer and winter from each geographical area. Personal samples were collected on a gold-coated Nucleopore filter in a conductive filter holder fitted with an extension cowl using an airflow of 1 L/min and analyzed using SEM. "Organic fibers" were defined as those with no sodium; no distinction was made between the different compositions of organic fibers or whether they were natural or synthetic. "Other inorganic fibers" were those fibers that did not meet the definition of asbestos, calcium sulfate, or "organic." Very few asbestos fibers were found. Organic fibers were approximately twice as common as "other inorganic" fibers with calcium silicates being the least prevalent. Organic fiber exposures were low, and there was not much variation between groups, individuals, or geographic locations. Person group geometric mean values for organic fibers with diameters <3 μm were 0.003 to 0.011 fibers/ml (f/ml) with lengths <5 μm, 0.009 to 0.019 f/ml with lengths >5 μm, and 0.0008 to 0.002 f/ml with lengths >20 μm. The numbers of organic fibers in the outdoor samples were much lower than in personal samples from the same geographic areas.

D. Consumer Exposures

Fiber shedding from commercial air filters was evaluated in laboratory simulations in which air was forced through various filtration media (Shumate and Wilhelm, 1990). Both man-made organic (polyester/polycarbonate) and synthetic vitreous (fiber glass) filter media were tested. The minimum level of detection using electron microscopy analysis of air samples was 0.0003 fiber/ml. The numbers of fibers/ml in down stream air from the two types of filter media were negligible compared to the number of fibers and particulates present in ambient outdoor air, and were not significantly different from each other. Fibers/ml averaged 0.0007 in the fiber glass-filtered air and 0.0003 in the organic fiber-filtered air. Some of the fibers in each air stream were determined to be in the respirable range. In each case, the chemical composition and dimensions of the downstream fibers suggested that they came from their respective filter types.

E. Occupational Exposures

1. Carbon Fiber

Exposure to carbon fibers was summarized in the WHO Environmental Health Criteria (No. 151) for Selected Synthetic Organic Fibers (1993). Jones et al. (1982) evaluated airborne dust in a pitch-based continuous filament carbon fiber production facility; mean concentrations were 0.08 to 0.39 mg/m^3 total dust, with 40% respirable dust. Concentrations were highest during cutting, grinding, and milling of carbon fiber-reinforced resins (0.39 mg/m^3). Gilliam (1986) reported gravimetric analyses of breathing zone samples from a

PAN-based carbon fiber production facility as 0.10 to 0.80 mg/m^3. Concentrations were much higher for chopping and winding operators (0.54 to 0.80 mg/m^3) than for line operators (0.10 to 0.12 mg/m^3). Henry et al (1982) analyzed airborne dust during preparation and machining of carbon fiber composites at a PAN-based production facility and reported 0.01 to 0.0002 f/ml (mean diameters >6 μm and mean lengths >30 μm). Lurker and Speer (1984) reported a mean concentration of 0.03 f/ml (PCOM and SEM analyses) for samples taken during the machining of carbon fiber composites at the Air Force Aerospace Materials Research Laboratories; however, fibers (aspect ratio >3) constituted <0.1% of the material released. Gieske et al. (1984) reported concentrations of 0.001 to 0.05 f/ml (mean diameters >5.5 μm and mean lengths >900 μm) during various phases of carbon fiber production. Familia (1986) reported PCOM analyses of "all areas of a pitch-based carbon fiber production facility in the USA where exposure was deemed likely". Counts were <0.1 f/ml in three facilities and a maximum of 0.27 f/ml in the fourth. Some dimension data suggested that fibers tended to be nonrespirable—diameters were 3.9 to 7.8 μm and lengths were 32.8 to 2342 μm.

2. Cellulose Acetate

Hengstberger et al. (1995) studied the levels of airborne fibrous dust in a plant that uses cellulose acetate tow to produce filter rods (which are subsequently used to produce filter cigarettes). Samples were collected on gold-coated polycarbonate filters in a metallic cassette and analyzed by SEM/EDX. The average concentration of airborne fibers meeting WHO criteria for respirable fibers was 0.04 f/ml in the filter rod production area and 0.02 f/ml in the cigarette production area. Most fibers were <10 μm in length. Fibers from the rod production area were mainly organic in nature, although about 20% were inorganic (gypsum, glass, etc.). The average concentration of airborne "other" fibers (i.e., not meeting WHO criteria) was 0.13 fibers/ml in the filter rod and 0.18 fibers/ml in the cigarette production areas.

Concentrations of cellulose RFPs, up to 57.3 $\times$ 10^6 f/m3 (0.05 f/cc) were measured in the processing of shredded paper insulation material. The number of fibers with diameters of $\leq$ 1 μm were 0.01 f/cc. It is noted that the material is physically different from the cellulosic fibers processed in the textile industry (Tiesler, 1992).

3. Nylon (Polyamide) Fiber

Bahners et al. (1994) evaluated fiber exposure for operators of ring spinning machines processing polyamide and a 80/20 blend of polyvinyl chloride (PVC) and polyamide (using PCOM). The total particle counts were 0.5 and 0.8 particles/ml, respectively, while critical particles (aspect ratio ≥3) were 0.060 and 0.020/ml. Evaluation of a double twist twisting machine processing polyamide gave a total particle count of 0.4 particles/ml, while critical particles were 0.003/ml.

4. Nylon Flock

An evaluation of airborne dust in a flock manufacturing plant was conducted by NIOSH (NIOSH, 1998; Washko et al., 1998; Burkhart et al., 1999) while attempting to discover the cause of an elevated incidence of interstitial lung disease among workers. Workplace air samples were collected using filter cassettes in series with nylon or stainless steel respirable dust cyclones, vertical elutriators, or direct-reading aerosol photometers with respirable dust cyclones. Cascade impactors were also used to collect and separate airborne particles by aerodynamic size. Total dust samples were measured with closed-face filter cassettes and direct-reading monitors. Polarizing light, PCOM, and SEM were used to examine particle morphology and size, and to estimate airborne concentrations.

In most of the general area air samples (87%), the gravimetric concentration of respirable dust was <1 mg/m^3. Overall concentrations of airborne respirable particulates ranged from 0.5 to 39.9 mg/m^3, with an average of 2.2 mg/m^3. The highest values were in the flocking area, with mean respirable dust of 7 mg/m^3. In the two work areas with the highest measurements, clogging of sample inlets with loose flock was noted, which may have limited the measurement of true airborne

concentrations. Five 30- to 90-min personal respirable dust samples collected during "blow-down" of flock equipment ranged from <1 to 76 mg/m^3 (with inlet clogging noted on all samples). Of four 2- to 3-h vertical elutriator samples from the flocking rooms, three were nearly 1 mg/m^3 and one (taken during "blow-down") was 8 mg/m^3. Real-time dust measurements identified short-term peak exposures; very high peaks were noted during "blow-down" operations.

Examination of the dust samples using polarized light microscopy revealed respirable birefringent particles that differed in size and shape from the much larger nylon flock fibers but were otherwise similar in terms of color and surface appearance. SEM examination of the ends of nylon flock fibers generally showed a clean cut, but some ends showed evidence of what appeared to be shredding of nylon fibers in the respirable size range. Impactor sampling showed "shreds" of nylon fibers in the stages corresponding to aerodynamic diameters of 4 to 8 μm. These smaller particles melted at 250 to 260°C, consistent with the melting point of nylon. Electron microscopy was used to measure the dimensions of the "shreds" that had a fibrous shape (length/width ratio greater than 3:1). Average width × length measurements of 400 randomly selected fibers (i.e., fibrous shreds) were 0.89×5.6 μm for a cutting/milling area sample and 0.75×3.5 μm for a flock room sample. Airborne concentrations of the small fibers were estimated to be 40 f/ml in the cutting/milling area and 90 f/ml in the flock room. It was noted that not all of these smaller particles were of nylon origin; some were identified as desiccant powder and potato starch agents, which are also used in the flocking process. (Note: see Section V.A for the results of short-term instillation studies in rats with nylon flocking material.)

5. Para-aramid

Merriman (1989) summarized data on evaluations of Kevlar® aramid fiber dust in numerous industrial operations, including cutting, staple yarn spinning, filament yarn twisting, roving, winding, weaving, friction material mixing and grinding, and gasket sheet making and cutting using NIOSH Analytical Method 7400 (NIOSH, 1987). The maximum 8-h. TWA reported by Merriman was 0.28 fibrils/ml (f/ml). Exposure concentrations were <0.2 f/ml during machining of composites in which Kevlar® fiber was a major portion of the material being cut. Exposure concentrations were <0.1 f/ml during continuous filament handling.

Verwijst (1990) measured a broad spectrum of para-aramid industrial exposures using PCOM. The mean values of WHO fiber concentrations from personal air sampling in a number of typical textile operations (fluff machine, papermaking machine, stufferbox/cutter, shortcut, winding machine, steam-drawing frame) and in textile laboratories were all <0.1 f/ml. Measurements were also made of epoxy composite tooling operations: drilling, grinding, milling, and sawing. For most of these, fibers were found to be embedded in the epoxy resin with only a few loose fibers being detected (no data provided). Personal air samples at a water-jet cutting machine gave values of 0.10 f/ml when using a movable nozzle and 0.94 f/ml when using a fixed nozzle. In the latter operation, the operator had to work close to the cutting nozzle and the water was partially recirculated so that it was "teeming with respirable fibers." (Corrective action was taken to stop water recirculation and better control water spray emissions.)

In 1992, Merriman reported in more detail on measurements (using PCOM) of a broad range of para-aramid fiber end-use operations. Brake pad manufacturing operations, which involve mixing para-aramid pulp with powdered fillers and resin followed by curing, grinding, and drilling, averaged <0.10 f/ml with the highest value being 0.19 f/ml. In gasket manufacturing, para-aramid pulp is mixed with fillers and rubber cement, rolled into sheets, and die-cut into smaller pieces that may be sanded. Mean personal exposures from all operations were <0.1 f/ml; the maximum personal sample was 0.15 f/ml and the maximum area sample was 0.25 f/ml. Machining of para-aramid-reinforced composites averaged <0.1 f/ml although one exposure (grinding) reached 0.25 f/ml. Processing of staple fibers was found to produce the highest fiber concentrations, which averaged 0.18 to 0.55 f/ml; most peak values were <1.0 f/ml, but one operation reached 2.03 f/ml.

In their first field trials, Bahners et al. (1994) performed measurements at several para-aramid

operations using PCOM. Two different lots of para-aramid being processed on a ring spinning machine gave somewhat divergent measurements. Total particle counts were 1.0 and 3.5 particles/ml with fibers (aspect ratio ≥3) constituting only 7% (0.07 f/ml) and 4% (0.140 f/ml) of the total particle counts, respectively.

Cherrie et al. (1995) conducted a comprehensive cross-sectional survey of para-aramid facilities in the UK. They used PCOM to determine the fiber concentrations in 63 different air samples taken during various operations. TWAs ranged from <0.01 to 0.56 f/ml, with about 10% of measurements exceeding 0.1 f/ml (Table 2). The highest concentrations were measured during staple fiber processing, followed by friction product and gasket manufacture from pulp. Area samples were generally similar to personal samples. Fiber dimensions were measured for two operations at one site using SEM/EDX. Very few para-aramid fibrils had diameters >3 μm. Geometric mean dimensions of the organic fibers were intermediate between asbestos fibers (which were longer and thinner) and SVFs (which were shorter and thicker). The SEM/EDX data suggest that most of the fibers counted by PCOM were para-aramid fibers.

Minty et al. (1995) evaluated 68 air samples from a broad variety of para-aramid end-use operations. They reported that the majority of exposures ranged from 0.01 f/ml to 0.15 f/ml. However, the maximum fiber dust concentration extended beyond this range for two operations: carding and spinning of staple fiber from spun yarns (0.32 f/ml) and blending, carding, drawing, and spinning of staple fiber for spun yarns (2.16 f/ml).

Thus, a relatively broad-spectrum evaluation of the para-aramid industry has been conducted by several groups in both the U.S. and Europe using appropriate analytical techniques. Exposure concentrations for most operations are generally below 0.1 to 0.2 f/ml. Three separate studies demonstrated that processing staple fiber had the highest exposure concentration, which, for the most part, was no greater than 1.0 f/ml. Two studies showed that the water used in water jet cutting of composites can become contaminated with para-aramid fibrils so that appropriate control measures need to be applied.

6. Polyacrylonitrile

Valic and Zuskin (1977) measured dust in two polyacrylonitrile fiber processing mills. They used a Hexhlet two-stage sampler, in which a horizontal elutriator traps the oversize fraction and a "soxhlet" thimble filter collects the "respirable" fraction (Wright, 1954). Total dust concentrations in these mills were 1.04 and 0.42 mg/m^3 with respirable dust concentrations of 0.53 and 0.16 mg/m^3.

In their initial survey, Bahners et al. (1994) evaluated exposures during the processing of a blend of polyacrylonitrile and modified polyacrylonitrile using a ring spinning machine. PCOM measurements gave a total particle count of 0.7 particles/ml, while critical particles (aspect ratio ≥3) were 0.035/ml. SEM analysis of critical particles gave 0.2 particles/ml or approximately six times the concentration of RFPs seen with PCOM. A double twist twisting machine processing polyacrylonitrile had a total particle count of 0.9 particles/ml, while critical particles were 0.018/ml.

7. Polyester and Polyester Blends

Bahners et al. (1994) reported the following polyester exposures: 0.7 total particles/ml and 0.010/ml critical (aspect ratio ≥3) particles during double twist twisting machine processing, and 10 total particles/ml but no critical particles dur-

TABLE 2
Summary of Para-aramid Workplace Exposures in the UK

Application	Sites	Jobs	Conc. >0.1 f/ml	Geometric mean
staple fiber processing	3	6	30%	0.06 f/ml
friction product & gasket manufacture	2	6	12%	0.035 f/ml
Composite manufacture from cloth	2	5	3%	0.02 f/ml
Continuous filament processing	4	8	3%	0.02 f/ml

Derived from data presented by Cherrie, et al (1995)

ing processing of polyester/polyacrylonitrile blend using an air nozzle loom with a single roll mangling machine (sample collected using a Gravikon VC25 sampler and examined by SEM).

Hengstberger et al. (1998a, 1998b) evaluated fiber exposures during ring spinning of a polyester/polyacrylonitrile mixture. WHO fiber counts were 0.15 f/ml (SEM counts) and 0.05 f/ml (PCOM counts). RFPs from this operation were relatively short and thick: by SEM, diameters ranged from 0.9 to 3 μm and lengths from 5 to 20 μm. Approximately 80% were less than 2 μm in diameter and 9 μm in length.

8. Polypropylene

Exposures to dusts and fibers were determined in three polypropylene manufacturing sites. Amounts were well below the voluntary fiber glass PEL of 1 respirable fiber/ml and also at or below the asbestos PEL of 0.1 respirable fiber/ml, with the exception of the "boom room" (Table 3; unpublished data; Johns Manville, Denver, CO). In the "boom room," scrap organic fibers consisting mostly of polypropylene, but some polyester are blown into long cloth tubes, which are then sold as products for containing and absorbing organic spills. Although the 8-h TWAs in these rooms were below 1 fiber/ml, infrequent spikes of >1 respirable fiber/ml were recorded. (Operators in the "boom room" wear respiratory protection.)

9. Textile Mills

In a health study of a textile mill in Isfahan, Iran, Parvizpour and Shadan (1981) reported that weavers were exposed to a mixed dust of cotton and synthetic fibers. The mean total dust concentration of samples collected on glass fiber filters in 28 locations was 2.63 ± 0.61 mg/m^3. The composition of the synthetic fibers used in this mill was not specified.

In a study that focused on exposure to cotton dust and symptoms of byssinosis, Fishwick et al. (1994) reported data from 11 Lancashire spinning mills of which two processed only synthetic organic fiber. Personal samples were collected using static air samplers and analyzed gravimetrically. Dust levels were lowest in the mills processing only "man made fibers" (≤0.37 mg/m^3) and in the "most modern cotton/polyester spinning mill" (≤0.27 mg/m^3). The authors noted that "these results (from personal samplers) are not comparable to the respirable fraction of dust measured in the United States." This study is limited in that the specific types and sizes of the airborne particulates were not determined.

IV. PULMONARY EFFECTS IN HUMANS

There have been at least 52 epidemiology studies that examine pulmonary health effects among workers with potential organic fiber dust exposure. Studies were included in the present

TABLE 3
Exposure Levels at Three Polypropylene Manufacturing Facilities

Location	Year			
		mg/m^3 Dust	Fibers/ml	n for F/ml [b]
1	1990-93	0.1 – 1.4	0.009 – 0.1	11
2	1996	0.2	0.03 – 0.04	2
3	1997	>0.1 – 0.8	0.01 – 0.09	17
		Operation	TWA[c]	n for TWA[b]
3	1999	Boom Rooms	0.069—0.907	12
		Die Houses	0.001—0.015	5

Data from: Johns Manville Industrial Hygiene Group, Denver, CO, internal reports, 1990, 1993, 1997, 1999.
[a] Fibers/ml according to B counting rules (NIOSH, 1987, Appendix C).
[b] number of samples/TWAs counted.
[c] Fibers/ml as time weighted average exposure for 8-Hr workday; A Counting Rules (NIOSH, 1987, Appendix B).

review if they examined nonmalignant pulmonary impairment, or cancers of lung, nasal cavity, and sinuses and the workers had potential exposure to fiber dust, including acrylic, cellulose acetate, cellulose triacetate, nylon, polyester, polyolefin, polypropylene, or exposure to nonspecific textiles. Many of these studies are large with well-defined exposed groups and health outcomes that are well documented. However, most of these studies have some weakness that limit the inferences that can be drawn from them. Most do not specify the level of exposures to fiber dusts, so it is difficult to determine if the workers had significant exposure. Few of these studies examined health outcomes by level of exposure, so again it is difficult or impossible to evaluate health outcome by exposure level. Frequently, other airborne exposures occurred in the workplace that could increase the risk of the diseases studied. The presence of asbestos (increased lung cancer risk), hardwood dust (increased nasal cancer risk), cotton dust (increased impairment of pulmonary function and byssinosis), and exposure to other substances in some textile operations makes it difficult to attribute findings to synthetic fibers. Also, many textile workers worked with several types of textiles in previous or subsequent jobs. There is also an initial selection of healthy workers into the work force and a survival of healthier individuals in the workforce (Arrighi and Hertz-Picciotto, 1994). This makes disease grouping such as nonmalignant respiratory disease difficult to evaluate. Workers in general have low rates of nonmalignant respiratory diseases when compared with the general population because of initial selection at employment, and because long-term workers often have lower rates of nonmalignant respiratory disease when compared with short-term workers because healthy workers remain in the workforce longer (Eisen et al., 1995). There is also the potential for reporting bias in the literature reviewed because positive findings are more likely to be reported and published (Dickersin et al., 1992). Consideration of reporting bias may be especially important for evaluating rare cancers, such as those of nasal cavity and sinus cancers (Collins et al., 1997). Studies with relative risks less than 1.0 may be underrepresented in these published studies.

Three reviews of studies of workers with MMOF dust exposure (Meek, 1993; ECETOC, 1996; IARC, 1997) have been published. We update and expand these reviews by examining cancer mortality and incidence of respiratory disease among workers with exposures to specific fiber dusts (Table 4), case control studies which examine cancer mortality and incidence in the textile industry (Table 5), and studies and case reports of nonmalignant respiratory effects among workers in various setting with the potential for synthetic organic fiber dusts exposure (Table 6).

A. Acrylic Fiber Workers

Valic and Zuskin (1977) examined 68 nonsmoking female workers at two acrylic fiber plants. Other workers at these plants also were exposed to cotton and hemp dusts. Exposures to cotton and hemp dusts have been associated with respiratory impairment including byssinosis in the case of cotton dusts. The mean airborne concentration of respirable acrylic fiber dusts was 0.5 mg/m^3 at one plant and 0.2 mg/m^3 at the other plant. The workers with only acrylic fiber exposure had none of the adverse symptoms associated with cotton dust exposure such as byssinosis, but did display some mild acute reductions in ventilatory capacity.

Four studies shown in Table 4 examined the mortality rates of acrylic fiber workers (Blair et al., 1998; Benn and Osborne, 1998; Swaen et al., 1998; Wood et al., 1998). There was no attempt to measure acrylic fiber dust in these studies. Rates of lung cancer, nasal cavity, and sinus cancer, and nonmalignant respiratory disease were consistent with expected levels. In the largest study of acrylic fiber workers, Blair et al. (1998) found the relative risk of death for workers at three acrylic fiber plants of 0.8 (95% confidence interval [CI] 0.6 to 1.0) for lung cancer, 0.8 (95%CI 0.0 to 4.5) for nasal cavity and sinus cancer, and 0.5 (95%CI 0.3 to 0.7) for nonmalignant respiratory disease. These studies indicate that while acrylic fiber dust at the exposure levels encountered in the plant studies may temporarily reduce ventilatory capacity, there were no long-term effects on ventilatory capacity or increased risk of death from lung cancer, nasal cavity and sinus cancer, or nonmalignant respiratory disease.

TABLE 4
Cohort Studies Assessing Mortality or Incidence Form Lung Cancer, Nasal Cavity and Sinus Cancer, or Nonmalignant Respiratory Disease among Workers Exposed to Synthetic Fiber Dusts

Authors (Year)	Industry	Number of workers	Follow-up period	Lung cancer (95%CI)	Nasal cavity and sinus cancer (95%CI)	Non-malignant respiratory disease (95%CI)
Acheson et al. (1981)	Textile	NR	1963-67	NR	1.0(0.5-1.8)	NR
Delzell and Grufferman (1983)	Textile industry	150,000[a]	1976-78	0.9(0.7-1.0)	NR	0.9(0.8-1.1)
Malker et al. (1986)	Textile	NR	1961-79	NR	2.4(1.0-4.7)	
Pifer et al. (1986)	Cellulose acetate	9,040	1972-82	0.7(0.5-0.9)	NR	0.4(0.2-0.5)
Dubrow and Gute (1988)	Textile	10,700[a]	1968-78	NR	NR	1.2 (0.9-1.5)
O'Brien and Decoufle (1988)	Carpet & Textile	NR	1970-84	1.0(0.9-1.1)	NR	NR
Olsen (1988)	Textile, clothing, & leather industries	NR	1970-84	NR	1.5(0.7-2.9)	NR
Hours et al. (1989)	Nylon	1,133	1952-86	0.9(0.4-1.6)	NR	NR
	Polyester	669	1956-86	1.7(0.8-3.2)	NR	NR
Lanes et al. (1993)	Cellulose triacetate	1,271	1954-76	0.8(0.4-1.4)	NR	1.0(0.4-1.9)
Goldberg and Theriault (1994)	Cellulose acetate, cellulose triacetate, and polypropylene	10,211	1947-86	0.8(0.6-0.9)	NR	0.8(0.6-0.9)
Gibbs et al. (1996)	Cellulose triacetate	3,211	1970-89	0.7(0.5-0.9)	NR	NR
Wood et al. (1998)	Acrylic fiber	2,559	1944-91	0.8(0.6-1.0)	0.0(0.0-4.1)[b]	NR
Swaen et al. (1998)[c]	Acrylic fiber	645	1962-95	1.2(0.6-2.1)	27.8(0.4-140.3)	1.2(0.7-1.9)
Blair et al. (1998)[c]	Acrylic fiber	12,596	1952-89	0.8(0.6-1.0)	0.8(0.0-4.5)[b]	0.5(0.3-0.7)
Benn & Osborne (1998)[c]	Acrylic fiber	2,208	1950-91	0.9(0.6-1.3)	NR	0.7(0.4-1.1)

NR = not reported

a - Estimated number of workers exposed in proportionate mortality ratio study.

b - The number of expected deaths was not report and was estimated using the ratio of nasal to lung cancers in the Blair et al. (1986).

c - Additional data by plant kindly provided by authors.

TABLE 5
Case-Control Studies Assessing Risks of Nasal Cavity and Sinus Cancer and Lung Cancer among Workers Exposed to Synthetic Fiber Dusts

Authors (Year)	Industry	Number of Exposed Cases	Nasal Cavity and Sinus Cancer Relative Risk (95% CI)	Lung Cancer RR (95%CI)
Kabat & Wynder (1984)	Textile related job	14(non-smoking females)		3.1(1.1-8.6)
Brinton et al. (1985)	Textile or clothing	34	1.3(0.8-2.2)	
Hayes et al. (1986)	Textile	NR	1.1(0.5-2.2)	
Ng (1986)	Textile	14	2.9(1.1-7.9)	
Siemiatycki et al. (1986)	Synthetic fibers	11		0.5(0.2-1.1)
Paci et al. (1987)	Textile	49		1.4(0.9-2.1)
Roush et al. (1987)	Textile	10	0.7(0.4-1.3)	
Bimbi et al. (1988)	Textile	5	2.9(1.0-8.6)	
Comba et al. (1992a)	Textile or clothing	4	17(1.9-162)	
Comba et al. (1992b)	Textile or clothing	2 (males)	4.5(0.8-26)	
	Textile or clothing	3 (females)	0.8(0.2-2.7)	
Zheng et al. (1992)	Textile	8	0.8(0.3-1.7)	
Magnani et al. (1993)	Textile	7	0.8(0.2-2.8)	
Wu-Williams et al.(1993)	Textile	31		0.7(0.4-1.1)
Zappa et al. (1993)	Mostly woolen textile	129		1.5(1.0-2.1)
Zheng et al. (1993)	Textile	3	1.8(0.4-8.1)	
Luce et al. (1997)	Textile or clothing (synthetic)	3 Squamous cell (males)	4.1(0.9-19.3)	
		3 Squamous cell (females)	6.9(1.1-44.9)	
		3 Adenocarcinoma (males)	3.0(0.3-31.0)	
Bruske-Hohlfeld (2000)	Textile or leather	180		1.2(0.9-1.5)

TABLE 6
Studies of Textile Workers That Examine Nonmalignant Pulmonary Health Effects

Authors (publication year)	*Industry*	*Description of study*	*Study's Conclusions*
Molyneux and Tombleson (1970)	Cotton and synthetic fiber mills	Cross sectional study of the prevalence of byssinosis and bronchitis among 1,359 cotton mill workers and 227 synthetic fiber mill workers.	The prevalence of byssinosis and bronchitis was lower among synthetic fiber workers compared to cotton mill workers.
Berry et al. (1973)	Cotton and synthetic fiber mills	Longitudinal study of 595 workers	Cotton fiber workers had a greater decline in FEV over time than did synthetic fiber workers.
Merchant et al. (1973)	Cotton, wool and synthetic fiber mills	Cross sectional study of respiratory function and prevalence of byssinosis among 1260 cotton mill workers, 803 blend mill workers, and 904 synthetic/wool mill workers	Synthetic/wool mill workers had lower prevalence of byssinosis, and respiratory impairment than did cotton or blend mill workers.
Wegman and Peters (1974)	Nylon flocking facility	Cross sectional evaluation of 13 workers where an influenza like syndrome occurred	Influenza like syndrome only occurred among smokers with exposure to fluorocarbon polymers.
Cortez Pimentel et al. (1975)	Synthetic fibers including nylon, polyester, polyolefin, and acrylic	Case report of 7 workers working with pulmonary diseases	Etiology of the pulmonary diseases could not be established but is likely occupational.
Valic and Zuskin (1977)	Cotton, hemp, and acrylic fibers	Cross-sectional study of respiratory symptoms among workers	Exposure to dusts of polyacrylonitrile synthetic fibers may be related to mild acute reductions in ventilatory capacity but does not induce symptoms characteristic of byssinosis.
Muittari & Veneskoski (1978)	Natural fibers (cotton, wool, flax & jute) & synthetic fibers (nylon, polyester, viscose, & acrylic)	Cross-sectional study of 233 workers with fiber exposure using nasal and inhalation provocation and tests for fiber allergens.	The allergy investigation suggests that synthetic fibers can cause IgE-medicated allergic rhinitis and asthma.
Parvispour et al. (1981)	Cotton and synthetic fiber	Cross-sectional pulmonary function testing on 162 worker in textile mill with cotton and synthetic fiber	All pulmonary function measures for both groups were within normal limits. Dusts

Authors (publication year)	*Industry*	*Description of study*	*Study's Conclusions*
	mills	exposure	produced from synthetic fibers did not produce the same level of adverse symptoms seen among cotton fiber workers.
Jones et al. (1982)	Carbon fiber	Cross-sectional pulmonary evaluation of 88 workers	No adverse pulmonary effects
Troitskaya (1988)	Carbon fiber	Cross-sectional health evaluation of 327 workers	68% of the workers had mucus membrane disorders of the upper respiratory tract
Hillerdal et al. (1990)	Synthetic fibers including acrylic and polyester	Case report of 3 workers with pulmonary fibrosis	Synthetic may be a cause of pulmonary fibrosis
Pal et al. (1990)	Para-aramid fibers	Cross-sectional evaluation of 167 workers	No change in lung diffusing capacity of workers exposed to para-amid fibers compared to workers not exposed to fibers.
Glindmeyer et al. (1991)	Cotton and synthetic fiber mills	Longitudinal study of lung function among 1,353 cotton mill workers and 454 synthetic fiber mill workers.	synthetic fiber workers had larger declines in pulmonary function than did cotton workers
Sigsgaard et al. (1992)	Cotton, wool and synthetic fiber mills	Cross-sectional study of 409 textile workers at a cotton mill, wool mill, and a man-made fiber mill.	Cotton and wool workers had higher rates of adverse pulmonary symptoms compared to synthetic fiber workers.
Nilsson et al. (1993)	Textile plant	Case report of 15 workers with asthma or dermatitis working in a textile plants with a dyehouse.	Exposure to dyes could be related to asthma and dermatitis.
Fishwick et al. (1994)	Cotton and synthetic fiber mills	Cross-sectional study of respiratory symptoms of 404 synthetic fiber and 1,048 cotton fiber workers	There were no work related respiratory symptoms among synthetic fiber workers.
Kremer et al. (1994)	Synthetic fibers (polyamide, polyester, para-aramide yarns and fibers).	Longitudinal study of airway hyper-responsiveness among 668 workers exposed to fumes and vapors	Exposure to some fumes and vapors was associated with cough, phlegm, dyspnea, wheese, itching or watery eyes.
Niven et al. (1997)	Cotton and synthetic fiber mills	Cross-sectional study on 2,991 workers in cotton textile plant compared to workers in man-made fibers plant	Cotton workers had greater risk of chronic bronchitis and decrements in lung function compared to synthetic fiber workers. Synthetic fiber workers had lower FVC than cotton

TABLE 6 (continued)

Authors (publication year)	*Industry*	*Description of study*	*Study's Conclusions*
			workers.
Kern et al. (1998)	Nylon flocking facility	Cohort study of all workers between 1990-96 who worked 18 months at a flocking plant	Worker at this plant were at increased risk of interstitial lung disease and nylon fiber is the suspected cause.
Zuskin et al. (1998)	Polyester fiber	Cross-sectional study of 400 synthetic fiber textile workers.	Inhalation of dusts in synthetic textiles plants may cause respiratory impairment.

B. Nylon Workers

Kern et al. (1997; 1998, 2000) examined an outbreak of interstitial lung disease (ILD) among workers who manufacture finely cut nylon "flock." Flocking is a process whereby a loose rope of thin, continuous strands of man-made organic fiber is chopped into short fibers, which are then applied to adhesive-coated surface (Burkhart et al., 1999). These studies found 8 cases of ILD among 165 flock workers (5%) in a Rhode Island plant. Since the first reports, a total of 20 cases have been identified in 500 nylon flock workers (4%) in three plants (Eschenbacher et al., 1999). The diseases in this investigation had transient clinical symptoms that distinguish it from other known progressive ILD such as asbestosis or silicosis. Indeed, pathological evaluation of biopsy material from affected workers characterized the interstitial disease as lymphocytic bronchiolitis (Boag et al., 1999). The incidence of ILD in the general population is unknown; an ILD registry in Bernadillo County, New Mexico, reports a prevalence of less than 0.03% (Coultas et al., 1994). The ILD observed in this study began with inflammation of the lung, which interferes with oxygen uptake by the blood and eventually can result in permanent functional impairment and scarring of the lung or fibrosis (Eschenbacher et al., 1999). The workers with ILD experienced improvement within weeks to months of leaving work. The improvement has not always been complete with some workers having persistent dyspnea, exercise limitation, or requirements for supplemental oxygen (Eschenbacher et al., 1999).

ILDs have been variously attributed to hypersensitivity (allergic reaction), drugs, radiation, inorganic dusts (e.g., silica, asbestos, hard metal dusts), organic dusts (i.e., bacteria, or animal protein), infections, and connective tissue disease, but most cases of ILD are of unknown origin (Coultas et al., 1994). Occupational exposures for the nylon flock workers include dyes, fiber coatings, titanium dioxide fiber fillers, adhesives, nylon fibers ≥12 μm diameter, nylon fibers in the respirable range, as well as other dusts, liquids, and gases. A wide variety of base fibers can be used in the flocking operations. Recently, textile dye products have been related to interstitial pneumonia (Romero et al., 1998). Eschenbacher et al. (1999) concluded that their findings indicate that fragments of nylon may cause ILD seen in these workers, but other particulate matter present in the flocking process or other exposures cannot be ruled out as a cause, particularly because few, if any, fibers have been observed in lung biopsies of patients. Exposure to dusts in this study was very high (80 to 100 mg/m^3) in some areas of the operation (Burkhart et al., 1999). Based on the current data, the association of nylon flock exposure to the development of lymphocytic bronchiolitis remains a correlative one and not a causal relationship has not been established.

Muittari and Veneskoski (1979) administered prick tests and nasal and inhalation provocation tests to 233 natural and synthetic organic fiber workers. They found that nylon workers had the greatest number of positive inhalation provocation results (7 of 20) when compared with other fiber workers, including cotton fiber (7 of 32) and acrylic fiber (1 of 10). The authors suggest that synthetic fibers such as nylon may act as haptens and cause an allergic reaction, which might lead to occupational asthma.

Hours et al. (1989) examined the mortality levels of 3086 men working in a polyamide-polyester plant in France. Workers working in the nylon operation, had lung cancer rates slightly less than expected (RR = 0.9, 95%CI 0.4 to 1.6) compared with the French male population. There were no levels of nylon dust exposure reported in this study. The rates of nasal cavity and sinus cancer and nonmalignant respiratory disease were not reported.

We conclude that workers exposed to high levels of nylon fiber dust may be at increased risk of ILD, although other exposures such as textile dyes, fiber finishes, and bacterial and/or fungal microorganisms cannot be ruled out as a cause. There is no evidence of increased cancer risk among nylon workers. However, there is only one study that examines cancer risk but the levels of nylon fiber dust in this study are not specified.

C. Carbon Fiber Workers

A study of 88 workers involved in the production of PAN-based carbon fiber did not show any adverse pulmonary effects (Jones et al., 1982).

However, the fibers in this study were probably too thick (8 to 10 μm diameter) to be respirable, and thus lower respiratory tract effects would be unlikely. Troitskaya (1988) studied 327 workers in a Russian PAN-based carbon fiber production facility; 68% of the workers had mucus membrane disorders of the upper respiratory tract and 40% showed adverse skin effects. However, in addition to carbon fibers, the workers were exposed to other substances in the workplace. We consider these studies of carbon fiber workers to be insufficient to establish the toxicity of carbon fibers for humans and our conclusion is shared by the International Program on Chemical Safety task force, which also considered these data insufficient to establish the toxicity of carbon fibers (Meek, 1993).

D. Aramid Fibers Workers

Pal et al. (1990) reported no change in the lung diffusing capacity of 167 workers exposed to para-aramid fibers and sulfur dioxide compared with 142 people with no workplace exposure. However, because of the healthy worker effect mentioned earlier, the control group used in this study may have been inappropriate (Meek, 1993). Kremer et al. (1994) reported that workers processing para-aramid fibers as well as polyester and polyamide fibers had higher prevalence of respiratory irritation, including cough, dyspnea, wheeze, and increased phlegm production. There was potential for exposure to fiber dusts as well as several potentially irritating chemicals, including sulfuric acid and synthetic oils. Fiber dust levels were not reported in this study, although the authors stated that all exposures measured were suggested control levels. Due to the small number of studies and the limitations of the studies done, it is difficult to evaluate the toxicity of aramid fibers in workers.

E. Cellulose Acetate and Triacetate Workers

Four studies shown in Table 4 report the mortality rates of workers with exposure to cellulose acetate or cellulose triacetate (Pifer et al., 1986; Lanes et al., 1993; Goldberg and Theriault, 1994; and Gibbs et al., 1996). All studies report rates of lung cancer and nonmalignant respiratory disease less than the comparison populations. Goldberg and Theriault (1994), the largest study of the four, reported on the mortality experience of 10,211 workers exposed to cellulose acetate, cellulose triacetate, and polypropylene from 1947 to 1986. The relative risk for lung cancer in this study was 0.8 (95%CI 0.6 to 0.9) and for nonmalignant respiratory disease is 0.8 (95%CI 0.6 to 0.9). The relative risk for nasal cancer was not reported. This study also examined cancer rates by duration of time employed in the plants but did not report any trends for lung cancer (presumably because there were none). There was no mention of levels of fiber dusts in this study. While cellulose and plastic fibers have been found in human lungs (Pauly et al., 1995; Pauly et al., 1998), exposures to cellulose acetate or cellulose triacetate in the plants studied were not associated with an increase respiratory cancer risk or mortality from nonmalignant respiratory disease.

F. Polyvinyl Alcohol (PVA) FiberWorkers

Polyvinyl alcohol (PVA) fibers used as a textile sizing agents usually exist as either short-cut fibers, staple fibers, or filaments. Although they are too large to be of respirable size as produced, they can recrystallize and can split longitudinally to form respirable fibrils. A retrospective cohort study of 447 exposed and 2416 nonexposed male workers using PVA fibers were followed from 1980 to 1996. The SMR for all cancers was 0.57 and the lung cancer SMR was 0.77 in the exposed workers (0.67% in the controls). The authors concluded that there was no difference in either the cause of deaths in the lung cancer incidence in PVA-exposed workers (Morinaga, 1999).

G. Textile or Clothing Industry

A few of the cohort studies (Table 4) and all of the case control studies (Table 5) examined mortality or cancer incidence rates of workers exposed in the textile and clothing industry. Also, several of the studies that examined respiratory

function and symptoms failed to specify the type of synthetic organic fibers studied (Table 6). This lack of specificity of exposure makes it impossible to draw any conclusions about the toxicity of fiber types, but does allow evaluation of the industry in general.

Nine studies compared the respiratory function or symptoms of impaired lung function of MMOF workers with workers exposed to cotton fibers (Molyneux and Tombleson, 1970; Berry et al., 1973; Merchant et al., 1973; Valic and Zuskin, 1977; Pavispour et al., 1981; Glindmeyer et al., 1991; Sigsgaard et al., 1992; Fishwick et al., 1994; Niven et al., 1977). Generally, cotton workers had greater risk of pulmonary impairment (e.g., byssinosis and chronic bronchitis) and greater decrements in lung function, but comparative levels of exposure were not presented. For instance, Niven et al. (1997) studying 2991 workers exposed to cotton or synthetic organic fibers found that cotton workers had a greater risk of chronic bronchitis and decrements in lung function after taking into account age, sex, ethnicity, and smoking history. Dust exposure levels were included for each worker in the study, although the range or average levels are not reported. One study did find synthetic organic fiber workers had larger declines in pulmonary function than did cotton workers. However, the authors conclude that a confounding exposure or a selection bias could not be ruled out as the reason for this finding (Glindmeyer et al., 1991). This finding was not reported in other studies.

Cortez Pimentel et al. (1975) reported on seven workers with varying degrees of respiratory impairment who worked with synthetic organic fibers, including nylon, polyester, polyolefin, and acrylic. Histopathological analyses from lung biopsies revealed a variety of adverse effects, including interstitial fibrosis and foreign body-containing granulomatous lesions. The authors speculated that the likely composition of the foreign material were acrylic, polyester, and/or nylon dust particles. Clinical symptoms were similar to allergic alveolitis. The authors observed similar lesions in guinea pigs exposed to aerosols of pulverized nylon or polyacrylonitrile dust for nearly 1 year. The potential role of other exposures or other potential confounding factors were not discussed. Quantitative exposure data for either the clinical studies or the experimental animal studies were not provided.

Hillerdal et al. (1990) reported on adverse pulmonary effects in three workers who had been employed for decades in cutting and measuring acrylic and polyester cloth and imitation leather. Histopathological analysis of lung biopsies revealed a diffuse pulmonary fibrotic effect with granulomatous lesions containing foreign bodies (presumed to be particles from synthetic organic fibers). Exposure data, including dimensions of the particles, were not available.

Three cohort studies (Acheson et al., 1981; Malker et al., 1986; Olsen et al., 1988) and 11 case-control studies (Brinton et al., 1985; Hayes et al., 1986; Ng, 1986; Roush et al., 1987; Bimbi et al., 1988; Comba et al., 1992a; Comba et al., 1992b; Zheng et al., 1992; Magnani et al., 1993; Zheng et al., 1993; Luce et al., 1997) examined nasal cavity and sinus cancer among workers in the textile and clothing industry. An important potential confounding exposure with fiber dusts among textile workers is wood dust. Wood dust has been associated with an increased risk of nasal cavity and sinus cancer. A previous review of the risk of nasal cavity and sinus cancer and exposure to wood dust indicated that the risk is limited to woodworkers mostly in Western Europe (Blot et al., 1997). The reasons that the high risk is limited to Western Europe is unknown but could be related to higher exposures, differing species of wood, or the presence of other carcinogens in the workplace (Blot et al., 1997). Eleven of these studies as shown in Table 4 were conducted on textile workers who worked in Western Europe and may have had potential wood dust exposure. A relative risk (RR) of nasal cavity and sinus cancer greater than 1 was reported in nine out of 11 studies on workers in Western Europe; three out of 6 studies in non-Western European textile workers reported an RR greater than 1.

The risk of lung cancer in the studies of textile workers in general was examined in two cohort (Delzell and Grufferman, 1983; O'Brien and Decoufle, 1988) and six case control studies (Kabat and Wynder, 1984; Siemiatycki et al., 1986; Paci et al., 1987; Wu-Williams et al., 1993; Zappa et al., 1993; Bruske-Hohlfeld, 2000). Some of the textile worker studies mentioned that asbestos and cotton dust were potential exposure

confounders (Buiatti et al., 1979). While both amphibole and chrysotile asbestos exposure increases lung cancer risks, cotton dust exposure might reduce lung cancer risk so it is important to consider the potential for multiple exposures in these studies. No study did this. Smoking also increases lung cancer risks and neither of the cohort studies examined rates of smoking. It is possible that the lack of findings in these studies is a result of confounding with cigarette smoking. The case controls were able to assess smoking. Four of the case control studies reported lung cancer rates greater than expected (Kabat and Wynder, 1984; Paci et al., 1987; Zappa et al., 1993; Bruske-Hohlfeld et al., 2000), but lung cancer rates in the remaining studies were below expected levels.

In summary, studies on textile industry workers there was an increased risk of nasal cavity and sinus cancer among workers, but this finding was limited to studies conducted in Western Europe, and hard wood dust exposure (known to cause nasal tumors) is a confounding factor. We find no consistent increased risk of nasal cavity and sinus cancer among workers with exposure to synthetic organic fiber dust who work outside of Western Europe. In general, the risks of lung cancer and nonmalignant respiratory disease do not appear to be increased among textile workers, but in the absence of exposure levels, type of exposure, and failure in some instances to account for the healthy worker effect, smoking, and exposure to other carcinogens, it is impossible to rule out an effect from exposure.

V. SHORT-TERM INHALATION AND INSTILLATION STUDIES IN ANIMALS

Short-term inhalation studies are used to evaluate several parameters relating to the biological effects of fibrous dusts, including the following: efficiency of lung deposition, acute pulmonary effects, and fiber persistence in the lung following the termination of exposure. These studies are also used to screen respirable fiber types for early pulmonary effects that could be predictive of more serious pathogenic effects (i.e., fibrosis and/or tumors) following chronic exposure. Intratracheal studies, although not a physiological route of exposure, have also been utilized to assess the pulmonary toxicity of fibers.

A. Nylon Flock Dust

Rats were exposed to nylon dusts by intratracheal instillation (IT) at a concentration of 10 mg/kg body weight (one dose) and examined for signs of lung inflammation at post IT days 1 and 29 (Porter et al., 1999). The nylon dust collected at a flocking plant contained respirable-sized nylon shreds that were fibrous. Rats exposed to this nylon flock dust showed elevations in several pulmonary inflammatory and injury parameters (protein leak, neutrophil infiltration, and alveolar macrophage activation) measured on post-IT day 1. Lung parameters of exposed rats were not significantly different from controls on day 29. Histological evaluation, however, revealed localized areas of histiocytic inflammation surrounding retained nylon fiber shreds. Additional groups of rats were exposed to either flocking plant dust that had been washed or the water extract from the dust. Again, on post-IT day 1, rats exposed to the washed dust showed substantial lung damage and inflammation, while rats exposed to the water extract showed only minimal inflammation. On day 29, parameters in both groups were similar to those of the control rats. In a third study, rats were intratracheally exposed to nylon shreds prepared from nylon tow that had not been treated with any dyes or flocking finishes. These rats also showed substantial lung damage and inflammation on post-IT day 1 (no evaluations were made for day 29). The investigators concluded that: (1) nylon flocking generated fibrous shreds of respirable size that interact with alveolar macrophages and are still visible in the lung 29 days after instillation; (2) instillation of the dust samples caused substantial acute inflammation in the rat lungs; and (3) the water extractable agent(s) from the airborne dust contributed minimally to the inflammatory lung response (Porter et al., 1999).

The results of intratracheal instillation studies with nylon flock fragments suggest that the material is inflammogenic in the lungs of exposed rats. However, preliminary results from a very recent 4-week inhalation study with nylon RFP in rats suggest that the inhaled RFP may produce different pulmonary results (less inflammogenic) from those reported in the pulmonary instillation model (Warheit et al., in press).

B. Biopersistence Studies of Para-Aramid RFP

Para-aramid respirable-sized fiber-shaped particulates (RFP) have been evaluated in several short-term inhalation studies using laboratory rodents. In one of the first studies (Lee et al., 1983), rats were exposed to para-aramid RFP for 2 weeks, then maintained without further exposure for a recovery period of 6 months. Rats exposed to 26 RFP/ml or less showed only a macrophage response, and those rats exposed to 280 RFP/ml or more developed granulomatous lesions at the alveolar duct bifurcations along with fibrotic thickening. By 6 months postexposure, the granulomatous lesions were nearly resolved and the fibrotic lesions were much reduced. During the recovery period, lung-retained RFP were fragmented and had decreased in length at a rapid rate (Lee et al., 1983).

In another study (Warheit et al., 1992, 1994), rats were exposed for 5 days to aerosols of para-aramid RFP (900-1344 f/ml) or wollastonite fibers (800 f/ml). Wollastonite, a natural inorganic fiber, cleared from the lung rapidly, with a retention half-time of less than 1 week. During 1 month of postexposure recovery, mean lengths of lung-retained wollastonite fibers progressively decreased from 11 to 6 μm. The numbers of para-aramid RFP/lung increased from time 0 to 1 week postexposure and then decreased thereafter, indicating a cleaving of lung-retained RFP (i.e., accounting for an increase in the number of RFP at that time point). Lung retention half-time was approximately 30 days for WHO-sized p-aramid RFP. During 6 months in the lung, mean lengths of lung-retained p-aramid RFP were progressively decreased from 12.5 to 7.5 μm, suggesting transverse breakage of longer RFP into shorter fragments. The investigators concluded that both para-aramid and wollastonite demonstrated relatively low biopersistence in the rodent lung (Warheit et al., 1992, 1994).

In a third study (Kelly et al., 1993), the lung deposition and clearance of para-aramid fibrils (RFP) were investigated in rats in a short-term inhalation study that paralleled a 2-year chronic inhalation study. The initial mean dimensions of lung-deposited para-aramid fibrils were 12 μm length and <0.3 μm diameter. After a 2-year exposure at 2.5, 25, or 100 fibrils/ml, or a 1-year exposure plus 1-year recovery at 400 fibrils/ml, mean lengths of lung-retained fibrils were <5 μm. The time required for fibrils to be reduced to <5 μm in the lung was markedly less at lower exposure concentrations. From these data, the investigators concluded that para-aramid fibrils are less biopersistent in the lungs of rats than would be expected from the known chemical resistance of commercial fiber (Kelly et al., 1993).

Searl (1997) conducted a study to evaluate the relative biopersistence of inhaled para-aramid fibrils, chrysotile asbestos, and JM Code 100/475 (special application) fiber glass in the lungs of rats following 2 weeks of exposure to similar aerosol concentrations (700 f/ml). During the 16-month postexposure period, each of the three fiber types appeared to be cleared rapidly from the lungs. During the first postexposure month, however, the lung burdens of both para-aramid fibrils and fiber glass decreased in numbers of long retained RFP, while they were *increased* in numbers of shorter retained RFP. This clearance pattern is similar to that observed in other studies with nonbiopersistent SVFs (e.g., building insulation fiber glass and HT stonewool; Hesterberg et al., 1996 and 1998). More rapid reduction of retained long RFP compared to retained short RFP is consistent with a mechanism of transverse breakage—the long fibers apparently break into shorter fragments, temporarily increasing the numbers of short fibers; macrophage-mediated clearance of the short fibers eventually causes their numbers to also decline. In contrast, the asbestos data showed the reverse clearance pattern, that is, more rapid clearance of short fibers concomitant with selective retention of lung-retained long asbestos fibers. The biopersistence of long (>15 μm) chrysotile asbestos fibers was very much greater than that of long p–aramid RFP or 475 glass fibers.

In another study, rats were exposed for 2 weeks to size-separated para-aramid fibrils or chrysotile asbestos at target concentrations of 400 or 750 RFPs/ml. Because chrysotile contained a much higher proportion of short fibers than the preparation of para-aramid RFP, the fiber sample containing chrysotile asbestos was size selected to eliminate some of the shorter fibers. Following exposure, the lung burdens were evaluated at six postexposure time points up to 1 year postexposure. Initial me-

dian lengths of lung-retained RFP were 8.6 μm for para-aramid but only 3.5 μm for chrysotile asbestos fibers. Para-aramid fibrils cleared rapidly from the lung, while clearance of long chrysotile fibers was negligible. Over time, the median lengths of lung-retained RFP in the lung decreased for para-aramid but increased for chrysotile fibers (Warheit et al., 1995a, 1995c, and 1996).

A study was conducted in hamsters to determine whether the inhaled para-aramid RFP were biodegradable in the lungs of hamsters as they had been demonstrated in the lungs of similarly exposed rats (Warheit et al., 1997). Hamsters were exposed whole-body to aerosols of size-separated para-aramid fibrils for 2 weeks at target fiber concentrations of 350 and 700 RFPs/ml. Lung burdens were evaluated at several intervals during a postexposure period of 3 months. Mean lengths of para-aramid fibrils recovered from hamster lungs were 10.4 μm immediately after the 2-week exposure, 6.3 μm at 1 month, and 6.1 μm at 3 months. Thus, the biodegradability of inhaled para-aramid fibrils observed in hamsters was similar to that observed in rats, in that, for both species, the mean and median lengths of lung fibrils progressively decreased during residence time in the lungs (Warheit et al., 1992, 1995a, 1995c, 1996; Kelly et al., 1993; Searl, 1997).

Pinkerton et al. (1999) assessed the pulmonary cellular effects at sites of fiber deposition following high-dose inhalation exposures to p-aramid RFP in rats. Rats were exposed to 419 and 772 p-aramid RFP/cc for 2 weeks. Animals were sacrificed and tissue effects analyzed immediately after 2-week exposure as well as 1 week, 1 month, 3 months, 6 months, and 1 year postexposure. Bronchiole alveolar duct junctions (BADJ) were identified, magnified, and analyzed. Morphometric analysis was implemented using the program Stereology Toolbox 13.3. The volume to surface area ratio (i.e., tissue density or thickness) of BADJ's from both p-aramid exposure groups were compared with sham control rats exposed to filtered air. The results showed that exposures to 419 RFP/cc p-aramid induced initial increases in tissue density at BADJs for the early postexposure time points, corresponding to prominent increases in alveolar tissue volume at the 1 to 4 week postexposure periods, but were not significantly different from controls at 3, 6, and 12 months postexposure. Exposure to higher concentrations (772 f/cc) of p-aramid RFP resulted in enhanced tissue thickening, and this response peaked at 1 month postexposure. Consistent with the effects at the lower concentration (i.e., 419 RFP/cc) no significant differences in tissue thickening were measured at 3, 6, and 12 months postexposure. Similarly, morphometric studies measuring alveolar macrophage volume/surface area at BADJs demonstrated a peak at 1 month postexposure but no significant difference thereafter. These investigators concluded that the early fibrotic lesions related to high-dose p-aramid exposure are repaired in the absence of continuing exposure. Therefore, the early tissue thickening response and corresponding cellular lesions measured at bronchoalveolar duct junctions following high-dose 2 week exposures appeared to be reversible.

Bellmann and colleagues (2000) evaluated the clearance of p-aramid RFP in rats following 90-day inhalation exposures. Male Wistar rats were exposed to aerosols of p-aramid RFP for 3 months at 50, 200, and 800 RFP/ml, as measured by scanning electron microscopy. The lungs of control and exposed animals were assessed through 9 months postexposure. The mean pulmonary retention of RFP for the 3 exposure groups was approximately 25×10^6, 122×10^6, and 576×10^6 RFP per lung, respectively, following a 3-month inhalation exposure. A decrease in the mean lengths of the retained RFP over the 9-month recovery period was measured, indicating a breakage of the long fibrils. Alveolar retention half-times were measured via gamma tracers at 0 and 3 months postexposure and indicated a dust overloading of the lungs at the high-dose exposure group. Bronchoalveolar lavage biomarkers revealed that p-aramid RFP induced pronounced inflammatory effects in the high- and medium-dose groups. Histopathological analysis revealed slight fibrotic and hyperplastic lesions in the medium- and high-dose groups immediately after the end of exposure, but were reduced at 3 months postexposure. No histopathological effects were measured in the low-dose group, and the NOAEL was determined to be 50 f/ml. The investigators concluded that the maximum functionally tolerated dose was exceeded for the high-dose group.

In the aggregate, the results of five independent inhalation studies have demonstrated the low biopersistence of inhaled p-aramid RFP. The mechanism of p-aramid biodegradability appears to be associated with transverse cleavage of the retained RFP in the lungs of exposed rats and hamsters. Shortening of the p-aramid RFP is followed by rapid pulmonary clearance.

C. Carbon Fibers

Guinea pigs were exposed to dust composed of chopped carbon fibers for 104 h (4.33 days). Dust concentrations ranged up to 20 mg/m^3 (Holt et al., 1978). Dust consisted of 99% nonfibrous particles of approximately 1 μm in diameter; only a small proportion of the fibrous particles were in the respirable range. The animals were sacrificed at intervals ranging from 1 to 144 days after termination of exposure. Histological evaluation of the lungs revealed only small increases in macrophage numbers, containing mostly nonfibrous carbon particles. A small number of extracellular fibrous particles were also observed. In a review article, Thomson (1989) concluded that the inhalation and intratracheal instillation studies with carbon fibers, although generally producing no adverse effects, are inadequate. In the inhalation study, only one exposure level was used and the fiber burden was inadequately characterized. In another study, the fibers were processed in a ball mill so that the bulk of the delivered dose was nonfibrous particulate (Thomson, 1989).

Rats were exposed by nose-only inhalation to aerosols of pitch-based or polyacrylonitrile (PAN)-based carbon fibers at 47 to 62 fibers/cm^3 for 5 days (6 h/day) and were monitored for 90 days postexposure (Warheit et al., 1995b). The PAN-based carbon fibers were considered a negative control because they were 9 μm in diameter and thus entirely of a nonrespirable dimension for the rat; they had no effect on any of the parameters tested. Pitch-based carbon fibers were respirable sized, with aerodynamic diameters <2 μm. Pitch-based carbon fibers produced a dose-dependent transient inflammatory response in the lungs of exposed rats, manifested by elevated levels of neutrophils and significant increases in lactate dehydrogenase, total protein, or alkaline phosphatase in bronchoalveolar lavage fluid at early postexposure time periods. Pigment-laden alveolar macrophages as well as minimal type II epithelial cell hyperplasia were observed primarily at the junctions of the terminal bronchioles and alveolar ducts. The inflammatory response was no longer apparent by 10 days postexposure. Exposure to aerosols of pitch-based carbon fibers also produced increases in cell proliferation in lung parenchymal cells at 10 and 30 days postexposure, as demonstrated by cell labeling studies.

There is a need for a longer-term inhalation toxicity study with respirable-sized carbon fibers. The test materials utilized in the two studies referenced above were brittle and likely were modified (shortened) during the aerosolization/exposure process. As a consequence, the carbon fiber preparations being tested contained significant nonfibrous particulate components. This mixture of fibrous to nonfibrous particulate composition in the workplace environment is common to commercial flocking operations. It remains to be determined whether this mixture simulates human exposures in carbon fiber processing operations.

D. Cellulose Fibers

The inflammatory effects of respirable cellulose fibers in the form of mechanical wood pulp were studied in two short-term animal models: intraperitoneal injection in mice, and inhalation exposures in rats. In the mouse study, both cellulose fibers and the positive control fiber, crocidolite asbestos, were injected in doses ranging from 10^4 to 10^8 fibers/mouse. Both caused marked, dose-dependent recruitment of inflammatory cells to the mouse peritoneal cavity. Crocidolite was much more active than cellulose, despite the mass dose of cellulose being 66 times greater for an equivalent number of fibers. In the inhalation study, rats were exposed daily, 5 days per week, to aerosols of cellulose dust for 3 weeks at a concentration of 1000 fibers/ml. Inhalation exposure induced an early inflammatory response in rats lungs, as determined by bronchoalveolar lavage, which peaked at 1 day following the start of inhalation and thereafter declined, despite a further 13 days of exposure. *In vitro* production of the proinflammatory cytokine tumor necrosis factor alpha (TNF-α) by lavaged alveolar macrophages was markedly depressed by the end of the exposure period in cellulose-exposed animals,

and this effect was still present in rats that had been allowed to recover for 28 days beyond the end of exposure. The cellulose material studied (i.e., mechanical wood pulp) is much less inflammogenic than crocidolite and that the extent of the inflammatory response within the lung appears to reduce with continued exposure over a 14-day period (Cullen et al., 2000).

There are numerous forms of cellulose fibers utilized in commerce today. Given the widespread nature of cellulose exposures in the paper and filtration industries, there exists a great need to evaluate the inhalation hazard potential of the several varieties of these natural fibrous materials.

E. Nonfibrous Polymer Dusts—Possibly Relevant to MMOF Toxicology

1. Water-Dispersible Polyester Dust

A rat inhalation study was used to test the potential health effects of a high molecular weight, water-dispersible, amorphous polyester used in water-based adhesives, coatings, emulsions, paint primers, cosmetics, and detergents (Katz et al., 1997). Following inhalation exposure for about 13 weeks to mean concentrations of either 0, 2.4, 19.6, or 199 mg/m^3 of nonfibrous polymer dust, no mortality occurred and body weights were unaffected. Exposure-related changes in the 199 mg/m^3 groups included increased mean absolute and relative lung weights, accumulations of macrophages and acute inflammatory cells in alveolar and bronchial lumina, and increased numbers of macrophages in peribronchial lymph nodes. Minor accumulation of macrophages in alveolar lumina was the only exposure-related change in the 19.6 mg/m^3 group. No exposure-related effects were seen in the 2.4 mg/m^3 group. The investigators concluded that aerosols of this form of polyester do not appear to be toxic to pulmonary tissues following subchronic inhalation exposure.

2. Polyacrylate Dust

Subchronic and chronic rat inhalation studies of polyacrylate (PA) respirable particulates were sponsored by the Institute for Polyacrylate Absorbents, Inc. (IPA) and reported to the US EPA (IPA, 1987, 1990, and 1994). PA particles, composed of cross-linked polymers of acrylic acid, are used as absorbent fillers in disposable diapers and other absorbent products. Although these particles are nonfibrous, this study is included because it demonstrates a potent adverse effect on the lung that is apparently caused by reactions to the chemical composition of an organic solid particle. Because the average diameter of commercial PA is 300 to 400 μm with less than 0.1% respirable, PA material was ground into particles of approximately 2 μm diameter for these studies. Inhalation exposure was by whole-body. In the subchronic study, PA at 1 mg/m^3 was considered to be the maximum tolerated dose because at that dose lung clearance was reduced. Thus, exposures for the chronic 2-year inhalation study in rats were 0.8, 0.2, and 0.05 mg/m^3. In the chronic study, inhalation of PA at 0.8 mg/m^3 resulted in inflammation, a 50% incidence of fibrosis, and a 30% incidence of lung tumors (adenomas + carcinomas). The tumor incidence in animals at risk (those surviving until the first tumor appeared at 78 weeks.) was 37%. PA at 0.2 mg/m^3 induced inflammation, a 25% incidence of fibrosis, and a 3.6% incidence of carcinomas. PA at 0.05 mg/m^3 was considered to be a no observable effect level (NOEL). Air controls had no lung tumors. Because human exposure levels during manufacture and simulated consumer use of PA products have been determined to be very low (i.e., below the NOEL of 0.05 mg/m^3), IPA contended that, despite the demonstrated inhalation hazard in rodents, PA did not pose a risk to human health.

F. Polypropylene

Rats were exposed by nose-only inhalation for 6 h/day, 5 days/week for 90 days to 0, 12, 20, or 48 polypropylene WHO f/ml or to filtered air (Hesterberg et al., 1992). (The WHO criteria for respirable fibers were defined by the World Health Organization for asbestos and SVFs [WHO, 1985] and may not be appropriate for respirability of MMOFs.) Test fibers had been size-separated from bulk polypropylene. The aerosolized fibers had geometric mean dimensions of 1.2 μm × 13 μm. The maximum dose was based on the maximum aerosol

concentration that could be generated for this test fiber. Six animals per exposure group were euthanized after exposure/recovery periods of 30/0, 90/0, and 90/30 days to evaluate pulmonary changes and lung fiber burden. The authors reported concentration- and exposure-duration-dependent changes in the lungs, characterized by increased cellularity and mild bronchiolitis but no deposition of collagen and no neoplasms. These cellular changes generally were considered to be reversible following cessation of exposure, and some reversal was observed in the animals euthanized at 90/30 days (90 days exposure followed by 30 days recovery; Hesterberg et al., 1992). Lung fiber burdens were directly related to both dose and duration of exposure, but no significant lung clearance occurred during the 30 days of post-exposure recovery (Hesterberg et al., 1992). However, 15 to 80% segmented fibers were observed among the fibers recovered from the lung, which suggested early stages of transverse breakage. The numbers of segmented fibers increased over time in the lung.

As a basis of comparison, the authors cite another study, in which rats exposed to refractory ceramic fiber (RCF1) at 200 WHO f/ml for 90 days developed minimal lung fibrosis (lung scarring characterized by excessive interstitial collagen deposition; considered to be irreversible) (Mast et al., 1995); the lung burden of RCF1 after 90 days was 183,000 WHO fibers/mg dry lung (39×10^6 WHO fibers/lung), which is fairly comparable to the 90 day lung dose of polypropylene (48 f/ml), 103,000 WHO fibers/mg dry lung (roughly 22×10^6 WHO fibers/lung). The authors concluded that inhaled polypropylene RFP at these doses and for this exposure period produces low pulmonary toxicity in rats. The lung fiber segmentation data might also suggest that, with a longer recovery period, significant lung clearance may occur as the fibers break into small enough pieces for macrophage-mediated clearance out of the lung.

VI. CHRONIC INHALATION STUDIES IN ANIMALS

A. Para-Aramid RFP

In a chronic inhalation study, groups of 100 male and female rats were exposed to para-aramid RFP at concentrations of 0, 2.5, 25, and 100 fibrils/ml for 5 days/week for 2 years (Lee et al., 1988). An additional group of 100 animals was exposed during the same period to 400 fibrils/ml for 1 year. Lungs exposed at 2.5 fibrils/ml exhibited normal alveolar architecture and a few dust-laden macrophages in the alveolar air spaces—this constituted a NOAEL (no observable adverse effect level). In rats exposed to 25 and 100 fibrils/ml, the following effects were observed: a dose-related increase in lung weight, inflammatory cellular responses, slight type II pneumocyte hyperplasia, alveolar bronchiolization, and minimal collagenized fibrosis in the alveolar duct region. In addition, 6% of the female rats (but none of the males) exposed to 100 fibrils/ml developed foci that were originally termed "cystic keratinizing squamous cell carcinomas (CKSCC)," but were later reclassified by a panel of expert pathologists to "proliferative keratin cysts (PKCs)" (Levy, 1994; Carlton, 1994). Female rats also had more prominent foamy alveolar macrophages, cholesterol granulomas, and alveolar bronchiolization. In the group exposed to 400 fibrils/ml for up to 1 year, 29 males and 14 females died due to obliterative bronchiolitis resulting from dense accumulation of inhaled para-aramid fibrils in the ridges of alveolar duct bifurcations. Rats in this exposure group that survived for 1 year postexposure showed significant reductions in lung dust content, average lengths of fibrils retained in the lung, and pulmonary lesions. However, these rats exhibited slight centriacinar emphysema and minimal fibrosis in the alveolar duct region; one male rat developed a carcinoma and six female rats (6/56; 11%) developed PKCs. The cystic keratinizing lung lesions produced following exposure to para-aramid and many other dusts appear to be unique to the rat. The general opinion was that these lesions are probably not relevant for human risk assessment of pulmonary cancer.

Para-aramid fibrils were evaluated recently by the International Agency for Research on Cancer (IARC, 1997) and were judged to be a Category 3 material (i.e., Inadequate Evidence for Carcinogenicity). This decision was based primarily on (1) the lack of carcinogenic effects in rats following long-term inhalation exposures and after intraperitoneal injection, and (2) strong evidence of biodegradability of inhaled para-

aramid fibrils in the lungs of exposed rats and hamsters.

B. Nylon

Guinea pigs were exposed to manually pulverized nylon or to acrylonitrile (Orlon) dust for 325 days (Cortez Pimentel, 1975). Animals were administered, whole-body, aerosols of 2 g of dust three times/day; this produced a dense dust cloud. Twenty-eight nylon-exposed and 10 acrylonitrile-exposed animals were histologically and radiographically examined either after the 325-day exposure period or after unscheduled deaths (six animals). Abnormal lesions were observed in 14 of the 28 nylon-exposed animals and in all 10 of the acrylonitrile-exposed—all of which survived at least until the 210th day of exposure (the six nylon-exposed rats that died prior to that time did not show pulmonary abnormalities). Macroscopically, the lesions were visible as small subpleural foci within small emphysemic areas. Microscopically, the lesions showed a tendency to conglomerate and form nodules. Lesions were localized in the intraalveolar septa and consisted of granulomatous cellular proliferative effects. In all lesions examined, particles were observed that were determined to be of the same composition as those inhaled, although the criteria utilized was not well described. Abnormal radiographic findings were reported for only one animal (dust-type not stated). Unfortunately, the investigators did not report the respirable particle concentrations or dimensions or the lung particle burden. The investigators remarked on the strong similarity between the lesions induced experimentally in the rats and those observed in human patients occupationally exposed to organic dusts.

VII. MECHANISTIC STUDIES

A. Introduction

A very limited amount of direct information regarding the bio-potency and mechanisms of toxicity of man-made organic fibers (MMOF) has been developed. Polypropylene and para-aramid are the only two synthetic organic fiber types purposefully studied in the laboratory in whole body inhalation designs. These investigations included a cadre of accompanying measurements intended to reveal how these RFP were producing their biological effects. In addition, a small number of man made organic fiber types have been investigated using standard *in vitro* tests in an effort to gauge their biopersistence. The limited results of these studies must be viewed in the context of a much larger body of information on the mechanisms of asbestos and synthetic vitreous fiber (SVF) toxicity. While the exact extent to which these data can be applied to MMOFs is unknown, the extensive number of studies conducted on SVFs, asbestos, and other natural inorganic fibers forms our base of knowledge in this area. Until we have direct mechanistic data on sufficient numbers of MMOFs to allow one to understand this class of fibers, it makes sense to draw our starting assumptions on MMOF mechanisms of toxicity from what is known regarding modes of action of SVFs and asbestos fibers. As experimental evidence on MMOF mechanisms is developed, our understanding of how this class of man-made materials impacts our pulmonary system will become clearer and perhaps distinct from the effects of SVFs and asbestos.

B. Lessons from Research on Synthetic Vitreous Fibers, the Three D's

Extensive and varied research on SVFs has demonstrated that the toxicity of inorganic fibers to the respiratory system is essentially determined by the three "D's": (a) Dose: the greater the number of fibers in the lower lung over time, the more severe the adverse health effects; (b) Dimension: long, thin fibers have a greater potential for pulmonary toxicity than short or thick fibers; and (c) Durability: Biopersistent fibers that are hard to remove from the lung have greater potential to produce significant lung injury.

RFP from MMOF have a variety of shapes and thus are quite irregular in their dimensional characteristics. Moreover, they have a strong tendency to aggregate both in air and in aqueous media. These factors could play important roles in determining biological activity in the respiratory tract following inhalation of MMOF dusts.

Although MMOFs have a significantly different physical-chemical composition than SVFs, the limited evidence we have so far (based primarily on the data derived from inhalation studies with p-aramid RFP) is not inconsistent with the notion that dose, fiber dimensions, and biopersistence will be important determinants in assessing MMOF bio-impact.

C. Dose to the Respiratory System

The general factors that determine the amount of fiber that ultimately moves from the environment and ends up as a burden in the respiratory tract can be assumed to be similar for SVFs and MMOFs. Dose to the respiratory system will depend on the airborne concentration of fiber, fiber dimensions, deposition fraction, length of exposure, minute ventilation, and retention kinetics. Experimental evidence and common sense support this assumption. In studies with size-separated polypropylene fibers the maximum dose attained was directly related to the maximum aerosol concentration that could be generated (Hesterberg et al., 1992). Inhaled MMOFs must first be removed from inspired air and make contact with respiratory tract surfaces. Basic factors that influence SVF deposition in the respiratory system are likely to be critical for MMOF deposition as well. Size, shape, density, charge, and hygroscopicity are the physical-chemical parameters likely to be important. The World Health Organization (WHO) uses the following size criteria as a definition for respirable SVFs: length to width ratio of 3:1 (minimum), width less than 3 μm and length greater than 5 μm. Long, thin fibers pose special problems for the respiratory tract. Fibers tend to orient with their lengths parallel to the direction of the air stream making fiber diameter a key determinate of fiber deposition. For more information on deposition characteristics related to inhaled inorganic fiber types, the reader is directed to studies by Timbrell (1965), Lippmann (1988), and Brody and co-workers (1981). Thus, very long respirable-sized fibers can be inhaled into the lower lung if they are very thin. The size criteria and deposition characteristics for respirable MMOFs may be similar but not identical to those established for SVFs. Overall, MMOFs are less dense than size-matched SVFs and may have different aerodynamic properties. It has been theorized that MMOFs with diameters slightly greater than 3 μm could be respirable due to reduced fiber density. Polypropylene fibers used in rat studies had geometric mean dimensions of 1.2×13 μm and the mean dimensions of lung-deposited para-aramid fibrils were 0.3×12 μm (Hesterberg et al., 1992; Kelly et al., 1993). Theoretical and experimental studies on the respiratory tract have identified a series of mechanisms thought to be important for understanding particle deposition in the pulmonary system. For particles, impaction, interception, electrostatic deposition, sedimentation, and diffusion may all take part depending on the physical characteristics of the inhaled particle/fiber. Of these mechanisms, interception and electrostatic deposition are likely to be most important for fibers in general and MMOFs specifically.

D. Fiber Dimensions and the Relationship to Toxicity

Low toxicity respirable particles (talc, titanium dioxide, etc.) have been studied extensively and found to have little adverse effect at ambient levels currently in the workplace. The body's standard clearance mechanisms are reasonably effective at removing these particles from the respiratory tract in situations where the deposition rate is below the clearance rate. These small diameter particles are efficiently phagocytized by alveolar macrophages and cleared through the airway mucociliary escalator. In contrast to small particles, research on SVFs and asbestos has demonstrated that once fibers have deposited in the lower lung, long fibers cannot be easily removed by the body's standard clearance mechanisms. In order for clearance by this mechanism to occur the fiber must first be completely phagocytized by a macrophage. This can only be readily accomplished for fibers shorter than the cell's diameter of 12 to 15 μm. Thus, long fibers have the potential to remain in the lung for much longer periods than nonfibrous particulates of the same composition. This is thought to be one of the main reasons for the difference in toxicity observed between low toxicity particulates vs. fibers. *In vitro* studies of

asbestos and SVFs have consistently demonstrated a direct relationship between cytotoxicity and fiber length (summarized in Hesterberg et al., 1993). Indeed, a significant difference in cytotoxicity and the ability to stimulate production of proinflammatory cytokines has been demonstrated in macrophage cultures between glass fibers 7 μm in length and those that measure 17 μm (Blake et al., 1998; Ye et al., 1999), with the 17-μm fibers producing greater toxicity than the 7-μm fibers. The relationship between length and clearing ability demonstrated by these examples may apply equally well to MMOFs. It is reasonable to assume that the body would attempt to clear MMOFs that reach the deep lung by the same physiological mechanisms. Experiments with size-selected polypropylene fibers measuring 13 μm in length showed dose- and exposure-duration-dependent changes in the lungs, characterized by increased cellularity and mild bronchiolitis. This fiber length is at the upper limit of what could be phagocytized and cleared by the macrophage. Lung fiber burdens in these experiments were directly related to both dose and duration of exposure, and no significant lung clearance occurred during the 30 days of post-exposure recovery (Hesterberg et al., 1992).

E. Biopersistence (Durability)

A series of SVF inhalation studies using rats showed a very strong, direct relationship between the biopersistence of a fiber in the lung and its toxic potential (Hesterberg et al., 1996 and 1998; Bernstein et al., 1996). Limited evidence suggests that this relationship may also be extended to include MMOFs. Durability (resistance to dissolution and fragmentation) plus fiber length are the most important determinants of lung biopersistence.

For fibers that are too long to be transported by macrophages, lung clearance is dependent on dissolution and fragmentation in lung fluids, which in turn is dependent on the fiber's chemistry.

A decade of rodent inhalation studies on 12 different compositions of SVFs and several asbestos types has provided little evidence that the chemical composition of SVFs plays a strong role in pulmonary toxicity. In these studies, when the 12 compositions of inorganic test fibers had comparable dimensions and initial lung depositions, biopersistence emerged as the primary toxic determinant. Recently adopted criteria for classifying SVFs in the European Union relies on measurement of biopersistence in the rat lung as well as other parameters.

The *in vitro* dissolution rates of various natural and synthetic fibers have been determined using Gamble's physiological saline solution at near-neutral pH 7.4, which is a surrogate for extracellular lung fluid. Dissolution rates are expressed as $k_{dis,}$ which is equal to the ng of fiber mass that dissolves per square centimeter of fiber surface per hour (k_{dis} = ng/cm^2). Thus, the greater the k_{dis}, the more rapid the dissolution. For example, the k_{dis} values are <1 for asbestos and 100 to 400 for fiber glass building insulation (Hesterberg et al., 1998). Carbon and aramid fibers were essentially insoluble and showed no evidence of alteration of the surface after examination with scanning electron microscopy with energy-dispersive spectrometry (Larsen, 1989). Law et al. (1990) compared the dissolution rates of three organic fibers (polypropylene, polyethylene, and polycarbonate), three fiber glasses, and chrysotile asbestos. During 180 days of leaching in a flow-through system, weight losses for the three fiber glasses were 37 to 75%, while chrysotile asbestos lost only 5% and the 3 organic fibers lost no weight. The fiber glasses also developed surface pitting, while asbestos and the organic fibers showed no surface changes when examined using electron microscopy. Based on these studies one would predict little degradation of MMOFs once they deposit in the lower respiratory tract.

However, studies in whole animals have shown that MMOFs and some natural fibers can clear from the lung by a multiple step process starting with fiber fragmentation. Multiple lung deposition and clearance studies in rats and hamsters with para-aramid fibers all show a tendency for mean para-aramid fibril length to progressively decrease over time, suggesting transverse breakage of longer RFP into shorter fragments (Warheit *et al.*, 1992, 1995c, 1996; Kelly *et al.*, 1993; Searl, 1997). Polypropylene RFP recovered from the lungs of exposed rats were segmented (15 to 80%), suggesting that fiber fragmentation may be an important step in the clearance of polypropylene RFP as well. The

numbers of segmented fibers increased over time in the lung (Hesterberg et al., 1992). Wollastonite, a natural inorganic fiber, is cleared from the lung rapidly by a similar, although more rapid mechanism, which involves fiber length reduction and clearance. Wollastonite shows low toxicity and has a retention half-time of less than 1 week. Lung burden analysis of rat lungs loaded with wollastonite showed a progressive mean lung fiber length decrease from 11 μm to 6 μm during 1 month of postexposure recovery (Warheit et al., 1992 and 1994).

Warheit and co-workers (2000b) investigated the mechanisms through which inhaled p-aramid fibrils (RFP) are biodegraded in the lungs of exposed rats and hamsters. Accordingly, based on the findings of Searl (1997), they postulated that lung fluids activate p-aramid RFP following deposition into the distal lung, and the RFP, which deposit at alveolar duct bifurcations, are then vulnerable to enzymatic attack in the lungs. To test the hypothesis, p-aramid or cellulose RFP (a more biopersistent respirable organic fiber-type) were instilled into the lungs of rats and the lungs digested 24 h postexposure using two different digestion techniques: (1) a conventional ethanolic KOH method, and (2) an enzyme method (which simulates lung enzymes). The results indicated that the enzyme but not the KOH method artificially cleaved the p-aramid RFP recovered from rat lungs. The enzyme digestion method had no discernible effect on the dimensions of the retained cellulose RFP. Next, p-aramid or cellulose RFP were incubated with saline or lung fluids and then processed by one of the two digestion techniques. Mean lengths of p-aramid RFP processed with KOH and evaluated by SEM were 13.4 μm; in contrast, mean lengths of p-aramid RFP samples, incubated in lung fluids and treated with the enzyme method, were significantly shorter (i.e., 8.8 μm). Similar to the *in vivo* experiments, neither the enzyme nor KOH digestions method had any discernible effect on shortening of cellulose RFP, indicating that the results with p-aramid were specific to the RFP type and not generalized for other organic respirable fiber types. The investigators concluded that components of lung fluids coat and catalyze the p-aramid as a prerequisite for enzymatic cleavage of the RFP. Moreover, it was suggested that this process could play an important mechanistic role in facilitating the transverse cleavage or shortening of inhaled p-aramid RFP, reported to occur in the lungs of exposed rats and hamsters.

F. Sustained Inflammation, Cytotoxicity, and Fibrogenesis

Inhalation of foreign particles or fibers can cause an inflammatory response in the respiratory tract characterized by cellular injury, increased permeability, and an influx of leukocytes (predominantly neutrophils). The physical and chemical characteristics of the foreign material in contact with the respiratory tissue will determine the duration of the inflammatory response that is stimulated. Both acute (short in duration) and chronic inflammatory responses are possible, the latter producing a greater chance for significant disease development. Pulmonary exposure to low levels of low-toxicity particulates will produce an acute dose-related, transient neutrophilic inflammation. Assuming lung clearance levels of retained particles are not overwhelmed, the inflammatory response will be of short duration and the particulate material will be gradually cleared. Pulmonary exposure to pathogenic materials, such as asbestos fibers or crystalline silica particles, can produce both acute and sustained inflammatory changes characterized by longer-term accumulations of alveolar macrophages and other immune cellular elements in the air spaces and interstitium of the lung (Mossman and Churg, 1998). Cellular injury and the associated release of chemokines and cytokines are theorized as responsible for the induction of cellular proliferation and fibrosis observed in the later stages of human lung disease produced by asbestos or silica. More recently, cell culture studies have identified some of the molecular details of the interactions between cells and inorganic particles, including the formation of reactive oxygen radicals and the cellular release of inflammatory cell mediators such as cytokines and arachadonic acid metabolites (Donaldson et al., 2000). A complex network of cytokines and other mediators are released when certain lung cell types come into contact with an inorganic particle. These mediators in turn activate and attract various populations of phagocytic

and inflammatory cells and coordinate their attacks on foreign particles and their attempts to translocate the particles out of the lung. The response of rat alveolar macrophages to respirable natural and man made fibers has been modified by components of the lung lining fluid. The main endpoint affected was the intensity of the superoxide release from the macrophage. Hill et al. (1996) demonstrated differences in the response of vitreous fibers and ceramic fibers when compared with long amosite asbestos fibers (Hill et al., 1996). Information regarding the ability of MMOFs to stimulate similar immune responses is quite limited. Inhalation of polypropylene fibers in the rat produced a dose-related increase in pulmonary cellularity and mild bronchiolitis without collagen deposition, fibrosis, or neoplastic change (Hesterberg et al., 1992).

G. Cell Culture Studies

1. Cellular and Molecular Effects of MMOFs

No cell culture studies have been found in the published scientific literature on the potential of MMOFs to activate reactive oxygen radicals or to induce the cellular release of inflammatory mediators, as have been reported for SVFs (see Introduction above). Therefore, whether the molecular events observed during cellular interactions with SVFs are applicable to MMOFs cannot be concluded from the available published literature.

2. P-Aramid RFP

Recent *in vitro* studies have been reported that are designed to elucidate the mechanisms of p-aramid RFP biodegradability. Using an *in vitro* noncellular system, Warheit et al. (2000b) reported that components of lung fluids coat and catalyze the p-aramid, thereby predisposing the RFP to enzymatic cleavage. The authors suggested that this mechanism could play a significant mechanistic role in facilitating the transverse cleavage or shortening of inhaled p-aramid RFP in the lungs of exposed rats and hamsters.

More recent strategies have utilized cellular *in vitro* studies, involving macrophages and macrophage-epithelial cell co-cultures to assess the mechanism(s) of biodegradability of p-aramid RFP (see Figure 1) (Warheit et al., 2001).

3. Carbon Fibers

Martin et al. (1989) established some degree of *in vitro* cytotoxicity in cultured rabbit alveolar macrophages exposed to any one of five graphite fiber composite materials machined by various operations (as characterized by Boatman et al., 1988). However, it was not clear in the report whether the test material was fibrous, particulate, or both, and apparently graphite and matrix material were both present. In studies conducted by Styles and Wilson (1973), "carbon dust" was not considered cytotoxic to cultured rat alveolar or peritoneal macrophages. Fewer than 2% of peritoneal macrophages and 5% of alveolar macrophages were killed following phagocytosis of carbon dust with particle diameters ranging from 2 to 15 μm.

VIII. CONCLUSIONS

A. Occupational Exposure

Available data suggest that exposure to respirable MMOF during standard fiber production and processing are, in general, very low and differ little from background exposures to total (natural and synthetic) organic fibers (Cherrie, 1995). The recent identification of flocking operations as a potential source of exposure to high concentrations of respirable fibers deserves further evaluation. There is a need for more data on the composition and dimensions of airborne MMOFs during production and processing. Such studies are time consuming, labor intensive, and expensive. Furthermore, the identification of the composition of respirable-size fibers requires specialized training and highly sophisticated instrumentation.

B. Epidemiology

Low occupational exposures to airborne MMOF dust were not associated with increased

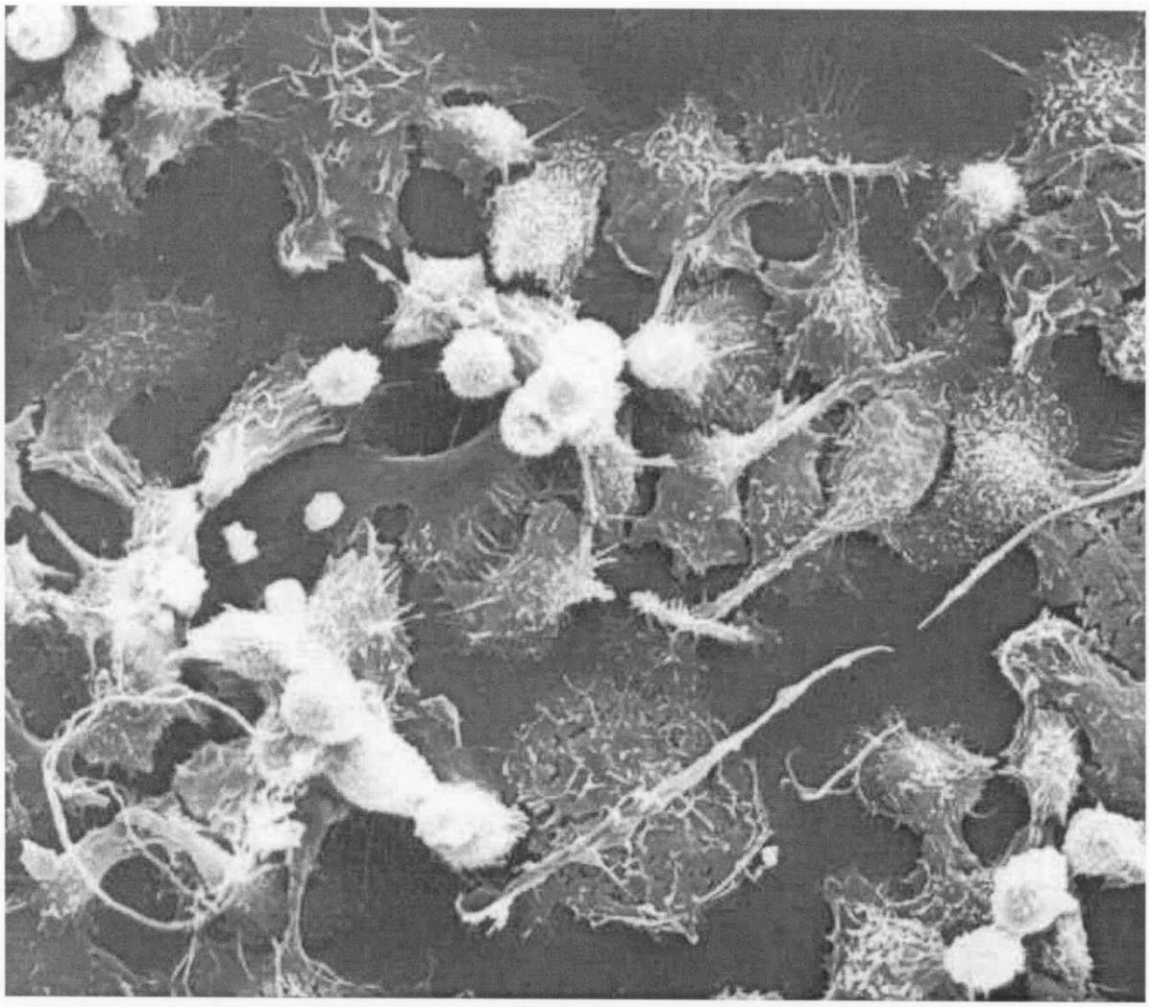


FIGURE 1. Scanning electron micrograph of a representative epithelial alveolar macrophage co-culture exposed to p-aramid RFP after 1 day; magnification = 1000×.

risk of pulmonary disease. Other types of natural organic particulates such as wood dust and processing of cotton have been linked to adverse effects. However, recent reports have associated interstitial lung disease with high exposures to MMOF dust (up to 40 mg/m^3) in the nylon flocking industry. Fibrous dust apparently was generated by chopping nylon fibers with 9 μm diameters (well above the range of respirability). The nylon flocking plant studies indicate the need for further investigations into the exposures and epidemiology of MMOF workers who are potentially exposed to respirable dust.

C. Toxicology Studies

Studies of pulmonary effects and biodegradation in rats are particularly useful in evaluating the hazard associated with exposure to a particular MMOF. However, animal inhalation studies are limited by the difficulties associated with producing a large volume of some RFPs for testing. Because production MMOFs are continuous in length and the vast majority have diameters well above the range of respirability, vigorous mechanical action is invariably required to produce respirable test fibers from production fibers; this action could alter the biological activity of the fiber.

In the one MMOF that has been studied extensively, chronic inhalation studies of para-aramid RFP have demonstrated a range of dose-related pulmonary effects in rats: no adverse effects for the lower doses, transient inflammation and minimal fibrosis for the intermediate doses, and proliferative keratin cysts in females for the high doses. Studies of inhaled para-aramid respirable

fibrils in rats and hamsters demonstrate evidence of biodegradability in the lung, which could explain the reversibility of lung fibrosis in rats after 6 and 12 months of post-exposure recovery.

Polypropylene was also evaluated in an inhalation study using rats; no persistent lung effects were observed following 90 days exposure to high concentrations of respirable fibers. However, no long-term studies have been conducted.

D. Mechanisms of Action

Basic mechanisms of respiratory tract effects of MMOFs may be similar to those revealed for SVFs from a variety of laboratory experiments. The toxicity of SVFs is determined by dose (in the lung), dimension, and durability (biopersistence) and strongly influences the degree of pulmonary inflammation and reactive oxidant generation following exposure. Other than its effect on biopersistence, composition does not appear to play a major biological role for SVFs. At this time, it is not known whether the toxicologic properties of MMOFs are determined by the three "D's" and/or other factors such as surface chemicals or polymer composition. Fiber toxicology differs from chemical or particulate toxicology. MMOFs differ from SVFs. While the database for p-aramid RFP toxicology is rather extensive, there exists a paucity of toxicological information on other MMOF dusts. With regard to mechanisms of action, it is unclear whether p-aramid is representative of other MMOF-types. It seems likely that a number of other MMOF dusts will have to be evaluated before one can determine whether the "3Ds" play an important role in MMOF pulmonary toxicology.

E. Future Directions

Risk is a combination of exposure and hazard. Priorities for future toxicologic studies of MMOFs should be based both on potential exposure and demonstrated bioreactivity. In the absence of indications of adverse human health effects in the vast majority of MMOF workplaces, the following steps for further research appear to be reasonable:

Step 1. *Assess Occupational Exposures*. Using PCOM, determine the numbers of airborne respirable fibers/ml in a variety of MMOF manufacturing and processing workplaces.

Step 2. *Identify Composition*. Starting with the higher levels of occupational exposures, identify the types of respirable fiber types using a variety of microscopy techniques.

Step 3. *Toxicology, Tiered Approach*. Again, toxicology studies should start with the MMOF compositions that are associated with the higher human exposures or that appear to be associated with adverse pulmonary effects.

Subchronic or short-term rodent inhalation studies can be used to study respirability (which affects lung dose), nonneoplastic pulmonary effects (persistent inflammation or fibrosis), biopersistence (likely to be associated with more severe biological effects) and mechanisms of action.

Vu and Lai (1997) discuss the need for further research to improve our knowledge base in fiber toxicology and stress the need to conduct toxicity studies and exposure assessment data to more accurately characterize the potential health risk involved. It should be noted, however, that generation of sufficient RFP numbers for inhalation toxicity testing may be difficult to achieve for many MMOFs.

Chronic inhalation studies using rats include an exposure period of 2 years, which requires a very large volume of test fiber. Whereas smaller amounts of relevant test fiber for subchronic studies may be feasible, the creation of a uniform, 2-year supply of respirable-sized organic test samples would be problematic for many fiber types. Furthermore, chronic studies require large numbers of laboratory rats, require several years to complete, and cost millions of dollars. Before embarking on chronic inhalation studies, it would seem logical to first evaluate lung deposition, biopersistence, and toxicity using subchronic and short-term inhalation studies.

In vitro dissolution/degradation studies have proven useful for screening SVFs, but, at this time, are probably of little or no value for MMOFs. The biodegradation of MMOFs is probably dependent on enzymes and other biological agents that are present in lung fluids but not in the current *in vitro* model for simulated lung fluid, which is an aqueous, inorganic physiological solution (Law et al., 1993). More recently developed *in vitro* biodegradability studies, using a different model, may be useful for predicting the biopersistence of MMOFs (Warheit et al., 2000b, 2001). The results of recent cellular and noncellular *in vitro* studies with p-aramid and cellulose RFP correlate well in terms of biopersistence with the findings of inhalation studies (Warheit et al., 2000b).

In this review, we have attempted to document the current database on MMOF dusts with regard to workplace exposures and pulmonary health effects. With the exception of p-aramid RFP, there exists a strong need for the development of hazard information on the potential pulmonary effects of numerous other MMOF dusts.

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