



Health Effects of Asbestos and Nonasbestos Fibers

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Exposures to asbestos and synthetic fibers remain areas of great concern in the field of occupational lung disease. Despite extensive study, the health effects associated with fibers remains an area of substantial controversy. In particular, effects of fibers at relatively low doses, particularly for mesothelioma, remain a matter of evolving opinion, especially when integrated with the divergence of opinion on relative pathogenicity of different fiber types. Mechanistic studies continue to provide a window into pathogenesis and some hope for understanding dose-response relationships at the lower levels seen in contemporary Western workplaces and the general environment. Changes in clinical assessment based on use of new chest imaging techniques beyond the traditional plain film are also an area of evolution and begin to challenge B-reading as the definitive tool for noninvasive assessment of disease. Public health concerns have to a great extent been transported to the developing world where there is a strong trend toward increased use of asbestos, although it has been virtually eliminated from commerce in most developed countries. For nonasbestos fibers, the major unsettled issues are their relative potencies as carcinogens for the human lung and mesothelium and the need to sort out the relation between physical and chemical properties of these fibers and their pathogenicity. The recent discovery of "flock worker's lung" due to synthetic fibers once again alerts us to emerging diseases associated with new technologies. **Key words:** asbestos, asbestosis, chrysotile, man-made mineral fibers, man-made vitreous fibers, mesothelioma, susceptibility. — *Environ Health Perspect* 108(suppl 4):665–674 (2000).

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In this article we examine the current state of knowledge regarding the association of natural and synthetic fibers with fibrotic and neoplastic lung disease. It is well established that inhalation by humans of all forms of asbestos can cause pleural plaques, pleural fibrosis, interstitial fibrosis (asbestosis) of the lung parenchyma, carcinoma of the lung, and mesothelioma, but potency and risk vary with fiber type and exposure history. Numerous epidemiology studies of workers in production, fabrication, and end use (largely construction) have been published, and asbestos is probably the best studied occupational and environmental health hazard. However, important controversies persist, partly because of gaps in science and partly because of different interpretations of existing data. Currently, the most important controversies concern the risks from low-level and ambient asbestos exposure, as well as the magnitude of mesothelioma risk from chrysotile inhalation. These issues are critical not only because of their inherent scientific importance but also because of their profound implications for future asbestos use and use constraints, especially from an international perspective.

Dust control regulations in developed nations have become progressively more demanding compared with the 10–100 fiber/cc exposure concentrations of the mid-20th century. The current U.S. Occupational Safety and Health Administration permissible exposure limit (OSHA PEL) is 0.1 fibers/cc, time-weighted average, for all six fiber types. Although some risk assessments still predict substantial morbidity at these

levels (1), others suggest the presence of thresholds for at least asbestosis (2). Thus, health research objectives have progressed to focus on the effects of much lower levels of asbestos fiber exposure, including ambient exposure in the vicinity of operations that use or process asbestos.

The major asbestos-exposed cohorts that continue to be studied for health effects are construction insulation workers (studied by Selikoff and colleagues), South Carolina textile workers (studied by Dement and NIOSH) and Quebec miners, millers, and factory workers (studied by McDonald and others). The latter two chrysotile-exposed cohorts have undergone detailed exposure reconstructions. Within limits, this has facilitated attempts to examine dose-response relationships and perform risk assessments (1). Although all these cohorts were originally reported on well before the 1990s, new information continues to appear that refines or revises that originally reported with respect to the associations between asbestos and disease. As asbestos uses have been phased out of commerce, many new fibrous materials have been used as substitutes, usually before the health hazard potential has been adequately evaluated.

In this article we discuss asbestos fibers, zeolites, man-made vitreous (mineral) fibers (MMVFs), as well as some newer nonvitreous (organic) synthetic fibers (nylon flock). We emphasize aspects of fibers and health such as fibrosis and mesothelioma not specifically addressed elsewhere in this monograph but cannot completely avoid discussion of lung cancer, which is addressed more specifically

elsewhere in this monograph. Concluding remarks address current policy and research implications of fiber health hazards. The focus of discussion is on information published in the last decade of the 20th century.

Nomenclature, Sources, and Production of Fibers

Asbestos

Asbestos is a commercial term for six different types of naturally occurring fibrous crystals (crocidolite, amosite, chrysotile, anthophyllite, tremolite, and actinolite) composed of hydrated aluminum-magnesium silicates with varying metal composition. The two major classes are serpentine (limited to chrysotile) and amphiboles, which include all the remaining asbestos fiber types, although only chrysotile, crocidolite, and amosite have experienced widespread commercial exploitation. Chrysotile has long relatively flexible fibers, whereas amphiboles are characterized by shorter, rigid fibers. Fiber types sometimes occur in combination, e.g., chrysotile from Quebec, Canada, typically contains approximately 1% of tremolite, an amphibole. Worldwide, about 95% of asbestos produced continues to be chrysotile, and total contemporary annual production of 2.9 million tons is comparable to that of the early 1960s (3). The former Soviet Union is the leading contemporary producer, followed by Quebec, China, and Brazil.

Man-Made Vitreous Fibers

Man-made vitreous fibers, a large subset of man-made mineral fibers (MMMFs), are synthetic, vitreous silicate fibers widely used in present-day insulation and construction industries in industrialized nations, following the decline of widespread use of asbestos materials. MMVFs are broadly categorized into insulation wools (rock wool and slag wool), glass fibers (glass wool, continuous glass filaments and microfibers), and refractory ceramic fibers (kaolin-wool and other high-temperature insulating fibers). There are over 70 varieties of synthetic inorganic fibers (4).

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MMVFs are produced from molten rock, slag, glass, and kaolin clay as well as from combinations of silicon and aluminum oxide. Processes used in manufacture include mechanical drawing, blowing threads or droplets through jets of steam, hot air, or flame, as well as attenuation of droplets of molten liquid by centrifugation. Several additives including fire retardants, binders, wetting agents, and antifungal agents are often incorporated in the production processes (5).

The common-purpose insulation wools, rock, glass, and slag constitute approximately 80% of MMVFs currently produced and are widely used for fire protection, acoustic and thermal insulation, acoustic ceiling tiles and panels, air-conditioning and ventilation ducts, and as growing media for horticulture. Continuous filament glass fibers comprise about 10–15% of MMVF production and are used in reinforcement of cement, plastics, resins, paper and rubber products, for textiles, and for electrical insulation. Refractory ceramic fibers (RCFs) constitute only 1–2% of MMVFs and are used in high-temperature insulation of furnaces and kilns. Other special purpose glass fibers comprise less than 1% of production and are used for high-efficiency thermal insulation in aircraft and aerospace, high-performance acoustic insulation, and as battery separation media. They constitute less than 1% of MMVFs produced and are used in aerospace, high-efficiency filtration, and other high-performance applications (4).

Rock and slag wools were first introduced in the late 1800s. Fiberglass came into use in the 1930s and refractory ceramic fibers have been produced since the 1950s (6). The industrial processes utilized in MMVF production facilities have changed over the years. In the early years of production, batch processes involving labor-intensive and hand-operated production methods as well as poorly ventilated facilities were commonplace. In addition, dust-suppressing agents were not used. Hence, workers employed during this period had high levels of fiber dust exposure. It is also noteworthy that in the early technological phase, contaminants such as asbestos, bitumen, pitch, silica, and formaldehyde were present in many workplaces. The recent phase of MMVF production is characterized by the use of more modern production methods as well as dust-suppressing agents (mainly mineral oil) and resin binders, with significant reductions in levels of respirable fiber exposure (7).

The annual worldwide production of MMVFs as of 1985 was in excess of 6 million tons (8). MMVF products release airborne respirable fibers during both their production and use, and it is estimated that exposure levels of respirable fibers in glass wool production generally have been in the region of 0.1 fibers/cm³;

recent exposures in rock wool and slag wool production are considered to be somewhat higher (8). Much higher exposures may occur among end users such as construction workers when MMVFs are used in confined spaces, as during application of insulation. This parallels the experience with asbestos in which early controls over exposure were applied solely in the production facilities and exposures in the construction/insulation setting were largely ignored until the dramatic epidemiologic reports of the 1960s and 1970s (9,10).

Mechanisms of Fiber-Induced Disease

A detailed account of fiber pathogenesis at the cellular, biochemical, and molecular levels is beyond the scope of this article. The study of the potential mechanisms of pulmonary health effects from fibers has been dominated by a concern for asbestos because of its much better demonstrated carcinogenic and fibrogenic properties, but many of the observations about asbestos have direct relevance or give perspective to understanding the effects of MMVFs and other synthetic fibers. The capacity for asbestos to induce pulmonary and pleural fibrosis in humans is indisputable, whereas the evidence supporting this for MMVFs is limited. Although all forms of asbestos are well-established animal and human carcinogens, the International Agency for Research on Cancer (IARC) (8) categorized insulation wools as Class 2b (possibly carcinogenic to humans), and glass fibers as Class 3 (indeterminate as to whether they are carcinogenic). Present-day concerns about the toxicity of all fibers are based on principles derived from experience with the toxicity of asbestos fibers. In particular, *in vitro* and *in vivo* studies of MMVFs are often designed to replicate studies that have been done with asbestos fibers (11).

Depositional characteristics, biopersistence, and the chemical composition are among the most important determinants of the intrinsic toxicity of any inhaled fiber. Many studies have attempted to understand pathogenesis by microscopic detection and quantification of different fiber types in different areas of the lung (see section "Lung Burden Studies"). Respirable fibers of concern have an aspect ratio of at least 3 and an aerodynamic diameter < 10 μ m, corresponding to a measured physical diameter of less than approximately 3–4 μ m. However relationships between measured diameters, shape, length, and aerodynamic diameter are quite complex as determinants of pulmonary penetrance and deposition of fibers (12). Beyond shape and size, increasing attention is being paid to particle (fiber) chemistry as a determinant of variables such as dissolution behavior, ion exchange, sorption properties, and surface reactivity (13).

Mechanistic studies of fiber health effects have recently proceeded along two major lines: those demonstrating biochemical mechanisms by which fibers induce disease, and those investigating human susceptibility and other host factors that contribute to or mitigate toxicity. New lines of investigation among the latter with important clinical applications are a group of studies beginning to investigate the role of certain enzyme polymorphisms in contributing to disease susceptibility.

Fibrosis from asbestos and other fibers appears to arise from a process of chronic inflammation associated with the elaboration and release of mediators such as lysosomal enzymes, intermediates of arachidonic acid production, proteases, cytokines, growth factors, and reactive oxygen species (ROS) from pulmonary macrophages, neutrophils, and other inflammatory cells. As the inflammation proceeds, fibroblast proliferation occurs and excess collagen is deposited in the lung parenchyma in the area of the offending fiber. Continued exposure and fibrosis results in asbestosis (2,14). The ROS, in particular, hydrogen peroxide, superoxide anion, and hydroxyl radical, can also be produced in cell-free systems, and thus presumably by direct chemical reactions between intrinsic metals on the fiber surface and extracellular fluids (15). Among the most prominent mechanisms hypothesized to account for fiber carcinogenesis is DNA damage from the ROS (15,16).

In recent years a number of investigators have shown the susceptibility hypothesis to have some clinical relevance. For instance, it has been shown that the glutathione S-transferases (GSTs) conjugate a variety of reactive, electrophilic substrates. Deletion of the gene coding for the mu class of GSTs is associated with increased risk for mesothelioma (17), lung cancer (18), and asbestosis (19,20).

Lung Burden Studies

Fiber biopersistence is defined as the retention of fibers in the lung, over time, with regard to their number, dimensions, surface chemistry, chemical composition, surface area, and other physical characteristics (21,22). Long fibers are generally believed to have more biologic activity and therefore greater pathogenicity than short fibers. Experimental studies have shown that fibers that are most carcinogenic for the mesothelium have fiber lengths > 8 μ m and diameters < 0.25 μ m (23). Asbestos fibers that tend to split longitudinally thereby producing thinner and longer respirable fibers are more pathogenic according to this hypothesis, whereas MMVFs (because of their brittleness) tend to split transversely resulting in shorter fibers of reduced aspect ratio (24). Long asbestos fibers are cleared less rapidly than short fibers (25). However, this does not hold

true for all MMVFs. Although long RCFs behave in a fashion similar to asbestos fibers (26), studies of glass wool fibers reveal that long fibers actually are cleared more rapidly than shorter fibers, perhaps because of differences between intracellular and extracellular pH. Thus, although the ability of fibers to induce tumors in lung tissue or serosa is thought to be related to their biopersistence, there are often conflicting data and no clear thresholds (27). These mechanistic approaches to differentiate fiber toxicity have parallels to more clinical investigations of fiber burden in exposed cohorts of asbestos and MMVF workers.

Lung burden studies involve the microscopic examination of lung tissue to identify, localize, and estimate the concentration of different fiber types in different parts of the lung. Light microscopy, electron microscopy, and more recently, energy dispersive X-ray analysis have been used. Although tremolite is present at a low concentration of approximately 1% in commercial chrysotile, lungs of workers exposed to chrysotile have a disproportionate amount of tremolite compared with chrysotile present in the pulmonary parenchyma at autopsy (28). McDonald et al. (29) analyzed autopsy specimens from 78 Canadian mesothelioma cases and matched controls and concluded that there were significant differences in amosite, crocidolite, and tremolite but not chrysotile between the two groups. The results of subsequent studies are subject to conflicting interpretation, but most report a better association of mesothelioma risk with lung concentrations of tremolite than chrysotile (30). Since chrysotile appears to be cleared from the parenchyma more rapidly than tremolite or other amphiboles, the concentration of tremolite may actually be a better exposure (dose) metric for chrysotile than the lung burden of chrysotile itself (31). The paradoxical observation that a number of studies have found higher concentrations of chrysotile than amphiboles in the pleura, even when amphiboles were the predominant exposure, limits the relevance of these parenchymal measurements for delineation of risk of mesothelioma (32,33).

Green et al. (34) examined lung tissue from Charleston, South Carolina, chrysotile textile workers compared with a demographically matched referent group of autopsy deaths from the same hospitals and found that chrysotile levels were 5-fold higher and tremolite levels were 15-fold higher in the workers. This study estimated lifetime individual inhalation exposures. Significant positive correlations were found between lifetime cumulative exposure to asbestos and total lung burden of all asbestos fibers, as well as chrysotile and tremolite fibers individually. Pulmonary fibrosis was correlated with both

cumulative exposure and the concentration of asbestos fibers in the lung, although tremolite provided a better correlation with pathologic fibrosis. The authors concluded that a component of fibrosis in these asbestos workers could be due to asbestos fibers that were subsequently cleared (i.e., chrysotile), which is consistent with current mechanistic understanding of the largely irreversible effects of inflammation in producing fibrosis. The most likely interpretation of these data is that tremolite concentrations in lung are a better metric of asbestos exposure than chrysotile concentrations but cannot necessarily be used to infer differential asbestos pathogenicity. We agree with Stayner et al. (33) that, for both technical and biologic reasons, the lung burden studies of differential fiber types do not clearly support a strong gradient in ability to cause fibrosis and mesothelioma and offer insufficient basis for discounting chrysotile as a cause of either condition.

Although previous work with asbestos indicates that long and relatively thick asbestos fibers have a tendency to become asbestos bodies, there are species-specific variations in the ability of asbestos fibers to become coated in the lung (35). Studies of MMVFs in animals indicate that the synthesis of ferruginous bodies depends on fiber dimensions as well as on the animal model. Holmes et al. (36) instilled glass fibers into hamsters and demonstrated partially coated glass fibers in lung tissue, with the frequency of the coated fibers varying according to the fiber dimensions. The proportion of coated fibers varied considerably in animals killed at the same time. Although Davis et al. (37) found ferruginous bodies in rats exposed to RCFs, Smith et al. (38) did not find ferruginous bodies in rats exposed to fiberglass or RCFs; they did, however, find some ferruginous bodies in hamsters exposed to the same MMVFs. Dufresne et al. (39) used a sheep model of pneumoconiosis to evaluate the long-term effects of glass wool, rock wool, and RCFs on lung tissue. Ferruginous bodies were not found for any of the MMVFs but were present in sheep exposed to crocidolite (the positive control group). Thus, evidence supporting MMVF ferruginous body production in animal models is limited, and it is unlikely that formation of ferruginous bodies from MMVFs could be used as a marker of exposure to MMVFs.

Human data from electron microscopic fiber burden analysis of MMVFs suggest some differences in persistence according to fiber type. Lung tissue samples from 131 workers in a cohort of glass, rock, and slag wool production workers did not show a convincing excess of any one fiber type compared to unexposed controls (40). A study by Sebastien (41) did not yield any evidence for

substantial long-term retention for MMVFs in the human lung. Roggli (24) examined lung tissue from three ceramic fiber workers, one of whom had adenocarcinoma of the lung and parietal pleural plaques. He identified substantial numbers of aluminum silicate fibers that were consistent with RCFs. In addition, he observed a few ferruginous bodies with RCF cores in one patient. These limited findings suggest that the RCFs are deposited in the lung but that other types of MMVFs, including those more commonly used, are not persistent in lung tissue.

Clinical and Epidemiologic Data on Asbestos Health Effects

Nonmalignant Disease

Asbestosis (interstitial fibrosis of the lung parenchyma) typically has a slow subclinical course for many years evolving to a symptomatic phase with the typical presentation of interstitial fibrosis: dyspnea, inspiratory crackles, basilar interstitial opacities, and physiologic restriction. In the 1990s a number of studies of highly exposed workers established that radiographic manifestations of interstitial fibrosis are more common among those who smoke (42). At the lower end of the exposure scale, non-occupational environmental exposure to asbestos in proximity to a factory has been implicated in some cases of asbestosis (43).

Over the past 10–15 years, considerable attention has been focused on the clinical and physiologic effects of asbestos-related pleural disease (44,45). Substantial evidence has accumulated that pleural fibrosis is associated with measurable decrements in forced vital capacity (FVC) and diffusing capacity independent of detectable fibrosis (by high-resolution computed tomography [HRCT]) or alveolitis (by bronchoalveolar lavage) (46).

Experience has accumulated with the use of computed tomography (CT) and HRCT for determination of asbestosis and asbestos-related pleural disease. HRCT is generally regarded as more sensitive than chest radiographs and conventional CT, and HRCT findings correlate with restriction, as described above. Pleural disease can be more readily distinguished from normal chest wall structures, and underlying parenchyma can be imaged in the presence of extensive overlying pleura (47,48). Newer investigations have begun to score HRCT readings quantitatively, and it is noteworthy that in one study that had histopathologic comparisons, the HRCT was normal or near normal in 5 of 25 asbestosis cases (49).

The International Labor Office (ILO) classification of chest radiographs for pneumoconiosis is the established standard for epidemiologic study of the clinical effects

of dusts. Improved imaging techniques such as HRCT may improve the sensitivity of readings, particularly at the low end of the spectrum, although the reading of plain films by two experienced B readers did comparably well in one controlled study (50). The challenge for the future is to integrate use of CT or other advances for screening and diagnosis in a cost-effective manner among the lesser-exposed cohorts of the future.

Mesothelioma

Mesothelioma is a malignant disease of the lining of the chest or peritoneal cavity. The more common pleural mesothelioma classically presents with dyspnea, chest pain, and opacification of one or both lung fields; the case fatality rate is extremely high, with few documented survivors and no effective standard therapy (51).

In the first half of the 20th century mesothelioma was an exceedingly rare disease, with background rates in the United States and Canada for the 1960–1970 period estimated at 2 per million, somewhat higher in males (52). Case reports in conjunction with asbestosis began to appear in the 1930s and 1940s, and by 1960 data from South Africa showed a strong association with asbestos exposure in miners, their family members, and other local residents [see McDonald and McDonald (52) for historical review]. Despite this, debates in the pathology community questioned the existence of primary malignant mesothelioma into the 1960s (53), suggesting the possibility of undercounting in some retrospective epidemiology based on clinical or death certificate records from before the 1970s. The existence of this devastating tumor, as well as its very strong relationship to asbestos exposure, is now undisputed, although some question the extent to which chrysotile causes mesothelioma and the lower limits of the dose-response relationship (54).

The Amphibole Hypothesis of Differential Fiber Toxicity

Over the last quarter century it has become widely acknowledged that crocidolite fiber is the most potent fiber type for causing mesothelioma, whereas chrysotile is the most widely used fiber type. But the relative potencies are controversial, with some, at one extreme, asserting that the potential for chrysotile to cause mesothelioma is minimal (55), and others maintaining that chrysotile because of its ubiquity and substantial although lesser toxicity is the predominant cause of mesothelioma cases (56). Although the evidence can be divided into toxicologic (laboratory) studies, human lung burden studies, and epidemiologic studies, it is the latter two that have engendered the greatest

controversy and disagreement. We now turn to the epidemiologic studies.

In the 1980s, various authors [e.g., (57,58)] began to suggest, primarily on the basis of laboratory pathology observations, that amphiboles were far more carcinogenic than chrysotile, and in particular, that carcinogenic properties of chrysotile, particularly for mesothelioma, were due to its contamination by tremolite fibers. This led to the development of the "Amphibole Hypothesis" (59), enabling some to argue that chrysotile is relatively innocuous with respect to its ability to cause mesothelioma. If this were true, it would allow the global economy to safely focus on strict control of amphibole exposure while expanding the use of chrysotile to take advantage of its many desirable commercial properties. These arguments have been updated (2) and reviewed in detail, with many authors finding them unpersuasive, largely from an epidemiologic perspective (33,60–63).

Substantial new epidemiologic data have emerged in just the past 5 years on the risk for mesothelioma from chrysotile, with or without tremolite contamination, and the nature of the dose response for causation of lung cancer by chrysotile. These are addressed in detail below.

McDonald and McDonald (64) reported a nested case-control study of miners and millers within subregions of Thetford Mines, Quebec, Canada. They found odds ratios (ORs) of 2.55 for mesothelioma and 1.98 for lung cancer (compared to general population controls) in the central mines area, which has been reported (on the basis of limited measurements) to have 4-fold higher contamination of its commercial chrysotile with tremolite than the peripheral area (65). They reported no elevated ORs in the peripheral (lower but nonzero tremolite) area relative to a general population comparison group. Liddell et al. (66) report for the same populations no increase in the standardized mortality ratio (SMR) for lung cancer at < 300 mpcf-years (millions of particles per cubic foot-years) of cumulative exposure, which they state is much lower than any currently permitted occupational exposure, although there are at least issues of noncomparability of the exposure metrics. They reported however, substantial numbers of mesotheliomas and pneumoconiosis deaths at this level, with data suggestive of a dose response.

McDonald (55) recently reexamined the so-called asbestos textile mystery, in which he estimates the risks of lung cancer in South Carolina textile workers to be "perhaps 50 times higher" than in the Quebec miner cohort, whereas the mesothelioma risk is similar and relatively low (between 2 and 5 per 1,000). These data are interpreted by the author to show that chrysotile poses little risk

of mesothelioma at any exposure level, and a fairly low risk of lung cancer at environmental, as opposed to textile-production, levels of exposure.

However, additional data have emerged that challenge the conclusions of these studies that chrysotile presents relatively little risk of mesothelioma. Recently Camus et al. (67) demonstrated a relative risk of 7.6 for mesothelioma in women living (but reportedly not working with asbestos) in asbestos-mining towns in Canada compared to other Canadian communities. There was no comparable excess of lung cancer in this non-worker cohort. The considerable controversy engendered by this article in terms of its relatively low risk for lung cancer (when compared to an existing U.S. Environmental Protection Agency [U.S. EPA] model for environmental lung cancer risk from asbestos) and its relatively high risk for mesothelioma attributable to environmental exposure, speaks to the continuing lack of consensus on the two issues: the carcinogenic dose response for lung cancer from chrysotile exposure and the presence of significant risk for mesothelioma following even nonoccupational chrysotile exposure.

Specifically, commentators argue that the low risk of lung cancer in this non-occupationally exposed group is most likely attributable to predominantly nonrespirable (too large) fibers characteristic of mining and milling (production) operations, as well as to methodologic problems inherent in the use of the U.S. EPA model altogether (68,69). Another criticism of the high risk of mesothelioma was that some of the women with mesothelioma may actually have had occupational or household bystander exposures to amphiboles (70,71). Unfortunately, it is true that explanations for these controversial lung cancer and mesothelioma findings are speculative (67). A definitive process for resolution of such competing explanations from observational data has yet to be identified, and competing interpretations of data are likely to continue because such an observational study cannot be repeated.

In an important effort to address the amphibole hypothesis, Smith and Wright (56) selected for reanalysis or reassessment published studies with the 25 highest incidence rates of pleural mesotheliomas and examined the fiber-type exposure in each study.

Of their top 10 studies, chrysotile was the primary exposure in 2 and was part of mixed exposure in 6; crocidolite was the primary exposure in 3 and was part of a mixed exposure in 5 others. Of their entire 25 studies, chrysotile was the main exposure in 8 and crocidolite in 5 studies. Thus, no clear dominance of amphiboles emerged.

Smith and Wright (56) also reanalyzed data from studies of gas mask workers, often cited as supporting the amphibole hypothesis (72). Because the chrysotile-exposed gas mask workers had only a 20% excess lung cancer risk, Smith and Wright (56) concluded that they must have actually had overall low asbestos exposure and relied on excess lung cancers as a marker of substantial exposure to chrysotile. Others have used a similar argument to proportionately adjust expected mesothelioma risk to observed lung cancer excess (61). Hence, they discount the relatively low mesothelioma rates in gas mask workers originally attributed to the lack of potency of chrysotile and ascribe it to overall low exposure.

Finally, Smith and Wright (56) added additional years of follow-up to a cohort of asbestos cement workers and found the excess of mesotheliomas to be 20% for chrysotile versus 72% for crocidolite, which gave the latter approximately a 4-fold greater potency rather than the often-cited 14-fold greater potency (73). They ultimately conclude that chrysotile is a potent cause of mesothelioma with 25–50% of the potency of crocidolite. Because chrysotile accounts for 95–98% of global asbestos use, they argue that chrysotile causes more actual mesothelioma cases worldwide than the amphiboles.

Low-Level Exposure

Cohort studies of workers have amply documented asbestos-related disease but provide very limited dose–response information at low exposure levels of ambient environmental health concern. Of relevance, Iwatsubo et al. (74) used a large-scale, population-based sample to identify 405 hospital-based cases and controls. Through individual interviews they generated an exposure metric for each case and control on the basis of the probability of exposure, its intensity, and the frequency and duration. This revealed a dose–response relationship with an OR of 1.2 (0.8–1.8) for the low-exposure category versus 8.7 (4.1–18.5) for the high-exposure category, with the categories corresponding to estimated cumulative exposures of 0.001–0.49 fibers/mL-year; 0.50–0.99 fibers/mL-year; 1–9.9 fibers/mL-year, and >10 fibers/mL-year. Although an accompanying commentary raises some solid methodologic questions about inadequacies and potential biases in the retrospective dose–response estimate by a panel of expert industrial hygienists (75), this study, with its detailed and individual exposure reconstructions, represents a benchmark for future investigations. It does not, however, attempt to distinguish exposures according to fiber type. They conclude that there is a significant excess of pleural mesothelioma at levels below regulatory limits. For example, 5 years

at the current OSHA PEL of 0.1 fibers/mL-year would produce a 4-fold excess of mesothelioma (74).

Nonasbestos Causes of Mesothelioma

Asbestos is clearly the main cause of mesothelioma and for a period of time was the only known cause of this disease. A series of studies in the late 1970s and early 1980s demonstrated that certain villages in central Anatolian Turkey had elevated incidences of mesothelioma (up to 50% of deaths) as well as pleural and parenchymal chest film abnormalities characteristic of asbestosis (76–78). Natural exposure from home construction activities using soil containing a fibrous zeolite known as erionite has been implicated as the causative agent. It is both fibrogenic and carcinogenic in animal models. Interestingly, small amounts of chrysotile and tremolite were found in soil from the same region (79). Conversely, mesothelioma has not been observed around geologically similar deposits in the Western United States, although zeolites are not commercially mined in the United States, as nonfibrous synthetics are used instead for commercial purposes (80). Tremolite asbestos has been found in the soil of inhabited California communities, and studies to examine relationships with mesothelioma are under way (81).

Is Asbestosis Necessary for Asbestos-Induced Lung Cancer?

A 1987 article (82) is frequently misinterpreted as strong support for the idea that asbestosis is necessary before there is a carcinogenic risk from asbestos exposure. The highly exposed insulation worker study from which our sample was drawn, with the requirement that all in our subsample had to have had a lung tissue sample available, makes it impossible to sustain such an unhypothesized generalization about causality. Also, there are strong arguments against the hypothesis that fibrosis is a prerequisite for carcinogenicity. This ties in with some of the concerns about the amphibole hypothesis.

Early observations finding an excess of lung cancers in asbestosis cases (83,84) led some researchers to argue that lung cancer occurred only in persons with pulmonary fibrosis. If this were true, it might reflect the increased susceptibility of damaged lung tissue to neoplasia. Alternatively, the fibrosis may simply be a marker of high exposure or of the process of ROS generation, as described previously. However, some recent studies have documented a significant excess of lung cancer incidence in workers who have no radiographic evidence of fibrosis. Hughes and Weill (85) studied a group with asbestos exposure but no radiographic fibrosis and no significant excess of lung cancer, reporting that asbestosis

was necessary. Jones et al. (86) studied 271 lung cancer patients and 678 referents and reported an OR of 1.56 [95% confidence interval (CI):1.02–2.39] even in workers with an ILO reading of 0/1. Case and Dufresne (70) studied the autopsy records and work histories of 111 Quebec chrysotile miners and millers and concluded that the community pathologists' diagnoses of asbestosis seemed arbitrary, and were not sensitive and effective predictors of lung cancer. Egilman and Reinert (87) reviewed 11 epidemiologic studies as well as histologic studies and concluded that these are all consistent with the hypothesis that asbestosis and lung cancer are two distinct pathologic processes with the same dose-related causative agent.

One interesting study of lung cancer has shown that mutations of the *k-ras* gene at codon 12 in lung cancer of asbestos-exposed individuals occurred independently of the radiographic presence of interstitial fibrosis, suggesting that the carcinogenic process, presumably dependent on some of the biochemical genotoxic mechanisms explained above, does not require that the inflammatory process advance to the point of producing visible scarring (88).

Controversy remains about the extent to which idiopathic pulmonary fibrosis is a risk for lung cancer (89), and if so, whether the risk is due to radiographically evident lesions or to the underlying inflammatory process. Despite being cleared from parenchyma sooner than amphiboles, chrysotile may well persist long enough to influence a carcinogenic process through generation of ROS or other mechanisms previously discussed. Many other human carcinogens, including ionizing radiation and benzene, do not require years of residence time to exert their neoplastic effects and are not identified in necropsy tissue with the tumors they cause. At this point there is insufficient evidence to conclude that pulmonary fibrosis (asbestosis) is a necessary antecedent of carcinogenic risk from asbestos.

Health Effects of MMVFs

Chronic Animal Bioassays of Malignant and Nonmalignant Disease

Animal studies of the toxicity of asbestos fibers indicate that there are several potential mechanisms for fiber-induced carcinogenesis. There is some evidence that asbestos fibers generate free radicals that cause DNA damage, interfere with mitosis, stimulate proliferation of target cells, and provoke chronic inflammatory reaction, resulting in the release of ROS, cytokines, and growth factors (15,16). We did not consider bioassays with respect to asbestos because of the widely accepted status of asbestos as a cause of fibrosis and cancer in

humans; however animal bioassays remain pertinent to consideration of the fibrogenicity and carcinogenicity of MMVFs.

The cytotoxicity of MMVFs has been examined in several studies. Luoto et al. (90) showed that MMVFs caused a modest but dose-dependent release of lactic dehydrogenase from alveolar macrophages, activated the release of ROS, and caused hemolysis in sheep erythrocytes. *In vitro* studies by Ruotsalainen et al. (91) examined the effects of glass wool, rock wool, and RCFs on human polymorphonuclear leukocytes (PMNLs) and erythrocytes. MMVFs did not affect the viability of PMNLs (as measured by the trypan blue exclusion test) or induce cell hemolysis, unlike chrysotile and quartz, which caused dose-dependent increases in lactic dehydrogenase and induced hemolysis. However, there is evidence that MMVFs caused a dose-dependent activation of ROS in human PMNLs, with RCFs being the most active inducer of ROS production among the MMVFs tested. Variation in fiber length did not modify the ability of MMVFs to induce ROS production. It is postulated that MMVFs activate ROS production, thereby causing DNA damage, cell injury, and eventually cell death.

The ability of fibers to induce tumors in lung tissue or serosa is generally thought to be related to their biopersistence, although, as we have discussed with chrysotile, this can be complex. Solubility and clearance studies of MMVFs in animal lung tissue indicate that in general, glass fibers are more soluble than rock wool, whereas RCFs are the most durable of MMVFs (92). However, studies of even the most durable MMVFs such as alumino-silicate RCFs show surface morphologic alterations after *in vivo* residence of 6 months in rat lungs, suggesting that RCFs show signs of dissolution and are physically cleared from the lung (93).

Animal experiments have been used in an attempt to determine whether exposure to MMVFs has health effects similar to asbestos exposure. Several studies have clearly demonstrated that MMVFs are highly carcinogenic when injected into the pleural and peritoneal cavities (11), whereas long-term rodent inhalation studies of MMVFs have yielded conflicting findings with respect to production of lung fibrosis and cancer (27,94).

Inhalation studies with glass wool, glass fiber, and slag wool are generally reported negative for fibrosis. Minimal fibrosis was observed in rock wool studies at the highest exposures, but no significant excess of lung tumors was reported (95). Ellouk and Jaurand (11) pooled data on glass wool inhalation studies and found a statistically significant increase in lung tumor development in rodents, whereas studies with slag

wool, rock wool, and glass microfibers were largely negative. Although intrapleural RCF injection studies for mesothelioma were largely negative, intraperitoneal inoculation studies showed statistically significant increases in tumors for glass wool, glass microfibers, and RCFs (11).

Inhaled RCFs induced lung tumors and mesotheliomas in both rats and hamsters, although with some inconsistencies between studies. In one study, inhalations of RCFs in rats and hamsters were negative for lung fibrosis or tumor (94). Mesothelioma was observed in hamsters, but this did not achieve statistical significance. In a subsequent RCF study, however, the results were positive for lung fibrosis and mesotheliomas in both rats and hamsters as well as for lung cancer in rats (6). The latter study also demonstrated a dose-response relationship for lung fibrosis. The differences in the results of the two studies have been attributed to the slightly larger diameter RCFs (4), hence reduced fiber penetration and retention, in the initial study by Smith et al. (94).

Because continuous glass filament fibers tend to have larger diameters, typically 4–7 μm , and were negative in injection studies, they are generally thought to have minimal potential to be carcinogenic. Sufficient animal bioassays for carcinogenicity have not been conducted to completely exclude this possibility, and IARC considers these fibers unclassifiable with respect to carcinogenicity (8,11).

Clinical and Epidemiologic Studies of Nonmalignant Disease

Rock and slag wool have been produced since the 1800s and glass fibers since the 1930s, with remarkably few reports of pulmonary disease due to MMVF exposure. The prevalence of nonspecific respiratory diseases (chronic obstructive pulmonary disease, emphysema, chronic bronchitis, and asthma) has been examined in a number of studies of MMVF workers. Even though there are variations in the study designs, the results have been largely negative (96,97). A study of ceramic fiber workers did not find any association between chronic bronchitis or wheezing and cumulative exposure to respirable fibers. However, there was a significant decrease in the forced expiratory volume and forced mid-expiratory flow related to cumulative fiber exposure in smokers (98). This study concluded that cumulative exposure to respirable ceramic fibers may contribute to airways obstruction by promoting the effects of cigarette smoke. A recent study by Lockey et al. (99) showed a significant decrease in FVC among workers employed in RCF production jobs prior to 1980 that did not persist with analysis of subsequent production

years. The reduction in RCF exposure levels after the 1980s was postulated to be responsible for eliminating any further effect of RCFs on pulmonary function. Lemasters et al. (100) also observed a significant decrease in FVC in men who smoked and manufactured RCFs. However, in women a significant decrease in FVC was found only in nonsmokers. The implications of this intriguing sex difference in response to combined RCF exposure and smoking require replication and further investigation.

Several studies examined chest radiographs of occupationally exposed individuals, and the results have been largely negative for evidence of pneumoconiosis (97,98,101,102). Weill et al. (103) reported radiographic findings of small irregular opacities (ILO grades 1/0 to 1/1) in 3% of glass, slag, and rock wool production workers during an initial cross-sectional survey in 1983. This study was not controlled and was subject to bias from a survivor effect. A follow-up survey of the same workers in 1993 (97) did not find any significant effect of MMVF exposure compared to local blue-collar worker controls and there was also no apparent progression of radiographic opacities in the MMVF workers.

A study of fiberglass workers (end users) by Kilburn et al. (104) reported a 13% overall prevalence of pleural abnormalities and small irregular opacities, profusion 1/0 to 2/1, due to fiberglass exposure. Possible limitations of the study were that there was insufficient information on individual historical asbestos exposure, as asbestos fibers were reportedly present in the production facility (105), and most of the chest film readings were not blinded to exposure. Using the ILO classification, Trethowan et al. (98) reviewed the chest films of employees of seven European plants that manufacture ceramic fibers. Small opacities profusion of 0/1 or greater were found in 13% of the radiographs. Profusion scores of 1/1 or greater were found in 18 of 592 (about 3%), 11 of whom had reported confounding exposures to other dusts. The prevalence of small opacities increased with age, smoking, and previous exposure to asbestos and importantly was not related to cumulative exposure to ceramic fibers. To date, the cumulative evidence of radiographic changes indicative of pulmonary interstitial fibrosis in MMVF workers is inconsistent.

Pleural plaques have been reported in a cohort of RCF manufacturing workers in an ongoing respiratory morbidity and mortality study in the United States. Twenty of 652 (3.1%) workers were found to have pleural changes (pleural plaques and thickening) on chest films. The prevalence was highest (12.5%) in those who began their production jobs more than 20 years ago, for an OR of 9.5. Additionally, 5 of 19 workers (26.3%)

with more than 20 years total employment in RCF production jobs had pleural plaques on chest films, for an OR of 2.2. A dose-response relationship with cumulative estimated exposure was also demonstrated. A nested case-control interview study showed that asbestos exposure did not account for the observed association between plaques and RCF exposure. There was no increase over historical control levels (0.5%) for small irregular opacities that would be indicative of lung fibrosis (99). It is noteworthy that pleural abnormalities were also observed in 16 of 592 films of ceramic fiber workers (two of whom had experienced previous exposure to asbestos) in the European study by Trechowen et al. (98). The pleural changes were related to age but not independently to estimated ceramic fiber exposure. Thus, although the evidence to date does not clearly indicate that radiographic changes of pulmonary interstitial fibrosis are clearly associated with MMVFs, there is substantial evidence in at least one cohort that RCFs caused pleural plaques. The fact that the worst degree of fibrosis reported in any individual from a cohort is 2/1 provides substantial reassurance that MMVFs are not as likely as asbestos or silica to cause morbidity from pulmonary fibrosis.

Epidemiologic Evidence That MMVFs Cause Malignancy

Human Studies

Several large population-based mortality studies of MMVF workers have been published. Enterline and Marsh (100) conducted a study of 7,049 MMVF workers in the United States. Even though SMRs were elevated for most major causes of death for workers with more than 20 years since exposure (4,120 workers), none of the observed excesses achieved statistical significance. In addition, there was no evidence of excess malignant or nonmalignant respiratory disease associated with fiberglass exposure. A Canadian study by Shannon et al. (107) actually found a reduced risk (SMR = 78) in glass fiber workers. There was a statistically insignificant increase in lung cancer deaths in this cohort. These results were supported by a subsequent study of glass filament textile workers in Ontario, Canada (108).

Bertazzi et al. (109) found an increased risk of laryngeal cancer (based on four deaths) in a cohort of 1,098 glass wool and continuous filament fibers workers in Italy. The risk for laryngeal cancer was highest in persons employed before 25 years of age, with at least 15 years of fiber exposure, and with onset of exposure before 1960. The authors could not attribute the excess risk observed to known confounders for laryngeal cancer, and no

other excess risks for cancer or mortality were observed in this study.

A study of MMVF workers in Finland did not show any significant difference in mortality or excess cancer risk (110). Gardner et al. (111) examined cancer mortality in a glass wool plant in the United Kingdom and observed a borderline increased risk of lung cancer among the workers compared to national cancer rates. However, the excess risk had little relationship to the length and duration of employment or to the level of exposure to MMVFs. Claude and Frentzel-Beyme (112) reported similar findings in a study of rock wool factory workers in Germany.

IARC conducted a historical cohort study of mortality of approximately 25,000 MMVF workers in seven European countries (7). This study found an increase in lung cancer mortality risk (SMR = 128) in rock/slag wool workers. The risk increased as the time since first exposure to rock/slag wool production increased. Exposures such as smoking and previous employment were considered unlikely explanations for the excess risk observed. The highest lung cancer mortality risk (SMR = 223) was observed in the early technological phase of production during which worker exposure to high levels of respirable fibers as well as arsenic (component of slag) and polycyclic aromatic hydrocarbons from furnace fumes occurred in the production facilities. Excess mortality was not observed in workers employed in the late technological phase of mineral fiber production when production changes reduced exposures. This study did not find an increased risk of mortality from non-malignant respiratory disease or from pleural tumors. The findings in the IARC study (7) are supported by Boffetta et al. (113), who also reported that workers employed in the early technologic phase of production, particularly rock/slag wool workers, were at higher risk of lung cancer mortality than those in other categories.

More recently, Boffetta et al. (114) reported follow-up data on the IARC cancer mortality study of European MMVF workers. The SMR for lung cancer was significantly increased at 134 for rock/slag wool workers, although not elevated compared to local mortality rates. The associations between lung cancer risk and time since first exposure as well as duration of employment were maintained as in the earlier study, although the trend for increased cancer risk according to the technological phase of production was less marked. This study also reported five deaths from mesothelioma, although the authors did not feel that this represented a clear excess over relevant national rates.

Marsh et al. (115) conducted a follow-up study of over 16,000 mineral fiber workers in the United States. They observed a small but

statistically significant excess of malignant neoplasms (SMR = 108.3) and respiratory tract cancer (SMR = 112.1) in the workers. Mineral wool fiber workers had higher respiratory tract cancer risks compared to glass wool/filament workers. This study reported 4 mesotheliomas. Wong et al. (116) and Chiazzie et al. (96) conducted case-control studies of lung cancer and MMVF exposure, and both studies reported no significant association with exposure, although, as expected, associations were found with smoking.

In summary, MMVFs are a diverse group of synthetic fibers that have biologic activity in both animal and human lung tissue. MMVFs generally differ from asbestos fibers in that a lesser proportion of them are respirable and the inhaled fibers are less durable than asbestos fibers. Nonetheless, there is convincing evidence that some of these fibers, in particular RCFs, are capable of inducing lung tumors in rats and mesotheliomas in hamsters. The data provided by mortality studies are not sufficient to conclude that rock/slag wool causes an excess in the risk of lung cancer, nor do they support complacency with respect to carcinogenicity. Many mineral fibers are respirable and may have contributed to increased lung cancer risk, possibly in combination with other work exposures, particularly in the early technological phases of mineral wool production. Recent convincing studies have demonstrated the occurrence of pleural plaques in RCF workers without concomitant interstitial fibrosis. It has yet to be determined if these pleural changes augur a risk for human mesothelioma. Long-term follow-up studies of the RCF worker cohorts may provide these answers over the next decade. At the present time, significant human carcinogenic risk from any inhaled MMVFs is neither clearly established nor refuted.

Nylon Flock-Associated Interstitial Lung Disease

In 1998, David Kern and colleagues from Brown University in Providence, Rhode Island, described an occurrence of radiographically visible interstitial lung disease that occurred among workers at a Rhode Island nylon flocking plant (117). There was both radiographic and functional improvement, although not complete resolution, after cessation of work. A subsequent pathologic review concluded that the pathologic findings, a lymphocytic bronchiolitis and peribronchiolitis with lymphoid hyperplasia represented by lymphoid aggregates, were distinctive compared with known lung conditions. Although not the only inhalation exposure in the plants investigated, the preliminary concern is that flock, from cut or pulverized fiber (synthetic or natural), used to produce a velvetlike coat-

ing on fabrics, is the causative agent. Preliminary reports of some toxicologic studies support that ultrafine respirable fibrous fragments of nylon can cause acute inflammatory lung injury in rodents (118). The popularity of the processes used in this plant suggests that more cases of "flock worker's lung" are likely to be identified. Additional organic fibers such as para-aramid fibrils, used in the manufacture of bulletproof vests, are being studied in animal models for toxicity. One study reported much less retention and inflammation than long chrysotile fibers (119); no human data are available.

Regulatory Policies for Exposure to Fibers and Research Recommendations

As of 1999, asbestos use was banned in Sweden, Norway, Denmark, the Netherlands, Finland, Germany, Italy, Belgium, France, Austria, Poland, and Saudi Arabia. Groups of knowledgeable scientists have called for a worldwide ban on asbestos mining and use (120,62). This effort is based on estimates of residual lifetime risk for lung cancer (5/1000) and asbestosis (2/1000) (1) at the present U.S. standard of 0.1 fibers/mL and the fact that few if any developing countries are expected to achieve such low levels of exposure (121).

The U.S. OSHA PEL for asbestos is based on fibers > 5 mm long with a 3:1 aspect ratio, counted by phase-contrast light microscopy. For many years the PEL was 5 fibers/cc, but it has been progressively reduced to 2 fibers/cc in 1976, 0.2 fibers/cc in 1986, and 0.1 fibers/cc in 1994. The American Conference of Governmental Industrial Hygienists lists different threshold limit values for different fiber types (2 fibers/cc for chrysotile vs 0.5 fibers/cc for amosite and 0.2 fibers/cc for crocidolite). OSHA does not recognize this distinction. There are no U.S. standards for MMMFs at this time. Sweden imposes an exposure limit for glass fibers of 2 fibers/cc (8).

Different nations have developed various regulatory and economic policies for exposure to asbestos and MMMFs. These range from banning of the former and encouragement of the latter, to increased use of asbestos and only tentative use of MMMFs. Most developed nations are at the former end of the spectrum and many developing nations are in the latter category, largely as a function of cost. Where asbestos is used, different countries (and indeed different agencies within countries) advocate different standards for workplace and ambient exposure. Central to the controversy over asbestos-related disease are observations of very different rates of disease in different parts of the world, related to different fiber types and industrial activities. Modern techniques of exposure assessment

should be applied to better quantify the exposures in these settings (at least, where exposures are ongoing), particularly with regard to differential distributions of particle size and shape. This approach may also contribute to resolution of controversy about relative risks of different types of MMMFs. Discrepancies in the epidemiologic literature must be examined more critically with respect to the type, intensity, constancy, and duration of exposure.

A systematic transnational study of the impact of these policies on the uses, exposure, and health effect consequences of fibers appears overdue. Where policies change, uses and exposures change, affording experimental opportunities to study the impacts of exposure on health consequences.

In some ways we are at a crossroads with respect to research into the health effects of fibers. In the developed nations powerful new advances are being made in exposure assessment and in basic toxicology, especially as applied to susceptibility. These advances, coupled with coherent epidemiologic designs, promise a more fundamental understanding, as well as a personalized risk assessment for fiber toxicity. Many inconsistencies in the current epidemiologic database may be eliminated if prospective studies of exposed individuals can be mounted with the new and developing tools to look at variations in individual responses to fibers and other toxicants.

With increasing use and new applications of asbestos in developing nations, there are ample opportunities to initiate new prospective cohort studies taking advantage of new research technologies. However, ethical concerns of such investigations must be addressed carefully because of the well-documented hazards of asbestos. Although some researchers feel that education and interdiction are a higher priority than further investigation, the fact remains that exposures are presently occurring.

Although new information about cell signaling involving free radicals, growth factors, and cytokines may yet identify interventions that can abort or retard the fibrotic process, the situation is more than complemented by the molecular epidemiology approach toward differential human responses to fibers. The latter seems a more direct approach, well-rooted in clinical exposure issues, toward identification of critical pathways of disease and development of responses. This is a rapidly expanding research area throughout environmental medicine. Although in terms of fibers, research has largely been limited to asbestos, it will greatly augment our understanding of the variation in response to other mineral fibers as well. To an increasing extent, health effects are dealt with through the surrogate of risk

assessment. Changing mechanistic and exposure models may alter how risk assessments for both asbestos and MMMFs should be done (122) as will the incorporation into risk assessments of susceptibility factors based on polymorphisms or other characteristics.

Epidemiologic studies have provided much insight into the pathogenicity and carcinogenicity of asbestos. Inconsistent results among studies, however, point to the omnipresent need to better characterize exposures and vulnerability. Continued tracking of the few long-term cohorts and the study of additional cohorts of people exposed to asbestos under different scenarios will play important roles in further defining the risks from asbestos. Fiber types and sizes, as well as intensity and duration of exposure to these fibers are obvious contributors to disease, yet practical exposure levels below which there is no appreciable risk have yet to be defined.

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