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Human Epidemiology: A Review of Fiber Type and Characteristics in the Development of Malignant and Nonmalignant Disease

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Consideration of the human epidemiology of diseases arising from exposure to naturally occurring and man-made mineral fibers encompasses the several forms of asbestos (chrysotile, crocidolite, amosite, anthophyllite, tremolite-actinolite), other naturally occurring silicates (talc, sepiolite, erionite, attapulgite, vermiculite, and wollastonite), and man-made mineral fibers (glass continuous filament, glass/rock/slag insulation wools, ceramic and other refractory fibers, and glass microfibers). The diseases arising from exposures to some of these fibers include pleural thickening (plaques, diffuse pleural thickening, and calcification), pulmonary fibrosis, lung cancers, mesothelioma of the pleura and peritoneum, and other cancers). Risk factors important in assessing these diseases include assessment of latency, duration of exposure, cumulative exposure, fiber origin and characteristics (length and diameter), other possible confounding occupational or environmental exposures, and smoking. Methodological issues commonly presenting problems in evaluation of these data include assessment of the adequacy of environmental exposures, particularly in regard to fiber identification, distribution, and concentration over the duration of exposure, and the adequacy of study design to detect health effects (disease frequency, latency, and cohort size). Research priorities include further assessment and standardization of pleural thickening relative to fiber exposure, uniform mesothelioma surveillance, further epidemiological assessment of certain silicate and man-made mineral fiber cohorts with emphasis given to assessment of tremolite and small diameter glass and ceramic fibers. Further assessment of possible health risks of the general public should await improved definition of relevant fiber exposure in ambient air.

Introduction

For the purposes of this presentation, only those fibers for which there is some human health effect data or reason for concern will be considered. Such fibers include the categories shown in Table 1.

Table 1. Fiber categories.

Asbestos	Other silicates	Man-made mineral fibers
Chrysotile	Attapulgite	Continuous filament (glass fibers)
Crocidolite (riebeckite)	Erionite	Insulation wool (glass wool, rock wool, slag wool)
Anthophyllite	Sepeolite	Refractory fibers (ceramic)
Amosite (cummingtonite-grunerite)	Talc	Special purpose fibers (glass microfibers)
Tremolite-actinolite	Vermiculite	
	Wollastonite	

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Assessment of Exposure

It has become clear that defining the mineralogical origin of fiber exposure is important to interpretation of epidemiological data. It is necessary to define whether the exposure was to asbestiform fibers or other fiberlike structures such as cleavage fragments. Although assessing the aspect ratio is useful where the general composition of the fiber exposure is known, where it is unknown, further assessment of bulk samples is necessary. This distinction has, for instance, become important in interpreting exposures to talc and vermiculite that may be contaminated with asbestiform fibers.

Previous exposures that members of a study cohort may have experienced may also influence interpretation of epidemiological data, yet data on the previous exposure is often not available or difficult to obtain. In these instances, pathological assessment of lung tissue by using electron microscopy may provide important data from which to better assess epidemiological findings. Occupational mortality data are usually inter-

preted without the benefit of adequate industrial hygiene data in the very important early phase of cohort exposure. When exposures can be reconstructed from previous exposure assessments, confidence in interpretation of results is greatly improved. The availability of previous exposure data has, for instance, increased the confidence in assessment of the risk to chrysotile exposure among South Carolina textile workers (*1,2*).

Assessing relevant fiber dimensions is important in assessing risk to these fibers among those occupationally exposed and also in assessing exposures to the general public, yet these data have not been adequate. Without this information, assessing risk from exposure of the general public must be done with caution. There is a clear need for better definition of fiber characteristics consistent with methods that are applicable to both occupational and community-based epidemiological studies (*3*).

Assessment of Health Effects

Health effects arising from exposure to asbestos are well documented and have been extensively reviewed. The relative importance of these health effects in terms of frequency and severity are, however, sometimes confused. Because mortality is often the only available data, a great deal of emphasis has been given to assessing mortality. Although vital status and cause of death can usually be determined with confidence, other health effects may be ignored or considered less important. When health effects arising from asbestos are ranked in terms of primary cause of death case-fatality rates, the probable ranking is mesothelioma > lung cancer > asbestosis > diffuse pleural thickening > pleural plaques. However, if one considers an estimate of the frequency of disease among those with 20 or more years of occupational exposure to asbestos, the ranking and approximate frequency of disease is significantly different (Table 2). The frequency of nonmalignant health effects and access to living subjects offer several epidemiological advantages not fully realized in assessment of fiber toxicity.

Asbestos-Related Health Effects

Pleural Disease

Until recently, pleural disease (except in cases of marked diffuse pleural thickening) was thought to be of little medical consequence. It is becoming clear that pleural thickening is not benign. Several epidemiological studies of asbestos-exposed occupational cohorts have found those with pleural plaques have significantly lower lung function than those without plaques, and those with diffuse pleural thickening have reductions in lung function more similar to those with asbestosis than those with plaques alone (*4–7*). These findings appear to be independent of smoking and profusion of small opacities. Determinants of pleural thickening manifestation and profusion include time from first exposure, duration of exposure, and average and cumulative dose (*8*). Decline in lung function over time does not appear to be as great as observed in initial cross-sectional results, possibly due to the effects of selection out of the cohort and from diminished fiber exposure (both on the job and from clearance from the lung). There is little information on the relationship between pleural disease and asbestos fiber type; however, a single study (*8*) reported there was a greater likelihood of progression of pleural disease among asbestos cement workers exposed to both chrysotile and crocidolite than among those with chrysotile alone.

Assessing pleural effects is likely to be useful, especially in instances where there is low exposure to asbestos, including assessment of consumers exposed to asbestos-contaminated talc and vermiculite, and certain occupational exposures to asbestos, such as school teachers and others working in asbestos-contaminated buildings. Low levels of exposure to fibrous minerals have been associated with pleural plaques among those living in proximity to those fibers (*9*). Assessment of pleural thickening among family members of shipyard workers has documented asbestos exposure and established increased cancer risk to these nonoccupationally exposed individuals (*10*). Similarly, chest radiographs from the National Health and Nutrition Examination Survey were evaluated by the International Labor Office (ILO) Classification for pleural thickening to obtain estimates of the U.S. population with pleural disease (1.3 million people) and with exposure to asbestos (8 million people) (*11*). It is well recognized that detecting pleural plaques from chest radiographs is much less frequent than detecting plaques at autopsy (*9*). Epidemiological assessment of autopsy data of those exposed to fibers therefore holds additional potential for the use of pleural plaques as useful indicators of fiber toxicity.

It has also become clear that high-resolution computerized tomography (CT) of the chest is very sensitive in detecting pleural abnormalities (*12,13*). The cost of this diagnostic technique, both in terms of radiation and dollars, however, makes it unlikely that this useful diagnostic tool will be widely applied to epidemiological studies. CT may, however, be used in case-control studies of those at increased risk for interthoracic malignancy, such as those with asbestosis and/or pleural disease. CT scans also provide the basis for improving the ILO Classification for pleural abnormalities, widely regarded as the priority for reassessment and standardization. Based on available information, it is unlikely

Table 2. Ranking and frequency of disease among individuals with 20 or more years of exposure to asbestos.

Disease	Frequency
Pleural plaques	40,000/100,000[a]
Asbestosis	20,000/100,000[a]
Diffuse pleural thickening	5000/100,000[a]
Lung cancer	2500/100,000[b]
Mesothelioma	1200/100,000[b]

[a] Estimates based on prevalence data.
[b] Estimates based on mortality data.

that assessment of pleural disease will contribute to our understanding of the epidemiology of manmade mineral fibers.

Asbestosis

Asbestosis has been a uniform finding among those occupationally exposed to asbestos. Studies of asbestos-related nonmalignant respiratory disease have been recently reviewed (*14,15*). The disease is determined primarily by cumulative dose of exposure to asbestos. Available data indicate that asbestosis progresses slowly, even in the absence of exposure, and that progression is significantly affected by average and cumulative dose (*8*) but also by the quality of the chest radiograph and reader variability. Although the ILO Classification has provided a very useful epidemiological tool for the assessment of chest radiographs, it is clear that for epidemiological studies, multiple readers are needed to assess radiographs, especially low profusion radiographs, where reader variability is highest and where any effect of smoking is more likely (*5*). Arbitrary modification of the ILO Classification to use category 1/1 or higher for diagnosis will reduce reader variability (*16*) but introduces a systematic bias that will further underestimate often clinically significant pulmonary fibrosis among those with category 1/0 opacities.

Autopsy results are of epidemiological importance to allow full characterization of pulmonary fibrosis and assessment of residual fibers. Use of autopsy data for fiber characterization is complicated by a lack of understanding of the dynamics of fiber removal from the lung over time. With improved data on this phenomenon by fiber type, such pathological data could be of even greater use to epidemiologists conducting case-control studies of fiber-related diseases.

Exposure to asbestos appears to be associated with the production of autoantibodies and with reduced lymphocyte function (*17*). Further epidemiological inquires are needed to assess the relationship between immune function, asbestosis, and related malignancies.

Lung Cancer

Assessment of lung cancer mortality patterns among those occupationally exposed are consistent with a linear dose-response relationship influenced mainly by cumulative dose of asbestos, an interaction with smoking, and no defined threshold. Lung cancer mortality associated with asbestos exposure has been recently reviewed by industrial sector and fiber type (*18*). Comparing these data is difficult because information regarding early exposures is rarely documented and because the vast majority of cohorts are exposed to mixed fibers. An additional risk factor is industrial sector, which is likely to significantly affect fiber exposure. Generally, those individuals working with industrial sectors where fibers are more likely to be contained in a matrix, such as mining and asbestos cement manufacturing, have lower cancer rates than those individuals working with processes such insulation and textiles who work with processed fiber.

A cohort study of chrysotile-exposed textile workers showed the steepest dose-response relationship for lung cancer and nonmalignant respiratory disease among asbestos workers (*2*). Such processing may well contribute to fragmentation fiber release and thus yield higher exposures to high aspect ratio fibers (*14*) (Table 3). Other explanations of this finding, including contamination with tremolite or exposure to mineral oil, have been suggested, but these explanations lack supporting data (*19*). For a confounding factor to explain an increased risk, documented evidence of the same health effect, sufficient exposure, and a pattern of exposure consistent with lung cancer mortality within the cohort is required. Because tremolite may be a contaminant of chrysotile ore and is known to have the same health effects of other asbestos fibers, further inquiries into tremolite contamination (or lack of contamination) in ore bodies and lungs of previously exposed asbestos workers hold promise for furthering our understanding of the epidemiology of asbestos exposures.

Estimates of the lung cancer risk from nonoccupational exposure to asbestos have been made to guide public policy regarding the use and removal of asbestos products (*14,20,21*). Such analyses necessarily rely on occupational mortality data to drive estimates and require the use of the best available data on both exposure and lung cancer incidence models. Perhaps the most important variable in making these assessments is the validity of the environmental data. Since a high proportion of fibers in community nonoccupational exposures are short and poorly characterized fibers of unknown origin, the extent of risk may be significantly overestimated if these fibers are not asbestos. It is for this reason that the National Academy of Sciences Com-

Table 3. Effects of comminution on properties of polyfilamentous asbestiform fibers.[a]

Fiber diameter, μm	Fiber number/mg[b]	Relative time of fall, $1/d^2$[c]	Aspect ratio, length/diameter	Relative surface area[d]
1.000	4×10^7	1	8	4
0.500	1.6×10^8	4	16	6
0.250	6.4×10^8	16	32	10
0.125	2.56×10^9	64	64	18
0.062	1.024×10^{10}	256	128	34
0.031	4.096×10^{10}	1,024	256	66

[a] Adapted from A. Langer (personal communication, 1983).

[b] If mineral density is assumed to be about 2.80 g/cm^3, 1 mg of dust would contain approximately the number of fibers shown in this column for the diameter shown. The increase in particle number is about three orders of magnitude when length is constant and the diameter of individual particles is decreased to about 3% of initial value.

[c] Falling speed of a fiber is approximately inversely proportional to the square of the fiber diameter ($1/d^2$). A chrysotile fiber with a 0.03 μm diameter takes approximately 1000 times longer to settle (neglecting other factors) out of an aerosol as compared to a 1-μm diameter fiber.

[d] Change in surface area with comminution. Units are relative. Ends of fiber not considered in these calculations. Relative surface area = $2N - 2$.

mittee on Nonoccupational Health Risks of Asbestiform Fibers included no biological effect in the confidence limits of all of its risk estimates (*14*). Detailed studies defining and quantifying relevant fiber exposure in urban air should be conducted in order to provide more accurate estimates of environmental exposure by fiber type from which to estimate cancer risk from community exposures.

Mesothelioma

It is now generally accepted that the risk for the development of mesothelioma is increased among those exposed to amphibole asbestos compared to exposure to chrysotile, which has been less frequently associated with mesothelioma (*22*). Review of mesothelioma data indicates that mesothelioma risk is associated primarily with exposure to crocidolite, amosite, or mixed fibers (*18*). There also appears to be a trend from lower risk exposure in mining and milling (dominated by chrysotile exposure), to manufacturing (dominated by mixed exposures), to insulation (including those in shipyard and railroads exposed to mixed fibers). As with pleural thickening, the risk from mesothelioma is determined primarily by time from first exposure and is independent of smoking. These similar findings are most likely attributable to patterns of deposition and retention of fiber within the lung. Hillerdal suggests that assessment of pleural thickening may provide a useful surrogate for mesothelioma risk (*23*).

As with pleural disease, tracking national mesothelioma rates, as suggested by McDonald (*19*), should provide a useful, but latent, biological marker for extent of asbestos exposure. While newly manufactured asbestos products are predominantly chrysotile, a great deal of amphibole fiber remains in building insulation which will result in future exposures. This is of particular concern among those with asbestos exposure early in life, as the risk from mesothelioma is dominated by time from first exposure. Risk estimates of the NAS Committee on Nonoccupational Health Risks of Asbestiform Fibers found that the lifetime risk to mesothelioma for all groups exceeds that of lung cancer for all groups except male smokers (*14*).

Other Cancers

Risk to other cancers from asbestos exposure has been reviewed by Alderson (*18*) and Doll and Peto (*24*). Apart from cohort mortality studies of insulators, there are inconsistent data regarding stomach cancer risk. Case-control studies for stomach cancer have been generally negative (*24,25*). Laryngeal cancer incidence suggests increased risk with all fiber types and industrial sectors (*18*). Ovarian cancer has been increased in four of the five mortality studies, but two case-control studies were negative (*18*). Further studies on the relationship between fiber type and these and other cancer sites that have been increased in individual studies are needed to better define these risks.

Other Silicate Exposures

Assessing the epidemiology of other fibrous silicate exposures is important, as many of these products are widely used as consumer products, potentially exposing millions of people, and also to extend our understanding of human fiber toxicity. With increasing regulation of asbestos, other silicates are increasing in use, as asbestos substitutes. As a result, there is a clear need to better understand the natural history of these products.

The principal epidemiological difficulty assessing these exposures is identifying adequate study populations (in size and latency). Currently there is but one epidemiological study of attapulgite exposure, which found a significant deficit in nonmalignant respiratory disease, a significant increase in lung cancer among white men, but a significant deficit in lung cancer among black men (*26*). Lung cancer risk was not associated with cumulative dose, latency, or duration of employment except for some increase among those employed for longer than 5 years. There are no data on the risk for pneumoconiosis or pleural disease. There is also only one study of health effects among workers exposed to sepiolite, which found 10 of 63 sepiolite trimmers to have radiographic evidence of pulmonary fibrosis (*27*). No information was provided about type of opacity or pleural disease. Villagers in this area of Turkey were found to have pleural plaques that were associated with white stucco which contained tremolite (*27*).

Assessment of the health effects of talc exposure has been reviewed by IARC (*28*), which evaluated each exposure in regard to whether the talc was contaminated with asbestiform fibers or not. Where exposure to asbestiform fibers has been reported as significant (*29–32*), rates of lung cancer have been increased and related to latency from first exposure. These studies all used interrelated cohorts in upper New York State. It is relevant to note that those occupationally exposed to talcs that are contaminated with tremolite and anthophyllite have also been found to have pleural plaques, diffuse pleural thickening and pulmonary fibrosis (typical of asbestosis), and mesothelioma (*28*). Other studies of talc populations, which are thought to be relatively pure, have trace contamination with tremolite but have not been found to be consistently associated with increased cancer risk. The five cases of lung cancer among Vermont talc miners (*33*) were thought to have had possible radon exposure and previous asbestos exposure at another mine. The question remains whether talc cleavage fragments with aspects ratios of fibers have toxic properties independent of, or similar to, asbestiform fiber contamination.

Recent studies of miners and millers exposed to vermiculite have, as with talc, raised the issue of tremolite exposure as a significant asbestos contaminant responsible for pleural thickening and pulmonary fibrosis typical of asbestos, mesothelioma, and significant dose-related increase in lung cancer. Environmental studies of the Libby, MT, mine and mill have documented significant exposure to tremolite fiber with high aspect ratios

(*34*). Radiographic findings by both Amandus et al. (*35*) and McDonald et al. (*36*) reported dose-related increases in small irregular opacities. Amandus et al. concluded, with certain assumptions, that 5 fiber-years was associated with a 1.3% increase in relative risk for small opacities and suggested, on this basis, that an 8-hr time weighted standard of 0.1 fiber/cc over a working lifetime was not unreasonable. Assessment of lung cancer risk in these cohorts found similar results (*37,38*).

McDonald et al. reported a steeper slope for lung cancer relative risk, possibly due to differences in calculating exposure. Amandus et al. (*38*) reported a slope for lung cancer relative risk intermediate to several other assessments of asbestos dose response. Based on a linear model for individuals examined more than 20 years since hire, an estimated percentage increase in lung cancer mortality risk was calculated to be 0.6% for each fiber-year exposure (*38*).

Two other small cross-sectional studies of vermiculite deposits have reported only trace contamination with tremolite and low levels of asbestos related morbidity (small opacities and pleural thickening) (*39,40*). These small study populations will be important to study over time to further assess the risk from low levels of exposure to tremolite. Those exposed to tremolite-contaminated vermiculite products, both in manufacturing products such as fertilizer and others (including consumers) handling these products, provide potential cohorts for further evaluation of low-level tremolite exposure.

A limited amount of human health effect data is available relative to exposure to wollastonite. Significant proportions of these fibers are longer than 5 μm and are similar to amphiboles in size and shape (*28*). This mineral is used extensively as an asbestos substitute. Evaluations of small study populations for respiratory morbidity in the U.S. (*41,42*) have revealed non-specific increase in bronchitis, reduced lung function and limited evidence of pneumoconiosis. No irregular opacities and no pleural disease was reported among U.S. wollastonite workers. Opacity type was not reported in the two Finnish quarry workers with 1/0 opacities (both had previous fiber exposure), but bilateral pleural thickening was found in 28% of men and one man with long exposure had calcified bilateral diaphragmatic thickening. Preliminary assessment of mortality in the Finnish cohort of 238 quarry workers (5,769 person years) was not positive for cancer, but one malignant retroperitoneal mesenchymal tumor (thought to be difficult to differentiate from mesothelioma) 30 years following first exposure was reported (*43*). Clearly, further follow-up of these cohorts and others exposed to this fibrous mineral is needed.

Exposures to erionite and tremolite in the Cappadocian Region of Turkey have resulted in epidemic pneumoconiosis, pleural plaques, and mesothelioma (*44*). Because of the strength of the association between erionite exposure and mesothelioma IARC (*28*) found sufficient evidence of human carcinogenicity from exposure to erionite. It is interesting to note that the opacities reported by Baris et al. (*44*) were described as rounded opacities, rather than irregular, and that the prevalence of both pneumoconiosis and pleural thickening was greatest in the town where both erionite and tremolite exposures occurred, suggesting a possible contribution from tremolite. These reports from Turkey on small numbers, but highly associated with disease, provide an important example of the value of investigating such unique exposures.

Man-Made Mineral Fibers

The epidemiology of man-made mineral fibers (MMMF) has been recently and extensively reviewed by IARC (*45*) and also by WHO as an Environmental Health Criteria (*46*). Studies of respiratory and other morbidity from occupational exposure to MMMF have revealed only low-level, small opacities, which are both rounded and irregular, depending on the study. There has been almost no pleural disease reported. Some cases of respiratory symptoms and decreased lung function have been reported, but not in association with epidemiological findings of radiographic abnormalities. There does not appear to be an association between MMMF and mesothelioma.

There does, however, appear to be a significant association between some segments of MMMF exposure and lung cancer (*46*). Significantly increased standardized mortality ratios (SMRs) for lung cancer among rock wool/slag wool production workers have been reported in both the large European and U.S. cohort studies (124 and 134, respectively) (*47,48*). Corresponding SMRs for the glass wool production industry were 103 and 109 and for the glass filament production industry 97 and 92 (WHO noted that there were too few data to assess a quantitative dose-response relationship in the latter industry). Potential confounding factors, including cigarette smoking and other occupational exposures (asbestos and arsenic), were not thought to significantly affect lung cancer mortality rates (*45,46*). Cancer rates among rock wool/slag wool production workers appear to be linked to the early technology phase of fiber production with no excess in lung cancer associated with lower fiber exposures in later industry phases (*46*). It was further noted, while not statistically significant, that there was an increase in lung cancer mortality with increasing latency among workers involved in the production of smaller diameter (< 3 μm) glass wool fibers in the U.S., possibly due to increased exposures in that segment of the industry. While there is no epidemiological data yet available on ceramic fibers, it has been observed that exposure levels are perhaps higher among those with this exposure. Given the long, thin fiber dimensions of ceramic fibers, this segment of the industry is a high priority for investigation.

WHO (*46*) concluded that epidemiological data on occupational cohorts were not yet adequate to allow quantitative estimates of cancer risk in the general population. It may be added that there is also a need for quantitative assessment of ambient air for both MMMF

and naturally occurring fibers. Relevant to the potential for any population at risk are analyses by Goldsmith (*49*) who found, based on comparison of dose-response data for certain asbestos pooled data and pooled U.S./European MMMF data, that MMMF appears to be at least as toxic as asbestos in regard to measures of chronic pulmonary disease, including lung cancer.

Priorities for Research

Further assessment and radiographic standardization of pleural thickening in regard to fiber type, distribution, industry, and exposed communities should be conducted. Mesothelioma should be monitored nationally, with further attention on diagnosis and follow-back for relevant occupational and/or environmental exposure.

Cohorts exposed to fibrous silicates, especially those used as asbestos substitutes and in consumer products, should be assessed further to more sharply define risk in relation to asbestiform and nonasbestiform fibers. Detailed studies of ambient community air should be conducted to define and quantify relevant fiber origin and distribution prior to any further quantitative risk assessments for any health risk to the general public from asbestiform, nonasbestiform, and man-made mineral fibers. Finally, we should continue to evaluate MMMF cohorts for cancer incidence, with emphasis on small diameter glass and ceramic fibers.

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