The risk of mesothelioma from exposure to chrysotile asbestos

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Purpose of review

This review assesses the risk of developing diffuse malignant mesothelioma of the pleura from exposures to chrysotile fibers and contrasts it with the known risk of amphibole asbestos.

Recent findings

Although a rare cancer, the mortality rates of pleural mesothelioma continue to be significantly elevated because of past occupational exposures to airborne asbestos fibers. New analyses of occupational epidemiologic studies for highly exposed workers show a substantially lower potency and suggest an empiric threshold for chrysotile compared with amphibole asbestos. Important kinetic and pathological differences between chrysotile and amphiboles have been substantiated that support chrysotile's impotency in causing pleural mesothelioma.

Summary

Excess risk of pleural mesothelioma from past exposures to asbestos, as evidenced by a trend of high incidence rates during the last half century, appears to be the result of nonchrysotile asbestiform fibers. Although scientific efforts and legal arguments continue, the risk of pleural mesothelioma in human populations is probably negligible for exposures to airborne chrysotile asbestos that is not known to be contaminated by amphibole. This distinction for asbestos fiber types is pivotal for understanding hazards and characterizing risks of continued use of natural chrysotile asbestos today and also new nanofibers.

Keywords

asbestos, chrysotile, mesothelioma, risk assessment

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Introduction

There appears to be an emerging assessment that chrysotile asbestos has relatively low mesotheliogenic potency. Comprehensive risk assessments and reviews have been published since 2000 [1–4], confirming that chrysotile fibers are substantially less potent than amphibole fibers in inducing mesothelioma. It has been argued for chrysotile miners in Canada that chrysotile exposure did not contribute to mesotheliomas [5]. A recent, comprehensive review of worker cohorts supports the conclusion that chrysotile fibers do not produce mesothelioma [6••]. Recent experimental data also support a low if existent mesotheliogenic potency of chrysotile.

Structure chemistry

Asbestos is a commercial term used to describe minerals that share certain physical properties and is categorized into two families: serpentine (chrysotile, white asbestos) and amphiboles (e.g. crocidolite, amosite, tremolite, anthophyllite and actinolite). Libby amphibole, erionite, balangeroite and other natural fibers appear to possess amphibole-like properties, but they are found in limited geographical areas.

Each asbestos type has a distinct chemical formula. Asbestos occurs both as asbestiform (fibrous) and nonasbestiform (massive) structures in nature, but each type retains its chemical composition in either form. Chrysotile is a sheet silicate that rolls into nano-sized tubular structures possessing a hollow core (also seen in carbon nanotubes), whereas amphiboles are chain silicates. Chrysotile breaks down into fibrils that have a surface layer of magnesium (brucite). The acid in lung macrophages (or stomach) weakens and destroys the fibrils [7••].

Fiber dose, fiber dimensions, and fiber durability are proposed to be the three primary factors affecting fiber toxicity [8]. Of the multiple clearance mechanisms from the lung to the pleura and other tissues, dissolution rate is a very important factor for comparing biopersistence of fibers, which is a major contributor to mesotheliogenic potency. Consistent with the lack of durability, chrysotile is considerably less biopersistent in the lungs compared with the amphibole fibers. The longer fibers break apart into small particles and smaller fibers that essentially become harmless amorphous silica [7••]. For fibers longer than 20 μm in animal studies, chrysotile asbestos from Calidria and Canadian mines cleared the lungs with a half life of 7 h and 11.5 days, respectively. By 2 days all long Calidria fibers had dissolved or disintegrated into shorter

pieces, and no long Canadian fibers were present after 1 year in the lung. For in-vitro studies under conditions analogous to biological systems, the measured dissolution rate for crocidolite is 40 times slower than for chrysotile [4,9–11].

Chrysotile asbestos exposures

Exposure assessment is required within the risk assessment paradigm along with hazard identification, dose–response assessment and risk characterization. Sustained high exposures to airborne asbestos of yesteryear are unlikely today since strict limits were established almost four decades ago. In work settings studied by epidemiologists, exposures to asbestos fibers were very high during the decades of the twentieth century, preceding progressively more strict exposure controls [6••].

Methods for measuring asbestos fiber exposures have changed greatly over the decades, and speciation of fiber types in air samples has been done infrequently after accurate measurement techniques were established. Count estimates of chrysotile fibers of the past are questionably valid because fibers were neither directly measured nor analyzed; they were not required by regulatory agencies. Phase contrast microscopy (PCM) is necessary for regulatory compliance of Occupational Safety and Health Administration (OSHA) and other agencies, but PCM does not distinguish fiber types, lacks analytical capability and has limited resolution. Transmission electron microscopy (TEM) addresses these limitations and is used in studies now in tandem with PCM, but there are still no health-based exposure guidelines for interpreting the results [12]. In addition, TEM was not available during the pertinent period of exposures in most asbestos epidemiologic studies used for risk assessment today.

In 1968 a specific hygiene limit for chrysotile in workplace air was proposed [13]. Only recently has a job exposure matrix been identified to provide information on exposure intensity and asbestos fiber type and length, designed for interpreting epidemiology results [14]. Exposure monitoring for fiber types obtained prospectively is being carried out. For example, asbestos-monitored truck drivers during World Trade Center (WTC) cleanup operations have exposures mostly to low levels of chrysotile with fiber lengths predominately less than 5 μm [12].

Merely using a chrysotile product does not indicate that exposures are significant (e.g. if fibers are encapsulated in a material). Working with naval gaskets and packing resulted in air concentrations indistinguishable from ambient ship levels or in the general environment [15]. Fiber exposures in the past while servicing car brakes with pads, a chrysotile-containing product with resin material, were found to be very low [16].

Asbestos concentrations in the ambient environment have been reconstructed for the entire twentieth century by using a combination of methods. It appears that chrysotile asbestos concentrations peaked mid century at approximately 0.1 fibers/cm^3, the current OSHA asbestos limit for 8 h, and then decreased in the last quarter of the century [17,18•].

Epidemiology

In the US, age-adjusted mortality rates for 1999–2001 show that males have a six-fold higher rate (22.34) than females (3.94), and the distribution of cases is predominately coastal [19••]. The incidence of mesothelioma in men in the United States increased from the 1970s through the 1990s but is now beginning to decline. Projections are that with reduced exposure, the number of new mesothelioma cases in men will continue to drop and will reach background levels in about 45 years in the US [20]. This pattern is consistent with the long latency of pleural mesothelioma and male workers being highly exposed to asbestos fibers in product manufacturing plants and shipyards until exposure limits became federally regulated in 1971.

Epidemiological studies are the preferred way to determine potential risks and the effects of substances on humans because they provide the most relevant kind of information. Analytical epidemiology includes cohort (i.e. from baseline, well defined populations) and case–control designs, which are sometimes grouped for metaanalyses.

The number of mesothelioma cases has been found to be very low or zero for occupational cohorts exposed to chrysotile. My research efforts in the area identified 71 occupational cohorts in the scientific literature and then classified each report by the type of raw asbestos fiber processed in the workplace (i.e. amphibole only, mixed chrysotile–amphibole, or chrysotile without any identified amphibole). Unless there was other reported evidence indicating that the cohort should be reclassified, this classification was based on information provided in the original study. Fourteen worker cohorts were identified that had exposures to chrysotile without identified exposure for amphiboles. Seven cases of mesothelioma were reported in these cohort studies among those workers exposed to chrysotile asbestos at the studies' plants; however, no pleural mesothelioma case that was reported in those cohorts could be confirmed. Careful review of these few cases illustrates that their exposures were likely mixed, the diagnosis questionable, and the latency period inadequate or unstated [6••].

Crude percentages illustrate the marked differences in reports of cases for the three classifications of cohorts. Among approximately 32 853 individuals exposed to amphiboles, 404 cases of mesothelioma (1.23%) were reported, and mixed fiber exposures resulted in an intermediate percentage of 0.67% cases (994/147 384). In contrast, only seven cases (at most) were observed for 32 039 individuals (0.04%) exposed to chrysotile [6••].

In addition to the chrysotile-only-exposed cohorts, several large cohorts that were exposed to chrysotile fibers contaminated with small amounts of amphibole contain subgroups that did not observe mesothelioma cases. The female cohort of the South Carolina textile workers and a chrysotile miner cohort in Québec are large and well characterized populations with no reported mesothelioma [21–23].

In a multicentered case–control study of 123 mesothelioma patients in South Africa [24], no case with a history of chrysotile mining was identified, and there was no case involving exclusively environmental exposure to chrysotile. Other case–control studies have been reviewed [2].

A metaanalysis of mesothelioma [25,26] was conducted for motor vehicle mechanics, which is another large population of potentially chrysotile-exposed workers that has been evaluated extensively but not as a single cohort. This study evaluated four proportionate mortality, eight case–control and four cohort studies of vehicle mechanics. The authors concluded that there was no association between work as a mechanic and mesothelioma. The consistency in the results of these studies indicates the strength of the reported absence of association.

Li *et al*. [27] published a metaanalysis of 26 cohort studies of chrysotile-exposed workers. They concluded that there is excessive mortality of mesothelioma among these workers. The authors, however, included 12 studies that reported amphibole or similar exposures. In addition to imprecise exposure definition, other methodological issues make their conclusions suspect.

A further metaanalysis [28] evaluated risk of pleural mesothelioma from environmental (not job-related) exposures by asbestos fiber type. The combined relative risk for chrysotile was not statistically elevated for neighborhood or household exposures.

Pathology

A review of the literature indicates that tissue (including the pleural lining) fiber studies cannot be used in isolation to reach conclusions regarding causation [29]. Chrysotile remnants are preferentially ignored because the majority of uncoated asbestos fibers less than 5 μm in tissues are not counted. The contention that very short asbestos fibers (particles) cause mesothelioma is not supported by comprehensive analyses [4,30]. Short (chrysotile and amphibole) asbestos fibers possess the ability to pass through the stomata of the mesothelial lining without causing tissue reaction [31]. In a video-thoracoscopic study of the 'black spots' of the pleura, normal appearing pleura and lung tissue of 14 patients with various pulmonary diagnoses, including three patients with mesothelioma and six without a history of asbestos exposures, amphiboles outnumbered chrysotile fibers in all samples [32]. These results contradict those of several other researchers [33].

Laboratory studies

While epidemiological studies indicate exposure to amphiboles is strongly associated with greater mesothelioma risk than exposure to chrysotile, this difference is not evident in animal studies. The reader is referred to reviews of experimental results that show chrysotile as having mesotheliogenic potency in laboratory animals [3,4,30].

For in-vitro toxicologic tests, some investigators have selected an amphibole – not chrysotile – as the test material because they concluded it has the greatest capacity to induce mesothelioma. Their experiments suggest that mesothelioma may result from the ability of crocidolite asbestos to generate free radicals and disrupt nitric oxide-mediated host regulatory mechanisms. In contrast to chrysotile (and pure tremolite), crocidolite contains much iron (approximately 27%), and iron generates free radicals directly via Fenton-type chemistry [34••]. Nitric oxide-related action of crocidolite is also reported for balangeroite [35]. Although its role is controversial, a recent report of hamster studies revealed that SV40 infection lowers the amount of crocidolite required to cause mesothelioma [36•].

Dose–response relationship

The human risk assessment prepared for the US Environmental Protection Agency (EPA) assigns zero risk to fibers thinner than 0.4 μm and less than 10 μm in length for its optimized exposure index for mesothelioma. Moreover, the hypothesis that chrysotile and amphibole are equally potent in causing mesothelioma, the assumption inherent in the 1986 EPA asbestos document, is clearly rejected ($P = 0.0007$) [4].

The human dose–response curve of chrysotile may exhibit a threshold level for mesothelioma. Ilgren and Browne [37] concluded that the concept of a mesothelioma threshold was supported by evidence from both animal and human studies but identified no specific threshold level for chrysotile-exposed populations. Browne [38] defined the threshold in asbestos-related disease 'as an exposure below which disease will not be epidemiologically detectable'

and reaffirmed identifiable thresholds for asbestos-related diseases. As described above, the epidemiologic studies of exposed workers suggest the existence of an empiric threshold for chrysotile.

Implications for new synthetic nondurable nanofibers

Elucidation of the actual mesotheliogenic potency of natural chrysotile fibers devoid of known contamination by amphiboles has added importance to the rapidly emerging field of nanomaterials. An example is a hemostat solution composed of rapidly biodegradable nanofibers that reportedly cause immediate hemostasis of liver wounds at the nanoscale level [39]. Also, synthetic chrysotile fibers have been manufactured recently that could be used in products, thereby potentially exposing workers and consumers [40].

Conclusion

In terms of medical assessments of causation and for public health evaluations, the contention that airborne exposure to only chrysotile fibers is a risk factor for pleural mesothelioma is disputable. The basis for determining whether chrysotile asbestos causes mesothelioma should rest primarily upon the results of analytic epidemiological studies. Studies have been published of cohorts that were exposed to high cumulative levels of chrysotile asbestos fibers not known to be contaminated with amphiboles, and the results do not justify a conclusion of causation. This finding is reinforced by other relevant investigations of asbestos fibers.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 354–355).

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