Further Evidence for Fiber Width as a Determinant of Mesothelioma Induction and Threshold—Anthophyllite, Bolivian Crocidolite, and Cape Crocidolite

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ABSTRACT

Crocidolite is a well-known causative agent for mesothelioma. However, studies have shown that the pathogenicity of the fiber from different mines varies considerably and it has been postulated the parameter that appears most likely to account for this variation is fiber width although this has never been formally confirmed. To date, crocidolite appears to be the only asbestos mineral for which an epidemiological study comparing the risk of mesothelioma in a population exposed to ‘thin’ fibers with another exposed to ‘thick’ fibers of the same species may be carried out. Finnish anthophyllite, South African amosite, and African Transvaal crocidolite can also be classified as thick fibers, and there is a paucity of mesotheliomas in populations exposed to them compared to those exposed to thin Cape crocidolite. No thin occurrences of these minerals are known. Our previous study looked at crocidolite from several sources. The present study considers the amphibole anthophyllite found in many places in the world. This mineral, regardless of source, does not show the same variation in fiber width found with crocidolite from different areas. All anthophyllite fibers that have been mined may be classified as thick and populations exposed show very low levels of mesothelioma. We suggest the most likely explanation is related to the fiber width distribution and a concomitant reduction in the ‘Stanton fiber size’ fraction.

Keywords: Crocidolite, anthophyllite, mesothelioma, pleural plaques, fiber width

INTRODUCTION

Fiber width has been claimed to be an important determinant of carcinogenicity.¹ However, this has never been formally confirmed despite the abundance of evidence. Thus, the risk of mesothelioma consequential upon exposure to long ‘thin’ amphibole asbestos fibers should be compared epidemiologically with that found in individuals exposed to long ‘thick’ fibers of the same amphibole species. This has not hitherto been done. As described in our recent report,² an opportunity arose several years ago to do so. Shedd³ examined the fiber dimensions of crocidolites from the world’s four crocidolite mining regions namely Cape South Africa, Wittenoom Western Australia, the South African Transvaal, and Bolivia. She found the crocidolite fibers from the Cape and Wittenoom were much thinner than those from the Transvaal and Bolivia, which resulted in a concomitant reduction in the corresponding percentages of ‘Stanton-sized’ fibers (those with length >8 µm and diameter <0.25 µm) (81%, Cape; 67% to 83%, Wittenoom; 45% to 53%, Transvaal; 18%, Bolivian fibers) that correlated with the incidence of mesothelioma being high in the Cape and Wittenoom and very low and apparently absent in the Transvaal and Bolivia, respectively. Shedd³ concluded this was due to the fact that the ‘crocidolites from Western Australia and the Cape Province had more thin (Stanton-sized) fibers than crocidolites from Bolivia and the Transvaal Province’.

The very high incidence of mesothelioma found in the Cape and Wittenoom is well known. Tracing problems preclude detailed studies in the Transvaal. Our recent demographic studies² confirmed the apparent lack of an attendant mesothelioma risk in Bolivia. Here, we provide further evidence for the low potential of thick amphibole asbestos fiber to produce mesothelioma from studies of populations exposed to anthophyllite from Finland and Japan. The findings compared to Cape and Bolivian crocidolite shown to have high³ and low² potential for mesothelioma induction.

ANTHOPHYLLITE AND MESOTHELIOMA INDUCTION

FINNISH ANTHOPHYLLITE

Anthophyllite was first mined from a remote rural area in Eastern Finland 4000 years ago and historically used widely throughout Scandinavia. Numerous studies of the modern (1918 to 1975) Finnish anthophyllite mining and milling workforce have been published.⁴ The mining and milling of Finnish anthophyllite was exceedingly dusty and resulted in numerous cases of asbestosis.⁵ Exposures from the extensive
Anthophyllite deposits in the region of the mine and mill were also sufficient to produce a very high percentage of endemic pleural plaques in residents without any occupational history. Noro said the pleural calcifications in rural Finns living near the anthophyllite districts probably came from contamination of soil or air. The people with endemic pleural plaques residing in the region of the mine failed to demonstrate an attributable mesothelioma excess. Noro said the pleural calcifications in rural Finns living near the anthophyllite districts probably came from contamination of soil or air. The people with endemic pleural plaques residing in the region of the mine failed to demonstrate an attributable mesothelioma excess. Despite such common sources of exposure to anthophyllite, no areas of endemic anthophyllite pleural plaques similar to those found in Finland and Japan have been identified in the United States thus far.

Commercially, anthophyllite asbestos was mined historically on a small scale in at least three states. To our knowledge, the health experience of those operations has never been described nor do we have information about the distribution and use of the products made by any of these mining concerns. Anthophyllite asbestos does not appear to have been used widely in the manufacturing sector in the United States possibly due to its very limited commercial application on a worldwide basis.

Japanese Anthophyllite

A high prevalence of pleural plaques was found in the region of Matsubase on the island of Kyushu. Forty-one percent of Matsubase inhabitants over the age of 40 years showed typical plaques. A large-scale open cast asbestos mine and mill had been in operation in Matsubase between 1883 and 1970, releasing asbestos dust into the environment for a period of approximately 80 years. Most patients had lived in the same residential areas for a long time (i.e. typical of Japanese rural areas). Many were farmers, and only one patient had been exposed to asbestos occupationally. He was a resident of Matsubase, and he showed accompanying pleural plaques. Since no occupational asbestos exposure could be determined in many cases, the pleural plaques were attributed largely to environmental exposure to asbestos originating from the contamination caused by the mining and milling as well as from exposure from non-commercial naturally occurring deposits. A special follow-up system was instituted for 5 years, from 1989 to 1993, to investigate the health of the inhabitants with pleural plaques. The center for respiratory diseases servicing the Matsubase area at the National Kumamoto Minami Hospital failed to find any evidence of a malignant mesothelioma excess. Mass screening programs for lung cancer in inhabitants over 40 years of age were also conducted in almost all towns in Kumamoto since 1986 and the incidence of lung cancer was not found to be higher than in other regions of the Kumamoto prefecture. Hiraoka et al. concluded that the ‘high prevalence of pleural plaques but low mortality rate from lung cancer and no evidence of mesothelioma was in accordance with the characteristics of anthophyllite asbestos exposure’ and said ‘These findings agree with those from an earlier study from Finland’. This noted: ‘anthophyllite is an interesting mineral, causing a high prevalence of pleural plaques but only rarely mesotheliomas’.

American Anthophyllite

There is limited evidence of anthophyllite-induced disease in the U.S. non-commercial anthophyllite asbestos deposits that occur in at least 12 different states. Some of these are in heavily populated areas. As a consequence, anthophyllite is commonly found in the lungs of non-occupationally exposed populations. The sources are not only the anthophyllite deposits but also anthophyllite contaminated chrysotile, talc, cordierite, and phlogopite. Geological similarities also exist between parts of Finland and the United States, thus accounting for the existence of large amounts of anthophyllite in association with cordierite. Despite such common sources of exposure to anthophyllite, no areas of endemic anthophyllite pleural plaques similar to those found in Finland and Japan have been identified in the United States thus far.

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South African Anthophyllite

Phillips and Murray reported a mesothelioma case allegedly due solely to anthophyllite. However, the exposure history given by the authors strongly suggests that crocidolite was also probably present but not detected due to the use of scanning electron microscopy (SEM). Certain aspects of the case also bring the diagnosis into question. The source of the anthophyllite was also not clear.
Australian Anthophyllite

Kottek and Kilpatrick\(^{26}\) said anthophyllite was mined outside of Perth during WWII and then brought to a suburb of the city to be milled. They commented that ‘as the milling of anthophyllite ceased 52 years ago, it is most likely that no environmental cases of mesothelioma have been caused by this source of environmental anthophyllite exposure’.

**THE ROLE OF FIBER WIDTH AND MESOTHELIOMA INDUCTION: ANTHOPHYLLITE COMPARED WITH CAPE AND BOLIVIAN CROCIDOLITE**

The low mesothelioma potential of Finnish anthophyllite has been recognized by various workers\(^{4,0,17,26–30}\) and attributed to increased fiber width.\(^{11,26–29}\) This is consistent with the relatively low percentage of Stanton size fibers found in Finnish anthophyllite (5%–26%) (see Table 2).\(^5\) The same is true for Japanese anthophyllite since increased fiber width was cited as being responsible for the rarity of mesotheliomas observed in rural Kyushu. Similarly, lung burden studies of Japanese residents with pleural plaques showed significantly increased mean fiber diameters (0.84 μm) (Table 1).\(^{31}\) The Cape Crocidolite used in Finland and Japan in some commercial processes was found to be comparatively very thin\(^{11,26}\) (Table 1) with a far greater percentage of Stanton size fibers (Table 2).

These observations also support the role of increased fiber width as an explanation for the low mesothelioma potential of Bolivian crocidolite.\(^2\) The mean width of Bolivian crocidolite (Table 1) and the percentage of Stanton size fibers (Table 2) are thus very similar to Finnish and Japanese anthophyllite. The exceptional width of Bolivian crocidolite\(^6\) is further supported by the fact that it could be mounted as

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**Table 1. Comparison of the Mean Diameters of Anthophyllite and Crocidolite**

<table>
<thead>
<tr>
<th>Country</th>
<th>Disease Type</th>
<th>Finnish Anthophyllite</th>
<th>Cape Crocidolite</th>
<th>Bolivian Crocidolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>Occupational asbestos disease</td>
<td>0.35 μm(^2)</td>
<td>0.15 μm(^1)</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>0.42 μm(^2)</td>
<td>0.09 μm(^3)</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Occupational (no disease stated)</td>
<td>0.61–0.73 μm(^4)</td>
<td>ND(^d)</td>
<td>0.3–0.48(^e); 0.40(^f)</td>
</tr>
<tr>
<td></td>
<td>Mesothelioma</td>
<td>0.35 μm (13% &lt; 0.1 μm)(^g)</td>
<td>ND(^g)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.35 μm(^h)</td>
<td>0.06 μm(^i)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 μm(^l)</td>
<td>ND(^i)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-occupational</td>
<td>0.4 μm(^m)</td>
<td>ND(^i)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6 μm(^n)</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>Non-occupational</td>
<td>0.25 μm(^e)</td>
<td>0.17 μm(^e)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meso (women)</td>
<td>0.33 μm(^l)</td>
<td>0.12 μm(^l)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mesothelioma</td>
<td>0.35 μm(^m)</td>
<td>0.11 μm(^m)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asbestosis (foundry worker)</td>
<td>0.22 μm(^n)</td>
<td>ND(^n)</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>Japanese Anthophyllite</td>
<td>'Cape' Crocidolite</td>
<td>0.84 μm (0.6% &lt; 0.2 μm)(^o)</td>
<td>(27% &lt; 0.2 μm)(^o)</td>
</tr>
<tr>
<td></td>
<td>Endemic plaque</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>'Finnish' Anthophyllite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mesothelioma</td>
<td>0.94 μm(^p)</td>
<td>ND(^p)</td>
<td></td>
</tr>
<tr>
<td>No disease</td>
<td></td>
<td></td>
<td>0.11–0.14(^f)</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\)Not found in Finland; sent from Bolivia to the USBUM.

\(^{b}\)SEM.\(^{25}\)

\(^{c}\)TEM.\(^{34}\)

\(^{d}\)TEM.\(^{35}\)

\(^{e}\)van Orden et al. (paper in preparation)/TEM.

\(^{f}\)TEM.\(^{7}\)

\(^{g}\)STEM.\(^{31}\)

\(^{h}\)TEM.\(^{4}\)

\(^{i}\)STEM.\(^{31}\)

\(^{j}\)TEM.\(^{35}\)

\(^{k}\)Reference.\(^{33}\)

\(^{l}\)Reference.\(^{36}\)

\(^{m}\)Reference.\(^{35}\)

\(^{n}\)Reference.\(^{34}\)

\(^{o}\)Reference.\(^{37}\)

\(^{p}\)Reference.\(^{25}\)

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single crystals under the microscope for fine scale x-ray diffraction (XRD) analysis (Whittaker, personal communication, 1991) and used to determine for the first time the detailed structure of an amphibole asbestos fiber. Similarly, the large width of Finnish anthophyllite also enabled it to be resolved under the optical microscope with phase contrast microscopy (PCM) for special biological studies.

Some suggest that anthophyllite fibers from non-occupational settings tend to be thicker than those seen occupationally. While that is not borne out by the data shown in Table 1, it would not be surprising to find commercial anthophyllite exposures to be composed of a finer fiber population if they had been highly processed. To the extent that was so, it might resemble the situation seen with amosite where fiber dimensional studies of the fiber as mined suggested it was relatively coarse and wide and very few mesotheliomas were consequently reported from the South African amosite mining fields. The intense fiberization required to use amosite commercially created significant thin fiber populations that appeared to be sufficient to cause a mesothelioma risk. However, it is difficult to strictly apply the analogy. Thus, it has been difficult to trace and follow-up the amosite miners and also to be sure that they, as well as those exposed to the commercially processed amosite, did not incur crocidolite exposures, a known potential confounder in those that worked at the UK Uxbridge plant and a probable confounder at the Paterson New Jersey amosite plant as well.

CONCLUSION

The findings of this report and the preceding contribution provide further support for the importance of fiber width in mesothelioma induction. In any sample of long amphibole asbestos fibers, there is a very sizable fraction that can penetrate the deep lung (width <0.6 μm). However, a significant proportion of such fibers particularly those wider than 0.2 μm appear to have a much reduced mesothelioma potential. This has important biological and regulatory implications. Biologically, those thinner than 0.2 μm are more likely to translocate to the pleura, thus explaining in part the reduced potency for mesothelioma of fibers greater than this width. A greater number of such ‘thin’ (<0.2 μm) fibers may accumulate intracellularly than those greater than this diameter. The appearance of a reduced mesothelioma potential for these thinner fibers may therefore also be another manifestation of ‘threshold’ at the cellular level. The regulatory implications are clear since most regulated PCM fibers are wider than 0.25 μm wide. Fiber counts restricted to those visible by PCM may fail to adequately assess the true attendant risks particularly when the mean diameter of the long fiber population is increased. Similarly, counts of fibers composed primarily of cleavage fragments and many types of ‘elongated particles’ will also overestimate the risks since their mean diameters will also be increased.

Table 2. Comparison of the Percentage of Stanton Size Fibers for Anthophyllite and Crocidolite

<table>
<thead>
<tr>
<th>United States</th>
<th>Finnish Anthophyllite</th>
<th>Cape Crocidolite</th>
<th>Bolivian Crocidolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-occupational</td>
<td>5%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ND</td>
</tr>
<tr>
<td>Mesothelioma (women)</td>
<td>26%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>68%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ND</td>
</tr>
<tr>
<td>Mesothelioma (US)</td>
<td>8%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>32%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>ND</td>
</tr>
<tr>
<td>Occupational</td>
<td>ND</td>
<td>8%&lt;sup&gt;d&lt;/sup&gt;</td>
<td>18.5%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>ND</td>
<td>ND</td>
<td>17%-25%&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

Notes

1. As evidenced by the fact that all four of them incurred very high [probably in excess of 50 f.ml (Ref. 29)], long term (13 to 31 years) sufficient to produce very high lung burdens (2.75-1100 f/g lung dry wt.) and concomitant asbestosis.

2. From an area that produced a few million pounds of copper.

3. There are anecdotal reports that anthophyllite was used at the Powhattan Point Baltimore operation making some friction products sent from the Powhattan anthophyllite mine in North Carolina [van Orden pers com]. Anthophyllite deposits in the Greater Region of the City of Atlanta have also been described from Soapstone Ridge and said to be a potential source of significant dust exposure.

4. Anthophyllite from Russia or Bulgaria or other major commercial sources, may also have been used.

5. The high end figure of 26% noted by Dodson et al. was seen in women with mesothelioma largely due to household exposure. Domestic exposures of this kind are thought by some to release a higher percentage of fine fibers, thus accounting for an enhanced mesothelioma inducing potential (Browne, personal communication).

6. To be distinguished from the small percentage of long ‘non-durable’, non-asbestiform Bolivian crocidolite cleavage fragments also found in the deposit. These are probably broken down and removed when the ore is fiberized.

7. Commercial use required special fiberizers (Browne, personal communication, 1997).

8. Earlier unrecognized exposures to asbestos in other facilities may also confound the Paterson studies.
REFERENCES


**Available on request from the authors.