

## LETTER TO THE EDITOR

### **Asbestos, Mesothelioma and Lung Cancer: A Letter From Russia** *Sergei V. Jargin*

To,  
The Editor in Chief  
Pakistan Journal of Chest Medicine

#### **Abstract:**

Health risks from asbestos have been previously estimated on the basis of the past experience, when occupational exposures were much higher than today. Extrapolations were made on the basis of the linear no-threshold dose-response pattern. However, its applicability to low exposures is unproven. Besides, asbestos-related research is loaded by biases. If small quantities of asbestos fiber are found in the lung and pleura, a lesion such as mesothelioma is sometimes attributed to asbestos. Interviews of patients and their relatives after a patient's death sometimes resulted in attribution of lesions to questionable historic exposures.

Histopathological diagnosis of malignant mesothelioma is difficult, the entity is not sharply delineated; and revisions of histological specimens often reveal uncertain diagnoses. Asbestos production and use are banned in some countries, while others continue its manufacturing and exports.

In conclusion, the asbestos-related policies should be reconsidered on the basis of scientific evidence, independent from industrial interests, and internationally coordinated.

**Keywords:** asbestos; mesothelioma; lung cancer; carcinogenesis

Asbestos is a known carcinogen; however, asbestos-related health risks have been estimated on the basis of experience from the past, when occupational exposures were much higher than today; and it has been usual to apply the linear no-threshold (LNT) approach for that purpose<sup>1</sup>. Applicability of the LNT dose-response pattern to the minimal levels of asbestos exposure has never been proven<sup>2</sup>.

Asbestos fibers may be present in the natural environment due to the erosion of surface deposits<sup>3</sup>; inhalation, degradation and discharge of the fibers occur normally, probably being in dynamic equilibrium. It can be compared to other factors that are present in the natural environment.

Use of the LNT hypothesis to estimate risks from low radiation doses was criticized<sup>7</sup>. By analogy with thyroid cancer after the Chernobyl accident<sup>8</sup>, the screening and attribution bias have obviously contributed to the increased incidence of malignant mesothelioma (MM) among people exposed to asbestos. MM is an uncommon tumor; its diagnostic accuracy is relatively low; and revisions of histopathological archives detected considerable percentage of uncertain diagnoses<sup>9,10</sup>. The histologic and immunohistochemical differential diagnosis of MM is complicated and depends on its histologic type: for example, for epithelioid MM it includes carcinomas and other epithelioid malignancies, for sarcomatoid MM - sarcomas and other spindle cell neoplasms, for mixed MM - biphasic tumors such as synovial sarcoma, etc.<sup>10</sup> There are standard approaches to the MM diagnostics in histopathology; however, on the author's opinion, the tumor diagnosed by the standard methods as MM is not necessarily a well-defined single entity, in all cases substantially different from adenocarcinoma or other tumors.

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Cytogenetic studies demonstrated that MM is not associated with any constant chromosomal aberrations<sup>11-13</sup>, thus being not sharply delineated as a separate entity. Together with the high expectancy of MM in exposed populations, all that must have contributed to an overestimation of the incidence. History of exposure to asbestos is not useful to a pathologist in making a diagnosis of MM.<sup>10</sup> In the most cases of MM diagnosed histopathologically no asbestos fibers are seen. However, some researchers, analyzing the cause-effect relationship between exposure to asbestos and MM, measure by special techniques (e.g. light or electron microscopy after digestion or ashing of tissue)<sup>14,15</sup>. At the same time, it is known that MM can be spontaneous also in the presence of asbestos fiber; and factors other than asbestos such as Simian virus 40 infection, ionizing radiation and inherited susceptibility, can play a role<sup>13,15</sup>. Some studies on asbestos and mesothelioma rely on work histories and on patients interviews. It is yet to be clarified what is the difference in carcinogenicity between different forms of asbestos: from the amphibole group (amosite, crocidolite, tremolite, anthophyllite, actinolite) and the serpentines (chrysotile). The US Environmental Protection Agency (EPA) and the Agency for Toxic Substances for Disease Registry (ATSDR) currently adheres to the concept "all fibers equal" in toxicity<sup>16</sup>. It was stated by responsible reviewers that it is only by further research that the controversial issue of fiber-specific potencies would be satisfactorily clarified<sup>17</sup>. There are published data in favor of lesser pathogenicity of chrysotile as compared to the amphiboles. It was also reported, partly in earlier studies, that there are no considerable differences in pathogenicity between the above-named asbestos fiber types. It should be stressed that there are strong economic interests to promote chrysotile, especially in the countries disposing of abundant deposits of this mineral. Some publications favoring chrysotile appear to be biased. There are also publications of questionable impartiality.

The following overview shows that current knowledge regarding comparison chrysotile vs. amphibole is partly conflicting.

Chrysotile was reported to be more rapidly cleared from the pulmonary tissues than the amphiboles<sup>19-21</sup>. However, accumulation of the fibers in the lung is not necessarily a good indicator of their retention in pleura and therefore of the carcinogenic effect. It was reported that chrysotile preferably accumulates in the pleura<sup>22-23</sup>, probably playing a significant role in the MM causation<sup>24</sup>. Chrysotile was reported to be the predominant fiber found in the pleura, while the amphiboles prevailed in the lung, obviously due to the preferential translocation of chrysotile to the pleura<sup>25</sup>. It was reported that there is no difference in potency between chrysotile and amosite in inducing MM<sup>23</sup>; while pure crocidolite, rarely used today, was associated with a higher risk<sup>23</sup>. However, according to<sup>26</sup>, the potency of chrysotile, crocidolite and amosite in producing both MM and lung cancer is approximately the same. Tremolite content in chrysotile products can be of importance for carcinogenicity<sup>27</sup>. It was pointed out in the review<sup>25</sup> that currently available scientific literature does not provide persuasive evidence for the hypothesis that tremolite contamination explains for mesothelioma excess observed in studies of chrysotile-exposed workers. The topic should be clarified by independent research

Some chrysotile fibers can be stiff and brittle like the fibers of the amphiboles, which can be associated with a higher health risk after an inhalation<sup>27</sup>. Longitudinal division of chrysotile (but not amphibole) fibers can result in formation of thin fibrils, not reliably identifiable by electron microscopy, so that the total number of the fibers would increase, possibly together with cumulative carcinogenicity<sup>30-31</sup>. In some animal experiments, the amphiboles and chrysotile were equally carcinogenic, also in the MM causation<sup>32-34</sup>. In vitro, chrysotile was shown to be toxic, to cause chromosomal aberrations and preneoplastic transformations<sup>32</sup>; it was reported to be the most potent inflammatory stimulus among all asbestos types<sup>35</sup>. At the same time, there is evidence from some epidemiological studies that chrysotile is less efficient in MM induction than

the amphiboles<sup>36, 37</sup>. Some epidemiological data favoring chrysotile have later been revised and revised<sup>38</sup>. Conclusions favoring chrysotile as compared to the amphiboles were made in the recent reviews<sup>3,39</sup>.

Human and animal studies indicated that potency of chrysotile was similar to that of the amphiboles. The same was pointed out also with regard to lung cancer<sup>40,41</sup>, which is essential because of its much higher incidence as compared to MM.

Russia is the greatest asbestos manufacturer and consumer in the world. Asbestos-related diseases were extensively studied in the former Soviet Union. The prevailing view in Russian literature is that, if all precautions are observed, contemporary methods of asbestos production and processing are safe; and restrictive measures applied by some countries are excessive<sup>43, 44</sup>. It was concluded on the basis of systematic review of 3,576 MM cases that asbestos and especially chrysotile-asbestos is neither leading nor obligate etiologic factor of MM<sup>45</sup>. Among 69 MM cases studied in Kazakhstan, asbestos exposure was not detected by anyone; while geographic association was found neither with asbestos mining nor with processing industry<sup>46</sup>. It was admitted that the concept about much higher carcinogenicity of the amphiboles as compared to chrysotile has not been confirmed by research<sup>47</sup>. At the same time, statements favoring chrysotile can be found<sup>48,49</sup>; for example (translation from Russian): "Chrysotile fibers are easily solved and discharged."<sup>49</sup> Considering possible translocation of chrysotile fibers to the pleura, discussed above, such a generalization appears to be not sufficiently founded. In any case, the hypothesis about easy solubility can be tested in vitro. Higher solubility of chrysotile was reported in some in-vitro studies reviewed in<sup>3</sup>; but this question should be clarified by experiments in conditions optimally mimicking those in pulmonary and pleural tissues. Decomposition by acids<sup>3</sup> does not automatically mean easy solubility in vivo. The more rapid clearance of chrysotile fibers from the lung can be partly explained by their splitting into thinner fibrils, which can be too thin to be reliably identified by electron microscopy, thus partly remaining uncounted<sup>30</sup>. After the splitting, the fibrils may remain in the pulmonary tissue or migrate towards the pleura<sup>24,31</sup>, continuing to exert their carcinogenic action.

On the author's opinion, current evidence does not provide sufficient support for separate handling of serpentine (chrysotile) and amphibole asbestos by the official regulations. At the same time, the international trade provides for mixing of different asbestos types<sup>50</sup>. The topic has been extensively discussed, being influenced by economic interests<sup>51</sup>. Carcinogenicity and other harmful properties of different asbestos fiber types, and of the man-made substitutes such as carbon nanotubes, should be tested in the large-scale animal experiments independently from economic interests. As discussed above, epidemiological research can be confounded by biases, the optimal approach being chronic animal bioassays<sup>52</sup>. In the meantime, considering the above, the "all fibers equal" approach to the asbestos-related regulations would be not only the simplest and technically most plausible one, it would be also compatible with current knowledge, conflicting as it is. Deviations from the "all fibers equal" concept, if there must be any, must be based on reliable independent research.

In conclusion, asbestos-related science should be separated from the economical interests. Only in this way the issue of carcinogenicity of chrysotile vs. amphiboles could be clarified and, which is increasingly important today, comparison with newly appearing man-made asbestos substitutes i.e. non-asbestos fibers could be reliably performed. In the meantime, considering argumentation from this letter, it would be reasonable to adhere to the "all fibers equal" concept in formulating of policies and regulations. Technologies of asbestos production and processing have improved, and exposures are much lower today than the average levels during the last century.

Thus in conclusion, asbestos-related policies are inconsistent: asbestos production and use are banned in some countries, while others are elevating its manufacturing and exports<sup>53, 54</sup>. Therefore, the policies should be reconsidered on the basis of independent scientific evidence and internationally coordinated.

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