

## **COMMENTS REGARDING THE U.S. EPA'S PROPOSED APPROACH FOR THE ESTIMATION OF BIN-SPECIFIC CANCER POTENCY FACTORS FOR INHALATION EXPOSURE TO ASBESTOS**

My name is Victor L. Roggli, MD, and I am Professor of Pathology with tenure at Duke University Medical Center in Durham, NC. My specialty is pulmonary pathology and I have spent the past 32 years of my career studying the biological effects of asbestos exposure. I have published some 160 articles in the peer-reviewed literature, approximately half of which have something to do with asbestos or asbestos-related diseases. I have also written 27 chapters in textbooks, at least 18 of which have something to do with asbestos or asbestos-related diseases. In addition, I have edited four books and two monographs, each of which has something to do with asbestos or asbestos-related diseases.

I have read the EPA's Office of Solid Waste and Emergency Response's Proposed Approach for the Estimation of the Bin-Specific Cancer Potency Factors for Inhalation Exposure to Asbestos. I commend the investigators at OSWER for all the hard work that they have put into the preparation of this document, and I believe that with this approach, the EPA is on the right track for dealing with exposures that might occur at various superfund sites to fibers of varying sizes and types. Based on the literature which has been published to date on this contentious issue, I would predict that the four-bin model will be the best fit for the available data. I have been asked by Caterpillar Inc., Honeywell, Chrysler, and International Harvester to provide comments. My comments in this regard are as follows.

An extensive review of the published epidemiologic studies on asbestos exposure and cancer by Hodgson and Darnton (2000) found a marked difference in potency between amphibole fibers and chrysotile with respect to the disease mesothelioma. Based on estimated exposures to asbestos fibers 5 microns or greater in length as determined by phase contrast microscopy, these investigators concluded that crocidolite is 500 times as potent as chrysotile, and amosite 100 times as potent as chrysotile. A smaller but still substantial difference (about 10 fold) was also found for lung cancer. An analysis of the literature by Berman and Crump (2003) came to similar conclusions. Based on estimated exposures to asbestos fibers 10 microns or greater in length as determined by electron microscopy, these investigators concluded that amosite and crocidolite are about 700-800 times as potent as chrysotile in the production of mesothelioma. A difference in potency for lung cancer similar to that reported by Hodgson and Darnton was also observed.

There are numerous other studies that have supported these observations. Much of my work has involved analyzing lung tissue samples for asbestos content and comparing the results with various diseases and occupational exposures. Scanning electron microscopic studies that we have performed have demonstrated that 80-90% of mesothelioma cases are asbestos related and that amosite is the main fiber type identified in lung tissue samples.<sup>1</sup> This observation holds across occupational groups and industries that we have examined.<sup>2</sup> Similar observations have been reported by laboratories using transmission electron microscopy.<sup>3,4</sup> Other observers have reported that the relative risk

of mesothelioma correlates with amphibole content of lung tissue samples but not with chrysotile content.<sup>5</sup>

The reason for these differences in potency between fiber types is apparently related to the more rapid clearance of chrysotile from the lung in comparison to the amphiboles. The estimated half life for chrysotile in the human lung is around 90 days, whereas the half life for amosite and crocidolite is 10-20 years. Toxicologic studies have long recognized that biopersistence of fibers is an important determining factor for pathogenicity, including carcinogenicity.<sup>6,7</sup> Manmade mineral vitreous fibers that have long pulmonary residence times are associated with the development of both fibrosis and cancers in the lungs of experimental animals, whereas fibers with shorter residence times are less associated or not at all.

Detractors from this potency difference among fiber types point out that there is a similar mesotheliogenic potential for amphiboles and chrysotile in inhalational studies in rats.<sup>8</sup> However, these studies used equal weights of dust, and it has been determined that the dust clouds in the chrysotile exposed animals contained at least ten times as many fibers as the amphibole exposed group.<sup>9</sup> Furthermore, differences in lifespan of the experimental animals compared to humans would also likely affect the relative potency of the fiber types as the half life of chrysotile becomes a substantial proportion of the animal's lifespan and the very high doses involved did not permit time for effective clearance of fibers.

Opponents of the potency difference also point out in vitro studies showing similar effects of different fiber types. However, these studies, although useful in exploring possible pathogenetic pathways, are not useful for determining relative potency because they cannot take into account in vivo repair of cellular injuries or in vivo differences in clearance and biopersistence of fiber types. Some opponents also raise the possibility of a "hit-and-run" effect, wherein chrysotile is deposited in the tissue, makes irreversible changes that set carcinogenicity in motion, and then is removed from the tissue by the time disease develops. There is no scientific evidence to support such an hypothesis, and indeed, the biopersistence studies of man-made mineral fibers noted above contradict this theory. Furthermore, there are no published studies of disease developing at an increased rate in chrysotile exposed animals in which fibers are not detectable in the lung tissue at the time of disease recognition. In fact, it has been shown that in rats exposed to asbestos for one day and examined one year later, in which subtle fibrotic lesions were found in approximately 25% of first alveolar duct bifurcations, long thin chrysotile fibers were still identified in the tissues by electron microscopy.<sup>10</sup> In addition, we have reported a case of an individual in which mild asbestosis and diffuse visceral pleural fibrosis occurred 39 years after a 7 year exposure to long chrysotile fibers while manufacturing asbestos blankets. Long chrysotile and tremolite fibers were still present in the lung tissue samples at levels in excess of background by scanning electron microscopy.<sup>11</sup>

The second issue that I would like to address is the role of short fibers in the pathogenesis of asbestos-related diseases. The classic studies by JMG Davis and

colleagues failed to demonstrate evidence of pathogenicity (including carcinogenicity) for asbestos fibers (amphibole or chrysotile) less than five microns in length.<sup>12, 13</sup> The reanalysis of the studies by Davis et al performed by Berman and colleagues failed to demonstrate evidence of pathogenicity for fibers less than ten microns in length.<sup>14</sup> An expert panel convened by the ATSDR in New York City in October, 2002 also concluded that there was no convincing scientific evidence that fibers less than 5 µm in length are capable of causing disease.<sup>15</sup> Fiber analysis studies in humans have come to similar conclusions.<sup>5, 16, 17</sup>

Critics of these analyses have pointed to the work of Suzuki and colleagues, who reported that the predominant fiber in mesothelial tissues is short chrysotile (less than 5 µm in length).<sup>18</sup> There are numerous problems with Suzuki's analysis, including the ubiquitous nature of short chrysotile fibers, which contaminate formalin fixative, paraffin embedding wax, Clorox bleach, and other reagents that may be used in preparation of tissue for analysis. Thus contamination issues must be carefully considered and addressed. In addition, many of the analyses performed by Suzuki and colleagues involved an unconventional technique not employed by other investigators. Furthermore, inappropriate controls were employed in the study (the only appropriate control for analyzing mesothelioma tissues would be pseudomesotheliomatous malignancies involving the pleura that are not asbestos related). Finally, analysis of tumor tissue is inappropriate, since whatever fibers may have been present at the time of malignant transformation would have been diluted by the growth of the tumor to form billions of cells. Even if these problems could be addressed, the finding of short fibers in pleural tissues would not prove pathogenicity no more than the finding of the much more numerous non-fibrous carbon particles in the pleura would implicate carbon in the pathogenesis of mesothelioma. In contrast with the studies of Suzuki and colleagues, Boutin et al have shown that long thin commercial amphibole fibers accumulate in 'hot spots' in the parietal pleura which correlate with the sites of origin of mesothelioma.<sup>19</sup>

I would like to make one additional comment regarding the data in Table 10-1 of the Proposed Approach for the Estimation of the Bin-Specific Cancer Potency Factors for Inhalation Exposure to Asbestos. In this table, the amphibole fraction for Chinese chrysotile as reported by Yano et al (2001) is 0. Tossavainen has shown that Chinese chrysotile is contaminated with tremolite at approximately the same level as Canadian chrysotile from Quebec.<sup>20</sup> Furthermore, analysis of the lungs of Chinese chrysotile miners and millers by Tossavainen demonstrated a similar ratio of tremolite to chrysotile as found in the lungs of Canadian chrysotile miners and millers. I would suggest that the amphibole fraction in Table 10-1 for Chinese chrysotile should be the same as for Canadian chrysotile, or at minimum, the analysis should be run with both assumptions to see which gives a better fit and agreement with other published data on cancer risks from chrysotile exposure.

Thank you for your time and consideration on these important issues.

**Victor Roggli**

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