

and Kuschner (Ex. 84-210) injected asbestos intratracheally into guinea pigs and found fibrosis only with fibers longer than 10 μm (Ex. 84-128). NIOSH (Platek et al., Ex. 84-240) conducted inhalation studies in rats with chrysotile fibers less than 5 μm in length and did not find increased incidences of pulmonary fibrosis or tumors compared with incidences in controls. Since NIOSH has difficulty in generating fibers with an aspect ratio of 3:1 or greater by the ball milling method and in counting the fibers, the NIOSH results only suggest that short fibers do not induce pulmonary fibrosis or tumors. However, studies conducted by Koler (1982) and Pott et al. (1972, 1976), as discussed by the National Research Council (Ex. 321, p. 182), suggest that amorphous asbestos and fibers shorter than 5 μm can induce mesothelioma in rodents, a finding that contrasts with the findings of other animal studies reviewed above.

One problem with the studies conducted by Stanton et al. (Exs. 84-193, 84-195) was the difficulty in generating asbestos samples with fibers of uniform lengths; because of this difficulty, the authors could not conclude that short asbestos fibers were safe despite the finding that exposure to shorter fibers were associated with lower tumor incidences in animals. At the hearing, Dr. Davis (Tr. 7/9, pp. 20-28) discussed some of his findings from rat inhalation and injection studies that used carefully prepared long- and short-fiber samples of amosite. For the inhalation experiment, rats were exposed for 12 months by inhalation to amosite samples of varying fiber lengths. Animals were observed for their full lifespans. Davis observed 13 tumors, as well as extensive lung scarring, in 40 animals exposed to the long-fiber dust. No tumors or scarring was found among animals exposed to the short-fiber dust (Tr. 7/9 p. 28). The amosite samples were also injected into the peritoneal cavities of groups of 25 rats. The long-fiber sample produced mesotheliomas in 95 percent of the animals treated, while the short-fiber sample produced only one mesothelioma tumor. Dr. Davis concluded from these studies that short asbestos fibers were "... unable to damage tissues" (Tr. 7/9, p. 28).

Researchers (Ex. 86-4) have also found that a significantly higher percentage of long fibers (greater than 5 μm) are retained in the lungs of mesothelioma and asbestosis victims. Morgan (Ex. 86-3) showed that anthophyllite fibers less than 5 μm in length were more easily cleared from rat lung than larger fibers. It has been well

established that shorter fibers are readily engulfed by lung macrophages and transported to the mucociliary escalator or to the lymph system (Exs. 86-3, 86-4, 236-A, 321, Tr. 7/9, pp. 5-6).

Several researchers (Exs. 86-3, 84-210, 86-4, 236-A, 321, Tr. 7/9, pp. 5-8) have theorized that the greater biological activity of longer fibers may be due to the inability of the macrophage to completely engulf the fiber. This may lead to the release of lysosomal enzymes and oxygen-free radicals from the macrophage, damaging alveolar epithelial cells and initiating fibrosis. In addition, the fibers may disrupt the normal proliferation and differentiation of lung fibroblasts either by directly interacting with the fibroblast or as a result of macrophage secretions.

Since the November proposal, OSHA has received much comment and testimony regarding the relative importance of fiber size, aspect ratio, and surface chemistry of the fiber to carcinogenic potential. Most of these commenters expressed the view that the surface chemistry of the fiber is an important determinant of disease. Dr. Dunnigan of the Université de Sherbrooke (Ex. 91-15, p. 391, attachment) cited studies and comments of several investigators that were presented at the World Symposium on Asbestos (1982) that point to chemical factors rather than geometric or physical factors as the important determinant of asbestos fiber effects on the cell membrane. They postulated that asbestos fiber interaction with cell membranes causes cell homolysis. Mossman et al. (Ex. 321, p. 39) found asbestos-induced cell damage to be initiated by the reaction of the fiber with the plasma membrane, which causes cell lysis or phagocytosis. The National Research Council, National Academy of Sciences (Ex. 321) cites the work of Wilkinson (1976) and Stossel (1972), who found that recognition of the asbestos fiber by phagocytes and their subsequent ingestion of the fiber may be due to physicochemical affinities between the fiber and the phagocyte. A study done by Light and Wei (Ex. 91-15) stated that "fiber dimensions are important in determining whether asbestos fibers are able to reach sites where critical cellular interactions take place, and thus could govern whether the potential biological activity of fibers due to their surface charge is displayed" (Ex. 91-15, p. 391, attachment).

Dr. Dunnigan (Ex. 91-15-2, p. 393) contended that, in view of studies suggesting that modification of the fiber structure affects the biological reactivity of the fiber, the "Stanton Hypothesis"

(see Exs. 84-193, 84-195) should be reassessed. He argues (Ex. 227-A, Table 4) that this hypothesis assumes that all comminution methods merely reduce the dimensions of the fibers without altering other fiber characteristics. To illustrate that this may not be the case, Dr. Dunnigan (Ex. 91-15-2) cites a 1978 study by Arthur Langer that showed that "ball milling of experimental [asbestos] samples results in important changes in the structural and surface characteristics of asbestos fibers, and reduces their effects on all membranes" (Ex. 19-15-2, p. 393). He also cites a 1980 report done by Dr. Spurny in Germany that concluded that "milling procedures change not only the size distribution, but also the shape and crystal structure of asbestos fibers" (Ex. 19-15-2, p. 393).

In a further elaboration of the evidence against the fiber size theory, Dr. Dunnigan cited a study done by Poole et al. (1983) that shows erionite fibers (in a concentration of 150 f/ μg mineral) of the "pathogenic" size range are more reactive than a larger number (1.6×10^6 f/ μg) of similarly sized crocidolite fibers (Ex. 227-A-4, p. 12). Studies by Suzuki (1980), Wagner, (1982), and Maltoni et al. (1982) were also cited by Dr. Dunnigan (Ex. 227-A-4) as evidence that fibrous erionite is the most powerful mesothelioma-producing agent, suggesting that these fibers may display disruptive or catalytic properties not shared equally by other types of fiber.

OSHA believes that the animal studies discussed above, in particular the recent work by Dr. Davis, point to a clear relationship between fiber dimension and disease potential. The finding in these studies that thin fibers (i.e., having an aspect ratio of at least 3:1 greater than 5 μm in length) are associated with elevated incidences of cancer and lung fibrosis is also consistent with current knowledge regarding lung clearance mechanisms, i.e., that shorter fibers are easily phagocytized and removed from lung tissue. OSHA also acknowledges recent findings that interactions between fibers and cell surfaces, in part, may also determine the course of asbestos-related disease. However, the mechanisms of fiber-cell interactions and their role in disease causation are not clearly understood at this time.

Some chemists have also suggested that the biochemically active sites or the electrical charge of the chemical groups on the asbestos fiber surface can be modified to reduce the hazardous potential of the fiber (Ex. 84-333). *In vitro* tests of modified asbestos fibers have shown decreased toxicity