

ASBESTOS MECHANISMS OF TOXICITY WORKSHOP



Chair's Summary of Workshop Comments **Workshop Chair – Dr. Kevin Driscoll**

The U.S. Environmental Protection Agency (EPA), Office of Solid Waste and Emergency Response, conducted the Asbestos Mechanisms of Toxicity Workshop in Chicago, IL on June 12-13, 2003, to review the most recent state of the science on asbestos toxicity. Discussions at the workshop focused primarily on molecular and cellular mechanisms of toxicity, lung disease, the pathogenesis of pleural plaques, and dose response.

EPA selected ten scientists to serve as expert panelists at the workshop. The panelists have extensive expertise in related fields, such as mechanistic toxicology, pulmonology, and risk assessment. Before the workshop, each panelist reviewed the recent peer-reviewed literature in his or her respective area of expertise. Following presentations, the panelists participated in discussions focused largely on charge questions submitted by EPA prior to the conference.

For detail on the workshop content see the individual speaker abstracts and speaker presentation slides. Below are summarized several areas related to asbestos toxicology, which were either areas of general agreement among the panelists or areas where it was clear consensus did not exist.

Chemical/Physical Properties Influencing Biological Activity

There was agreement that the size and shape of asbestos fiber are important determinants of bioactivity. It was also generally recognized that size and shape do not entirely explain the biological activity of asbestos. Other factors such as surface composition and, in particular, iron that is available to catalyze or otherwise participate in chemical reactions, are important factors influencing asbestos fiber bioactivity.

It was generally agreed that long thin fibers are of particular importance in contributing to the mesotheliogenic activity of amphiboles.

A point of disagreement was the importance of short, thin, high aspect ratio fibers in pleural reactions to amphiboles. Existing animal or other data do not appear to have adequately addressed the potential importance of short (e.g., ≤ 5 micrometer) very thin amphibole fibers in pleural disease.

Role of Fiber Type in the Mesothelioma Response Associated with Asbestos Exposure

The panelists agreed that the amphiboles studied to date in animal or epidemiological studies are more potent than chrysotile at producing mesothelioma. It was noted that some comparisons have suggested a potency difference of 10-500 fold between the amphibole and serpentine fibers.

Role of Fiber Type in the Lung Cancer Associated with Asbestos Exposure

There was not agreement with respect to asbestos fiber types and ability to produce lung cancer. Several panelists suggested the amphiboles might be more potent. However, other factors such as the dominant role of cigarette smoking in lung cancer and potential interactions between cigarette smoking and asbestos

as well as uncertainties about mechanism of action preclude a clear determination of fiber type specific effects at this time. It was agreed that the current epidemiology data does not clearly differentiate between amphibole and serpentine asbestos for human lung cancer risk.

Fiber Biopersistence/Clearance

Based on the presentations and discussion, it was apparent that there is general agreement that fiber biopersistence is considered an important factor contributing to the potential to produce adverse responses in the lung and pleura. The biopersistence of chrysotile was generally accepted as being less than the biopersistence of crocidolite, amosite, and tremolite.

Mechanisms of Asbestos Lung and Pleural

The precise mechanisms of asbestos-induced disease have not been fully elucidated and it is likely that multiple and overlapping mechanisms exist. Studies have clearly shown that asbestos fiber can stimulate mesothelial and lung cell proliferation, activate intracellular signalling pathways and modify protooncogene/tumor suppressor gene expression. There was disagreement amongst the panel about the requirement for direct fiber-cell interactions to produce pleural responses versus secondary effects on the pleura due to inflammatory mediator or cytokine release.

Confounding Effects

There was general agreement that cigarette smoke exposure has confounding effects on asbestos mechanisms and lung disease progression.

Characteristics of Libby Tremolite

As part of the discussion, the characteristics of Libby tremolite became a topic of debate. An audience participant from the US Geological Survey stated that the Libby tremolite fiber is not much thinner than other tremolite fibers. However, panelists held the view that Libby fibers are not classic tremolite cleavage fragments, but are very thin with high aspect ratios. It was also noted that the Libby fiber is a long, often thin, fiber that resembles amosite in size characteristics. Such long fiber tremolite behaves more like amosite and is a relatively potent mesothelial carcinogen; it also is fibrogenic at sufficient doses.