MULTIPLE MODES OF ACTION OF ASBESTOS AND RELATED MINERAL FIBERS

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“Asbestos” is a generic term that encompasses multiple fiber types but may mean different things, depending on the scientific discipline. This lack of consistency among asbestos research communities can lead to a disconnect when comparing studies in asbestos research. Differences in the interpretation of asbestos definitions between disciplines lead to discrepancies in the results and their interpretations from the research analyzed. A comparison of the health and environmental impacts of various asbestos fibers is not possible without consistency in how these fibers are defined. A grasp of these issues is important to fully understand the state of the science of asbestos research.

A respirable environmental dust like asbestos may work through more than one mode of action (MOA), with multiple MOAs for various health outcomes following exposure to the same particulate (e.g., interstitial fibrosis versus lung cancer versus mesothelioma). A mode of action encompasses a sequence of key events and processes that begin with the interaction between fibers and cells that may result in both cancer and complex noncancer health effects. The complexities of fiber toxicity make it difficult to define one MOA for asbestos in general. Further, the potential overlap of multiple MOAs makes it feasible to assume that there is more than one MOA acting at any given time to lead to the same adverse health effect. Key questions still remain to be answered in understanding asbestos-induced health effects, particularly related to the mode of action of asbestos. Discussion of the different viewpoints and supporting data surrounding these ongoing questions, including the role of short versus long fibers in asbestos-induced disease, translocation of different fiber types to nonpulmonary tissues, and variable potencies of multiple fiber types, are included in the following review papers. Despite decades of research, many questions still remain about the role of specific fiber characteristics in disease. Unfortunately, many early research papers in the field did not describe all specific characteristics in the publications, and these details are needed to inform the role of specific characteristics in specific effects from fibers. There continues to be a discussion about what characteristics of fibers lead to specific adverse health effects, and the relative potency of the different types of fibers. Understanding of the role of these characteristics in different MOAs may shed some light on this issue and help to address these differences in biologic response to various fibers. When studying fibers, the determinants of toxicity include length, width, chemical composition, durability, surface areas,
and surface reactivity (such as surface charge or associated reactive elements).

Individual determinants may play a key role in specific toxic endpoints; however, it is more likely that the adverse health outcomes are the result of the interaction of multiple determinants of toxicity. This may help to explain the large variability in response to fiber exposures. When possible, any known fiber characteristics should be described in order to determine the role for these characteristics in toxicity. While there are many opinions and theories on which fiber characteristics are the key determinants of toxicity, there is no consensus in the field on specific endpoints.

To address these issues, a workshop was held in December 2009 to discuss the current state of the science for the mode of action of asbestos. The main goal of this workshop was to review the current knowledge related to mechanisms resulting in asbestos-induced health outcomes and to define data gaps and research needs for understanding the role of asbestos and thus potentially other morphologically similar structures in inducing disease.

The basis of the following review articles is the current state of the science of asbestos research as it relates to mode of action and mechanisms of different disease endpoints. These are divided into health endpoints by tissue (pulmonary, pleural, and nonpulmonary) or overarching issues, including susceptibility, genotoxicity, and effects from environmental exposures. With these arbitrary divisions of topics, there is some overlap of topics in the review articles expected. In many cases, varied viewpoints are discussed and cross-referenced between the articles when this occurs.

**SUMMARY**

It is recognized that there are still many data gaps in the field of asbestos research. Workshop participants agreed that these gaps should be addressed with a structured, interdisciplinary, and well-funded research program. Despite the breadth of literature available on many asbestos fiber types, there is a lack of cohesiveness between most studies. There is considerable literature regarding mechanisms of asbestos-induced diseases; however, there often exists difficulty in comparing findings between studies and the models used and the characterization of the asbestos used, not to mention the variations of terminology for defining the fibrous particulates in a given study. The comprehensive reviews from this workshop will assist in better defining research approaches and initiatives that will advance our ability to prevent adverse health effects arising from exposure to asbestos and morphologically similar particulates.

This issue of the *Journal of Toxicology and Environmental Health* includes all of these critical reviews of asbestos, with the goal of informing the mode of action of asbestos and determining data gaps and research needs in the field.