Comments on "Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research" – By Paul Middendorf, Ralph Zumwalde, and Robert Castellan, NIOSH Mineral Fibers Work Group

David Lai, Ph.D., OPPT/U.S. EPA
Feb. 28, 2007

Thank you for the opportunity to review this draft document.

The document identifies several current issues concerning asbestos and other mineral fibers and outlines a research strategy to reduce the uncertainty and provide the scientific foundation for potential development of new policies for NIOSH.

Specifically, this *Roadmap* proposes to address three strategic goals: (1) to develop improved sampling and analytical methods of fibers; (2) to develop information on occupational exposure and health outcomes of various types of fibers and fiber-like cleavage fragments; and (3) to develop broader understanding of the important determinants of toxicity of fibers and fiber-like cleavage fragments.

This *Roadmap* is timely addressing these fiber issues as they are not only related to occupational exposure and important to NIOSH but are also important to EPA as they are also related to a number of recent findings concerning health hazard of the general public: *e.g.*, asbestos contamination at the vermiculite mine near Libby, MT.; asbestos-laden dust in El Dorado Hills, CA.

The research program proposed by this *Roadmap* is comprehensive and scientifically sound. The first two strategic goals proposed are especially important as the sampling and analytical methods used earlier are outdated and these goals are dealing directly with occupational exposure settings and studies on workers. In real situations (as in Libby, Mont. and El Dorado Hills), workers are actually exposed to mixtures of fibers with diverse sizes and chemical structures. Human data are particular valuable not only because rodents may be less sensitive but also because of the evidence there is synergistic effects between fibrous and nonfibrous particles in toxicity. For the same fiber exposure, the RCF test sample contained more short fibers and nonfibrous particles has been shown to be more toxic (Brown et al., Inhal. Toxicol. 3: 99-107, 2000). Davis et al. (Int. J. Exp. Pathol. 72:501-525, 1991) exposed rats to mixtures of asbestos and either TiO2 or quartz particles by inhalation. Mixed fiber particle exposures induced twice the incidence of lung cancer and mesothelioma compared to that in the asbestos alone groups.

Regarding the third goal, the mechanisms of carcinogenic action and important determinants of toxicity of fibers have been well established based primarily on studies on asbestos (e.g., IARC Sci. Pub. No.140, 1996). There appears to be a general belief that fiber dimension and tissue burden, which is determined by rates of deposition and clearance, are of primary importance. Experimental evidence accumulated over the last three decades has shown that long, thin fibers are more carcinogenic than short and thicker fibers. This can be explained by the aerodynamic of fiber deposition and the clearance mechanism of fibers in the respiratory tract. The deposition of fibers in the lungs is determined by the fiber dimensions. Only fibers

having a diameter of 3 μm or less are respirable and are readily deposited in the lung. Thin fibers with a length up to 200 μm, on the other hand, may be able to travel to distal segment of the lung and deposited in the alveoli. Once deposited in the lung, short fibers are cleared much readily than long fibers. Some short fibers (less than 5 μm) are phagocytized by alveolar macrophages while some are transported to the gastrointestinal tract by the mucociliary system. Some short fibers may also enter the pleural and peritoneal cavities via lymphatic drainage. Long fibers [longer than about 10 μm (rat) or 20 μm (human), the size of rat and human macrophages, respectively], on the other hand, are only partially engulfed by macrophages and may remain in the lungs for longer periods of time. There is evidence that the carcinogenic effects of inhaled fibers are most strongly associated with the lung burden (which is determined by biopersistence) of long fibers. The chemical composition of the fiber is an important determinant for the biopersistence of the fiber. Long fibers in the lung can disintegrate (disintegration rate is dependent on their chemical properties), leading to shorter fibers that can be removed by the macrophages. Therefore, fiber chemistry influences fiber carcinogenesis primarily through its role in determining biopersistence. A direct mechanistic role, if any, of chemistry in fiber carcinogensis is believed to be of secondary importance. While short fibers and particles may be less toxic/carcinogenic, it does not necessarily mean that short fibers/particles are always inert. In fact, the induction of mesotheliomas by asbestos fibers shorter than 5 μm has been shown in rats (Pott et al., Ann. Anat. Pathol. 21: 237, 1976; Kolev, Environ. Sci. 29, 123, 1982). It has been suggested that the carcinogenicity of the fiber may be a function of the aspect ratio, the dose, and other chemical properties (*e.g.*, surface charge density) of the fiber/particle; a sufficient quantity of short, thin fibers/particles (*e.g.*, crystalline silica) may also be carcinogenic. The carcinogenicity of crystalline silica has been associated with its unique surface reactivity (Fubini, Environ. Health Persp. 105S:1013-1020,1997). So, it appears that in addition to dimension, the surface property/activity of fibers may be important. In order to develop a unified theory of toxicity of thoracic-sized mineral fibers, the association of toxic/carcinogenic responses and changes in surface chemistry/activity of fiber-like cleavage fragments appears to be the missing puzzle.

It is hoped that with the completion of this research program, all interested Federal Agencies sponsor a workshop convening an expert panel to review the data to support the inclusion of other mineral fibers and fiber-like cleavage fragments (with similar physicochemical characteristics compared to carcinogenic fibers such as asbestos and RCF) for cancer classification/regulation based on a unified theory/mechanism of toxicity/carcinogenicity of thoracic-sized mineral fibers.