Miller, Diane M. (CDC/NIOSH/EID)

From: Joseph Manuppello [JosephM@peta.org]

Sent: Thursday, May 31, 2007 4:32 PM

To: NIOSH Docket Office (CDC)

Subject: Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research, NIOSH Docket Number NIOSH-099

Attachments: Asbestos Roadmap comments.pdf

Attached please find comments of the American animal protection community on Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research, NIOSH Docket Number NIOSH-099. I would appreciate acknowledgement of receipt.

Thank you,

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NIOSH Docket Number NIOSH-099
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To Whom It May Concern,

The following comments are submitted on behalf of the more than 1.7 million members and supporters of People for the Ethical Treatment of Animals (PETA) and the Physicians Committee for Responsible Medicine (PCRM) in response to the draft document *Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research*, NIOSH Docket Number NIOSH-099. PETA and PCRM are committed to using the best available science to protect animals from suffering and to promoting the acceptance of alternatives to animal testing.

Exposure to asbestos fibers is etiologic for several life-threatening respiratory diseases including fibrotic lung disease (asbestosis) and cancers of the lung, pleura, and peritoneum. The NIOSH draft document *Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research* envisions a research program designed primarily to address inconsistencies in the definition and application of the term asbestos for health protection guidance and regulatory purposes. Specifically, while mineral fibers that grow in asbestiform habits are clearly of health concern, NIOSH contends that controversy remains as to whether particles with similar dimensions from similar minerals that grow in nonasbestiform habits, represent a similar health concern.

We are very concerned that the research program described in this document relies heavily on animal studies. Short-term animal studies are envisioned to investigate fiber deposition, translocation and clearance, biopersistence and disease mechanisms as well as chronic inhalation studies to evaluate the effects of fiber dimension, morphology, chemistry, and biopersistence on cancer induction and fibrosis. Such an approach would cause the suffering and death of many thousands of animals while not moving the ball forward to protect workers.

The fact that the evidence for the role of asbestos in human lung cancer comes from studies of the cause of death of occupationally-exposed workers and does not derive from animal studies is undisputed. In its Toxicological Profile for Asbestos, ATSDR summarizes more than 40 epidemiological studies that provide reliable dose-response information on the inhalation effects of asbestos in humans. Animal studies, on the other hand, are described as providing only supporting evidence for the fibrogenicity of asbestos.[1] Further, ATSDR cautions that extrapolation of exposure-response relationships for asbestos-induced lung fibrosis in animals to humans is not recommended due to inter-species differences. These differences include the longer biopersistence of fibers in humans, the relatively short life-span of animals used in laboratories, and the anatomical and physiological differences

between animals and humans that influence rates of lung deposition and clearance of asbestos fibers.

In its *Roadmap*, NIOSH also notes similar problems with extrapolating results from animal studies to humans. For example, fibers that are capable of being deposited in the bronchoalveolar region of humans cannot even be evaluated in animal inhalation studies due to differences between rodents and humans in fiber deposition characteristics. In addition, the low incidence of lung tumors and mesotheliomas occurring in rats exposed to asbestos suggests that rats are less sensitive to asbestos than humans.

In fact, Rödelsperger and Woitowitz (1995)[2] and Muhle & Pott (2000)[3] concluded that rats are two-to-three *orders of magnitude* less sensitive to asbestos than humans and are therefore not sufficiently sensitive to detect risks to humans exposed to other fibers. In the six chronic toxicology/carcinogenicity studies of asbestos already conducted by the NTP, no evidence of the very high carcinogenicity of asbestos seen in humans was found in 17 out of a total of 18 groups of animals that included rats and hamsters. In only one group was a result of "some evidence" produced.[4]

NIOSH's answer to the historically difficult problem of reproducing the known adverse effects of asbestos and other mineral fibers in animals is, unbelievably, to conduct even more animal studies. The agency's difficulty in deciding which species supposedly best predicts the health risk for workers exposed to different fiber types leads it to conclude that future animal inhalation studies must consider using a "multianimal testing approach" – *in other words, more uninterpretable tests on more species of animals.* But the fact remains that similar problems exist with all suitable species. Hamsters, for example, may be more sensitive to developing mesothelioma than rats, but they also appear to be even more resistant to developing lung cancers.[5]

The main rationale that NIOSH provides for proposing new animal studies is that the heterogeneity of fibers in the workplace, in which a range of sizes and types of fibers are present, limits the ability of epidemiological studies to evaluate the influence of fiber size, chemical composition, and biopersistence on toxicity. NIOSH argues that animal inhalation studies are needed to investigate the biopersistence and toxicity of pure fiber samples representing discrete lengths and uniform diameters.

However, at a May 4th public meeting held to discuss the *Roadmap*,[6] Dr. Wayne Berman, co-author of EPA's 2003 *Asbestos Risk Assessment Protocol*, demonstrated that this rationale is based on a misconception. Even when a range of sizes and types of fibers are present, as in workplace epidemiological studies, the relative potency of each size and type of fiber can still be calculated exactly. No additional information is obtained from animal studies in which pure fiber samples are used, since fundamentally the same calculations are necessary.

In fact, more information is likely to be obtained from workplace epidemiological studies in which a range of sizes and types of fibers are present. Studies in which pure fiber samples are used are not designed to detect interactions between different sizes and types

of fibers. In addition, if the pure fiber sample chosen for a particular animal study yields no interpretable results, the effort has been wasted, along with the animals' lives. In contrast, if a range of sizes and types of fibers are present as in the workplace, the categories dividing the range can be redefined to test different hypotheses. Dr. Berman concludes that new animal studies would not necessarily be more informative than better characterizing the human exposures in existing epidemiology studies directly. "After all," he said "we are interested in disease among humans."

Dr. Emanuel Rubin of Thomas Jefferson Medical College echoed these observations, noting that although the risk of developing lung cancer following asbestos exposure is increased many fold by smoking, "in experimental animals, it has not been possible at all to produce lung cancer by inhalation of tobacco smoke." He concluded that "[t]his shows the discrepancy between experimental data and epidemiologic data." Explaining the importance of the surface properties of asbestos fibers, Dr. Rubin observed that these properties cannot be determined simply by viewing the fiber. "[T]hat's why the epidemiologic studies are so important, because there are genetic differences between animals and man, exposure times, routes of administration, et cetera, et cetera." He urged "that no decisions be made on the role of any type of fiber until good epidemiologic studies have been done."

Lastly, NIOSH should be aware that at the recent International Science Forum on Computational Toxicology at EPA's RTP Laboratories, numerous models of human organs, including lung, were presented. Dr. Richard Corley from the Pacific Northwest Laboratory in Richmond, CA, outlined the progress of the Respiratory Program, which has eleven different collaborators around the US examining the respiratory system. Using MRI imaging technologies, they have developed 3D models of the architecture and tissue mechanics of the respiratory systems of rats, mice, rabbits, monkeys and humans. The not unexpected results clearly demonstrate the *"tremendous differences in architecture and thus responses of the respiratory systems of laboratory animals and humans to a variety of gases, vapors or airborne particles* [emphasis added]."[7] It would thus be a tremendous waste of resources and animals to conduct any inhalation studies in rats with asbestos and other mineral fibers, and the modeling techniques being developed in the Respiratory Program coordinated by Pacific Northwest Laboratories would be better applied, using human 3D models, to predict deposition of airborne fibers and potential toxicity in the human lung.

Inexplicably, NIOSH anticipates that the results from the animal studies envisioned in its *Roadmap* will provide a "gold standard" that can be used to validate the utility of long-term inhalation studies in animals as predictors of human disease. Given the demonstrated difficulty in reproducing the known adverse effects of asbestos in animals, the historical failure of animal test results to produce more protective regulatory decisions, and the existence of more appropriate analytical methods, we find this automatic call for yet more animal testing to be unjustifiable. The proposed animal studies will instead only waste thousands of animals' lives, along with resources that would be better spent using new human-relevant methods such as computational toxicology, as well as better characterizing the existing epidemiological data.

Thank you for your attention to these comments. I look forward to hearing from you on this important matter and can be reached at 610-586-3975 or by e-mail at josephm@peta.org.

Sincerely,

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[1] Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Asbestos. U.S. Department of Health and Human Services. 2001.

[2] Rodelsperger, K. and Woitowitz, H. J. Airborne Fibre Concentrations and Lung Burden Compared to the Tumour Response in Rats and Humans Eeposed to Asbestos. *Ann Occup Hyg.* 1995; 39(5):715-725.

[3] Muhle, H. and Pott, F. Asbestos as Reference Material for Fibre-Induced Cancer. *Int Arch Occup Environ Health.* 2000; 73(Suppl): S53-S59.

[4] National Toxicology Program. Toxicology and Carcinogenesis Studies TR-246, TR-249, TR-277, TR-279, TR-280, TR-295. *Available at*: http://ntp.niehs.nih.gov/index.cfm?objectid=084801F0-F43F-7B74-0BE549908B5E5C1C

[5] Dorger, M. et al., Early inflammatory response to asbestos exposure in rat and hamster lungs: role of inducible nitric oxide synthase. *Toxicol Appl Pharmacol.* 2002; 181:93-105.

[6] Transcript of the Public Meeting on *Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research.* 2007. NIOSH. *Available at*: http://www.cdc.gov/niosh/docket/NIOSHdocket0099.html.

[7] Corley, R. A. Towards the Virtual Human: Development of Three Dimensional Organ Models for Human Health Risk Assessment. *International Science Forum on Computational Toxicology.* 2007. U.S. EPA. *Available at:* http://www.2007comptoxforum.com/abstracts/abstract_corley.htm.