From:	David Bernstein
To:	Holm, Stewart E.
Sent:	3/19/2010 5:15:53 AM
Subject:	Fw: TOXSCI-10-0139: Manuscript Decision

Privilege

----- Original Message -----
From: toxsci@toxicology.org
To: davidb@itox.ch
Sent: Thursday, March 18, 2010 10:37 PM
Subject: TOXSCI-10-0139: Manuscript Decision

18-Mar-2010

Re: Manuscript TOXSCI-10-0139

Dear Dr. Bernstein,

Thank you for submitting the manuscript entitled "The pathological response and fate in the lung and pleura of chrysotile in combination with fine particles compared to amosite asbestos following short term inhalation exposre -- interim results." for publication consideration by Toxicological Sciences. Three scientists knowledgeable in this field have reviewed the paper and their comments are below.

I recognize that this manuscript represents the combination of two papers that were previously reviewed, and I appreciate your efforts to combine the two papers. However, I am concerned by the issues and concerns raised regarding the appropriateness of the experimental design, interpretation of the results and the overall descriptive nature of the research. Furthermore, the general consensus from the reviewers was that the paper did not represent important and novel information consistent with a manuscript in the top quartile in its field. Collectively, I regret that my review of the paper and the comments from the other reviewers lead me to conclude that the paper is not acceptable for publication in Toxicological Sciences.

We appreciate your interest in publishing in Toxicological Sciences and hope that this experience will not deter you from submitting manuscripts for consideration in the future.

Sincerely,

Lois D. Lehman-McKeeman, PhD
Editor in Chief
Toxicological Sciences

Reviewer: 1
Comments to the Author
This manuscript is extremely well-documented and provides important information about kinetics of translocation andpersistence of amphibole asbestos fibers in the pleura following inhalation. The morhphological changes are beautifully-illustrated and the quantitative results summarized well. Minor suggestions are:
p. 17 line 21: The authors refer to lymphatic ducts in the lungs - a more appropritate term is lymphatic vessels or channels. The authors shoulc describe this histopathologic appearance of the mediastinal lymph nodes in the text and

include images in the supplemental data.
p.18 line 12: It is not clear whether neutrophils are present in this SEM; mast of the cells appear to be activated macrophages.
P. 18 line 32: The authors describe a granulomatous mass in the pleural space; however, it appears to be only 20um in diameter and may represent a small aggregate of pleural macrophages.

Did the authors visualize any fine particles in the pleural space or parietal pleura?
Reviewer: 2
Comments to the Author
Author: General Comments: The purpose of this study, as stated in the first paragraph of the Introduction, was to compare the response of the lung and pleura of male rats to an inhaled chrysotile-containing commercial product versus a positive control, amosite. This is a report of a testing of a commercial product and so there is no real hypothesis other than the hypothesis that the commercial product will be less toxic than the positive control, which it was. In agreement with the stated purpose, the final sentence of the Conclusions states that the commercial product would not be expected to cause an inflammatory response in the lung following inhalation and the chrysotile fibers in the product do not migrate to the pleural cavity where mesotheliomas form.
The only thing new in the study is the fact that a commercial product containing chrysotile was used in the testing rather than pure chrysotile. The report will be helpful for those wanting to use or sell the commercial product (if such people still exist); otherwise, there is little new information provided by the paper. The authors suggest that it is new information that exposure to the commercial product did not result in transfer to chrysotile to the pleura. If the hypothesis was that chrysotile transfer to the pleura would be altered in the commercial product, one would think the experimental design would have been to expose rats to chrysotile alone and in the commercial product, and then examine the pleura. The actual experimental design, however, suggests otherwise and confirms that this is a report of a test of a commercial product compared to a positive control.

Specific Comments
Page 1: There is no abstract.
Page 2, line 50: This reference is not listed in the Reference Section. Therefore there is no description of the fiber exposure methods.
Page 3, lines 40-41: It would be helpful to state in the text what the "fixed exposure levels" were.
Page 6, line 1: It would be helpful to list the questions posed by the study as part of the experimental design.
Figure 9:Even with a magnifying glass, I had a hard time reading the print in the figure.
Figure 12: Why is this needed?
Figure 13: This figure was not interpretable for me. Why do you need it?
Figure 16: Need to indicate what the exposure was.

Reviewer: 3
Comments to the Author
Major Concerns:

The purpose of the study was to understand the pathological effects and biopersistence of chrysotile asbestos that had been included in joint compound, and to compare this to the effects of amosite asbestos. To adequately recreate the potential exposures, the chrysotile material should have been incorporated in the joint compound, then sanded and the sanded material collected. The amount of asbestos in the sanded material could have been determined and the corresponding amount of amosite used for comparison. The joint compound by itself should have been used as a control.

The comparison of chrysotile asbestos, in combination with the sanded fine particles, and amosite asbestos could not be made because of the gross differences in particle characteristics between the two fibers as demonstrated in Figures 1, 2 and 3, and Table 3. There was no discussion of these differences. In addition, there were major differences in the amount of material found in the lung at different time points between the CSP and amosite exposed animals (Table 4 vs Table 5, mass of fibers per lung in mg), with the day 0 data implying that there were different amounts of the fibers in the exposure airflow. The differences described as biological consequences of these exposures could be

due to the major differences in dose between the fibers. No mention of this was made in the results nor the discussion sections of the paper. The simple argument can be made that there is less chrysotile in the lungs after 90 days because there was less in the lungs to begin with as measured at day 0, and thus the inflammation seen in the amosite-exposed lungs was due to the increase in dose compared to the chrysotile-exposed lungs.

No statistical analyses were presented for any of the data in the tables, thus it is unknown if the differences in the data presented are significant.

No rationale is presented for the large time-frame difference between the rest of the presented data and the Pleural method 2 -chest wall procedure and data. There was no description of which treatment group or time point the chest wall photographs belonged to in Figure 16. In general, the time frames do not correlate with the rest of the data presented and do not add any information relevant to the rest of the manuscript. The data presented in Table 2 for the extended time points is not presented in the results section nor is it discussed.

No data were presented to support the "validation of lung digestion procedure" results (p11).

The conclusions of the paper are overstated.

Minor concerns:

There are typographical errors throughout the paper, including in the title (...inhalation exposre..., p1 line34, etc.).