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REFERENCE: Comments on the EPA's Office of Solid Waste and Emergency Response "Proposed Approach for Estimation of Bin-Specific Cancer Potency Factors for Inhalation Exposure to Asbestos."

Dear Ms. Turner,

I am pleased to provide below my comments to the EPA's Office of Solid Waste and Emergency Response, "Proposed Approach for Estimation of Bin-Specific Cancer Potency Factors for Inhalation Exposure to Asbestos."

The proposed re-evaluation by the EPA of their cancer risk assessment for asbestos using a multi-bin approach is a potential improvement over the previously used model. Certainly, separation of the effects of amphiboles from those of chrysotile is very important. In addition, consideration of fiber length and width would also be potentially very valuable if there is sufficiently good data to support such a model.

SECTION 2.1 MINERALOGY OF ASBESTOS:

In the background information on asbestos, while the two families of asbestos are briefly described, it would be important as well to present the important differences in mineralogical structure between chrysotile and amphiboles.

The amphiboles are double chain silicates which form solid rod-like fibers. They are encased by the silica matrix which has very low solubility in both acid and bases.

Chrysotile (serpentine) fibers are sheet silicates composed primarily of magnesium and silica. Because of the different molecular spacing of these two elements, chrysotile fibers form as rolled sheets of approximately 8 angstroms thickness with

the magnesium on the outside of the roll. Chrysotile is soluble in acid. This has been described by Pundsack, F.L., 1955 (The properties of asbestos. I. The colloidal and surface chemistry of chrysotile. *J. Phys. Chem.* 59 (9), 892–895).

SECTION 3.0 OVERVIEW OF ANIMAL STUDIES:

The overview of animal studies does not mention the studies on the biopersistence of amphibole versus chrysotile asbestos. These studies have been reviewed recently (Bernstein, David M. & Hoskins, John A. 2006. The health effects of chrysotile: current perspective based upon recent data. *Regulatory Toxicology and Pharmacology* 45/3 pp. 252-264.) The importance of fiber biopersistence and fiber length to toxicity is one of the most recent scientific findings and should be addressed.

Concerning the inhalation studies there is no discussion or assessment of the dose used in many of these studies in comparison to human exposure. Table 4 in Bernstein, D.M. 2007 (*Synthetic Vitreous Fibers: A review toxicology, epidemiology and regulations. Critical Reviews in Toxicology*, 37:10, 839 – 886), illustrates that the alveolar dose used in most of the studies cited was more than 175,000 times human exposure. Based upon current knowledge on the use of the rodent as a model for inhalation toxicology, the particle component of this dose would be considered as “lung overload” (Oberdörster, G., 1995. Lung particle overload: implications for occupational exposures to particles. *Regul. Toxicol. Pharmacol.* 21 (1), 123–135.) The studies cited should be assessed for validity and only studies that do not overload the lung should be considered.

SECTION 8.0 CURRENT APPROACH PROPOSED BY OSWER

On Page ES-3 the reports states concerning the estimation of bin-specific exposures that occurred in each of the published epidemiological studies that “OSWER proposes to estimate these needed values by finding published data sets based on transmission electron microscopy (TEM) that are most closely matched to the workplace exposures reported in each epidemiological study, and using these particle size data sets to extrapolate from PCM-based to bin-specific exposures.”

Yet in Section 2.2 on Particle Size Variability, it is stated that “The length of the fibers depends on the source of the asbestos and on the degree to which the ore has been processed.”

Of major concern in this approach is that the source of the asbestos will not be the same compared to the “closely matched to the workplace exposures” mentioned above.

- Even if the asbestos comes from same mine, each mine produces a large variety of different asbestos fiber lengths (Cossette, M., and Delvaux, P. 1979. Technical evaluation of chrysotile asbestos ore bodies. In *Short course in mineralogical techniques of asbestos determination*, ed. R. C. Ledoux. Mineralogical Association of Canada, Toronto, Canada, pp.79–109, May).

- In addition, when considering chrysotile, the inter-mine variability in tremolite levels is important and as tremolite occurs in distinct and separate veins in the mines, and the level of tremolite present can be very different for each sample (Williams-Jones, A. E., C. Normand, J. R. Clark, et al. (2001). "Controls of amphibole formation in chrysotile deposits: Evidence from the Jeffrey Mine, Asbestos, Quebec." *Canadian Mineralogist*: 89-104).
- Even if original samples of the fibers to which the cohort was exposed are available, there are often very few samples with no long term history of original fiber exposure by type and length possible. Extensive care should be taken in using the proposed approach which has the risk in introducing considerable uncertainty and bias.
- Prior to proceeding with the use of these exposure estimates in computing risk, full disclosure should be made by OSWER with a subsequent open scientific forum of the assumptions, caveats, and the actual TEM data compared to the original workplace exposures.

TABLE 8-2, BIN LENGTH

In section 3.2, the report states that "As seen, fibers longer than 40 μm accounted for 99.8% of the total potency, with most of that (85%) being contributed by fibers $\leq 0.3 \mu\text{m}$ in diameter." As shown in section 3.2, the shorter fibers have very little potency prediction even though there are many more fibers in this size range. Bernstein, D.M., 2006 (Asbestos chapter, In *Inhalation Toxicology – 2nd Edition*, H. Salem, Editor, Taylor & Francis Group, Boca Raton, Fl.), described the iterative analysis of the relationship of fiber length to carcinogenic response in long-term inhalation toxicology studies. In this analysis fibres longer than 20 μm in length were found to be the best predictor of toxicity. When fibers longer than 10 μm in length were used, no association with toxicity was found.

However, in Table 8-2, the longest bin length mentioned is > 10 μm . With a maximum bin length of > 10 μm , there appears to be little if any possibility of differentiating exposure effect relationships in the epidemiological studies (other than by chance) based on fiber length. It is highly recommended that the maximum bin length be at least > 20 μm in length.

SECTION 9.1 CRITERIA FOR STUDY SELECTION:

The inclusion conditions are very important in choosing studies for inclusion in this analysis. However, using studies without assessing the validity and plausibility of what was reported is scientifically irresponsible. As an example, the study by Yano et al., is included as a chrysotile only exposure study.

However, when examining the details of the Yano et al., 2001, study it is very difficult to interpret the results reported.

- The pleural mesothelioma death occurred 13.8 years after first exposure. This would suggest some prior exposure elsewhere if the mesothelioma is due to fiber exposure.
- There are no consistent industrial hygiene measurements over the history of the study (respirable dust concentration was measured once every 4 years!). Yano et al. don't say if they determined what fiber types were on these filters.
- Using microscopy to find amphibole fibers when present at less than 1 % concentration is statistically unviable. The only way to have a large enough sample of what was used is to determine amphibole by chemical digestion (Addison and Davies, 1990). We know that if amphibole was present that it is not distributed uniformly in the chrysotile sample. They also don't say how many fibers they analyzed. Was it 100 or 10,000? With the well known UICC chrysotile sample, Frank et al., 1998 'showed' it was pure chrysotile by light microscopy counting of approximately 12,000 fibers. When chemical digestion was used for analysis tremolite was found in the UICC sample (Bernstein, D.M. 2006. Asbestos chapter, In Inhalation Toxicology – 2nd Edition, H. Salem, Editor, Taylor & Francis Group, Boca Raton, FL.).
- More importantly, the fiber concentration measurements (0.1 - 58 fibers/cm³) certainly don't account for the 6.1 to 320 mg/m³ dust burden. Even 58 f/cm³ would correspond to less than 0.1 mg/m³ by weight. There is no discussion of what is the rest. This is especially worrisome as it appears that at the highest concentration of 237 mg/m³, they were using rubber products.
- There is no indication that the control cohort had similar exposures. In fact there is no presentation of what the control was exposed to. Considering that the dose makes the poison, this very high unaccounted dose which was clearly not chrysotile should be of major concern. This study clearly is not a pure chrysotile exposure as 99.96 % of the exposure was to something else.
- Lastly, there is no lung burden analysis even on the small biopsy samples. This has always been the bottom line in determining exposure.
- This study should not be included in this assessment.

The validity and plausibility of what was reported in each study proposed for inclusion should be evaluated and presented.

FIBER SPECIFICITY OF THE STUDIES INCLUDED:

More care should be taken in identifying what fibers these cohorts were exposed to.

As an example, in Table 9-1, the study marked as Index 4 shows Henderson and Enterline 1979; United States Cement Product Manufacturing; Chrysotile, that is a pure chrysotile exposure. However, on Page 121 of Henderson and Enterline 1979 they state “moreover, there was some indirect crocidolite asbestos exposure among men in the shingle and sheet operation” to which this appears to refer.

With the very important difference in response between chrysotile exposed in a 90 day inhalation toxicology study which at 5000 times the TLV produced no effect and amphibole (tremolite) asbestos which after only 5 days of exposure at one-half this dose produced interstitial fibrosis and intense inflammatory response (Bernstein, D. M., Rogers, R., Chevalier, J. and Smith, P. 2006. The toxicological response of Brazilian chrysotile asbestos: A multi dose sub-chronic 90-day inhalation toxicology study with 92 day recovery to assess cellular and pathological response. *Inhalation Toxicology*, Vol. 18, Issue 5, pp. 313-332) even a small exposure to crocidolite in the Henderson and Enterline 1979 cohort can have an important effect.

Based upon recent studies fiber length appears to be very important in assessing amphibole exposure with even a relatively small exposure to long fiber amphibole having a significant potency. Errors in characterisation of both exposure fiber type and fiber length and diameter have the potential of introducing significant bias in risk assessment.

Sincerely yours,

David M. Bernstein, Ph.D.