National Institute of Environmental Health Sciences (NIEHS) Comments on the Interagency Science Discussion Draft IRIS Assessment of Libby Amphibole Asbestos (dated August 2014)
Date: September 9, 2014

DEPARTMENT OF HEALTH &. HUMAN SERVICES Public Health Service

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To whom it may concern:

Thank you for the opportunity to comment on the Toxicological Review of Libby Amphibole Asbestos. We've focused the following comments on the sections of the draft pertaining to the toxicological outcome (Critical Effect) used to derive the reference concentration and the mode of action of the Libby Amphibole.

Selection of the Critical Effect:

We agree with the selection of localized pleural thickening (LPT) as the appropriate toxicological outcome for derivation of the RfC. Localized pleural thickening as supported by the analysis presented in the draft Toxicological Review represents an irreversible physiological alteration of the lung resulting from asbestos exposure. We independently agree with the Science Advisory Board and the American Thoracic Society that LPT is more than a "marker for asbestos exposure" and represents an irreversible and progressive pathological alteration of the pleura and is generally associated with reduced lung function and decrements in quality of life.

Furthermore, In Libby specifically, 64/84 vermiculite workers with pleural disease had progression of their disease over time.[1] In addition to reduced lung function, individuals with LPT also experience increased symptoms, such as dyspnea, which increases with the extent of their disease.[2] Lastly, as individuals age there is natural loss of lung function. The additional loss due to LPT further compromises the aging adult populations, adding unnecessary burden to the health care system. This loss of lung function reduces functional reserve and compromises overall pulmonary health and capacity. This is critically important for the elderly with additional health conditions and medical care needs involving surgery, when even small compromises in lung function can be critical to medical decisions and outcomes.

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[1] Larson TC, Meyer CA, Kapil V, et al. Workers with Libby amphibole exposure: retrospective identification and progression of radiologic changes. 2010. Radiology. 255 (3):924-33.

[2] Bourbeau j; Ernst P, Chrome J, Armstrong B, Becklake MR. (1990). The relationship between respiratory impairment and asbestos-related pleural abnormality in an active workforce. Am Rev Respir Dis 142:837-842.

It should be noted that the selection process EPA used for including studies that only reflect "LPT" is very conservative given that fibrosis of the pleural compartment is an ongoing process of varying speed and severity (depending on individual and exposure risk factors). LPT may progress from unilateral to bilateral disease as well as from LPT to more DPT over time. Thus, the included studies only reveal the low-end functional findings associated with the most minimal radiographic findings along a spectrum of evolving pathology and disease.

Mode of Action:
NIEHS agrees with the analysis of mode of action (MOA) of Libby Amphibole as presented. We support inclusion of the newer in vitro studies based, in part, upon the work completed by Dr. Phil Cook as presented in Duncan et al. 2014.[3] These studies demonstrate a high degree of correlation between surface area and mineral length with respect to pro-inflammatory response in human airway epithelial cells. Notably, this work explored inflammatory response following exposure to fiber populations that were largely shorter than the commonly measured size range used for regulatory purposes. Additionally, although indirectly related to the development of an inhalation risk concentration, the work of Pairon et al. (2013)[4] supports the paradigm of a spectrum of progressively detrimental physiological changes following exposure to Libby amphibole minerals.

The discussion regarding the individual versus population level impacts of decreased pulmonary function in association with LPT (or pleural plaques) is adequately addressed. It is important to note that the studies and meta-analyses reflect the mean loss of lung function and thus a significant number of individuals will have losses of function that are higher. Additionally, the selected studies are of workers that typically are healthier than the general population ("healthy worker effect") and adverse pulmonary function impacts among the general population of Libby, MT, which includes children, the elderly, individuals that have other health conditions, and those with other susceptibilities, may be considerably more severe than a healthy worker cohort.

The use of HRCT appears to have increased sensitivity and specificity for pleural disease as compared to x-rays. For example, the ability to discern actual pleural fibrosis versus subpleural fat adds an element of improved specificity among individual with increasing BMI.[5] Again asbestos-related pleural disease comprises an evolving spectrum of visible and functional pathology from mild to severe. The ability of HRCT to visibly detect very mild early pleural changes will enable researchers to more closely follow and elucidate risk factors associated with the clinical course of disease. Additionally, HRCT can help

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[3] Duncan K.E, Cook, P.M., Gavett, S.H. et al. *In vitro* determinants of asbestos fiber toxicity: effect on the relative toxicity of Libby amphibole in primary human airway epithelial cells. In: *Particle and Fibre Toxicology.* 2014, **11**:2

[4] Pairon, J.C., Laurent, F., Rinaldo, M. et al., (2013). Pleural plaques and the risk of pleural mesothelioma. J Nat Cancer Inst 105:293-301.

[5] Larson TC, Franzblau A, Lewin M, Goodman AB, Antao VC. (2014). Impact of body mass index on the detection of radiographic localized pleural thickening. Acad Radiol 21(1) 3-10.

to evaluate the absence of interstitial disease for independent assessment of pleural disease.

Of note, the absence of pulmonary function abnormalities with early pleural changes identified on HRCT should not be construed to indicate that such functional abnormalities will not occur in the future. The current research indicates that as the severity of LPT disease progresses over time (becoming increasingly visible on x-rays) so does the associated functional abnormalities. Thus, it should not be surprising if the improved sensitivity to detect early LPT by HRCT is not associated with pulmonary function abnormalities until later in the clinical course of the disease.

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