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Title: Relative Mesothelioma Potencies for Unregulated Respirable Elongated Mineral and Synthetic Particles

ABSTRACT

For decades uncertainties and contradictions have surrounded the issue of whether exposures to respirable elongated mineral and synthetic particles (REMPs and RESPs) present health risks such as those recognized for exposures to elongated asbestiform mineral particles from the five federally regulated types of asbestos. Dose-response Models for predicting relative potencies and risks for a broad range of human exposures to REMPs and RESPs have not been well developed and appear to produce contradictory predictions depending on the data and assumptions utilized. Epidemiological data are the basis for established asbestos fiber specific air standards for protection of human health but have uncertain applications for much needed prospective risk assessments for a broader array of exposures of concern. The complex mixtures of REMPs and RESPs associated with different dust materials and sources vary with respect to particle length, width, elongation/aspect ratio, crystal structure, surface area, mass, chemical composition, etc. Thus, derivation of more holistic dose – response models based on asbestos associated health effects such as mesothelioma, lung cancer, and asbestosis requires development of quantitative structure activity relationships (QSARs) for REMPs and RESPs as accomplished for chemicals having a common mechanism of action but differing relative potencies.

Based on rat intrapleural exposures to a total of 50 unique *in vivo* doses using 29 different mineral and synthetic particle types with all doses extensively TEM quantified and characterized for this purpose in the 1980s, we have determined for mesothelioma incidence that:

1. The fundamental dose metric is the sum of each elongated particle's surface area.
2. Determination of changes in the *in vivo* dose particle number, size, and shape characteristics through dissolution are critical for accommodating bio-durability and splitting/comminution impacts on the *in vivo* effective dose.
3. Contrary to long standing hypotheses for no potency for short fibers versus full potency for very long fibers, all lengths of fibers seem to contribute potency in proportion to their external surface areas with some evidence for additional potency for rare wide asbestiform amphibole fibers due to some internal bioavailable surface area contribution.
4. A model adjustment involving setting the aspect ratio (L/W) minimum greater than 3.0 improves the surface area dose-response data fit but post exposure tissue dose data do not yet reveal a clear explanation for the well reproduced statistical results.
5. The findings seem consistent with pharmacokinetic data and models for post inhalation particle transport and current mechanism of action models for a variety of endpoints.

This presentation will conclude with comments on how these new findings may help reduce uncertainties and provide support for better extrapolations of human epidemiological data.