Persistent Elongated Particle Total Surface Area Dose to Rat Pleura is Optimum Predictor of Mesothelioma Incidence

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Based on preliminary statistical analyses of 29 reanalyzed (quantitative TEM) diverse elongated particle (EP) test samples from the well known and often cited study of Stanton et al. 1981, total surface area (TSA) of biodurable EPs was reported at the 2008 Johnson Conference to be a good predictor of pleural mesothelioma incidence in intrapleural (IP) exposed rats. This conclusion was important because TSA could be most representative of the toxicologically relevant dose of active particles in the pleural membranes and would be consistent with the particle surface as the locus for mechanism of action. This further would provide a general, holistic, mechanism of action relevant model based on graded relative potencies associated with EP size and shape *in vivo*. The existence of such a model contradicts models which ascribe high potency for unique size fractions of long, thin EPs and negligible potency for all other EPs in the dose. The TSA dose metric does support the concept of increased individual particle potency as a function of greater length. The TSA model, on an individual particle basis, appears to contradict the perception of greater potency as a function of individual particle thinness because a wider EP has greater surface area than a thin EP of the same length. However, for toxicity tests based on comparisons of equivalent mass dose exposures, it can be shown that the strong correlation of EP thinness with both greater particle number and surface area concentrations should result in greater tumor incidence as is observed.

Since 2008, we have applied logistic regression with Akaike information criteria (AICs) to evaluate thousands of alternative dose-response models using tumor incidence data for a master bivariate/trivariate TEM data set comprised of 50 rat IP dose samples with greatly divergent particle size distributions, chemical and structural compositions, and both unleached and acid leached (simulated *in vivo* exposure) dose characterizations. Only dose measurement data accomplished at our lab in the 1980s are used in conjunction with published tumor incidence data for rats. The approach requires that all dose modifications and alternatives tested and the statistical data analyses be based on biological, toxicological, pharmacological, physical-chemical, and mineralogical plausibility. Systematic dose cut off and dose addition experiments to seek optimum dose-response models based on fiber number, TSA, mass/volume, L·W, L/W, etc. have utilized individual size/shape data points for each EP across a matrix containing 2948 discrete L, W cutoff points. Resultant optimized models based on either TSA or fiber number dose involve highly significant contributions from shorter EPs in part because of their abundance in EP exposure sample size distributions. Consistently better predictions based on acid leached EP data provide evidence for the need to understand short term EP dose alterations *in vivo* when judging relative potencies and EP bioavailability/persistence requirements for toxicity. Evidence for reduced SA related potency for EPs with aspect ratios < 8 is observed. These model evaluation results appear to have general applicability to the extent they have been found to apply to independent data sets as well as data subsets. (This abstract does not represent US EPA policy)