Measurement of Elongated Particle Dissolution Rates and Consequent Size/Shape Distribution Alterations in Support of Relative Potency Determinations and Human Dosimetry Model Development.

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Clearance of inhaled bio-persistent elongated particles (EPs) from the lungs and their associated translocation to pleural and other extra-pulmonary tissues involves a number of inter-related and coincidental physicochemical and physiological processes. These can result in EP dissolution, splitting/separation, comminution and associated impacts on particokinetics. Depending on an EP's structure, chemistry and initial point of deposition in the lungs, the collective contributions of each of these processes to resultant EP persistence and relative potency will be different. Despite the complexity of these *in vivo* dose realities, exhaustive analyses of compatible rat pleural dose-mesothelioma response data show clearly that dose characterizations based on TEM analyses of short term acid leached test samples consistently provide better predictions of dose-response than the unleached sample dose TEM data. Acid leaching (HF/HCL/citric acid mixture), used in previous studies conducted by P.M. Cook, provides a rapid bio-durability assay for EP's. This convenient model focuses on particle propensity for transformation through dissolution but is not a direct model for much slower lung fluid or other tissue/cell residence associated particle changes *in vivo*. However, comparisons of the acid treatment results for the same samples after residence for up to two years in rat lungs or five months in rat pleural membranes reveal consistent outcomes for EP size and shape distributions and EP number and surface area concentrations when adjusted for apparent EP clearance rates.

J. K. McGee is currently conducting *in vitro* dissolution studies of Libby amphibole (LA) EPs in comparison to UICC amosite and other well characterized EP samples. These experiments will include dissolution using both the acid solution and a solution of a synthetic lung lining fluid (SLF) commonly used in *in vitro* dissolution studies of manmade and naturally-occurring fibrous materials (Zoitos et al., 1997). The SLF data have been reported to correlate well with toxicity and to provide useful particokinetic information (Hesterberg et al., 2002). Comparison of results using the two types of solutions will allow assessment of potential impacts on both short term and longer term particle *in vivo* doses. Both the SLF and acid *in vitro* dissolution rates can be calibrated to rates observed *in vivo* based on intratracheal instillation and inhalation studies. Once calibrated, the *in vitro* assays can provide a rapid way to compare key dosimetry determinants that play an important role in fiber persistence and durability. This will support determination of rate parameters for LA dissolution and potential splitting as needed for modeling lung clearance and translocation of LA using an extended dosimetry model for lung deposited fibers (Asgharian et al., Johnson 2011 abstract) to predict tissue specific retained doses over time for LA EPs. These studies will also provide a dataset that can be used to assess LA's relative biopersistence compared to other types of fibers and to previous studies conducted both *in vitro* and *in vivo*. Preliminary LA results and their significance will be reported as available.