Elongate Mineral Particles (EMPs) characteristics and mesothelioma: Summary and resolution for Session I of the Monticello II conference

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The session addressed the current state of the science in the area of characteristics of EMPs impacting their carcinogenic potential. With understanding that cancer potency of EMPs is impacted by numerous parameters, the session agreed that special attention should be paid to measurable, attainable, and predictive characteristics, with special attention to the dimensions of particles.

In her talk, Lucy Darnton (HSE) updated the results of the landmark Hodgson, Darnton (2000) study, confirming the main conclusions that mesothelioma potency of crocidolite, amosite, amphiboles from Libby MT, and chrysotile are substantially different. Ms. Darnton demonstrated the deviation from linearity in mesothelioma dose-response, in which a sub-linear relationship for peritoneal mesothelioma dominates at higher doses and a supra-linear relationship dominates at lower doses. However, the latter is driven particularly by data for chrysotile

cohorts where there is less consistency and where the influence of occult amphibole exposure may be important. The relative potencies of major mineral types of fibers hold when comparing linear and nonlinear models. A paper containing main conclusions of Ms. Darnton's talk titled "Update on the meta-analysis for mesothelioma and lung carcinoma risk related to exposure to various mineral types of asbestos" is included in this volume.

Dr. Ann Wylie summarized a series of her studies on the dimensional metrics of EMPs, most predictive for mesothelioma potency factors and mortality. She demonstrated that mesothelioma potency factors for various mineral types of amphiboles and their localities can be predicted by fractional metrics, including the fraction of thin fibers (width lower than 0.15 or 0.25 μm) among all fibers longer than 5 μm (EMPA and EMPB criteria). The results of Monte Carlo simulation were shown confirming that the maximum correlation between potency and dimensional fraction is achieved at about 0.2 μm for mesothelioma and 0.28 μm for lung carcinoma. Also, Dr. Wylie presented the results of factor analysis for the potential predictors of mesothelioma potency and pointed out to geometric mean of width and specific surface area (proportional to the reciprocal of width), along with EMPA and EMPA, express the highest correlation with cancer slope factors. It was also demonstrated that specific surface area of particles allows for an efficient discriminating between asbestiform and non-asbestiform populations of particles. A manuscript with A. Korchevskiy summarizing dimensional studies and their applicability to mesothelioma in the paper entitled "Dimensions of amphibole fibers and their carcinogenicity: The review." is included in this volume.

Dr. Eric Chatfield elaborated on the differentiation between asbestiform and non-asbestiform particles in the respirable fractions of crushed amphibole in data analysis and laboratory fraction. Dr. Chatfield utilized the criteria for asbestiform particles which included the range of width (0.04 to 1.5 μm) associated with aspect ratios (AR) of three categories, depending on the length of particles (AR>35 for length > 5 and < 10 μm, AR> 30 for length > 10 and < 20 μm, AR>20 for length > 20 μm). He demonstrated that geometric standard deviation of the aspect ratio, as well as the number of respirable EMPs longer than 5 μm per gram of respirable dust are strong predictors of particle habit. Dr Chatfield's paper found in this volume entitled "Asbestiform fibers and cleavage fragments: Conceptual approaches for differentiation in laboratory practice and data analysis." details this work.

Dr. Wolfgang Losert emphasized that numerous physical factors can elicit a cellular response to surrounding materials, including the size, stiffness, or shape of the material. Excitable systems, with their characteristic fast positive feedback and

delayed negative feedback, have fascinating dynamical properties such as repeated bursts that can couple in space to form waves and oscillations, demonstrating a whole cell response rather than a response at the molecular level. Dr. Losert introduced the foreign materials to a THP-1 macrophage cell model and image the interaction of the materials with the actin cytoskeleton. It was found that the touching of asbestiform fibers trigger actin waves in most cases, but the intensity of actin waves interacting with the materials is dependent on the geometry of the materials. In particular, thin fibers trigger a stronger response than rounder control materials. The outline of future research was presented to investigate whether one of the consequences of asbestos exposure may be a change in the excitable systems state, which makes cells more active and motile. A paper by Losert and co-workers entitled "An excitable system on cell response to asbestos fibers." describes initial results from this work using asbestos and nonasbestos amphibole in their paper in this volume.

Professor Julian Peto focused on the relationship of amphibole lung burden and mesothelioma risk based on a comprehensive case-control study in UK. It was shown that a linear relationship exists between mesothelioma risk and amphibole lung burden measured by TEM. The lifetime mesothelioma risk is approximately 1 in 10,000 in people with 1 amphibole fiber per mg of dry lung. The risk per fiber for crocidolite was higher than for amosite, though the difference was not statistically significant. Chrysotile burdens were uniformly low, presumably reflecting its rapid clearance from the lung, and showed no consistent relationship with occupation. The Peto model describing the dependence of mesothelioma mortality on time since first exposure was presented.

Drew Van Orden presented a conceptual model for distinctions between asbestiform and non-asbestiform amphibole particles based on dimensional categories. For modelling, 59 designated as dominantly asbestiform (73,845 particles) and 39 designated as dominantly non-asbestiform (235,247 particles) datasets were evaluated. Discriminant analyses were used to determine functions that separate populations by source type with random cross-validation subsets. For particles longer than 5 μm, the function 2.99log10(Length) – 5.82log10(Width)-3.80 was selected as the best discriminator of particles in the asbestiform populations, with a misclassification rate of about 15% total. It was recommended that regulatory agencies utilize the developed discriminant analysis methodology for revising risk assessment and related regulatory policies that cover excavation activities and industrial mineral dusts. A paper by Drew Van Orden entitled "Discriminant analysis of asbestiform and non-asbestiform particles: Testing and validation" describes applications of the developed discriminant model.

Dr. Andrey Korchevskiy presented the approaches for using quantitative structure-activity relationship (QSAR) modeling as an efficient tool to characterize potency factors of various types of asbestiform fibers. Based on OECD criteria for validation of QSAR models, it was demonstrated that cancer risk can be predicted by dimensional parameters with high precision. In particular, the dimensional fractions (like EMPA and EMPB), the "corrected" aspect ratio (length in a certain power divided by width in a certain power), and specific surface area can serve as independent variables for regressions with R in the range from 0.86 to 0.98. The "leave-one-out" validation algorithm was proposed for the situation when the number of available epidemiological data points for asbestos potency factors appeared to be low. Several models were demonstrated with dimensional parameters of fibers combined with such parameters as iron content to achieve high predictability for cancer potency in several classes of fibrous minerals. In particular, peritoneal mesothelioma rates in humans and in rats were modeled by the combination of log-transformed specific surface area and log-transformed iron content of the amphibole fibers. The work will be discussed in the review paper with A. Wylie.

After the discussion, the participants of the session agreed on the following:

1. The difference between mesothelioma potency of elongate mineral particles with different characteristics has been confirmed in numerous studies. The parameters associated with this difference include such interrelated population characteristics as mineral occurrences and dimensions.
2. Non-asbestiform particles and asbestiform fibers can be distinguished based on their dimensions measured by electron microscopy with precision of 85-90 %.
3. Length and width of elongate mineral particles impact their mesothelioma potency. Growing epidemiological evidence has been reported that mesothelioma mortality increases with the fraction of very thin amphibole fibers (width less than 0.15-0.25 μm). It was also demonstrated that as a rule, non-asbestiform particle populations do not contain particles thinner than 0.15 μm, and contain only a small fraction of the < 0.25category. These differences are expected to drive the difference in potency for asbestiform and non-asbestiform mineral varieties. The length appears to be much weaker predictor of mesothelioma potency than width at the studied range (length greater than 5 μm).
4. Several of the reports during the session were based on the new database on the dimensions of elongate mineral particles containing at this point more than 400,000 records. The session recognized the efforts to create the database and suggested that further steps to expand the database should be

undertaken. The quantitative structure-activity relationship (QSAR) modeling demonstrated its potential for elongate mineral particles and represent a promising area for further studies and practical applications.

5. The current regulatory requirements for asbestos were developed for applications to its commercial forms and focused on occupational exposure. For this reason, the regulations related to asbestiform and non-asbestiform EMPs do not always recognize the differences in their toxicity. Also, chrysotile and amphibole forms of asbestos have substantially different toxicity but are regulated identically. The regulations and practices regarding EMPs need to be revised to better protect workers and communities. The sampling methodology accurately reflecting the health risks from EMPs should be developed. The NIOSH 7402 electron microscopy method should be expanded to take into account the exposure to particles with the width lower than 0.25 μm. Different occupational exposure limits should be proposed for chrysotile and amphibole forms of asbestos.
6. Further studies are needed to continue collecting scientific facts about EMPs including:

    - Analysis of dimensional distribution for the mineral particulate lung burden in mesothelioma cases and controls particularly for persons born after 1960;
    - Toxicological experiments in vitro and in vivo with varying dimensional parameters and mineral identity of exposure;
    - Development of toxicokinetic models for the behavior of various dimensional categories of EMPs in human lungs using in silico and physical lung prototypes.