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Non-Cancer Outcomes Session

Differential Non-Cancer Outcomes of Fibrous Amphiboles in Mice
Jean C. Pfau and Deborah E. Keil, Montana State University

Novel research findings are forcing us to consider a paradigm shift in the assessment of health outcomes of asbestos exposure. First, non-cancer outcomes must be considered as sensitive and impactful measures, potentially occurring at very low levels of exposure. The experience with Libby Amphibole (LA) has taught us that exposure predominantly causes a non-malignant pleural disease that has a progressive and atypical clinical presentation, and can increase the risk of systemic autoimmune diseases. Our studies also suggest that the two may be related mechanistically. Further, it is clear that we cannot assume that different types of fibers will have the same outcomes; therefore, fiber-specific risk assessments must take these non-cancer outcomes into account. The public health impacts of these findings are highlighted in the growing awareness of "naturally occurring asbestos" in places where it was not previously predicted to occur, leading to environmental exposures in wide areas of the U.S. A mouse model has been used to compare the non-cancer effects in mice of exposure to LA with those of a newly discovered mixture of amphibole fibers from Arizona. We now know that the immune system plays a profound role in directing the outcomes of exposure, including cytokine shifts and development of autoantibodies, which can affect the ability to fight cancer, produce fibrosis or result in autoimmunity. We hypothesized that subtle differences in size and chemistry of fibers can affect the resulting immune dysfunction, and that the immune profile may predict ultimate health outcomes. The results demonstrated that LA is not unique in producing autoimmune outcomes in mice, and yet supported our hypothesis that the Arizona amphibole would have a somewhat unique immune profile despite chemical and morphological similarities with LA. Importantly, we are demonstrating immune changes and autoantibodies at very low exposure levels in mice.

Non Cancer Exposure-Response Modeling for Libby Amphibole Asbestos
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The United States Environmental Protection Agency (EPA) developed a quantitative exposure-response model for the non-cancer effects of Libby Amphibole Asbestos (LAA). The model is based on the prevalence of localized pleural thickening (LPT) in workers exposed to LAA at a workplace in Maryville, Ohio, that used vermiculite ore from Libby, Montana, to produce commercial products. These modeling results were summarized in the Toxicological Review of Libby Amphibole Asbestos and was posted on the IRIS site in 2014. The modeling results were used to derive the Reference Concentration (RfC) for LAA. These modeling results will be presented and discussed. In addition, modeling results for an alternative cohort were also summarized in the Toxicological Review of Libby Amphibole Asbestos. These additional modeling results, which support the RfC, will also be presented and discussed.

Subsequent to the development of EPA’s RfC, Lockey et al. (2015) published a follow-up study on the health status of surviving Marysville workers. The data from this study increases the number of cases of LPT, Diffuse Pleural Thickening (DPT), and Small Interstitial Opacities (SIO) and extends the observation period in these workers. EPA Region 8 combined these new data with the previous data to update the exposure-response modeling for LPT and also modeled the DPT and SIO endpoints (Benson et al., 2015). These new modeling results will be presented and compared to the previous results.
Fibrous Amphibole in Libby, Montana: Unique Biologic Response?
Brad Black, MD, Center for Asbestos Related Disease, Libby, Montana

The asbestos paradigm has held to the belief that asbestosis is on the decline, and pleural plaques are simply a marker of exposure and not associated with significant disease. In the early 1990s, a Spokane pulmonologist recognized a progressive pleural disease in Libby patients he had been following who had been exposed to the unique mineral fiber mix called Libby Amphibole Asbestos (LAA) that contaminated the mined vermiculite. The general phenotypic pattern is of pleural progression, whether plaque or diffuse pleural fibrosis, usually with relatively mild interstitial fibrosis. Nonmalignant morbidity/mortality from environmental exposure as well as occupational exposure has been observed. Additional atypical clinical patterns associated include 1) severe, intractable chest pain 2) episodes of rapid progression 3) prevalence of positive ANA serology (in 25%). Observations in the Libby Amphibole cohort (over 7,000 patients) followed by the Center for Asbestos Related Disease in Libby, MT for over 16 years suggest atypical mechanisms of disease. Furthermore, radiographic features have created new challenges in screening detection and quantification of disease.

SEM, TEM and IHC Reveal the Deposition Pattern and Translocation Pathways of Inhaled Asbestos Fibers That Cause Lung Injury, Fibroproliferative Disease and Cancer
Arnold R. Brody, Ph.D., Professor Emeritus, Department of Pathology, Tulane University Medical School, New Orleans, LA

All asbestos varieties cause asbestosis, lung cancer and mesothelioma. The fundamental mechanisms through which inhaled fibers mediate these diseases are being uncovered. Before we could embark on studies at the molecular level, it was necessary to determine the deposition and distribution patterns of the inhaled fibers after exposure and through the consequent levels of injury that result in disease. We used SEM and TEM to establish that inhaled fibers are intercepted at the bronchiolar-alveolar duct (BAD) junctions where they are transported by the Type-1 alveolar epithelium to the underlying interstitial space that includes connective tissue, blood and lymph flow and macrophages. About 20% of the fibers that deposit on the epithelium reach the interstitium, and a proportion of those are translocated to the mesothelial surfaces of the thoracic and peritoneal cavities. There is rapid injury to the Type-1 epithelial gas-exchange surfaces as evidenced by an alveolar leak containing plasma proteins, including the third component of complement (C) that is activated by asbestos to form C5a, a powerful chemo-attractant for macrophages and other inflammatory cells. To repair the asbestos-induced injuries, Type-2 epithelial cells, bronchiolar Clara cells and vascular smooth muscle and endothelial cells undergo rapid and prolonged proliferation, largely driven by the expression of transforming growth factor (GF) alpha (TGFα) and platelet-derived growth factor (PDGF) A and B chain peptides. Over the next few days, fibroblast, myofibroblast and smooth muscle cell proliferation are mediated by PDGF, and there is an increase in interstitial matrix, mediated by transforming growth factor beta (TGFβ). My laboratory has focused on genes that control cell proliferation, including tumor necrosis factor alpha (TNFa) that controls the expression of TGFβ by the MEK/ERK pathway and AP1 transcription in various lung cells. In situ hybridization of the genes that code for these GFS, as well as laser capture micro-dissection and real time-polymerase chain reaction showed that the genes coding for these growth factors were expressed in a dose responsive manner with the highest expression at the BAD junctions and the lowest at the pleural regions. Even though there was low gene expression at the pleural surfaces, there were significant increases in the number of proliferating mesothelial cells at 2 and 8 days post-exposure to chrysotile asbestos. Mice that had the genes coding for both TNFa receptors knocked out were significantly protected from the asbestos-induced fibroproliferative disease process. Inasmuch as proliferating cells are more likely to undergo genetic alterations that lead to neoplastic events, it will be essential to control the expression of these factors that mediate cell proliferation consequent to asbestos exposure.
Quantitative analysis of the role of fiber length on phagocytosis and inflammatory response by alveolar macrophages
Trudy Padmore, Carahline Stark, Julie Champion, and Leonid A. Turkevich
Georgia Institute of Technology, Atlanta GA, and CDC/NIOSH

Background In the lung, macrophages attempt to engulf inhaled high aspect ratio pathogenic materials, secreting inflammatory molecules in the process. The inability of macrophages to remove these materials leads to chronic inflammation and disease. How the biophysical and biochemical mechanisms of these effects are influenced by fiber length remains undetermined. This study evaluates the role of fiber length on phagocytosis and molecular inflammatory responses to non-cytotoxic fibers, enabling development of quantitative length-based models. Methods Murine alveolar macrophages were exposed to long and short populations of JM-100 glass fibers, produced by successive sedimentation and repeated crushing, respectively. Interactions between fibers and macrophages were observed using time-lapse video microscopy, and quantified by flow cytometry. Inflammatory biomolecules (TNF-α, IL-1α, COX-2, PGE2) were measured. Results Uptake of short fibers occurred more readily than for long, but long fibers were more potent stimulators of inflammatory molecules. Stimulation resulted in dose-dependent secretion of inflammatory biomolecules but no cytotoxicity or strong ROS production. Linear cytokine dose-response curves evaluated with length-dependent potency models, using measured fiber length distributions, resulted in identification of critical fiber lengths that cause frustrated phagocytosis and increased inflammatory biomolecule production. Conclusion Short fibers played a minor role in the inflammatory response compared to long fibers. The critical lengths at which frustrated phagocytosis occurs can be quantified by fitting dose-response curves to fiber distribution data. General Significance The single physical parameter of length can be used to directly assess the contributions of length against other physicochemical fiber properties to disease endpoints.

Arizona Amphibole Asbestos Induces Autoimmunity and Fibrosis in Mice
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Asbestos is a well-known carcinogen that contributes to autoimmunity and other health consequences. Libby Amphibole (LA) asbestos was a contaminant of vermiculite mined near Libby MT for decades, leading to asbestos diseases not only in mine workers, but in the entire community. Amphibole asbestos fibers in Arizona (AzA) have recently been discovered in the Lake Mead Recreational Area, but their health impact is unknown. The goal of this study was to determine whether these fibers, with similar chemistry to LA, induce autoimmune and fibrotic responses at a very low dosage that might represent environmental exposures. Seven months after exposure, blood, urine, diaphragms and lungs were collected from mice. Serum was used to determine autoantibody (ANA) levels and T helper cytokine responses. Urine was used to measure protein excretion, suggesting kidney involvement. Results revealed ANA levels were statistically significant with positive results with AzA. Urine analysis indicated significant amounts of excreted proteins by treated mice, consistent with an autoimmune process. Also, all three Th-17 cytokines were shown to have increased levels in treated mice that were statistically significant above controls. Analysis of lungs and diaphragms revealed significant interstitial and pleural fibrosis in the fiber-treated mice. Therefore, our results show that the AzA poses a serious health risk, even in small doses.
The development of diagnostic and prognostic plasma biomarkers for thoracic malignancies requires novel technologies as well as appropriate case/control cohorts for discovery and validation. Specifically, the asbestos related malignancy, mesothelioma, is often detected in later stages with little chance for long term survival. The EDRN Mesothelioma Biomarker Discovery laboratory represents institutions with unique expertise in the development and technical validation of innovative platforms using plasma or imaging algorithms for the diagnosis of thoracic malignancies. Building on promising preliminary data, three plasma mesothelioma markers (FBLN3, SOMAmer 13 classifier, and HMGB1 Isoforms), will undergo further refinement and potential validation. The consortium will have access to discovery and validation cohorts from the mesothelioma (N=202), lung cancer (n=760), and control (n=419) plasma archives at NYU. The NYU Biomarker Discovery Laboratory, with technical assistance from its EDRN associate member SomaLogic, will construct a novel Luminex based assay (LuSoma) which will consist of 13 slow-off-rate-modified-aptamers (SOMAmers) and a newly constructed FBLN3 SOMAmer. The new assay will undergo technical validation, followed by further validation of previous published work from the NYU BDL that the AUC differentiating MPM from AE remains greater than 0.9. The University of Hawaii, using 202 pleural effusions from the NYU BDL, will investigate the sensitivity/specificity of HMGB1 and its isoforms with a unique, technically validated, electrospray ionization liquid chromatography tandem mass spectrometry to differentiate MPM from non-PMP benign and non-PMF malignant effusions. The HMGB1 effusion results will be compared to those obtained with the LuSoma assay described above. Validation cohorts from the already approved EDRN MPM screening program in Santiago, Chile, as well as from University of Toronto and South Glasgow University Hospital are already in place. Research Support from U01 CA 086402, NCI/NIH, 2U24OH009077-08, CDC, 2U01CA 111295-04 (Subaward), NCI/NIH, and CA150671P2, DOD.

Serum protein biomarkers of mesothelioma and asbestos exposure
Ian A. Blair, PhD and Liwei Wang, PhD, University of Pennsylvania, Philadelphia PA

High mobility group box-1 (HMGB1) is a non-histone chromosomal protein that is highly conserved in eukaryotic cells. It is known to play a regulatory role in inflammatory immune responses and has recently proved to be a potential novel therapeutic target in malignant mesothelioma (MM). HMGB1 normally locates in the nucleus. During cell necrosis due to asbestos fibers, HMGB1 undergoes acetylation followed by translocation from the nucleus to the cytoplasm, and then secreted to extracellular space, where it binds to and activates pro-inflammatory mediators. Given the role it plays in inflammatory processes, HMGB1 may hold promise as a biomarker of cell transformative processes and thus hold utility as an indicator of asbestos exposure. A recent study revealed that serum levels of HMGB1 were increased in asbestos-exposed individuals as compared to both smoking and non-smoking controls by using an ELISA kit. This finding indicates the potential usage of serum HMGB1 levels in assessing asbestos exposure in human populations. In agreement with this finding, serum levels of HMGB1 have also been reported to be elevated in MM patients using an HMBG1 ELISA kit. Herein, we developed a stable isotope dilution HPLC-MS method, which has higher sensitivity and specificity compared with currently available HMBG1 ELISAs, to accurately quantify the HMGB1 levels in serum. Glu-C digestion of HMGB1 yields specific peptides including two nuclear localization signal (NLS) fragments. These two key peptides are highly acetylated, which prevents HMGB1 from reentering the nucleus. Thus, detection
and accurate quantification of these two highly acetylated peptide may provide a useful biomarker to assess the progress of MM and/or exposure to asbestos. For expressing isotopically labeled HMGB1, HEK293 cells were cultured in the RPMI media containing [13C6,15N2]-lysine and [13C9,15N1]-tyrosine for at least 3 split before transfection. The plasmid of the conjugation of GST and HMGB1 was transfected into HEK293 cells. The cells were lysed 24 h after transfection and the cell lysate was incubated with GSH Sepharose beads at 4°C overnight. TEV enzyme, 1 mM DTT and the buffer were added to the beads afterwards, and the mixture was incubated at 4°C overnight. The supernatant was then collected and solution was stored at -20°C until use. Pierce protein A/G beads were incubated with HMGB1 antibody (Sigma) and the mixture was rotated and tilted at r. t. for 1 h. After removing the supernatant, the beads were mixed with the human serum (50 mL). The mixture was rotated and tilted at 4°C overnight. Acetylation of HMGB1 was conducted with acetic anhydride. To purified/enriched HMGB1 was added 1 mM TCEP, 25 mM NH4HCO3, 10% CH3CN and Glu-C (protein:protease = 10:1). The digestion was carried out at 37°C overnight. The digested peptides were purified by C18 column and analyzed by ultra-high performance liquid chromatography-high resolution mass spectrometry. Immunopurification coupled with stable isotope dilution methodology made it possible to reliably quantify bioh free and acetylated forms of HMGB1 in the serum of mesothelioma patients and asbestos-exposed individuals.

**Novel Diagnostics and Therapeutic Modalities for Mesothelioma**

Raphael Bueno, MD  
Division of Thoracic Surgery, Brigham and Women’s Hospital, Boston, MA

Malignant Pleural Mesothelioma is an aggressive cancer usually resulting from prior exposure to asbestos fibers. We have been engaged in the study of tumor biology from the point of view of biomarkers that may facilitate diagnosis, prognosis and prediction of response. We previously developed a gene expression signature to define the risk of recurrence after surgery for Mesothelioma. We recently validated this signature and a multi-platform prognostic test that includes molecular biomarkers as well as pathological and radiographic data in a large prospective cohort of patients including both surgical and non-surgical cases. In parallel, we recently completed and reported in Nature Genetics a comprehensive Omic profiling of 216 mesothelioma tumors. We demonstrated that the tumors cluster into at least 4 concensus groups based on gene expression and that these groups have inherent additional prognostic features. We also described the most common mutations associated with mesothelioma. Finally, we embarked upon window of opportunity trials with biological compounds with some significant response in mesothelioma, likely associated with immune modulation, to define predictive tests. Some of these studies have been funded by grants from the NCI.

**Asbestos-induced mesothelial cell pathogenesis: What is new?**

Arti Shukla, PhD  
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Asbestos causes mesothelial cell pathogenesis leading to fibrosis or malignant mesothelioma (MM). Although there is no dispute about the role of asbestos in the process, how asbestos fibers reach mesothelial cells and initiate these diseases is still not well understood. Our lab focuses on understanding the role of recently discovered inflamasomes in the process of asbestos-induced mesothelial to fibroblastic transition (MFT) leading to MM. We have also learned from our studies that chemotherapeutic drugs can modulate inflamasomes in MM tumor cells, and a combination of chemotherapeutic drug and IL-1receptor antagonist may be a better strategy to treat MM than chemotherapy alone. In addition, we are exploring the possibility that asbestos can affect epithelial cells and macrophages, resulting in the secretion of exosomes loaded with specific signature molecules. These
exosomes can then target mesothelial cells of pleural and peritoneal cavity, unload their cargo and initiate the process of transformation. Some related data will be shared with the scientific community at the workshop. This research is financially supported by NIEHS (RO1 ES 021110) and DoD (W81XWH-13-PRCRP-IA)

POSTER SESSION (Biomarkers)

**microRNA as Exosomal Biomarkers for Mesothelioma**
Phillip B. Munson and Arti Shukla. Ph.D.

Malignant mesothelioma is a highly aggressive tumor directly associated with exposure to asbestos with median survival post-diagnosis of less than 1 year. Up to the present time, there are no useful means of diagnosing mesothelioma before the patient is experiencing symptoms of this invasive neoplasm, and it is effectively too late to meaningfully intervene. This lack of suitable detective biomarkers, taken with the fact that the mechanism of tumor development is mainly unknown, heralds the fact that more innovative approaches to understanding this disease are needed. Our lab is currently focusing on utilizing a novel approach to biomarker identification in the form of exosomes. Exosomes are small (40-140nm) membrane bound extracellular vesicles of endosomal origin that are currently a hot trend in scientific research for identifying unique biological disease signatures and uncovering the mechanistics of many vital processes of malignancy. We initially hypothesized that exosomes secreted from mesothelioma tumor cells carried a unique microRNA (miRNA) cargo compared to non-cancer cells. We uncovered that there is indeed a unique miRNA signature secreted in exosomes from mesothelioma cells, and more interestingly that a set of the significantly upregulated miRNAs happen to be tumor suppressive. At first, this appears counter-intuitive but led us to an altered hypothesis that mesothelioma tumor cells preferentially secrete tumor suppressor miRNAs in order to avoid the deleterious effects they may have on the tumor’s progression. This study currently focuses on miR-16-5p, and provides evidence that this tumor suppressor miRNA is secreted significantly more from tumor cells than non-cancerous cells, and that cancer cells themselves have less of this miRNA expressed within the producer cells when compared to their non-cancerous counterparts. This work is supported by funding from DoD W81XWH-13-PRCRP-IA and NIH RO1 ES021110 grants.

**Cancer Outcomes Session**

**Tumor immunology and immunotherapy for pleural mesothelioma**
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Abstract - Malignant pleural mesothelioma has been marked historically by poor prognosis. Current standard of care for this disease results in sub-optimal improvements in overall survival, which has prompted researchers to explore innovative treatment alternatives. Investigating solid tumor immunology and translating the knowledge to develop immunotherapy is an emerging therapeutic modality that harnesses the power of the human immune system. Even in a deadly disease such as pleural mesothelioma, our laboratory has shown that patients with good tumor-specific immune responses show improved survival. We developed cancer-antigen specific chimeric antigen receptor (CAR) T-cell therapy and translated to a clinical trial. Keeping the regional aggressive nature of pleural mesothelioma with rare metastases, the CAR T cells are being delivered intrapleurally in our clinical trial. We also summarized the different methods of immunotherapy for malignant pleural mesothelioma - immune checkpoint blockade, immunotoxin therapy, anticancer vaccines, oncolytic viral therapy, and adoptive cell therapy as the most common and pertinent methods of immunotherapy currently being assessed in clinical trials. In
addition to highlighting some of the successes of immunotherapy, we also have identified limitations that must be overcome to improve the efficacy of these therapies.

The Asbestos Paradigm in Unraveling the Mechanisms of Alveolar Epithelial Cell Mitochondrial DNA Damage: Implications for Lung Cancer
Dr. David W Kamp, Northwestern University Medical School, Chicago

ABSTRACT: Asbestos exposure remains an important cause of pulmonary fibrosis (asbestosis) and lung malignancies. Notably, patients with asbestosis, similar to idiopathic pulmonary fibrosis (IPF), have an increased risk for lung cancer. Alveolar type II (AT2) cell injury and apoptosis is evident in patients with asbestosis and IPF. Careful research by our group and others has begun to unravel the molecular events linking asbestosis with the development of lung fibrosis that can be targeted for therapy. The ability of asbestos fibers to induce alveolar epithelial cell (AEC) injury and repair are critical determinants of their fibrogenic and, presumably, their malignant potential. We have shown that mitochondrial reactive oxygen species (mt-ROS) mediate asbestos-induced AEC DNA damage, endoplasmic reticulum (ER) stress, and apoptosis by a p53- and mitochondria-regulated (intrinsic) death pathway. Our group established a key role for a novel mechanism by which mitochondrial (mt)DNA base excision repair enzyme, 8-oxoguanine-DNA glycosylase 1 (mt-OGG1), prevents oxidant-induced AEC apoptosis by preserving mitochondrial aconitase (ACO-2) and preventing mtDNA damage. We showed increased asbestos-induced lung fibrosis in mice deficient in OGG1 (Ogg1<sup>−/−</sup>) due in part to AT2 cell mtDNA damage, p53 expression, and intrinsic apoptosis while transgenic mice overexpressing mitochondrial catalase (MCAT) are protected from AEC mtDNA damage, apoptosis and lung fibrosis following asbestos exposure. Our more recent studies suggest that mice globally over-expressing mtOGG1 have reduced asbestos-induced lung mtDNA damage and lung fibrosis. SIRT3, the major mitochondrial NAD-dependent deacetylase with tumor suppressor functions, attenuates mt-ROS-induced mtDNA damage in part by deacetylating manganese superoxide dismutase (MnSOD) and mitochondrial 8-oxoguanine DNA glycosylase (OGG1). We recently reported that IPF lung AT2 cells have increased MnSOD<sub>K68</sub> acetylation compared to controls while oxidative stress (asbestos or H<sub>2</sub>O<sub>2</sub>) diminishes AEC SIRT3 protein expression and increased mitochondrial protein acetylation, including MnSOD<sub>K68</sub> and OGG1<sub>K338/341</sub>. SIRT3-over-expression reduced oxidant-induced AEC OGG1<sub>K338/341</sub> acetylation, mtDNA damage and apoptosis whereas SIRT3 silencing promoted these effects. Asbestos- or bleomycin-induced lung fibrosis, AEC mtDNA damage and apoptosis in WT mice were amplified in Sirt3<sup>−/−</sup> mice. Collectively, these studies are informing our understanding of the mechanisms by which asbestos-induced AEC mtDNA damage promotes apoptosis and pulmonary fibrosis. We reason that AEC mtDNA is a key target that integrates cell survival / death signals following exposure to fibrogenic / carcinogenic agents, such as asbestos fibers. Importantly, the asbestos paradigm is providing insights into the pathophysiologic events of other lung diseases that may identify novel molecular approaches useful in preventing pulmonary fibrosis and/or lung cancer following exposure to environmental toxins (e.g. asbestos, cigarette smoke, particulate matter etc.).

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Erionite Carcinogenic Potency: Epidemiological Assessment and Toxicological Considerations
Andrey Korchesvskiy, Chemistry and Industrial Hygiene, Inc, Arvada, CO 80005

Erionite had become known as “the most toxic mineral on the Earth” when mesothelioma mortality rates skyrocketed in Cappadochia, Turkey, where this zeolite rock was used as a building material. However, fibrous erionite can also be found in different locations in the United States (for example, in North Dakota, California, Oregon, and Nevada). Recently, a death from mesothelioma, apparently caused by erionite exposure, was reported in Mexico. In spite of significant toxicological concerns, erionite fibers are still not specifically regulated in the U.S. or internationally for workplace and ambient air permissible levels, or for transportation. This talk will explore approaches to a determination of erionite potency.
factors for mesothelioma. The data about air concentrations of PCME erionite fibers in Turkish villages will be juxtaposed with published mortality rates: for example, with mesothelioma mortality in a Swedish cohort of Karain emigrants. Monte Carlo simulation results show that erionite mesothelioma potency in terms of a Hodgson, Darnton RM metric has an average level of 3.46 (95 % CI 1.48, 7.13), approximately 7 times higher than for Australian crocidolite. It will be demonstrated that a similar estimation of erionite potency maximizes the F value of a predictive toxicological model deriving the mesothelioma potency from silicon/magnesium ratio, iron content, and the median dimensional characteristics of various fiber types. The presenter will compare this estimation of erionite potency with other published assumptions regarding carcinogenic potential of erionite in animal studies and epidemiological observations. The results of a new sampling and analysis of erionite-containing materials from Karain village in Turkey will also be presented. Various estimations of a potential occupational exposure limit (OEL) for erionite fibers will be compared and discussed.

Mysteries at the Biotic Interface
Christopher Weis, Ph.D., National Institute of Environmental Health Sciences/NIH, Bethesda, MD

Much work has been done to demonstrate human disease and characterize its epidemiology following exposure to elongated mineral particles (EMP). Yet, specific mechanisms involved in internal transport and toxicology of EMP leading to cancer and other health outcomes remain a matter of great concern. Recently, biophysical investigations into the nature of engineered nano- and micro-sized particles have expanded our understanding of particle-membrane physics. This presentation will explore particle behavior at the biotic interface with an eye toward advancing the biophysics and toxicology of EMP. The role of hydration shells, coulombic attraction, and particle dimension will be explored as important measures at the level of the cell membrane.