## 1082 BERYLLIUM-INDUCED SENSITIZATION AND GRANULOMATOUS LUNG DISEASE IN MURINE MODELS.

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Beryllium (Be) exposure is an occupational hazard that can cause chronic beryllium disease (CBD), an irreversible, debilitating granulomatous lung disease, in as many as 3-5% of exposed workers. CBD may be viewed as a biphasic disease: first with peripheral sensitization occurring, and then, in some, progression to pulmonary granuloma formation. To look at both aspects of the disease process, we performed a mouse ear-swelling test (MEST) to correlate with the sensitization process and a 5-month oropharyngeal aspiration study to examine pulmonary granuloma development in mice. Previously, a MEST was utilized to see if different inbred mouse strains would exhibit varying hypersensitivity responses to Be. In the present study, 21 inbred mouse strains were tested for sensitization to Be and distinct strain differences were observed with the mouse ear-swelling test with the SJL/J strain being the most sensitive while the FVB/N strain was resistant. The data were analyzed using an *in silico* approach to uncover genes associated with sensitization to beryllium and Vav3, involved in the activation of T cell receptors, became a likely candidate. In the current aspiration study, 26 inbred strains were aspirated with either 20μg of beryllium metal particles or water monthly. Clear strain differences in beryllium-induced lymphogranulomatus nodules were observed. *In silico* analysis was performed on the data and candidate genes implicated in granuloma formation were uncovered and compared to the results of the MEST study. Elucidating genes responsible for the hypersensitive phenotype and granuloma formation in mice may prove useful in learning more about the mechanisms involved in the progression of CBD.

## 1083 USE OF A MOUSE MODEL TO EVALUATE PULMONARY INFLAMMATION CAUSED BY FLOOR DUST FROM A WATER-DAMAGED BUILDING.

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Although the causes of building-related respiratory illness are still unclear, epidemiological research has indicated that fungi and endotoxin in floor dust are associated with such health risks. In the present study, we used a mouse model to evaluate pulmonary inflammation caused by floor dusts collected from the workstations of employees in a water-damaged office building. The dusts were tested in an endotoxin-sensitive strain of mouse - C3HeB/FeJ, and pulmonary inflammation was determined. We examined correlation among markers of inflammation and levels of endotoxin and (1→3)-β-D-glucan. Each mouse was treated with dust sample (2.5 mg/kg of body weight suspended in 40 μL of saline) by pharyngeal aspiration. Control mice received an equivalent volume of saline by aspiration. At 18 hrs after aspiration, bronchoalveolar lavage was done postmortem on lungs and the following inflammatory and lung injury markers were measured: (1) neutrophil infiltration, (2) albumin and lactate dehydrogenase levels, and (3) inflammatory cytokines levels. The results demonstrated significant dust-induced inflammation in mice. Significant positive correlations were found between endotoxin levels and IL-6 ($r=0.30$, $p<0.05$), IFN-γ ($r=0.47$, $p<0.05$) and MCP-1 ($r=0.33$, $p<0.05$). However, most inflammatory markers showed no correlation with extractable-glucan levels, except for albumin which had a negative correlation. This may be due to the fact that fractions of (1→3)-β-D-glucans which induced inflammation are generally not water soluble, but the commercially available analytical method can only measure the water extractable glucan in the dust. Alternative indicators of fungi, such as culturable fungi, may exhibit a better correlation with pulmonary inflammatory potential of floor dusts. Additional studies are ongoing using this animal model with the endotoxin-insensitive strain of mouse (C3H/HeJ) to further examine such correlations.

## 1084 REFINEMENT OF TRADITIONAL RESTRAINED WHOLE-BODY PLETHYSMOGRAPHY (WBP): DEVELOPMENT OF A MODULAR RESTRAINED WBP CHAMBER FOR NOSE-ONLY INHALATION EXPOSURE STUDIES IN MICE.

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Restrained WBP is used to monitor breathing frequency and tidal volume in many applications including the Standard Test Method for Estimating Sensory Irritancy of Airborne Chemicals (RD50; concentration required for a 50% depression in breathing frequency; ASTM Designation: E 981-04). Traditional restrained WBP relies on the use of a sealed chamber with a tight-fitting neck collar which isolates the exposure chamber from the body where the plethysmography takes place. Compression around the neck due to the tight-fitting collar is a recognized physiologic stressor that has been shown to cause pituitary injury. This potential for injury limits the utility of the procedure for repeated dose measurements. As a refinement to traditional restrained WBP, we developed a modular restrained WBP chamber for use in mice which was constructed specifically to eliminate the tight-fitting neck seal. Measurements of breathing frequency in CD-1 mice using this system (296±52 breaths/min) were similar to those previously reported using traditional restrained WBP. To test the utility of the newly developed modular restrained WBP chamber for use in determination of RD50, we conducted a series of experiments using well-characterized materials with established RD50 values and standard test methods (ASTM Designation: E 981-04). Data collected indicate that the new modular restrained WBP chamber can be used to determine the RD50 value of gases and vapors. The modular design permits optimal sizing of the body tube for the strain and age of mouse used and adaptation of the instrumented exposure tube to any nose-only exposure chamber system. The system can be used during single & repeated exposure studies to refine estimation of inhaled dose to individual animals. This modified WBP can be used to determine the sensory irritancy of inhaled materials, providing valuable data to aid in human risk assessment, while eliminating the physiologic stress induced by traditional systems which use a neck seal.

## 1085 DIFFERENTIAL PHYSICOCHEMICAL PROPERTIES OF PARTICLES FROM WOOD COMBUSTION AND TRAFFIC DETERMINE PRO-INFLAMMATORY POTENTIAL.

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The importance of different sources and the contribution of different components to effects of particulate matter still deserves investigation. Wood combustion particles have been suggested to be less potent than particles from motor vehicles. The aim of this study was to determine the pro-inflammatory potential of wood combustion particles (WCP) from different combustion phases and motor vehicle particles (MVP); to study the role of TNFα and IL-1 in cytokine release by these particles; and to investigate the importance of the organic fraction. THP-1 monocytes and A549 lung epithelial cells in contact co-culture were used in these studies. Cytokine levels were measured by ELISA. Roughly similar levels of IL-8 release were induced by MVP and WCP, whereas the levels of IL-6 tended to be higher after exposure to MVP compared to WCP. Whereas IL-1 seemed to be the primary determinant for the IL-6 levels induced by MVP, IL-1 did not seem to influence the IL-6 response to WCP. Particles from the different phases of the wood combustion process elicited roughly similar responses, but the coarse fraction of the WCP induced higher levels of cytokines than the fine fraction. The organic fraction of WCP was of greater importance for the cytokine response than the organic fraction from MVP. In contrast, the washed particles from MVP induced a greater cytokine release than the organic fraction. The toxicity of the particles included in the study was generally low. A reduction in cell number seemed to be due to inhibition of cell proliferation and not cell death. This reduction in cell number was associated with the organic fraction of the particles. In conclusion, the particles from two different sources elicited differential cytokine release in a co-culture of monocytes and lung epithelial cells. The organic fraction was the most important determinant of the effects of WCP.

## 1086 THE PROTECTIVE EFFECT OF THE UPPER AIRWAYS AGAINST WATER SOLUBLE IRRITANT GAS EXPOSURE – A CASE STUDY OF ACUTE AMMONIA EXPOSURE.

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Background: It is a commonly held toxicological principal that highly water soluble irritant gasses (i.e. hydrogen chloride, ammonia, sulfur dioxide, etc.) are first deposited in the upper respiratory tract, resulting in a filtering effect that protects the lower airways from damage. As exposure concentrations and durations increase, water soluble gases are able to penetrate more deeply into the respiratory tract to cause effects within the lungs. Following this toxicological principal, one would hypothesize that chronic respiratory effects from irritant gases would occur only after high-level exposures that first cause significant upper respiratory tract effects. No systematic evaluation of this hypothesis could be identified in the scientific literature.
Methods: This review examined reports of over 200 cases of acute ammonia exposure identified in the scientific literature. Reported cases with and without chronic respiratory effects were evaluated based on the severity of clinical signs at initial presentation and duration of hospital stay in order to determine the severity of exposure associated with chronic pulmonary effects.

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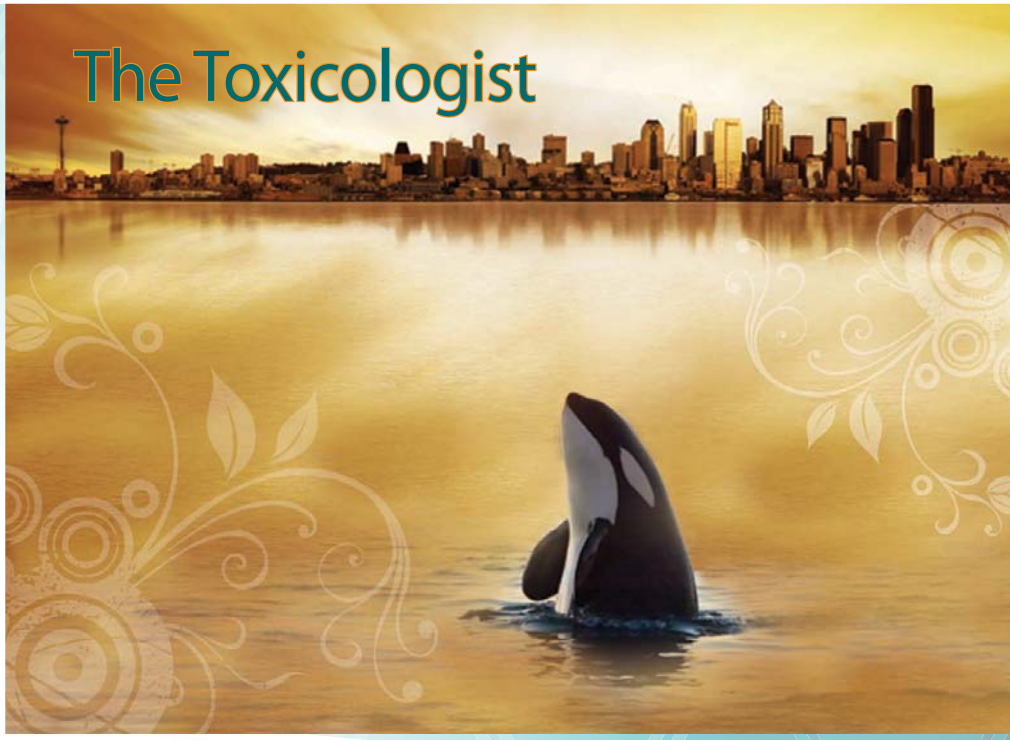

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