1281 Persistent Increases in Inflammatory Cytokines, Akt, and MAPK/ERK Pathways After Inhalation Exposure of Rats to Libby Amphibole (LA) or Amosite: Comparison to Effects After Intratracheal Exposure to LA or Naturally Occurring Asbestos

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Human exposure to LA and other mined or processed asbestos increases risk of lung inflammation, fibrosis, and cancer. Health risks from exposure to naturally occurring asbestos (NOA) are not as well-understood. Mechanisms of long-term toxicity were compared in male F344 rats exposed by nose-only inhalation (IH) or intratracheal (IT) instillation. Responses to IH LA (1.0, 3.3, or 10.0 mg/m3), amosite (AM; 3.3 mg/m3, as positive referent group), or air (all 6 hr/d, 5 d/wk, 13 wk) were evaluated 1 d, 1 mo, and 3 mo post-exposure. Responses to IT LA and NOA samples Sumas Mountain chrysotile (SM), El Dorado Hills tremolite (ED), and Ontario ferroactinolite (ON) (all at 0.5 or 1.5 mg/rat), or dispersion media (DM) only, were evaluated 1 d and 3 mo post-IT. Inflammatory cytokines, Akt, and MAPK/ERK pathway proteins were examined in lung tissue. Three mo after IH LA at 10.0 mg/m3, MAPK/ERK components (STAT3, MEK1/2) were significantly elevated 40-50% over air control. One day after IT LA or SM, STAT3, MEK1/2, and ERK1/2 were increased 2-5x over DM control. These IT effects were not present (MEK1/2, ERK1/2) or strongly attenuated (STAT3 for LA) at 3 mo post-exposure. Akt pathway components (S6RP, Akt) were increased 2x over air control 3 mo after 10.0 mg/m3 IH LA. One day post-IT, S6RP was increased 4x by 1.5 mg LA and 9x by 1.5 mg SM, and Akt was increased 2x by SM. By 3 mo post-IT, only Akt was significantly increased (2x by SM). TNF-α, IL-1β, and CXCL1 were persistently increased 1 d to 3 mo after IH AM or LA. These targets were also increased 1 d post-IT LA and SM, but by 3 mo only CXCL1 and TNF-α remained elevated (for LA and ED). At 15 mo post-IT and 18 mo post-IH, LA promoted lung fibrosis and tumor development. We conclude that LA inhalation causes more persistent inflammation and activation of growth factor pathways than IT exposure, which may contribute to lung disease long after initial exposure. Pro-inflammatory effects of IT SM and LA were greater than those of ED and ON. (This abstract does not represent US EPA policy.)

1282 Inflammatory Effects of Acrolein, Crotonaldehyde and Hexanal on Air-Lifted Primary Bronchial Human Epithelial Cells

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Acrolein (ACR) and crotonaldehyde (CRO) are formed during incomplete combustion and are found in e.g. cigarette smoke and restaurant kitchens. Hexanal (HEX) is emitted from wood pellets, MDF board and used as flavoring additive in cigarettes. The aim of the study was to compare the inflammatory effects of aldehydes in an air-liquid interface (ALI) exposure system with on air -lifted primary bronchial human epithelial cells (PBEC). The air-liquid interface (ALI) exposure system was used to achieve a closer resemblance with inhalation exposure *in vivo*. PBEC were obtained from multiple donors and cultured and grown in the ALI system. After 8-10 days at ALI, these cells were exposed to ACR (0.05, 0.1 and 0.5 ppm), CRO (0.5, 1.0, 2.0 and 5ppm), HEX (5, 10, 20 and 50 ppm) or clean air for 30 minutes. Samples of basal and apical media were collected at 8 h and 24 h after exposure and analyzed for Interleukin-8 (IL-8) and Matrix Metalloprotein-9 (MMP-9) by enzyme-linked immunosorbent assays (ELISA). Cell viability was tested at the same time points by trypan staining. Reduced cell viability (70-80% cell survival) was only seen at the highest tested aldehyde concentrations. Both ACR and CRO caused elevated IL-8 levels in basal media after 8 h and more so after 24 h. The IL-8 levels tended to increase with concentration but started to decrease at the highest tested concentrations. A different pattern was seen in apical media, with an inverse relation between aldehyde and IL-8 concentrations. None of these trends were statistically significant. There were no effects of HEX on IL-8. No clear effects were seen on MMP-9 for any of the aldehydes. Our study (1) shows that the ALI system can be used to study the inflammatory response of aldehydes, (2) supports that the potency to induce an inflammatory response follows the order ACR>>CRO>>HEX, and (3) indicates that the IL-8 response patterns seem to differ between the basal and apical side in the ALI system.

1283 Dung Biomass Smoke Exposure Attenuates Immune Responses to Toll-Like Receptor Ligands in Airway Epithelial Cells and Mice

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Worldwide, 3 billion people use biomass fuels, including animal dung, for cooking and heating their homes. According to the World Health Organization, over 4 million premature deaths every year are attributed to biomass smoke inhalation. Women and children, who often spend the most time around cooking fires, are at high risk of biomass smoke exposure. Epidemiological studies associate biomass smoke with an increased risk for respiratory infections, and nearly half of the pneumonia-related deaths in young children are related to biomass smoke. However, there is currently little experimental data examining how dung biomass smoke exposure impacts host-pathogen interactions. We hypothesized that dung biomass smoke impairs innate immune responses in the lung. To test this hypothesis, we generated dung biomass smoke using a novel, automated system. Primary human small airway epithelial cells (SAEC) were grown on transwell inserts, moved to the air-liquid interface, and exposed to air or dung smoke. Subsequently, cells were stimulated with Poly I:C (a Toll-like (TLR)-3 ligand) or MALP-2 (a TLR-2 ligand). Cytokine production was assessed by ELISA, IFN-β gene expression was measured by qPCR, and interferon levels were determined using ISRE-reporter cells. For *in vivo* experiments, mice were exposed to dung biomass smoke 2x1 hour per day (TPM = 50 mg/m3) for 2 weeks. After smoke exposure, mice were treated with LPS (a TLR-4 ligand) via inhalation. Inflammatory mediators and proteins were measured in the lung and BALF by ELISA and Western blot. Histology was used to examine lung inflammation. We found that SAEC exposed to dung biomass smoke had heightened IL-8 secretion in response to MALP-2 and attenuated upregulation of cytokines and interferon levels after Poly I:C treatment. Mice exposed to dung biomass smoke for 2-weeks had reduced levels of neutrophil chemoattractants and more inflammation after LPS inhalation. Our results show that dung biomass smoke exposure dysregulates pulmonary innate immune responses to pathogen-associated molecular patterns. We propose that impaired innate immunity due to dung biomass smoke inhalation may contribute to an increased risk and severity of respiratory infections, especially in vulnerable populations living in developing countries.

1284 Pulmonary Responses Following Inhalation of Sand Dust Collected From Hydraulic Fracturing Operations

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Workers at gas well fracking operations are exposed to fine fracking sand dust (FSD) which is generated from the movement of sand as it is prepared for injection into the well as a proppant. The worker exposures to FSD have been reported to exceed the exposure limits for crystalline silica promulgated by OSHA, NIOSH and ACGIH. Characterization of the FSD indicated that 88% of the particles were ≤2 µm, very low in Si•, $SiO_•$, or $SiOO_•$ radicals, and >95% quartz. We investigated the effects of FSD inhalation on the lung using Sprague-Dawley rats. Animals were exposed in whole-body chambers to 10 or 30 mg/m3 FSD collected from a fracking site or filtered air (control) for 6 h/d for 4 d. Measurements were made at 1, 7 and 27 d post-exposure. Neither 10 nor 30 mg/m3 FSD affected basal pulmonary function (lung resistance, RL; dynamic compliance, Cdyn) at any post-exposure time. At 10 mg/m3 FSD Cdyn responses to inhaled methacholine (MCh) were decreased 7 d post-exposure. At 30 mg/m3 FSD reactivity to MCh (RL) was increased at 7 and 27 d post-exposure. No other changes in reactivity to MCh were observed. Lung injury, measured as lactate dehydrogenase activity in bronchoalveolar lavage (BAL) fluid, was not increased following exposure to either dose of FSD. Neutrophil influx into the lung, an index of inflammation, increased at 7 d following exposure to 10 mg/m3 FSD, whereas neutrophils were elevated at 1 d post-exposure following inhalation of 30 mg/m3 FSD. BAL phagocyte oxidant production was increased at 7 d following inhalation of 30 mg/m3 FSD. Inflammatory responses were resolved by 27 d post-exposure for both doses of FSD. The results indicate that a four-day exposure of rats to FSD elicits modest changes in pulmonary function and lung inflammation.

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Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 55th Annual Meeting of the Society of Toxicology, held at the New Orleans Ernest N. Morial Convention Center, March 13–17, 2016.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 603.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 629.

The abstracts are reproduced as accepted by the Scientific Program Committee of the Society of Toxicology and appear in numerical sequence. Author names which are underlined in the author block indicate the author is a member of the Society of Toxicology. For example, J. Smith.

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