inflammatory response to ozone in a hyperthyroid state include an increase in NF-kappa B activation and an up-regulation of chemokine production.

707.2

Induction of CYP1A1 and NADPH quinone oxidoreductase (QR) with concomitant attenuation of CYP2B1 in the lung: Effects of paving asphalt fume exposure

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Polycyclic aromatic hydrocarbons (PAHs) in asphalt fumes require bioactivation by cytochrome P-450 to exert toxic/carcinogenic effects. Exposure to asphalt fume may alter phase I (P-450) and phase II (QR and GST) enzymes in the lung. The objective of this study was to evaluate this hypothesis in a rat model. Rats were exposed to air or asphalt fume generated at paving temperature (~150°C, ~20 mg/m^3, 3.5h or 6h/day for 5 days). Lung microsomes and cytosol were isolated. The activities for P-450 isozymes (CYP1A1 and CYP2B1) and phase II enzymes (QR and GST) were monitored. Protein levels were determined by Western blot analysis. The results show that asphalt fume exposure significantly induced the activity and protein levels of CYP1A1, but markedly reduced CYP2B1 levels and activity in the lung. By immunofluorescence, CYP1A1 induction was localized in airways, blood vessels, and alveoli. Cytosolic QR activity was significantly elevated after asphalt fume exposure, whereas, GST activity was not affected by the exposure. This induction of CYP1A1 and QR with the concomitant attenuation of CYP2B1 after asphalt fume exposure may alter PAH metabolism leading to potential carcinogenic/mutagenic effects.

707.3

Alternation of Innate and Cell-Mediated Immunity to *Listeria monocytogenes* by Short-Term Exposure to Diesel Exhaust Particles

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The effects of diesel exhaust particles (DEP) on functions of pulmonary host defense were studied using a rat Listeria infection model. Short-term DEP inhalation (50 and 100 mg/m3, 4 h) by rats resulted in a slowed lung bacterial clearance, suppressed alveolar macrophage (AM) phagocytosis and reduced AM production of tumor necrosis factor (TNF)-alpha, interleukin (IL)-1 and IL-12 in response to Listeria. The combined DEP/Listeria exposure was also characterized by increased CD4+ and CD8+ cell counts, and percentage of CD8+ cells in lung draining lymph nodes. The lymphocytes from DEP-treated rats showed increased IL-2 production when challenged with concanavalin A (ConA). Cells from the combined exposed rats produced increased interferon (IFN)-gamma at day 7, but decreased IFN-gamma at day 3, when challenged with either ConA or heat-killed Listeria (HKLM). Listeria significantly induced lymphocyte secretion of IL-6 in response to HKLM, which could be increased by DEP preexposure. These results indicate that short-term DEP exposure aggravates Listeria infection by suppressing AM phagocytosis and the production of TNF-alpha, IL-1 and IL-12, and by eliciting an adverse effect on T-cell-mediated immunity.

707.4

Effects of paving asphalt fume exposure on genotoxic and mutagenic activities in the lung

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Asphalt fumes are complex mixtures of aerosols and vapors containing various organic compounds, including polycyclic aromatic hydrocarbons, and have been demonstrated to alter the cytochrome P-450 system in the lung with significant induction of CYP1A1. The present study was carried out to characterize the potential mutagenic and genotoxic effects of inhaled asphalt fume in a rat model. Rats were exposed to air or asphalt fume generated at paving temperature (~150°C) at ~98 mg/m^3 and 6h/day for 5 days. Alveolar macrophages (AM) were obtained by bronchoalveolar lavage. S9 was isolated from the lung tissue. Mutagenicity was monitored using the Ames test and genotoxicity was determined by Comet assay. In comparison to controls, AM from asphalt fume-exposed rats showed significant DNA damage as demonstrated by the Comet assay. However, the S9 fraction from asphalt exposed rat lungs used for metabolic activation of 2-aminoanthracene or benzo[a]pyrene in Ames tests, did not induce mutagenic activity in either *S. typhimurium* YG1024 or YG1029. These results suggest that short term inhalation of asphalt fume did not induce any metabolic activity-dependent mutagenicity, but caused significant DNA damage in AM.

707.5

Induction of Apoptosis from Instillation of Agricultural Dust

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In this study, we test the hypothesis that induction of alveolar macrophage (AM) apoptosis plays a role in lung injury from particulates. We examined AM apoptosis in F344 rats following intratracheal instillation of 1ml of saline containing 4mg of particles. Particles used included crystalline silica, titanium dioxide and particulates from air sampling of citrus and grape fields. After 4 weeks, rats were sacrificed and lung sections analyzed for the number of apoptotic cells per lung using TdT labelling. Apoptotic macrophages, expressed in millions of cells per lung (mean±SE,N=4), were 43.4±4 for crystalline silica, 10.50±0.2 for grape, 8.1±0.5 for citrus and 3.1±0.4 for titanium dioxide. Saline controls were 1.6±0.4. The degree of apoptosis correlated well with inflammation and damage suggesting a role for apoptosis in lung injury resulting from particulates.

707.6

Enhanced Nitric Oxide Production Associated with Silica-Induced Disease in Rats.

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This study investigated the relationship between silica-induced lung damage, inflammation and fibrosis and nitric oxide (NO) production in rats exposed by inhalation to silica (15 mg/m^3 silica, 6 hr/day, 5 days/week, for 116 exposure days). Markers of pulmonary inflammation and damage rise rapidly (5-16 days of exposure) and are maintained at a relatively stable new set point through 40 days, before rising explosively at 79 and 116 days of exposure. Fibrosis is evident only during this explosive period of inflammation and damage. Silica inhalation results in a rapid (5 days) rise in NO-dependent chemiluminescence from alveolar macrophages (AM). NO products in bronchoalveolar lavage fluid increase significantly, exhibiting a time course similar to that for parameters of inflammation and damage. Immunohistochemical analysis of pulmonary inducible NO synthase (iNOS) and nitrotyrosine identified elevated iNOS and NO-induced damage in AM and type II cells after 79 days of exposure. This NO production is associated with granulomatous regions of the lung. These data indicate that NO production is associated temporally and anatomically with silica-induced lung disease in a rat inhalation model.

707.7

Increased lung permeability accompanies homeostatic decline in aging mice

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Epidemiological studies show elderly populations are at greater risk for adverse health effects from inhaled environmental particulate matter. To determine whether enhanced particle uptake contributes to increased risk, we studied 99mTc-DTPA clearance from the lung in mice with genetically accelerated aging(AKR/J). Onset of weight loss in this strain predicts lifespan and is a reliable estimate of homeostatic decline(34±3SEM, Tankersley, AJP 2001). Both stable adult(wild type:25g, AKR/J:45g) and AKR/J mice after 9.3% weight loss were anesthetized, intubated, and given 25µl 99mTc-DTPA by tracheal instillation. 30min clearance from the lung was measured by gamma scintigraphy. Results indicated that mice showed an increased rate of particle clearance after weight loss compared to stable adult controls. Particle retention in the lung of stable adult wild type(n=4), AKR/J(n=2), and senescent AKR/J(n=8) averaged 56%, 50% and 40%($p<0.05$), respectively. Thus during the period of homeostatic decline

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