(i.e., the airborne concentration which causes a 50% decrease in respiratory rate) for D-α- and D-β-pinene, and D-Δ^3-carene were almost equal: 1053 ppm, 1279 ppm and 1345 ppm in outbread OF1 mice, respectively. L-β-pinene was about 4 to 5 times weaker as sensory irritant with RD_{50} of 4663 ppm. For L-α-pinene, the RD_{50} could not be determined because its very weak sensory irritating properties. The RD_{50} of turpentine was 1173 pmm. The turpentine used consisted mainly of D-Δ^3-carene (53.1%), L-β-pinene (14.7%) D-α-pinene (10.6%), L-α-pinene (3.8%) and limonenes (5.6%) indicating that D-monoterpenes might be responsible for the sensory irritation caused by turpentine. For nonreactive chemicals, vapor pressure (P^o) and olive oil-gas partition (L_{Oil}) can be used to estimate their potency as sensory irritant. Thus, for enantiomers with close physicochemical properties, the estimated RD_{50}s will be similar. This can be used to estimate the RD_{50} of a mixture. However, because of the inactivity of L-α-pinene, the 3-dimensional structure must be taken into account. Thus, the target site for nonreactive sensory irritants is most likely a receptor protein capable of chiral recognition and physicochemical descriptors alone may overestimate the potency of some enantiomers in a mixture.

609 GENOTOXICITY AND IMMUNOLOGICAL CHANGES IN ISOCYANATE EXPOSED BROWN NORWAY RATS.

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Methylene di-phenyl diisocyanate (MDI) is an important chemical used to make many polyurethane products such as foams and wood binders. The predominant occupational disease attributed to isocyanates including MDI is asthma, however, the potential for genotoxicity has also been of concern. Diisocyanates are very reactive. MDI can be hydrolyzed to methylene dianiline (MDA), and/or react with primary amines and thiols under physiological conditions. MDA is a carcinogen in animals and is a suspected carcinogen in humans. Brown Norway rats (BNR) were exposed to either 7 (LOW) or 113 mg/m^3 (HIGH) MDI aerosol for 1 hr, 1x/week for 3 weeks with sacrifice 1 week later. A third, acute 135 mg/m^3 (ACUTE) MDI aerosol, 1 hr exposure group was sacrificed within 1 hr of exposure to assess acute eosinophilic inflammation. Bone marrow was recovered from HIGH and LOW groups to assess micronuclei formation in polychromatic erythrocytes (PCE) and peripheral blood for measurement of specific antibodies. Trachea and bronchial alveolar lavage were assessed for inflammatory changes. Dose dependent formation of PCE micronuclei formation was noted in MDI exposed BNR. Preliminary *in vitro* evidence suggest that the genotoxicity may have been mediated through the formation of MDA and/or thioester MDI conjugates. Eosinophilic inflammation measured by histochemical diaaminobenzidine staining of tracheal sections was present only in the acute inflammatory response. T-cells were slightly elevated in the BAL of half of the HIGH MDI exposed BNR, and the cd4/cd8 ratio was normal. MDI-specific IgE was detected in 5/6 and 4/6 of the rats from the LOW and HIGH groups, respectively. MDI-specific IgG was detected in all rats from both groups. These data demonstrates the genotoxic potential along with the allergenic effects of MDI aerosol exposure in the BNR model.

610 RESPONSE OF SHEEP HEMOGLOBIN TO NOSE-ONLY, INHALED NITROGEN DIOXIDE AND CARBON MONOXIDE MIXTURE.

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Nitrogen dioxide (NO_2) and carbon monoxide (CO) are gases produced during fires threatening life and health, because they cause lung injury and impair hemoglobin (Hb) O_2 carrying capacity. If the brain's O_2 supply is reduced, the ability for timely and rational response may be impaired. To study the changes in Hb oxygenation after exposure to NO_2+CO mixture, we used 5 healthy crossbred ewes weighing 70-80 kg, each prepared with a chronic carotid artery loop a month earlier. The sheep inhaled a mixture of (150±10 ppm NO_2+3500±400 ppm CO) for 30 min via the nose using a plastic canine anesthesia mask. Gas concentrations were measured. Arterial (A) and venous (V) blood samples were collected before (Pre), and at 0h, 1h, 4h, and 24h post exposure. Blood was immediately analyzed using a Hemoximeter, and packed cell volume was measured. All sheep survived the exposure, and packed cell volume was not altered. Maximum effect in blood was at 0h post exposure where carboxyHb (COHb) increased 40-fold from <1% to 39.5%, and metHb doubled from 0.8 % to 1.6%. Both returned to control levels by 24h. To follow the kinetics of COHb and metHb formation, we collected blood from two sheep every 5 min during exposure. We found that COHb increased 1% / min, whereas metHb increased at 0.025% / min only. Exposures of rats to similar levels of NO_2 + CO were lethal. This raises a question about extrapolating single species data to humans, and whether small animals alone are suitable for predicting human response or setting environmental and occupational standards.

611 TRICHOTHECENE TOXINS ARE PRESENT IN NON-VIABLE *STACHYBOTRYS CHARTARUM* SPORES.

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Fungi are a significant etiological factor in Sick Building Syndrome. Buildings whose occupants register complaints concerning indoor air quality (IAQ) frequently have high concentrations of Penicillium sp. present in the air and/or Stachybotrys on building surfaces. Stachybotrys sp. are thought to be involved in IAQ problems by virtue of their production of trichothecene toxins. This study determined if spore viability was a prerequisite for the toxigenic properties of S. chartarum, or if the trichothecene toxins were contained in the spores. Toxigenic S. chartarum spores were washed with phosphate buffered saline and incubated with rat alveolar macrophages (RAM) attached to microtiter plates. This treatment caused a dose- and time-dependent loss of RAM viability. Rendering the spores non-viable (NV) with ultraviolet-irradiation did not reduce spore toxicity. Washing S. chartarum spores with absolute methanol extracted the trichothecene toxins and rendered the spores NV. Methanol extraction reduced the toxigenic effect, but, overtime, the RAM were still killed by the S. chartarum spores. These data suggest that at least some of the trichothecene toxins are embedded in the S. chartarum spores and emphasizes the importance of removing S. chartarum spores from the indoor environment regardless of their viability. (These studies were supported in part by QIC Systems.)

612 BIOMARKERS OF CELL PROLIFERATION AND FIBROSIS IN MICE AFTER INHALATION OF ASBESTOS: APPLICATION TO TRANSGENIC MODELS USING LUNG EPITHELIAL CELL-SPECIFIC PROMOTERS FOR MODIFICATION OF MITOGEN-ACTIVATED PROTEIN KINASE SIGNALING CASCADES.

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Work in our laboratory has linked activation of certain Mitogen-Activated Protein Kinases (MAPK) to the advent of asbestos-associated apoptosis and proliferation in rodent mesothelial and alveolar type II epithelial cells *in vitro*. These phenotypic endpoints may be linked to the development of pulmonary or pleural fibrosis and/or repair. To address this question, we are developing transgenic mouse models using dominant negative mutant constructs of the Extracellular Signal-Regulated (ERK) and c-Jun-N-terminal (JNK) kinases using lung epithelial cell-specific promoters. The goal of work here was to characterize the development of inflammation, epithelial cell proliferation, and fibrosis in the parental mouse strain, C57Bl/6, after inhalation of NIEHS chrysotile asbestos (~7mg/m^3 air, 6hr/day, 5d/wk). Mice (2 month old, N=5/group/time period) were exposed for periods of time up to 30 days and evaluated for 1) total protein and cell counts in bronchoalveolar lavage fluid (BAL); 2) hydroxyproline content in lung; 3) increases in incorporation of 5-bromo-2'-deoxyuridine (BrdU) in bronchiolar and alveolar type II epithelial cells; 4) histopathology; and 5) procollagen type I message levels in lung. Data show that inflammation occurs in chrysotile-exposed mice as evidenced by increases ($p<.05$) in total protein and increased neutrophils in BALF after 10 and 20 days of exposure. These changes preceded increases in cell proliferation ($p<.05$) at 30 days in bronchiolar and alveolar epithelial cell compartments. Histopathology revealed the development of focal pulmonary fibrosis at 30 days in the absence of increases in lung hydroxyproline or elevations in procollagen type I mRNA levels. Comparative studies using NIEHS crocidolite asbestos are in progress to determine if patterns of inflammation, proliferation and fibrosis are more striking with use of this asbestos type. (Supported by a NIEHS Environmental Pathology Training grant (T32ES07122) and grants from NHLBI and NIEHS.)

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