LC50 is >5 mg/L and there is mortality or significant clinical signs; otherwise the substance is not classified. Data were available from 8 acute inhalation studies with aerosolized oils. In three of these studies, groups of 20 rats (10/sex) were exposed to ~0.1, 0.5, or 2.5 mg/L. In two similar studies, one group of rats was exposed to aerosol levels of 1.0 or 2.6 mg/L. Viscosity of these 5 mineral oils ranged from 15 to 460 cSt at 40°C. Five rats/sex in each group were sacrificed 18 hours after exposure; the remaining 5/sex were sacrificed after 2 wks. Endpoints in these 5 studies included body weight, clinical signs, gross necropsy, and weights of lung (wet and dry), liver, and kidney. Lungs, nose, kidneys, liver, and thoracic lymph nodes were examined microscopically. No treatment-related changes were noted in any study relative to controls. Three additional oils with viscosities ranging from ~9 to 32 cSt at 40°C were also studied. Endpoints were periodic body weights, clinical observations, and a gross necropsy on day 14. Mean aerosol concentrations ranged from 4.0 to 5.5 mg/L. All animals survived until termination and appeared normal within the 2 wk observation period, except those exposed to the 9 cSt oil. Those animals showed a lack of grooming, reddened skin, hunched posture, and reduced body weight gains. Based on the absence of mortality or significant clinical signs at maximum aerosol levels of 2.5 to 5.5 mg/L, mineral base oils with viscosities =>15 cSt at 40°C would not be classified as acute inhalation hazards under GHS.

1078 IN VIVO EVALUATION OF LUNG STRUCTURE BY MAGNETIC RESONANCE IMAGING (MRI) FOLLOWING ELASTASE INDUCED EMPHESEMA IN RATS.

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Emphysema and chronic bronchitis comprise the clinical complex known as chronic obstructive pulmonary disease (COPD). Cigarette smoke is a primary risk factor for COPD, with emphysema resulting in tissue destruction and airway expansion. MRI was used to non-invasively assess emphysema in a rodent model. To measure the extent of airway remodeling, the apparent diffusion coefficient (ADC) of inhaled hyperpolarized ^{3}He was quantified by MRI. Groups (3/time-point) of adult male rats were intratracheally administered saline or elastase (250 U/kg) and serially imaged. ^{3}He gas was generated using spin-exchange optical pumping, and animals were anesthetized and maintained on a mechanical ventilator. A Varian UnityPlus console with a 2 T wide bore magnet was used for imaging. The ^{3}He ADC was measured from three-dimensional (3D) images of control and treated animals acquired at 1-, 2- and 3-weeks post-exposure. The body-weight normalized median global ADCs in control rats, including airways, were (in units of cm^2/s/kg) 0.288, 0.254, and 0.239, respectively, and in elastase treated rats were 0.326, 0.343, and 0.244. Although global changes were quantifiable, the overall elastase lung response was heterogeneous. For example, in 3-week elastase-treated rats ADCs in random 5 x 5 x 2 mm^3 regions, which excluded major airways, typically ranged from 0.178 to 0.455 cm^2/s/kg, indicating a wide range of disease severity. Current efforts are aimed at correlating local ADC values with lung morphometry to determine whether MRI can be used as a noninvasive tool to assess the time-course of localized disease progression in individual animals. This technology will advance the evaluation of subtle changes in lung structure resulting from exposure to a broad range of xenobiotics. Most importantly, the ability to conduct repetitive measurements in the same animal offers a unique opportunity to advance the evaluation of toxicological response and mechanism of action. (Supported by NIH/NHLBI grant R01 HL073598-01 and Battelle ILA)

1079 PROGRESSIVE PULMONARY AND PLEURAL EFFECTS OF INDIUM PHOSPHIDE IN B6C3F1 MICE: PARTICULATE INDUCED PLEURAL FIBROSIS AND PROLIFERATION.

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Indium phosphide (InP) is a synthetic metal used in the microelectronics industry. Previous chronic inhalation exposure of mice to InP particles caused alveolar/bronchiolar adenomas and carcinomas, alveolar proteinosis, chronic inflammation, pleural fibrosis, hyperplasia of the pleural mesothelium and inflammation of heart arteries (NTP 2001). Although fibers are known to cause lesions in pleural tissues, pleural effects are uncommon after inhalation of a non-fibrous particulate. This study was conducted to investigate the mechanism of InP induced pleural fibrosis and hyperplasia in male B6C3F1 mice. Mice were treated with saline, 1 or 2 mg/kg InP by oropharyngeal aspiration (OA). Pleural lavage (PLF) and bronchoalveloar lavage fluid (BALF) was collected from mice 1, 3, 14 and 28 days post-aspiration. Cell number, LDH, total protein and cytokine levels were assayed from PLF and BALF. BALF cell number demonstrated a delayed increase, and total protein and LDH were increased in a time-related manner. Complex changes in BALF cytokine levels were observed. InP induced a pronounced pleural effusion on day 28. Cytokine analysis of PLF from day 28 demonstrated increased concentrations of osteopontin, C-RP, fibrinogen, MMP-9, MIP-1g TIMP-1, VCAM-1, vWF and other cytokine/growth factors in the pleural cavity of InP treated mice. Intrapleural injection of InP or indium chloride did not demonstrate an equivalent pleural effusion at day 28. Aspiration of InP caused progressive inflammation at weeks 1, 2, and 4 and subsequent multifocal regions of severe chronic inflammation with associated proliferative pneumonia, perivascular inflammation with extensive lymphoid proliferation and extensive areas of fibrotic thickening in the visceral pleura evident at week 14. InP may cause pleural fibrosis by causing a chronic pleural effusion, secondary to lung injury, which eventually results in pleural fibrosis and pleural hyperplasia.

1080 TOXICOLOGICAL CHARACTERIZATION OF INHALED CUSTOM PEPTIDES.

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In recent years, a number of new therapeutic peptides and proteins have been developed, but they must be injected in order to avoid rapid degradation by gastrointestinal enzymes. Significant development in new drug delivery systems such as nasal and lung delivery has been growing. Unfortunately, new therapeutic macromolecules are too large to pass through the epithelial and endothelial barriers without an absorption enhancer. A preliminary experiment was performed to determine the toxicity and efficacy of a Custom Peptide when administered by inhalation exposure once daily for 5 consecutive days to Sprague-Dawley rats. The proposed use of the inhaled Custom Peptide would introduce an excipient that can be used to enhance nasal and pulmonary drug delivery in tandem with a variety of inhaled pharmaceuticals. The results of this experiment demonstrated that dose levels up to 26.0 mg/kg/day did not produce any adverse test article-related findings. The Custom Peptide was well tolerated and there were no adverse clinical observations or systemic effects detected by assessment of clinical pathology parameters or following histopathological examination of all major organs. The respiratory tract (nasal cavity, nasopharynx, larynx, trachea, carina, bronchi and lungs) was examined histologically and there were no indications of local toxicity. The stability of the Custom Peptide in dose formulation solutions (2, 10, 50 mg/mL) was determined in vitro by assessing the biological activity on epithelial cell-cell adhesion. The Custom Peptide was capable of disrupting adhesion of confluent epithelial cells.
This study was supported by the Canadian Institutes of Health Research (CIHR PPP 82569)

1081 INHALATION OF STAINLESS STEEL WELDING FUME RESULTS IN DISSIMILAR INFLAMMATORY RESPONSES IN THE LUNGS OF A/J AND C57BL/6J MICE.

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Epidemiology studies suggest that inhalation of welding fume increases lung cancer risk in welders. Stainless steel (SS) fume, in particular, contains carcinogenic chromium and nickel. However, animal studies are lacking to conclusively link exposure to an increased lung cancer risk. An ongoing study in our laboratory has been to compare the inflammatory and tumorigenic responses to welding fume in lung tumor susceptible (A/J) and resistant (C57BL/6J) mice. Age and weight-matched male mice were exposed to gas metal arc-SS welding fume at 40mg/m^3 x 3hr/d for 10 days. Control mice were exposed to filtered air. At 1, 4, and 7d after the final exposure, bronchoalveolar lavage (BAL) was done postmortem. Lung cytotoxicity (LDH activity), air-blood barrier damage (albumin), inflammatory cytokines (IFN-γ, IL-6, IL-10, IL-12p70, MCP-1, TNF-α), total BAL cell counts, and differentials (≥300 cells identified) were analyzed. Inhalation of SS fume caused significant cytotoxicity and damage at all time points in both strains. Air exposure caused no effect and BAL cells were >99% alveolar macrophages. In SS fume-exposed A/J mice, total cell numbers were increased 3.5, 5.6 and 7.6 fold compared to control at 1, 4, and 7d, respectively. The inflammatory response was dominated by an increasing neutrophilic component that reached 36% by 7d. A minor influx of macrophage/monocytes and lymphocytes (<2%) was found. No cytokines were increased at any time point in the A/J. In the C57BL/6J, total cells were increased 5.2 fold versus control and this increase was maintained among all time points. The response was dominated by macrophage/monocytes and lymphocytes (7-10%) with minimal neutrophils (<5%). MCP-1 and IL-6 were increased at all time points, which confirmed the cellular response in the C57BL/6J. In conclusion, the dissimilar responses to inhaled SS fume may be due to the genetic background of these strains. Chronic inhalation studies are planned to further evaluate these strain differences.

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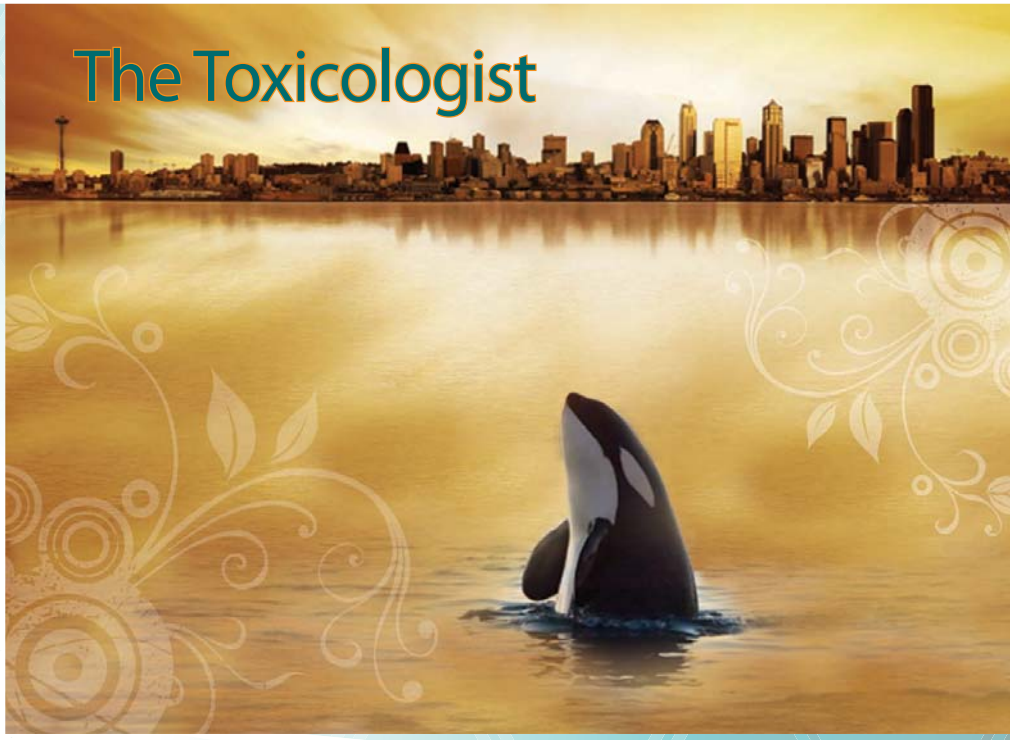

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