## 214 INFLAMMATORY EFFECTS OF QUARTZ SAMPLES AFTER INTRATRACHEAL INSTILLATION IN RATS.

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Objectives: This 28-day study compared the inflammatory potential of quartz with geologically ancient surfaces to well-characterized reference quartz DQ 12 (RQ). A differentiation of subspecies of quartz dusts is important in regard to a wide exposure and a potential carcinogenicity. Methods: A quartz sample in a naturally occurring respirable size (quartz isolate-QI) was separated centrifugally from an unprocessed bentonite dispersion, as were clay minerals (clay isolate-CI). QI contained approx. 67% quartz with the remainder being predominantly clay minerals, and CI contained <0.035% quartz. Lung effects of QI and CI were evaluated in rats at 3 and 28 days after administering a total dose of 15.2 mg/kg in 4 equal doses. To rank the effects, a positive control (RQ) and a negative control (TiO2) were included. Results: Bronchoalveolar lavage showed a severe acute inflammatory effect in the CI group at 3 days after last dosing, which recovered mostly after 28 days. QI induced moderate inflammatory effects after 3 days, which did not change significantly by 28 days post treatment. In contrast, RQ showed a high acute inflammatory response on day 3, persisting through day 28. Histopathologically pulmonary inflammation in lungs at day 28 was most pronounced in the RQ group, whereas QI and CI showed significantly lower effects. In contrast to the quartz groups, inflammation in the CI group was not persistent or progressive but was a late recovery phase of a severe acute inflammatory effect. Conclusion: Pulmonary inflammatory effects of various quartz subspecies were significantly different.

## 215 PULMONARY TOXICITY OF ADVANCED COMPOSITE MATERIAL COMBUSTION ATMOSPHERES IN RATS.

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Advanced composite materials (ACM) provide a lighter alternative to their metal counterparts without compromising strength. A downside to the use of ACM is their ability to burn. To investigate the toxicity of ACM combustion atmospheres F-344 rats were exposed for 1 hour in whole-body chambers to the smoke produced from the pyrolysis of 60 g of carbon-graphite/epoxy material. Control rats were exposed to filtered air. After 1, 3, and 7 days post-exposure, the animals underwent bronchoalveolar lavage. The lavaged cells were quantitated and identified morphologically. The lavage fluid was analyzed for the inflammatory cytokines Interleukin-1 beta (IL-1β), IL-6, and Tumor Necrosis Factor-alpha (TNF-α) by ELISA. The results included significant increases in cell counts, polymorphonuclear leukocytes (PMN)s, IL-1β, IL-6, and TNF-α as compared to controls. In conclusion, exposure to ACM combustion atmospheres produces time-dependent pulmonary toxicity manifested by the recruitment of inflammatory cells, release of inflammatory cytokines and the development of pulmonary inflammation.

## 216 ACUTE PULMONARY RESPONSE OF INDUCIBLE NITRIC OXIDE SYNTHASE KNOCKOUT *VERSUS* WILD TYPE MICE FOLLOWING ASPIRATION OF LIPOPOLYSACCHARIDE PLUS INTERFERON-γ OR QUARTZ.

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Exposure of mice to lipopolysaccharide (LPS) plus interferon-γ (IFN-γ) or to quartz increases nitric oxide (NO) production, which has been proposed to play a role in the resulting pulmonary damage and inflammation. To determine the role of NO in these acute lung reactions, the responses of inducible nitric oxide synthase knockout (iNOS KO) versus C57BL/6J wild type (WT) mice to aspiration of LPS+IFN-γ or quartz were compared. Male mice (6-8 weeks) were exposed by aspiration to LPS (1.2 mg/kg) + IFN-γ (5000 University), quartz (40 mg/kg), or saline vehicle. At 24 hours post-exposure, lungs were lavaged with 10 aliquots (1 ml each) of Ca+2 and Mg+2 free phosphate-buffered saline. The acellular fluid from the first bronchoalveolar lavage (BAL) was analyzed for total antioxidant capacity, lactate dehydrogenase (LDH) activity, albumin, tumor necrosis factor-α (TNF-α) and macrophage inflammatory protein-2 (MIP-2). The cellular fraction of the total BAL fluid was assayed for alveolar macrophage (AM) and polymorphonuclear leukocyte (PMN) counts, and AM zymosan-stimulated chemiluminescence (AM-CL). Exposure to LPS + IFN-γ decreased total antioxidant capacity, increased BAL AMs and PMNs, LDH, albumin, TNF-α and MIP-2, and enhanced AM-CL to the same extent in both iNOS KO and WT mice. Exposure to quartz decreased AM yield, increased PMNs, LDH, albumin, TNF-α and MIP-2, and enhanced AM-CL. However, iNOS KO mice exhibited less AM activation (activation status was defined as an increased AM-CL and decreased AM yield) than WT mice. These data suggest that NO may play a role in the acute pulmonary response to quartz exposure; however, evidence for a role of NO in the acute reaction to LPS+IFN-γ was not obtained.

## 217 INTERACTION BETWEEN PRIMARY ALVEOLAR MACROPHAGES(AM) AND PRIMARY ALVEOLAR TYPE II (TII) CELLS UNDER BASAL CONDITIONS AND AFTER LIPOPOLYSACCHARIDE (LPS) OR QUARTZ EXPOSURE.

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This study evaluated the mutual interactions between AM and TII cells under unstimulated or LPS (10 μg/ml) or quartz (100 μg/ml) exposure conditions. AM were obtained by bronchoalveolar lavage of rats, while rat TII cells were isolated by enzymatic digestion and purified by panning (~20 million cells/rat, 95% pure). AM and TII cells were co-cultured either separated by transwell inserts or in a single well to allow physical contact. After an 18 hour culture period in the absence or presence of stimulant, the medium was assayed for tumor necrosis factor-alpha (TNF-α), macrophage inflammatory protein-2 (MIP-2), interleukin-6 (IL-6), interleukin-1 beta (IL-1β) and nitric oxide (NO). Cell viability, which was measured as lactate dehydrogenase (LDH) released from the cells into the medium, was not affected by either transwell or contact co-culture under basal or stimulated conditions. Under basal conditions, co-culture of AM and TII cells in transwells significantly potentiated the release of TNF-α, MIP-2, IL-6 and NO above the sum of the production by these cells cultured separately. Physical contact between AM and TII cells mitigated this potentiation, which was further decreased by exposure to LPS or quartz. Indeed, under stimulated conditions, physical contact actually decreased the production of some of these inflammatory products below the sum of the production by these cells cultured separately. These results indicate that cross-talk between AM and TII cells is complex. It appears to vary with the distance and/or contact between the two cell types, and with exposure to different stimulants.

## 218 CYTOTOXICITY OF SIZE-SELECTED MANVILLE CODE 100 (JM-100) GLASS FIBERS ON HUMAN ALVEOLAR MACROPHAGES.

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A previous study using rat alveolar macrophages (AMs) demonstrated that glass fibers > 17μm long were larger than these pneumocytes and resulted in frustrated phagocytosis, while fibers < 7μm long were completely engulfed. Frustrated phagocytosis was associated with a substantially greater cytotoxicity of long versus short fibers (Blake et al. J Toxicol Environ Health. Part A, 54:243, 1998). Human AMs are larger than rat AMs, approximately 18 and 13μm in diameter, respectively. Therefore, the objective of this study was to evaluate the cytotoxicity of fibers of different lengths on human AMs. JM-100 glass fiber samples of 8, 10, 16, and 20μm lengths were obtained by classification of airborne fibers by dielectrophoresis. Human AMs were obtained by segmental bronchoalveolar lavage of healthy, non-smoking volunteers. AMs were treated with three different doses (determined by fiber numbers) of the sized fiber samples for 18 hours *in vitro*. Cytotoxicity caused by the fiber samples was then determined by monitoring membrane damage (leak of lactate dehydrogenase [LDH]) and loss of function (decrease in zymosan-stimulated chemiluminescence [CL]). Microscopic analysis indicated that human AMs were large enough to completely engulf fibers which were 20μm long. All fiber length fractions tested exhibited equal cytotoxicity, i.e., increasing LDH and decreasing CL in the same dose-dependent fashion. The data indicate that because human AMs are larger than rat AMs they are able to phagocytize longer fibers and the absence of frustrated phagocytosis results in lower fiber toxicity in human AMs. These differences in the AM response to long fibers between human and rat phagocytes should be considered when designing *in vivo* exposures using the rat model.

## 219 SILICA-INDUCED TOXICITY: *IN VITRO* AND *IN VIVO* PROTECTIVE EFFECTS OF TAURINE.

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Taurine has been suggested to have cytoprotective actions through different mechanisms including antioxidant effects. Taurine has been proposed to be a membrane stabilizer thereby preventing oxidative damage. The aim of the present studies was