

209 ASSESSMENTS OF THE BARRIER EFFECTIVENESS OF PROTECTIVE CLOTHING FABRICS TO AEROSOLS OF CHRYSOTILE ASBESTOS FIBERS.

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This study measured the performance of flashspun polyethylene clothing fabrics and the spunbonded polypropylene composite (spc) fabrics as barriers to chrysotile asbestos fibers. The spc fabric samples were taken from clothing samples obtained from several manufacturers. Ten fabric samples and two controls were concurrently exposed to chrysotile asbestos aerosols. Fibers that penetrated the fabric specimens were captured on sub-micron filters. These fibers were counted and sized from SEM micrographs of random sections of those filters. The aerosol challenge concentration was obtained from filters directly exposed to the asbestos aerosol without an intervening fabric. Penetration percentage was based on the number of fibers that penetrated the fabric versus the number of fibers observed on the uncovered filters. Five different exposures were performed. The penetration of chrysotile fibers through flashspun polyethylene fabrics ranged from 0.24% to 1.0%. In contrast, the penetration of chrysotile fibers through the commercial spc fabrics ranged from 13.4% to 26.8% under the conditions at which these evaluations were conducted. The results demonstrated that the method consistently differentiates performance of protective clothing materials to chrysotile fiber penetration and that flashspun polyethylene fabrics provide greater resistance to asbestos fiber penetration when compared to several different spc fabrics available from several manufacturers.

210 SILICA EXPOSURE *IN VITRO* STIMULATES THE ACTIVITY AND EXPRESSION OF MATRIX METALLOPROTEINASES IN MOUSE MACROPHAGES. .

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Exposure of mouse macrophages *in vitro* to crystalline silica elicits numerous inflammatory mediators including the matrix metalloproteinases (MMPs) which participate in extracellular matrix remodeling. MMP activity has been implicated *in vivo* in the development of pulmonary fibrosis in rodents and humans. In a rat model of silicosis, MMP-2, -9, and -13 were found in silicotic granulomas (Perez Ramos et al: Am J Respir Crit Care Med. 160:1274, 1999). Furthermore, gene analysis of lungs of both humans and mice implicate MMP-7, matrilysin, as a mediator of fibrosis (Zuo et al: PNAS 99:6292, 2002). However, few studies have examined the profile and regulation of MMP expression *in vitro*. To investigate the expression and activity of MMP-2, -7, and -9, RAW 264.7 cells were stimulated with LPS (1 ug/ml), TNF α (20 ng/ml), crystalline silica (cristobalite), and amorphous silica for varying times and with different concentrations of particles. The results were analyzed using zymographic and western blot methods. The zymogram indicated constitutive levels of MMP-9 activity in cells stimulated with silica; no activity for MMP-2 was detected. Increased gelatinolytic activity was detected in the silica treated cells (25, 12, and 6 ug/cm²) after 48 hours of stimulation that was not apparent in the LPS, media, or amorphous silica treated groups. The apparent molecular weight of this active moiety was ~28kDa, consistent with that of MMP-7. Western blot analysis and further zymographic analysis will confirm the identity of this moiety. These data suggest that MMP expression and activity are integral to the cell's response to a silica insult. (Funded by R15ES09433 and the University of CT Research Foundation)

211 BIOMATHEMATICAL MODELS OF EXPOSURE-DOSE-RESPONSE TO RESPIRABLE QUARTZ IN FISCHER 344 RATS, CYNOMOLGUS MONKEYS, AND HUMANS.

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A biomathematical model was developed to describe clearance and retention kinetics of respirable quartz and pulmonary responses, including the recruitment of alveolar macrophages (AMs) and polymorphonuclear leukocytes (PMNs) and the production of superoxide dismutase (SOD) in bronchoalveolar lavage (BAL) fluid, as well as hydroxyproline (HP) in lung tissue. The model was first calibrated in Fischer-344 rats exposed to respirable crystalline silica (15 mg/m³ for up to 6 months) and validated using data from two additional rat studies (respirable quartz exposures 0.74 mg/m³ for 2 years, and 10 mg/m³ for 75 days). The model was then extrapolated to cynomolgus monkeys and humans by adjusting model parameters for species differences such as breathing rates, lung mass, and surface area. To evaluate model fit, BAL data and limited quartz lung burden data were available in cynomolgus (10 mg/m³ quartz for up to 26 months) and in coal miners (<0.1 mg/m³ mean quartz in respirable coal mine dust for 17 years). The model predicted well the end of study lung burden in monkeys and the lavageable quartz mass in two humans; however, it overpredicted the pulmonary cell responses by several fold. This was consistent with the observed dose-response, in which the rat PMN

and AM counts were several times greater than those in monkeys at higher doses (cell counts relative to controls and normalized to lung surface area). Human predicted dose-response data were in the low dose region, where responses were similar across species, except for two individuals, whose PMN counts exceeded those expected from the rat data. The relative increases in SOD and HP were comparable across species. Despite some differences in magnitude, similar patterns of nonlinear dose-response were observed in all three species. These biomathematical models may be useful in risk assessment by providing a mechanistic basis for extrapolating rat responses to various inhaled particulates in humans.

212 EVALUATION OF THE CHEMICAL AND PHYSICAL PROPERTIES OF CELLULOSE INSULATION AEROSOLS AND THE POTENTIAL ACUTE PULMONARY TOXICITY.

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Cellulose insulation (CI) is a type of thermal insulation produced primarily from recycled newspapers. The newspapers are shredded, milled and treated with fire retardant chemicals. CI is installed by a blowing process that generates significant quantities of airborne material. These studies were conducted to characterize the chemical and physical properties of the CI aerosol and to evaluate the potential acute pulmonary toxicity of the respirable particles. An aerosol generation system was designed to simulate the process used during installation of CI at work sites and to separate CI particles based upon aerodynamic size. Aerosols were generated using CI from four different manufacturers. The mean equivalent diameter of aerosol particulates ranged from 3.5 to 11.4 microns in the cyclone collection bag and 0.6 to 0.7 microns in the sampling chamber. For all four CI samples, less than 0.1% was collected as the small respirable particle fraction. X-Ray diffraction analysis of the respirable particle fraction did not indicate the presence of any cellulose material. The fraction consisted mainly of fire retardants and smaller quantities of clays. Concentrations of the toxic elements lead, chromium, arsenic, and selenium were very low in all samples tested. The respirable fraction was administered by intratracheal instillation to male F344 rats at doses of 0, 0.125, 0.25, 0.5, and 1 mg/rat, and the bronchoalveolar lavage fluid (BALF) evaluated 3 days later. BALF was evaluated for cellularity and cell differentials. The total number of cells in the BALF was significantly increased only in the high dose group. The %PMNs was increased and the %AMs was decreased in a dose-related manner. These results indicate that few respirable particles or fibers are generated during the application of CI, and that intratracheal instillation of respirable particles in rats resulted in only a minimal inflammatory response.

213 PULMONARY TOXICITY OF CARBON NANOTUBES IN MICE 7 AND 90 DAYS AFTER INTRATRACHEAL INSTILLATION.

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Single-walled carbon nanotubes (SWNT; individual tube: ~1 nm x 1,000 nm) are a novel material possessing many desirable properties and potentially have widespread applications in the electronics, computer, and aerospace industries. NT are light and could become airborne. Little is known about the toxicity of this fiber/rope-like material. The pulmonary toxicity of three NT products, obtained from Rice University or Carboxol Inc. was investigated in mice by intratracheal instillation. These products were made by different methods, and contained different types or amounts of residual catalytic metals. Metal analysis showed that the Rice HiPco-prepared NT contained 27% (w/w) iron in the raw form, and 2% iron after purification; Carboxol electric-arc product contained 26% nickel and 5% yttrium. Male mice (B6C3F1, ca. 30 g, 4 to 5 per group) were each intratracheally instilled once with 0, 0.1 or 0.5 mg of NT suspended and ultrasonicated in 50 μ l of mouse serum. Carbon black and quartz, two standard reference dusts, were prepared similarly for instillation. Carbon black elicited minimal effects and high-dose quartz produced moderate inflammation in the lung. All the NT products, regardless of the type or amount of metal, induced a dose-dependent formation of epithelioid granulomas in the centrilobular alveolar septa and, in some cases, interstitial inflammation in the animals of the 7-d groups. These lesions persisted and, in most cases, became worse in the 90-d groups. The granulomas in NT-treated mice consisted of aggregates of macrophages laden with black NT particles. Our results show that, for the test conditions described here, if SWNT reach the lung, they can be more toxic than quartz.