Evaluation of Cellular Toxicity of TAFMAG, a Natural Substitute for Asbestos from China

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A[illegible] ustrial use. However, the need for a [illegible] rise due to its high disease causing [illegible]-hazardous effects of TAFMAG, a [illegible]mparison with chrysotile, a typical [illegible] properties of TAFMAG were very similar to those of chrysotile when it was examined by a scanning electron microscope (SEM) and X-ray diffraction (XRD) analyses. Both of TAFMAG and chrysotile showed high content of Magnetite and Fenton activity when compared with wollastonite, a non-asbestos fiber with a known low toxicity. When their cellular toxicity was assessed, TAFMAG showed no or less comparable to that of chrysotile in the hemolysis and lipid peroxidation of erythrocytes, and also on a MTT assay in RLE-6TN, a rat alveolar epithelial cell line. Pre-treatment of fibers with desferrioxamine, an iron chelator, showed that iron content of TAFMAG and chrysotile might be important in their cellular toxicity.

These results suggest that TAFMAG is potentially toxic when inhaled into the lung and appropriate laws and regulations should be established for its use.

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Seasonal Allergic Rhinitic and Normal Subjects Congest Differentially to Nasal Provocation with Acetic Acid Vapor

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R[illegible] llergic rhinitis (SAR) show more nasal obstruc- [illegible]s (Cl_2) than do non-rhinitic (NR) controls. We [illegible]ferential responsiveness was also apparent after [illegible]Methods: Sixteen non-smoking, non-asthmatic [illegible]vided by gender and nasal allergy status, were enrolled in a single-blinded crossover study involving exposure to acetic acid (AA) vapor (15 ppm) or air for 15 min. on separate days a week apart. Symptoms were rated on visual analog scales (VAS) and NAR measured in triplicate before, immediately post-, and 15-minutes post-exposure. NAR values for each testing condition were normalized to baseline and expressed as "Net proportional NAR," representing the ratio of post-exposure to baseline NAR on the AA minus air exposure days. This metric was then log-converted to achieve normality and compared between groups (SAR vs. NR) using ANOVA. Results: Mean peak sensory ratings of odor were 1.77 (between "slight" and "moderate") and nasal irritation 0.98 ("slight") on a 0-5 scale. The mean $\log_e$ of [Net proportional NAR] was 0.22 for SAR subjects and -0.11 for NR subjects immediately post-exposure ($p < 0.05$); the corresponding values 15 min. post-exposure were 0.24 and -0.08, respectively ($p < 0.05$). Conclusions: Inhalation of acetic acid at the (NIOSH-recommended) short-term exposure limit of 15 ppm for 15 min. produces greater nasal airflow obstruction among SAR vs. NR subjects. This differential responsiveness is consistent with our previous findings with Cl_2, indicating that there may be a generalized susceptibility factor associated with allergic rhinitis.

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Factors Affecting the Recognition of Excessive FEV_1 Decline: Analysis of 30 Years of Data from an Industry-Based Monitoring Program

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RATIONALE: Spirometry is often performed annually to monitor worker lung health. Excessive FEV_1 loss in an individual employee can be a useful indicator of the development of lung disease, while differences in FEV_1 declines between exposure groups may suggest continuing workplace hazards. However, the operating characteristics of the test are highly dependent on test performance and quality standards. METHODS: We evaluated factors affecting FEV_1 using 21821 test results from 1884 workers who participated in the annual spirometry screening program at a single chemical plant between 1973 and 2003. Testing procedures and each of the four models of volume spirometers used by the program met ATS standards. The influence of multiple factors on repeated measurements of FEV_1 was examined using a mixed model. RESULTS: The FEV_1 level was significantly associated with birth cohort and spirometer type, as well as age, gender, race, body weight, and tobacco smoking. FEV_1 loss averaged 24.8, 17.9, 16.7, and 9.8 ml/yr for white and black males and females, respectively, after controlling for birth year, age at the first test, weight, pack-years of smoking, and spirometer type. Testing using different spirometer types gave FEV_1 results differing by as much as 90 ml, over 3 to 9 times the observed annual declines. CONCLUSIONS: The accurate classification of individuals or worker groups as demonstrating either excessive or normal declines requires attention to multiple factors which have been recognized to affect lung function. Based upon these results, future analyses of job and exposure information should account for these factors, in order to facilitate recognition and prioritization of potential workplace hazards.

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Late-Phase Airway Response to Trimellitic Anhydride in Brown Norway Rat: Effect of Dexamethasone and Salbutamol

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Trimellitic anhydride (TMA) is a reactive, low-molecular-weight (LMW) chemical known to induce IgE and occupational asthma. We have previously shown that dermal powder sensitization with subsequent TMA airway challenge produces both early (EAR) and late-phase airway responses (LAR) in Brown Norway rats (BNR). The response to TMA challenge is characterized by pulmonary eosinophilia, hemorrhage and early, short and late, prolonged (hrs) increases in Penh (an index of airway resistance). The pathological and physiological responses in this model are consistent with that seen in TMA asthmatics. Clinically, bronchodilators have been noted to be effective in reversing EAR, but not LAR; corticosteroids, given prophylactically, inhibit LAR, presumably due to their anti-inflammatory activity. The effect of the corticosteroid, dexamethasone, and the β_2 agonist, salbutamol, on the TMA-LAR was examined in the present study to further assess the utility of the BNR-TMA asthma model. BNR were sensitized by 4 weekly, 4 hr dermal applications of 40 mg TMA powder. Two weeks after the final dermal application they received a 10 min, 40 mg/m^3 TMA inhalation challenge with or without prior treatment of dexamethasone (2mg/kg i.p. for 3 days). Following TMA challenge, Penh was recorded for 16-20 hrs. In a separate group, BNR were exposed to a 1% salbutamol aerosol for 10 min either 30 min before TMA challenge or during the LAR. All TMA sensitized, non-treated BNR (8/8) developed LAR following challenge. LAR Penh increase and airway (bronchoalveolar lavage) eosinophilia were completely inhibited in all animals when treated with dexamethasone. Salbutamol had no effect on LAR when given either prior to challenge, or during the LAR. It is concluded that the effects of corticosteroid and β_2 agonist in the LAR BNR-TMA model are similar to that observed in human TMA asthma suggesting the potential utility of this model in the study of LAR to LMW asthmagens.

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Diisocyanate Antigen Specific Antibodies Are Detectable in a Non-Worker Population without Diisocyanate Exposure

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Rationale. Specific IgG for toluene diisocyanate (TDI) human serum albumin (HSA) was reported in 8% of residents living close to a foam manufacturing facility that used TDI (*Environ Health Perspect 106:665:1998*). However, because comparable data were not obtained in settings without such facilities, the significance of this finding is uncertain.

Methods. Serum was collected from 139 anonymous donors who were without known exposure to diisocyanates at home or work as assessed by questionnaire. Specific IgG and IgE were assayed by ELISA for antigens prepared by conjugation of HSA with TDI, diphenylmethane-diisocyanate (MDI) and hexamethylene-diisocyanate (HDI). Positive tests [optical density (OD) $\geq$ 3 SD above the mean of 8 negative laboratory controls] were rerun 3 times for confirmation; specificity was assessed by an ELISA inhibition assay in sera with high levels of antibody (OD $\geq$ 0.2).

Results. Serum specific IgG reactive with at least one diisocyanate-HSA antigen was detected in 22 subjects (16%); there was binding with HDI-HSA in 18 of those subjects (13%) and with TDI-HSA in 7 (5.0%). Specific IgG reactive with MDI-HSA or HSA were not detected. Antigen specificity was demonstrated by ELISA inhibition in 6 of 9 subjects (67%) with high HDI-HSA-specific IgG binding and in 3 of 7 subjects (43%) with high TDI-HSA-specific IgG binding. TDI-HSA specific IgE was detected in 2 (1.4%) subjects.

Conclusions. Specific and non-specific IgG antibodies reactive with HDI- and TDI-HSA were detected in subjects without known exposure to isocyanates, indicating these tests may not be reliable markers of diisocyanate exposure in non-worker populations.

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Interleukin-1 Plays a Critical Role in Airway Inflammation and Hyperresponsiveness in a Murine Model of Toluene Diisocyanate Asthma

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Rationale: Interluekin-1 (IL-1) is a pleotropic cytokine that has been shown to play a prominent role in large molecular weight protein asthma in mice. IL-1 is also an important mediatory of eosinophil infiltration into the lung. Human studies have demonstrated increased IL-1 immunostaining in the submucosa of patients with toluene diisocyanate (TDI)-induced asthma and increased production of IL-1β is evident in the airways of mice with TDI asthma. **Hypothesis:** We hypothesized that IL-1 signaling plays a critical role in the pathogenesis of TDI asthma through regulation of airway inflammation. **Methods:** C57BL/6 mice were sensitized to TDI by vapor inhalation (20 ppb; 4hrs/day, 5 days/week, 6 weeks) and then challenged 2 weeks later by inhalation of 20 ppb TDI vapor for 1 hr. **Results:** Sensitized/challenged mice showed increased airway hyperresponsiveness (AHR) to methacholine challenge and a TDI-specific late asthmatic reaction 4-5 hours following challenge. Significant airway inflammation was also evident, consisting of lymphocytes and eosinophils as well as increased lung IL-4 expression. Mice deficient in IL-1 receptor type I (IL-1RI) did not show any increase in AHR nor airway inflammation. Airway inflammation was prevented in mice treated with neutralizing antibodies to IL-1β and IL-1α. In contrast, antibodies to IL-1β and IL-1α alone, only partially reduced AHR, whereas treatment of mice with IL-1β/IL-1α completely abolished AHR. TDI asthmatic mice showed increase lung expression of VCAM and ICAM, adhesion molecules important for the recruitment of eosinophils and lymphocytes and disruption of IL-1 signaling prevented this effect. **Conclusions:** These results suggest that IL-1 signaling is critical for the recruitment of inflammatory cells to the lung and AHR in TDI asthma. Increased expression of adhesion molecules represents a plausible mechanism.

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