Importance of Surface Properties of Quartz Particles for Cellular Uptake and Lung Clearance

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In earlier studies it has been shown that particle surface properties have an influence on quartz pathogenicity. We have recently demonstrated that surface modification with polyvinylpyridine-N-oxide (PVNO) or aluminium lactate (AL) reduces inflammatory responses in the rat lung compared to native quartz (DQ12). At chronic time points (90 days) the inhibitory effects of PVNO were more pronounced than by AL. Since particle clearance mechanisms are suggested to play a key role in the chronic particle effects, our aim was to investigate *in vitro* particle endocytosis by macrophages and epithelial cells, as well as *in vivo* lung clearance of the different quartz preparations (i.e. native DQ12, PVNO-DQ12, AL-DQ12). Determination of the silica burden up to 360 days post intratracheal instillation of 2 mg DQ12 quartz showed a significantly higher clearance rate of PVNO-DQ12 (i.e. 1.3%/day) compared to the native or AL-DQ12 (i.e. 0.7%/day). In parallel *in vitro* experiments, NR8383 rat alveolar macrophages (AM) as well as rat lung epithelial cells (RLE) were treated with these different quartz preparations for 48 h at a concentration of 10 $\mu g/cm^2$. Particle uptake was quantified using light and electron microscopy. Surface modification of quartz with PVNO resulted in a significantly enhanced uptake by AM, whereas AL-modification did not affect uptake in these cells. In contrast, surface modification of quartz with PVNO caused a reduced uptake in RLE. In conclusion, surface properties of quartz particles appear to be important for particle uptake in both AM and RLE as well as clearance from the lung. The enhanced AM uptake as observed *in vitro* with PVNO may explain the higher lung clearance for this quartz modification as observed *in vivo*. Whether the reduced uptake by RLE of the PVNO-DQ12 may serve as an additional protective mechanism needs further investigation.

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Silicosis in Stone Carvers: Correlation between HRCT and Standard Radiographs

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Rationale: A high prevalence of silicosis has been described among stone carvers in Brazil. This study was aimed to determine the correlation between two methods of radiological evaluation of silicosis in this population. **Methods:** Forty-one workers and 9 healthy controls were studied with chest radiographs (CR) and high resolution computed tomography (HRCT). The radiographs were independently interpreted by 3 "A" readers (according to ILO/1980 rules), and 3 radiologists experienced in the evaluation of pneumoconiosis read the HRCTs. All readers were blinded with respect to exposure. The results of each CR and HRCT examination was summarized as the median of 3 readings. A small opacity profusion of 1/0 or greater was considered as silicosis. A systematic protocol was used for grading silicosis on HRCT. **Results:** All CR and HRCT from the control group were considered normal. Silicosis was identified in 22/41 workers (53.7%) by CR, and in 23/41 workers (56.1%) by HRCT. The inter-reader agreement (generalized kappa) for major profusion categories (0, 1, 2, 3) was k=0.44 by CR and k=0.62 by HRCT ($p<0.001$). When only the diagnosis of silicosis was considered, k=0.54 for CR and k=0.84 for HRCT. The Spearman correlation coefficient for the two exams, considering 4 categories of profusion, was 0.84. HRCT demonstrated higher profusions than CR, mostly in categories 1 and 2. Coalescence of small opacities was noted on 7 exams by HRCT that were not noted on CRs for the same patients. Large opacities "A" were noted on 6 exams by HRCT (3 of which were coded with symbol "AX" by CR) and on no exams by CR. **Conclusions:** Despite the high correlation of CR and HRCT, this study found higher small opacity profusion and apparent greater sensitivity to coalescence and large opacities for HRCT compared to CR. In addition, the inter-reader agreement was higher for HRCT than for standard CR.

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Predictors of Lung Cancer among Asbestos-Exposed Men in the Carotene and Retinol Efficacy Trial (CARET)

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Rationale: Despite numerous published studies, debate continues regarding the risk of lung cancer in men exposed occupationally to asbestos, particularly those without radiographic or functional evidence of asbestosis. **Methods:** The beta-Carotene and Retinol Efficacy Trial (CARET) for chemoprevention of lung cancer has followed 3,897 men with occupational asbestos exposure for 9-17 years. 241 cases of lung cancer were observed in this cohort through 10/31/02, an incidence rate of 5.9 per thousand person-years. Chest radiographs obtained prior to randomization in the trial were classified using the 1980 ILO scheme. Spirometry was also performed prior to randomization. Lung cancer incidence was analyzed using a stratified proportional hazard model. **Results:** The analysis confirmed excessive rates of lung cancer among men with asbestosis. Among those with normal lung parenchyma on chest x-ray (ILO grade 0), there was also evidence of dose-related risk; men with > 40 years exposure in high risk trades had a risk almost 5-fold higher than those with 5-10 years, after adjustment for smoking and other risk factors. The presence of pleural plaques was associated with an approximately doubling of risk. FEV1 and FEV1/FVC were significantly lower in lung cancer cases compared to participants without lung cancer suggesting increased risk in those with evidence of airway obstruction. **Conclusions:** Among current and former smokers exposed occupationally to asbestos, risk of lung cancer increases with increased exposure duration, even among those without clinical evidence of asbestosis. Those with radiographically apparent pleural plaques or airway obstruction also appear to be at higher risk.

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Longitudinal Changes in Lung Function and Airflow Limitation in Pulp Mill Workers Reporting Ozone Gassing Incidents

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We investigated whether occupational exposure to ozone gassings in pulp mills was associated with increased airflow limitation and decline in lung function. We used both cross-sectional and longitudinal data in our analysis. Bleachery workers potentially exposed to ozone (n=179) from three Swedish pulp mills were studied, as was a comparison group of paper mill workers not exposed to ozone (n=62) from two of the three pulp mills. Initial and follow-up surveys took place in 1996 and 1999, respectively. Participants underwent spirometry testing and provided answers to a questionnaire regarding history of accidental exposure to ozone gassings. Several analyses suggested that bleachery workers with a history of four or more ozone gassings (n=25) had obstructive changes when compared to paper mill workers. The group of workers with at least 4 ozone gassings had lower forced expiratory volume in one second (FEV_1) and lower ratio of FEV_1 over forced vital capacity (FEV_1/FVC) in 1999, controlling for potential confounders (age, gender, height, weight, smoking) by linear regression analyses (-0.219 L, p=0.06; -2.69%, p=0.05, respectively). In another regression model controlling for potential confounders, this exposed group also had an additional 17 ml longitudinal decline in FEV_1 (L/yr) between 1996 and 1999 in comparison to paper mill workers, although this difference was not statistically significant (p=0.21). In 1999, workers with at least 4 gassings were also more likely to have airflow limitation (i.e., FEV_1/FVC < 70%), although the association was not statistically significant at the $p<0.05$ level (prevalence ratio: 3.72, 95% CI: 0.66-20.94, p=0.14). These findings suggest that obstructive changes in lung function among pulp mill workers are associated with multiple ozone gassings.

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A Prospective Cohort Study among New Chinese Coal Miners – The Early Pattern of Lung Function Change

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RATIONALE: Associations between coal mine exposures and pulmonary function have been studied in the US and abroad. Studies in new coal miners have suggested that spirometry changes may be non-linear, possibly an initial rapid decline followed by partial recovery. METHODS: We investigated the early pattern of lung function change in a cohort of 317 newly hired Chinese coal miners, compared to 132 referents. The 3-year study included a pre-employment and 15 follow-up health surveys (questionnaires and spirometry), performed monthly for 3 months, then bi-monthly for 6 surveys, every 3 months for 5 surveys, and a final survey at a 6-month interval. Area sampling for total and respirable dust was done bimonthly. We used a mixed effects model to analyze longitudinal spirometry data, allowing the detection of both linear and quadratic time trends, and differences between groups in FEV1 change over the study period, controlling for age, height, pack-yrs of smoking, mean respirable dust concentration, and room temperature during testing. The model included interaction terms for both group*linear time, and group*quadratic time. A spatial power law covariance structure was used, which has the property of larger correlations for proximate than distant times. RESULTS: The new miners experienced an initial rapid FEV1 decline, primarily during the first year of mining, with a leveling-off in the second year, and partial recovery during the third year. Both linear and quadratic time trends in FEV1 change were highly significant. Referents did not demonstrate rapid initial declines. CONCLUSIONS: The findings are consistent with previous studies, indicating that FEV1 change over time in new miners is non-linear. Better definition of longitudinal FEV1 patterns should assist in both design of medical monitoring programs and interpretation of results among dust-exposed workers.

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Effect of Fume Exposure on FEV1 in Early COPD

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Occupational exposures, in addition to smoking, may contribute to development and progression of COPD. SUBJECTS: Data are for 5734 subjects in the Lung Health Study (LHS), a study of smoking cessation interventions for persons with early COPD (defined as FEV1/FVC ratio < 0.70 and FEV1 55% - 90% predicted). Each had baseline and up to 5 annual follow-up spirometry tests. METHODS: FEV1% predicted post-bronchodilator at each follow-up year was modeled as determined by both baseline characteristics and time-dependent variables using a repeated-measures general linear model with first-order autoregression. Baseline characteristics included age, airway responsiveness by methacholine challenge, baseline FEV1, and self-reported dust exposure, fume exposure, and mask use. Time-dependent variables included smoking (smoking status, cigarettes/day, or smoking intensity as a categorical variable) and self-reported dust exposure, fume exposure, and mask use. RESULTS: Exposure to "fume" (both as a baseline characteristic and as a time-dependent characteristic) showed relationships to FEV1 in many models. Significant results were found in men, but not in women. Subjects reporting fume exposure at baseline had 0.44% lower FEV1% predicted than those not reporting ($p < 0.06$), and fume exposure at any follow-up year was associated with a 0.21% lower FEV1% predicted ($p < 0.05$) when adjusted for age, baseline FEV1% predicted, smoking status, and baseline cigarettes/day. No significant effects of dust exposure or mask use were observed. CONCLUSIONS: There is an indication that self-reported fume exposure adversely affects FEV1 in persons with early COPD. The effect may be additive to that of smoking and be present even if smoking ceases.

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