app. 200 g). A control group received one single it-instillation of 0.5 ml sodium chloride. The experimental periods were 3 and 6 months. The lungs and the lymph nodes were histologically examined.
Results: Already after 3 and 6 months we observed pre-neoplastic alterations in the lung tissue of the group instilled with a DQ12 particle size of 0.78 µm and with a dose of 3.55 mg per animal. In addition the fibrogenic effect was shown in all groups except the control group.
Conclusions: An interrelation between particle size and carcinogenic effect of quartz dust may be discussed – already after 3 month. These results provide supplementary information to the long-term investigations known from literature.

54 Time course of pulmonary responses to inhalation of crystalline silica in the rat model: evidence for a threshold burden beyond which silicosis progresses without further exposure

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Exposure to crystalline silica has been associated with pulmonary disease in sand blasters, rock drillers, miners, tunnelers, granite workers, etc. However, the molecular and cellular events which trigger the shift from an exposed state to a pathologic condition remain to be elucidated. This study investigated the relationship between silica-induced pulmonary responses (lung damage, inflammation and fibrosis) and nitric oxide production in rats exposed by inhalation to crystalline silica (15 mg/m^3, 6 hr/day, 5 days/week, for 116 exposure days). In addition, recovery (a decrease) or progression (an increase) of pulmonary pathology was evaluated in rats exposed to silica for 20, 40 or 60 days and sacrificed either immediately or 36 days after exposure. Markers of pulmonary inflammation and damage were significantly elevated by 5-16 days of exposure and were maintained at this relatively stable new set point through 40 days of exposure. Exposure beyond 40 days was associated with an explosive increase in inflammation and damage. Only during this explosive inflammatory phase was the development of granulomas and fibrosis in the lung parenchyma and the bronchus-associated lymphoid tissue (BALT) observed. No recovery of pulmonary inflammation and damage was noted in rats exposed for 20 days and sacrificed 36 days after the cessation of exposure. In contrast, after 40 or 60 days of silica exposure, inflammation, damage and granulomas progressed during the 36 day period of non-exposure. Nitric oxide (NO) products in the bronchoalveolar lavage fluid exhibited a time course which preceded fibrosis and was similar to that for inflammation and damage, i.e., a significant but stable elevation from 5-40 days of exposure followed by an explosive increase thereafter. As with inflammation and damage, during the 36 day period of non-exposure NO production did not recover after a 20 day exposure and progressed after a 40 day exposure. Immunohistochemical analysis of pulmonary inducible NO synthase (iNOS) and nitrotyrosine identified elevated iNOS and NO-induced damage in alveolar macrophage and type II cells which co-localized with areas of silica deposition, phospholipidosis, and granulomatous lesions. Progression of iNOS staining after cessation of exposure was evident in alveolar macrophages and BALT. The results suggest that there is a threshold burden of silica beyond which disease progresses without further exposure, and that NO production appears to be associated both temporally and spatially with the pathogenic response to silica exposure.

55 *In vivo* expression of COX-2 in macrophages and epithelial cells after instillation of quartz and surface modified quartz

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Objectives: Overexpression of cyclooxygenas[redacted]
seen in several neoplastic lesions in eg. colon, breast and lung. Additionally COX-2 is abundant in alveolar type II cells of lung cancer-sensitive mouse strains. Recently the induction of COX-2 after quartz treatment in the mouse macrophage cell line RAW 267.7 was demonstrated. The activation of carcinogenic aromatic and heterocyclic amines due to COX-2 overexpression may lead to toxicological alterations in lung metabolism. In this study we investigated the expression of COX-2 in epithelial cells and macrophages from rat lungs after quartz treatment.
Methods: 2 mg of DQ12 quartz, DQ12 coated with polyvinylpyrrolidine-N-oxide (PVNO) or aluminium lactate (Al) were instilled in female Wistar rats. As vehicle control, animals were treated with saline. At 7 and 28 days after exposure, epithelial cells and interstitial macrophages were isolated from lavaged lungs. RNA was prepared and a reverse transcription PCR (RT-PCR) was performed determine the expression of COX-2. Additionally lungs were embedded in paraffin and analysed by immunhistochemistry with a COX-2 antibody.
Results: COX-2 mRNA was detected in epithelial cells and in macrophages. COX-2 signal was not altered in epithelial cells after exposure to DQ12 or surface modified DQ12. In contrast COX-2 expression was increased in macorphages 7 and 28 days after quartz exposure. Immunhistochemical staining confirmed increased expression of COX-2 protein in rat lungs after exposure to quartz and surface modified quartz at both time points investigated.
Conclusions: COX-2 is constitutively expressed in lungs of Wistar rats. Treatment with DQ12 or surface modified DQ12 leads to modified COX-2 expression only in macrophages after short time (7 days) and subchronic (28 days) exposure. Our results underline the relevance of macrophages in changing lung metabolism. These alterations may be important factors for the toxicological effects of quartz in the lung.

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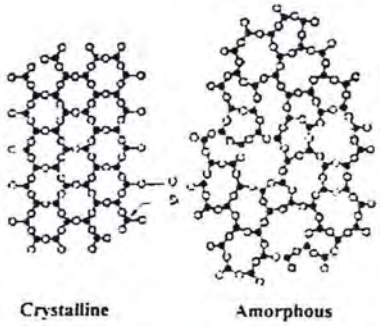

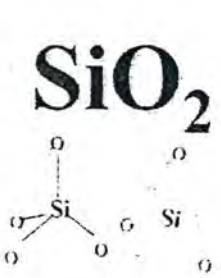

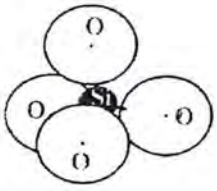

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