PL 1398 PULMONARY TOXICITY OF CERIUM DIOXIDE PARTICLES IS MODULATED BY SIZE AND COATING: INHALATION STUDIES WITH NANO-, AGGREGATED NANO-, AND MICRON-SCALE PARTICLES AND PARTICLES WITH DIFFERENT SURFACE CHEMISTRY.

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Pulmonary toxicology studies in rats suggest that nano-particles are more toxic to the lungs than larger, micro-scale particles of similar chemistry at identical mass concentrations (Oberdoerster et al. 2000, Res Rep. Health Eff. Inst. 96, 5-86, Stoeger et al. 2006, EHP 114, 328-333 Wittmaack 2007, EHP 115: 187-194). In this study we used CeO_2 as model substances with different particle sizes, agglomeration states and surface chemistry designed for different applications. Male Wistar rats were head-nose exposed to test atmospheres of CeO_2 for 6 hours a day on 5 days. Toxicity was assessed by examination of broncho-alveolar lavage fluid (BALF) shortly after the exposure and after a recovery period of 2 months or 3 weeks. Exposure to nano-scale CeO_2 (spark generated) caused pronounced effects at a mass concentration of 0.14 mg/m^3 (increased levels of ALP, GGT, LDH, NAG, protein, neutrophiles and lymphocytes). Aggregates of CeO_2 particles of similar size induced milder changes (ALP, GGT, protein and neutrophils) at more than 10 times higher mass concentration. Similar mass concentration of the micro-scale material failed to induce any measurable signs of toxicity. Agglomerates of unmodified CeO_2 and alumina doped CeO_2 (similar particle size and surface area) were administered at three concentrations to rats by inhalation exposure as described above. Both materials caused concentration-related changes of BALF parameters, increased lung weights and inflammation in the lung. However, the concentration-response relationship of the doped CeO_2 was steeper than that of unmodified CeO_2. It can be concluded that size as well as aggregation/agglomeration state and surface chemistry strongly influence the pulmonary toxicity of nanomaterials.

PL 1399 INTRATRACHEAL EXPOSURE TO MULTI-WALLED CARBON NANOTUBES CAUSED GRANULOMATOUS INFLAMMATION ON MURINE LUNG.

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Carbon nanotubes attract the attention of many scientists because of their high potential of industrial application, however, several reports have shown that carbon nanotubes may cause toxicity. In this study, we compared acute and chronic pulmonary toxicity and clearance of two different types of MWCNTs; pristine multi-walled carbon nanotube (PMWCNT), and acid treated multi-walled carbon nanotube (TMWCNT). We administered PMWCNTs, TMWCNTs and sterilized saline as vehicle control into murine lung by intratracheal instillation and the animals were sacrificed at the time point of 24 hours, 1 week, 2 weeks, 4 weeks and 4 months following injection (n=6/group). Inflammatory response and clearance of granuloma were analyzed by histopathological studies and planimetric analysis using Image-ProPlus software. In the histopathological study, both PMWCNTs and TMWCNTs induced multifocal inflammatory granulomas in time- and dose-dependent manner. Although the area of granuloma was largely decreased 4 months after post-exposure in the lungs of 1month post exposure mice, characteristics of dysplasia like clear mitotic figures, anisocytosis, anisokaryosis and binucleated cells were observed in bronchial epithelial cells. These findings demonstrate that MWCNTs can cause genetically unstable status even though the status is transient. Although most of MWCNTs are able to clear from the body, careful toxicity studies need to be undertaken particularly to take strict industrial hygiene measures to regulate exposure during their manipulation.

PL 1400 ASSESSMENT OF PULMONARY TOXICITY FOLLOWING INTRATRACHEAL EXPOSURE TO SILICON NANOWIRES.

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Silicon nanowires (NW) are manufactured for use as bio-sensors, gas sensors, and field effect transistors for various circuit applications. The goal of these studies was to assess the potential pulmonary toxicity of silicon NW using an *in vivo* model. Single-crystal silicon NW were synthesized by the vapor-liquid-solid method in an ultrahigh vacuum-chemical vapor deposition chamber with silane as the silicon precursor and gold as the catalyst (~20-30 nm Diameter x ~15 μm Length, with a 20 nm gold nanoparticle catalyst at one end). NW were isolated, suspended in a physiologic dispersion medium (DM, phosphate-buffered saline + 0.6 mg/ml rat serum albumin + 0.01 mg/ml dipalmitoyl phosphocholine), and sonicated. On day 0, Sprague-Dawley rats were intratracheally-instilled with the NW in DM at a dose of 10, 25, 50, 100, or 250 μg or DM alone (control). Rats were humanely sacrificed 1, 3, and 7 days post-exposure and the right lung was lavaged. The lavage fluid and cells were analyzed for indicators of lung injury and inflammation. On days 1 and 3, there was a dose-dependent increase in lung injury, indicated by elevations in lactate dehydrogenase and albumin in lavage fluid. There was also a dose-dependent increase in inflammation indicated by the presence of neutrophils in the lung on day 1, which persisted on day 3 in the rats treated with the highest dose. In addition to neutrophils, there were also significant increases in alveolar macrophages, lymphocyte, and eosinophil influx into the lungs. Macrophage uptake of NW was observed in cells recovered at all time points and this uptake was paralleled by increased oxidant production in these cells. These initial lung injury and inflammatory responses resolved by day 7. To summarize, the NW were found to induce a transient lung injury and inflammation accompanied by cellular oxidant production. Studies are ongoing to assess long-term pulmonary responses to NW as well as to assess lung distribution and clearance of NW over time.

PL 1401 *IN VIVO* AND *IN VITRO* ASSESSMENTS OF MICRONUCLEUS INDUCTION BY AMORPHOUS SILICA PARTICLES.

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The development of a risk management system for nanoscale particle-types requires a base set of hazard data. These data could include screening-type genotoxicity studies. However, there is little agreement on the appropriate tests for evaluating genotoxic responses to particulate materials. One objective of this study was to assess the induction of micronucleated reticulocytes in rats exposed to aerosolized amorphous silica (AS) nanoparticles. Male rats were exposed for 1 or 3 days, 6 h/d, to freshly generated, AS nanoparticles (37 or 83 nm) at concentrations ranging from 3.1 x 10E7 to 1.8 x 10E8 particles/cm3. Control animals were sham-exposed to room air. Peripheral blood samples were collected 24 hours postexposure, fixed and analyzed by flow cytometry according to the In Vivo MicroFlow Plus Rat Micronucleus assay kit. Approximately 20,000 reticulocytes were analyzed per animal. For both particle sizes and exposures there were no statistically significant increases in micronucleated reticulocytes vs. controls. These data were compared with an in vitro assessment of another form of AS fine particles, using a Micronucleus assay kit in CHOK1 cells. There were no significant increases in the percentage of micronucleated cells at any concentration tested, although cytotoxicity was observed at concentrations > or = 5.2 μg/cm2 (plate surface area), with a dose dependent decrease in the percentage of cells in the G0/G1 cell cycle phase, along with a higher percentage in G2/M. A second objective was to determine whether identification of cytotoxicity endpoints correlated with genotoxicity parameters. Increased cytotoxicity (LDH and MTT assays) and inflammatory cytokine releases (TNF-a and IL-6) were measured at concentrations > or = 5.2 μg/cm2 in rat alveolar epithelial (L2) and macrophage (N8383) cell lines. Studies are ongoing to develop appropriate in vivo and in vitro screening assays with fine-sized and/or nanoscale particles to detect genotoxicity.

PL 1402 TISSUE DISTRIBUTION OF FULLERENE AFTER INJECTION INTO TAIL VEIN IN RAT.

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Engineered nanoparticles as nanotechnology materials have been designed intentionally with the physiochemical characteristics for the specific application. In the industry field that relates the human to direct ingestion, engineered nanoparticles are applied to pharmaceuticals, foods, cosmetics, and so on. Among these engineered nanoparticles, it is feared that the exposure risk of fullerenes and their derivatives increases from the occupational and/or living environment through the oral, dermal and inhalation route by the rapid commercialization. However, the effect on the human health and the biological behavior by the exposure have not studied sufficiently. In this study, we have examined the behavior of C60 fullerene after injection into the tail vein in rats. The C60 fullerene was extracted with toluene from