automated for long-term studies. Here we present the performance of this method and system. *This work was supported by the Health and Labour Sciences Research Grant, Japan.*

2224 Pulmonary Toxicity Associated with Different Zinc Nanoparticles after Intratracheal Instillation in Rats

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Zinc nanoparticles (Zn NPs) are used extensively in variety products including cosmetics, personal hygiene products, paints, food additives, and cancer therapeutic agents. As Zn NPs production increases, pulmonary toxicity related to occupational exposure becomes a concern. The goal of this study was to assess pulmonary toxicity of Zn NPs of different size, shape, solubility, and composition. In the first study, 2 doses (0.05 and 0.125 mg) of 6 particles were examined: fine-sized ZnO (FZnO), nano-sized elemental Zn (EZn), nano-sized ZnO (NZnO), ZnO nanowire (WZnO), and comparable nano-sized TiO_2 ($NTiO_2$) and TiO_2 nanowire ($WTiO_2$) as highly insoluble control materials. Male Sprague-Dawley rats were exposed by intratracheal instillation (II) to 0.05 or 0.125 mg of particles or vehicle control DM (dispersion medium) following a 5 min sonication on day 0. Body weights were recorded throughout the study. Parameters of lung injury and inflammation were measured in bronchoalveolar lavage (BAL) at 1 D, 7 D, 1 M and 3 M post-exposure. In a second study, rats were exposed to FZnO, EZn, and NZnO at the high dose in DM following a 30 sec sonication that resulted in less release of soluble Zn prior to II. The same time points and endpoints as in the first study were analyzed. In the first study, NZnO had the greatest specific surface area (SSA) and solubility prior to II. FZnO and NZnO agglomerates were smaller than the other samples, and consistent across studies. Study 1 showed the high dose of FZnO and NZnO caused decreased body weight on 1-3 D, which gradually increased by 1 M, followed by normal weight gain up to 3 M. All particles caused transient lung injury and inflammation at 1 D post-exposure except $NTiO_2$, with NZnO>FZnO>EZn>WZnO≥$WTiO_2$. At 7 D, lung injury and inflammation remained increased in the groups exposed to Zn NPs only. Inflammation persisted up to 3 M post-exposure to the greatest degree in the NZnO group followed by FZnO then EZn, while there was recovery in the groups exposed to TiO_2 and WZnO. Eosinophils were increased to the greatest degree in the NZnO > FZnO > EZn groups at 1 and 7 D. Study 2 showed a similar trend as the first study in changes of body weight, lung injury, and inflammation, although the difference between the NZnO and FZnO was not as pronounced. Material characterization studies suggested differences in toxicity may be associated with increased solubility as a function of composition (oxide vs elemental) and increased SSA.

2225 Bioactivity of Boron Nitride Nanotube Preparations That Differ in Purity *In Vitro* and *In Vivo*

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Boron nitride nanotubes (BNNTs), due to their wide band gap and thermal and chemical stability, are expected to be incorporated into a myriad of industrial applications. Currently, commercial production of BNNTs occurs through different processes including a pressurized vapor/high temperature process (PVTH) or an induction thermal plasma process (plasma), both resulting in 30-60 % residual compounds and impurities. In the current work, we evaluated the pulmonary and systemic toxicity arising due to acute exposure of BNNTs from the plasma process. Four BNNTs with a gradient of purity (from 50% to 90% tubes) were used to assess toxicity and evaluate bioactivity. Hexagonal boron nitride (less than 100 nm in diameter) was used as a reference material. All BNNTs tested were agglomerated bundles of few multi-walled tubes (~3 to 5 walls/tube). Electron microscopy (EM) confirmed a visible decrease in impurities and an increase in tubular structures across the gradient samples. *In vitro* and *in vivo* experiments were performed following sonication of BNNTs in dispersion media (DM). Preliminary EM sizing showed that the BNNTs dispersed in DM had a length of ~0.5 - 1.5 µm and a diameter of ~5 - 30 nm. Electron paramagnetic resonance measurements showed no change in surface hydroxyl radicals among the BNNTs with various purities. *In vitro*, the toxicity was evaluated in human monocyte cells (THP-1) wild-type and NLRP3-deficient cells at a concentration range of 0-100 µg/ml. At the high doses, there was a small but statistically significant increase in lactate dehydrogenase (LDH) released in the highest purity BNNT exposures. This increase in toxicity was attenuated in NLRP3-deficient cells. *In vivo* toxicity was evaluated in male C57BL/6 mice exposed by oropharyngeal aspiration to 4 or 40 µg of BNNT sample/mouse. Animals were euthanized 1 and 7 d post-exposure and lung lavage was performed to evaluate lung injury and inflammation. At day 1 there was a significant influx in neutrophils, a marker for lung inflammation, as well as an increase in LDH activity in particle-exposed groups. The response was highest in animals exposed to the high dose of the highest purity BNNT mixture. Inflammation and injury began to resolve by 7 d. The results indicate that BNNTs made by plasma process induce acute toxicity and inflammation only at high concentrations and ongoing studies will evaluate histopathological changes and clearance up to 3 mo post-exposure.

2226 Activities of Mitochondrial Enzymes in Heart and Brain of Rats Exposed to Titanium Dioxide Nanoparticles

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Titanium dioxide Nanoparticles (TiO_2 NPs) have found wide application in various products making exposure to this metal oxide nanoparticle inevitable. Information about toxic effects of TiO_2 NPs after oral exposure are extremely limited. Since mitochondrionopathies are being recognized as subtle and insidious biochemical events in the toxicity associated with various toxicants, this study determined the activities of mitochondrial enzymes (Malate dehydrogenase, MDH; Succinate dehydrogenase, SDH; Combined Complex I+III, CPI+III; Combined Complex II+III, CPII+III; Complex IV, CPIV) in rats exposed to TiO_2 NPs. Male albino rats were exposed orally to TiO_2 NPs (8-12nm) (50, 150 and 250mg/kg body weight) for 4, 8 and 12 weeks. Control rats (n=18) received distilled water for the same period. At the end of TiO_2 NPs exposure, brain and heart were removed from the rats and activities of mitochondrial enzymes determined. Enzymes in the two organs exhibited different patterns on exposure to TiO_2 NPs. While cardiac MDH was down-regulated throughout the study, brain MDH increased at 4 and 8 weeks of 50 and 12 weeks of 150mg/kg body weight doses respectively. In both organs, SDH activity was up-regulated at 4weeks. While the up-regulation in cardiac SDH was dose-dependent, brain SDH did not show any dose dependency. In contrast however, CPI+III in both organs was down-regulated, except at 4weeks of 150- and 12weeks of 50mg/kg body weight where increases ranging between 2 and 7 folds were observed. While cardiac CPII+III was decreased at 8 weeks of 150mg/kg body weight dose, the brain enzyme was up-regulated by 50 and 250mg/kg body weight doses of TiO_2 NPs. Unsystematic changes characterized the response of brain CPIV, whereas the cardiac enzyme was down-regulated, except at 8weeks of 50 and 250mg/kg body weight doses of TiO_2 NPs. Our findings indicate that TiO_2 NP-induced alterations in cardiac and brain mitochondrial energy metabolism might be important in pathologies associated with exposure to TiO_2 NPs.

2227 Crystalline Nanocellulose-Induced Lung Toxicity and Global Gene Expression Changes in the Rat

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Crystalline nanocellulose (CNC) is an emerging nanomaterial with multiple commercial and industrial applications. Occupational exposure to CNC during the production and/or use of products containing the nanomaterial potentially resulting in adverse health effects among workers is possible. Therefore, there is an immediate need to determine the toxicity potential and mechanisms underlying CNC toxicity. Male Fischer rats were exposed by whole body inhalation exposure to air or CNC (20 mg/m^3, 6 hours/day, 14 days), and pulmonary toxicity and lung gene expression changes were determined one day following the last exposure. CNC particles were detected in the lung alveoli of the exposed rats. Compared with the air-only exposed controls, significant increases ($p<0.05$) in the incidence of bi-nucleated alveolar macrophages (AM), lactate dehydrogenase activity, pro-inflammatory cytokine levels, phagocyte oxidant production, and AM and neutrophil counts were detected in the bronchoalveolar lavage of the CNC exposed rats. Mild lung histological changes, such as the accumulation of AM and neutrophils, were observed in the CNC exposed rats. Global gene expression profiling by next generation sequencing identified 573 genes whose expressions were significantly different (fold change >1.5 and FDR $p<0.05$) in the lungs of the CNC exposed rats, compared with the controls. Bioinformatic analysis of the lung gene expression data identified significant enrichment of several biological functions and canonical pathways related to inflammation (cellular movement, immune cell trafficking, inflammatory diseases and response, respiratory disease, and free radical scavenging, complement system, acute phase response, leukocyte extravasation signaling, granulocyte and agranulocyte adhesion and diapedesis, IL-10 signaling, phagosome formation and matu-

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