2799 Differential Effects of Silver Nanoparticles (AgNP) and Silver Acetate (AgOAc) on the Accumulation, Distribution, and Potential Toxicity of Silver in Rats Following Daily Oral Administration for 13-Weeks

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AgNP have broad applications in consumer products, and reports indicate that ingested AgNP distribute to numerous organs in mammals. This study examined particulate and ionic forms of silver and particle size for differences in tissue silver accumulation, distribution, morphology, and potential toxicity when administered by daily oral gavage to Sprague-Dawley rats for 13 weeks. Test materials and dose formulations were characterized by transmission electron microscopy, dynamic light scattering, and inductively-coupled mass spectral analyses. Seven-week-old rats (10 rats per sex per group) were randomly assigned to treatments: AgNP (10, 75, 110 nm) at 9, 18, and 36 mg/kg; AgOAc at 100, 200, 400 mg/kg; and controls (2 mM sodium citrate (CIT) or water). At termination, complete necropsies were conducted, histopathology along with hematology, serum chemistry, micronuclei and reproductive system analyses were performed, and silver accumulations and distributions in tissues were determined. Male and female rats exposed to AgNP did not show any significant changes in body weights or feed and water intakes relative to controls. Hematology and serum chemistry values, micronuclei, reproductive system analyses, and absolute or relative organ weights did not differ from controls. Distributional and morphological differences of silver were observed by transmission electron microscopy for 10 nm AgNP and AgOAc, and silver showed significant dose-dependent and AgNP size-dependent accumulations in all tissues examined. Furthermore, sex differences in silver accumulations were noted for a number of tissues and organs, with accumulations significantly higher in female rats, especially in the kidney, liver, jejunum, and colon.

2800 Effects of Pre-Exposure Dispersion Status on Nanoparticle Distribution and Fibrosis in the Lung

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An important aspect of nanoparticle toxicity is the deposition and translocation of the particles once they reach the lung. In the form of agglomerates deposition characteristics can change, as the agglomerates will have a greater aerodynamic diameter than singlet nanoparticles. We hypothesize that pre-exposure dispersion status of the nanoparticle will correlate with particle deposition and translocation within the lung. Specifically, we postulate that well dispersed (WD) particles will be more likely to move into the interstitial space of the lung, while poorly dispersed (PD) particles will primarily be taken up by the alveolar macrophages (AMs). To test our hypothesis, nano-sized NiO was suspended in four different dispersion media (PBS, dispersion medium (DM), Survanta, or Pluronics F-68). At each respective dose, WD and PD suspensions (sonicated at 25W continuous output, 20 min or 5 min, respectively) were created. Mice (male, C57BL/6J, 7 weeks old) were given 40 or 80 µg/mouse of nano-sized NiO in the different states of dispersion via pharyngeal aspiration. At 2 hours, 7, and 56 days post-exposure, lungs were collected and fixed by intratracheal perfusion. Lung sections were then viewed using a CytoViva microscope. At 2 hours post-exposure both PD and WD NiO structures were primarily distributed in the airspaces of the first few alveolar generations. However, the forms of distribution were quite different between PD and WD NiO at 7 and 56 day post-exposure. The majority of the PD particles were in large clumps in the airspaces. Many of the large clumps induced granulomatous nodules. The majority of WD NiO particles were in AMs or found within the interstitium. By 7 and continuing out to 56 days post-exposure, there was significant fibrotic development within the granulomatous nodules with PD NiO. However, granulomatous nodules and the associated fibrotic development were not observed with WD NiO particles. This work was supported by NIH grant F32 ES021341.

2801 Inhaled TiO_2 Nanoparticles Induce Morphologic and Biochemical Changes in the Lungs of Golden Syrian Hamsters

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TiO_2 is a metal oxide that has found diverse applications from sunscreens to food additives. Inhaled metal nanoparticles have been shown to deposit in the parenchyma of the lungs causing generation of ROS, inflammation, cell death and fibrosis. NIOSH has classified TiO_2 as a potential carcinogen following development of tumors after chronic inhalation in rats exposed to 250mg/m^3 of TiO_2. From such studies NIOSH set an exposure limit of 0.3mg/m^3 while OSHA set a permissible exposure limit of 15mg/m^3. The current study investigated the toxicity of TiO_2 NP in Golden Syrian Hamsters. Hamsters were exposed in a whole body chamber to aerosolized vehicle (control) or aerosolized TiO2 NP at concentrations of 0.3mg/m^3, 3mg/m^3 or 15mg/m^3 (4 hrs/day for 14 days). 24hrs post exposure, hamsters were euthanized, lungs were lavaged and either fixed or frozen for further analysis. Bronchoalveolar lavage was assessed for levels of LDH, SOD and TNF-α. Average size of TiO_2 NP was determined to be 36.9 ±14.4nm by TEM evaluation. Lavage from the lungs of hamsters treated with 0.3, 3.0 or 15mg/m3 NP had a 33%, 73% or 138% increase in TNF-α as compared to controls. SOD levels were significantly higher by 137% (3mg/m^3 group) and 337 % (15mg/m^3 group) while LDH levels were increased by 73% and 108% (3mg/m3 and 15mg/m3 groups respectively) as compared to controls. H & E evaluation of lung tissue revealed significant hyperplasia in animals exposed at 3mg/m3 and 15mg/m^3 while TUNEL assay revealed the presence of apoptotic cells in the 15mg/m^3 group. Scanning electron micrographs of animals exposed to TiO_2 NP showed presence of blebbing in airways while the control group had cells that appeared normal. Such findings indicate that inhalation of nanosized TiO_2 particles induce apoptosis and histopathological changes in lung tissue, increase in SOD levels suggest induction of oxidative stress while the increases in LDH and TNF-α indicate induction of parenchymal injury.

2802 Effect of Ascorbic Acid Pretreatment on Brain Perivascular Injury Induced by Prenatal Exposure to Carbon Black Nanoparticle in Mice

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Objective: Our previous report* showed that maternal exposure to carbon black nanoparticle (CB-NP) alters histological feature of the brain perivascular macrophages and astrocytes of mouse offspring. The aim of the present study was to investigate protective effects of ascorbic acid, one of the antioxidant reagents, on the brain perivascular cell damages induced by maternal exposure to CB-NP in offspring mice. Methods: Pregnant ICR mice were treated with CB-NP suspension without bulk agglomerates (95, 73, 15, 2.9 µg/kg/time) by intranasal instillation on gestational days 5 and 9. Ascorbic acid (500 mg/kg) were intraperitoneally administered at 1 hour before every administration of CB-NP. Brains and dissected frontal cortex were collected from offspring mice at 6 and 12 after birth. Phenotypes of perivascular cells were examined by western blotting for glial fibrillary acidic protein (Gfap) and aquaporin-4 (Aqp4), immunohistochemistry, comprehensive gene expression profiling by microarray, and gene ontology (GO)-based annotation analysis. Results: Quantitative analysis by western blotting indicated that the expression levels of Gfap and Aqp4 were dose-dependently increased in the frontal cortex by CB-NP. Gfap expression was increased in the astrocytic endfoot attached to denatured perivascular regions in the gray matter and Aqp4 expression was increased in brain parenchyma, not in perivascular region, of frontal cortex. The increase in Gfap and Aqp4 protein expressions levels were not suppressed by ascorbic acid pretreatment. Analysis of gene expression using GO terms indicated that expression levels of genes associated with angiogenesis, chemotaxis, and cell proliferation were altered in the frontal cortex of offspring by CB-NP maternal exposure, and these gene expression levels were not altered by ascorbic acid pretreatment. Conclusion: The present study indicated that maternal exposure to CB-NP induced chronic perivascular injury with an increase in Gfap and Aqp4 of frontal cortex, which was not protected by ascorbic acid pretreatment. The present study suggests that the mechanism of brain perivascular injury induced by prenatal exposure CB-NP may not related to increase in oxidative stress of a pregnant mother. *Onoda A et al., PLoS One. 2014.

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Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 55th Annual Meeting of the Society of Toxicology, held at the New Orleans Ernest N. Morial Convention Center, March 13–17, 2016.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 603.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 629.

The abstracts are reproduced as accepted by the Scientific Program Committee of the Society of Toxicology and appear in numerical sequence. Author names which are underlined in the author block indicate the author is a member of the Society of Toxicology. For example, J. Smith.

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