PS 1457 GLOBAL GENE PROFILING REVEALS DOSE AND TIME PROGRESSION OF KEY BIOLOGICAL RESPONSES OF LUNG EPITHELIAL CELLS TO NANOSCALE AMORPHOUS SILICA *IN VITRO*.

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Nanoscale amorphous silica is used widely in consumer products and is a representative for poorly soluble, low toxicity metal oxide nanoparticles. We used global gene expression profiling to identify key mode-of-action related cellular processes and to quantify impacts on these processes as a function of time and target cell silica particle surface area dose. Mouse C10 lung epithelial cells in submerged culture were exposed to four concentrations of 33-nm carboxylated amorphous silica (10, 50, 100 and 250 μg/ml) for 2, 4, 8 and 24 hours. Cell viability was unaffected by silica at concentrations ≤ 50 μg/ml, while treatment at 100 and 250 μg/ml decreased cell viability by 6% and 17%, respectively. Global transcriptomic profiling (Affymetrix DNA arrays) showed a distinct progression, increasing with dose and time, with unique expression patterns where toxicity was evident and absent. Among the gene products most robustly up-regulated by non-cytotoxic exposures were transcripts linked to inflammation (Ccl7/Cxcl1/Cxcl5/Cxcl15/ Ptgs2), angiogenesis/wound repair (Ankrd1/Ang2/Ang4/Angptl2/figf), oxidative stress (Olr1/Cybb) and lung tissue remodeling/injury response (Mmp3/Mmp8/Mmp10/Mmp13). Most of these changes in transcript level progressed in intensity from low non-cytotoxic exposures to cytotoxic exposures. We calculated the delivered particle surface area for each exposure using a particokinetic model for particles in vitro, which enabled separation of the individual roles of cellular dose and exposure duration. By de-convoluting exposure-duration and dose, the dependence of the response for key biological processes could be quantified and related to comparable acute human exposure levels by the inhalation route.

PS 1458 PULMONARY TOXICITY OF AMORPHOUS SILICA NANOMATERIAL: A COMPARISON OF INHALATION AND INSTILLATION STUDIES.

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The inhalation and deposition of air-borne nanomaterials in the lung is a complex process. Their potential pulmonary toxicity should thus be studied by inhalation exposure. Those studies demand, however, special equipment and large quantities of test material. Intratracheal instillation appears as a simple and less substance-consuming alternative, although bolus dosing and the more central distribution of the particles in the lung are a well known trade-off. We compared the response of the lung to amorphous silica (AS) after instillation and inhalation. For inhalation the established short-term protocol for nanomaterials was employed (Ma-Hock et al. Inhal. Tox. 21:102, 2009): Rats inhaled for 6 h/day on 5 consecutive days 0, 0.5, 2.0 or 10 mg/m3 of either uncoated or polyacrylate coated AS nanomaterial. The bronchoalveolar lavage fluid (BALF) and lungs (histopathology) were examined 3 days and 3 weeks after the end of the exposure. In parallel, rats were intratracheally instilled and equally evaluated. The instilled dose corresponded to the aerosol concentration used for inhalation. After instillation, coated and uncoated AS elicited significant changes in BALF and moderate to massive multifocal granulomatous inflammation in the lungs. In contrast, inhalation of the coated and uncoated silica caused no, or minimal inflammatory effects. Coated AS applied by both exposure techniques caused a significant but reversible increase of spleen weights. An increased spleen weight was also observed after instillation, but not inhalation, of the uncoated AS. Results show that inhalation and instillation of nominally equal mounts of AS elicit different results in the lung with inhalative treatment being less harmfull. This difference may be due to the bolus effect inevitable linked to instillation. Instillation stuldies with AS may, therefore, be of limited value with respect to dose-response assessment.

PS 1459 NANOPARTICLE INHALATION ENHANCES CARDIAC PROTEIN PHOSPHORYLATION AND NEUROTRANSMITTER SYNTHESIS IN THE NODOSE GANGLIA OF RATS.

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Growing evidence from epidemiological studies indicates that an increase of the small sized particle, particularly nanoparticle, component in ambient air is strongly associated with increased incidence of cardiovascular diseases. Animal studies demonstrated that pulmonary inhalation of nanoparticles stimulates the development of atherosclerosis and impairs vascular function. However, the effect of inhaled nanoparticles on cardiac muscle has not been reported. The present study investigated the effect of ultrafine titanium dioxide (UFTiO2) on the heart. We found that direct exposure of rat cardiac myocytes in vitro to UFTiO2 (1 μg/ml) for 4 hrs did not alter myocyte contractility, calcium handling, or the phosphorylation level of cardiac proteins, such as p38 mitogen-activated protein kinase (p38 MAPK) and cardiac troponin I (cTnI). In contrast, pulmonary inhalation of UFTiO2 (6 mg/m3) for 4 hrs significantly increased the phosphorylation status of p38 MAPK and cardiac cTnI in the heart. In addition, pulmonary exposure to UFTiO2 also increased neurotransmitter substance P synthesis in nodose ganglia, which is involved in the integration and control of lung and heart function. However, neither mRNA expression nor protein synthesis of TNF-α, IL-1 and IL-6 was detected in the heart or peripheral blood respectively. Blood cell counts and differentials did not indicate significant systemic inflammation. Our results suggested that pulmonary exposure to UFTiO2-enhanced the phosphorylation level of p38 MAPK and cTnI in cardiac tissue. Such responses may contribute to cardiac dysfunction which is independent of the direct interaction of UFTiO2 with the heart or systemic inflammation, but may involve a lung-neuron-regulated pathway.

PS 1460 DISTRIBUTION, ELIMINATION, AND BIOPERSISTENCE TO 90 DAYS OF A SYSTEMICALLY-INTRODUCED 30 NM CERIA ENGINEERED NANOMATERIAL IN RATS.

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Background: Nanoscale ceria is a diesel fuel additive, among other applications. Objectives: To extend our prior work showing no reduction of cerium in reticuloendothelial tissues up to 30 days after a single dose of nanoscale ceria, determine the routes and rate of its excretion, and further characterize its distribution, persistence, and effects in the rat. Methods: An ~ 5% aqueous dispersion of citrate-stabilized 30 nm ceria, synthesized and characterized in-house, was iv infused into 16 rats (87 mg/kg), which were terminated 1, 7, 30 or 90 days later. Fifteen control rats received vehicle. Three rats received 50 mg/kg cerium(III) ion. Rats were housed in metabolism cages for up to 2 weeks to quantify urinary and fecal cerium output, cage-side observations recorded daily, and weighed weekly. At termination, nine organs were weighed and samples were collected from 14 organs/systems, blood and CSF for cerium determination by ICP-MS. Results: Nanoscale ceria was less acutely toxic than the cerium ion. Less than 1% of the ceria or cerium ion dose was excreted in the first week; 98% was in feces. Body weight gain in ceria-treated rats was significantly lower than controls. Ceria was primarily retained in the spleen, liver and bone marrow. Spleen weight was significantly increased in some ceria-treated groups, associated with visual evidence of abnormalities. Conclusions: Nanoscale ceria and the cerium ion were retained by reticuloendothelial tissues from which it was very slowly cleared. These results further support the concern about the long term fate and adverse effects of inert nanoscale metal oxides that reach systemic circulation, from which they can distribute throughout the body, resulting in persistent retention and potential adverse effects in multiple organs. Supported by U.S. EPA STAR Grant RD-833772.

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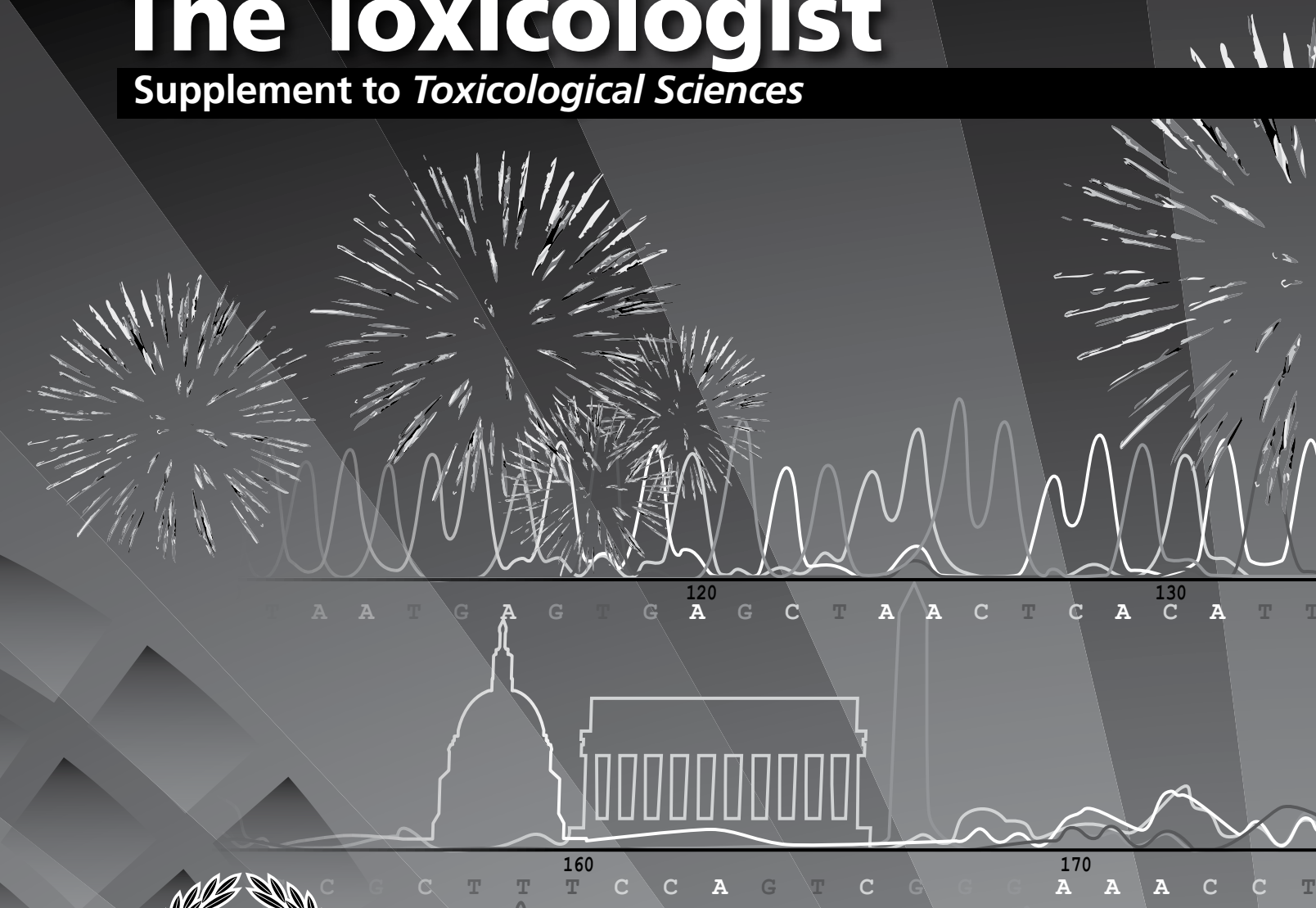

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 50th Annual Meeting of the Society of Toxicology, held at the Walter E. Washington Convention Center, March 6–10, 2011.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 578.

The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 606.

The abstracts are reproduced as accepted by the Scientific Program Committee of the Society of Toxicology and appear in numerical sequence.

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