1390 NEUROINFLAMMATORY RESPONSES FOLLOWING EXPOSURE TO ENGINEERED NANOMATERIALS.

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Multi-walled carbon nanotubes (MWCNT) and fine crystalline silica are largely used in the manufacture of composites and as blasting abrasives. While the widespread application and economic benefits of manufacturing such materials are highly promising, their adverse effects on the nervous system have not been fully investigated. Populations at greatest risk for exposure are industrial workers involved in the manufacturing, handling or utilization of such materials. Here, we evaluated the potential neurotoxic effects of exposure to MWCNT (67nm diameter, 5-13μm length) and silica (<2μm) in a murine model. Exposure (by pharyngeal aspiration) of mice to MWCNT (10, 20 or 40μg/mouse) or silica (1mg/mouse) elicited neuroinflammation in discrete brain areas. Specifically, the expression of CCL2, TNFα and IL6 increased (2 to 10-fold; P<0.05) in the olfactory bulb, hippocampus and frontal cortex, within 24h following exposure. This inflammatory outburst is a consequence of microglial activation, in response to perturbation of the neuronal microenvironment and function. Silica also induced the expression of IL1α, OSM, TLR2 and FGF2, effects not observed with MWCNT at the doses tested. In addition, both MWCNT and silica induced region-selective expression of metallothioneins I and II (>2-fold, P<0.05), metal binding proteins that are regulated by inflammatory stress signals and afford protection against oxidative injury. Whether the region-specific neurotoxicity observed following pharyngeal aspiration is due to systemic responses or possible redistribution of these materials to the brain remains enigmatic. In summary, our findings indicate that exposure to engineered nano- and fine particles can elicit neuroinflammatory changes.
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1391 TOXICOLOGY OF TITANIUM DIOXIDE (TIO2) NANOPARTICLES: 2. IMMUNOLOGICAL EFFECTS IN SUBCUTANEOUSLY AND INTRAVENOUSLY INJECTED MICE.

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Nanoparticles that are internalized are very likely to interact with the reticuloendothelial system (RES). This will be more important with therapeutic nanoparticles that may require multiple injections in significant quantities. We evaluated effects of TiO2 particles injected either subcutaneously (SC) or intravenously (IV) on several standard measures of the immune response. Suspensions of ~ 4.7 nm uncoated TiO2 (W470X, Degussa) particles were injected at total doses of 5600 mg/kg (SC) or 560 mg/kg (IV) over two days. At +1 day, there was no significant change in any cell population in peripheral blood except CD8+ in SC mice. In contrast, at day +5 there was a dramatic increase in granulocytes in circulation in SC as well as proportional decreases in circulating lymphocyte percentages. Macrophage percentages were not affected. No changes were observed in any cell population in draining lymph nodes. In SC mice, there was an increase in granulocyte number in the spleen, mirroring the increase in peripheral blood. In the spleen of IV injected mice a number of macrophages containing TiO2 aggregates were observed in the marginal zone of the white pulp, suggesting a pathway for the interaction of TiO2 with T cells. After 3 days of culture with Con-A, an apparent lack of T-cell proliferation was seen in lymph nodes from SC but not IV injected animals. This was seen by both direct measurement of proliferation and from B-cell:T-cell ratios after culture. Cytokine analyses of the mitogen stimulated spleen and lymph node cells indicated increased production of TNF-alpha, IL-6 and gamma-interferon. These results indicate that the acute inflammatory response seen in SC injected mice may well have secondary effects on the immune response. These findings, along with earlier results with polystyrene nanoparticles suggest that the immune system may be especially sensitive to effects of nanoparticles.

1392 SIZE AND SURFACE COATING DIFFERENCES IN SILVER NANOPARTICLE TOXICITY AND INFLAMMATORY RESPONSE IN JURKAT CELLS.

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The use of silver nanoparticles (Ag NP) in many commercially available products for their strong antibacterial and antiviral properties has led to questions about their toxicity to mammalian cells. Our studies show that their toxicity is dependent upon their size, concentration, and chemical surface composition. First, we examined the effect of toxicity measures due to size for uncoated Ag NPs (10, 25, and 80 nm, Nanotechnologies, Inc.) and surface coated Ag NPs (15, 30, 80nm, Clarkson University). The primary NP sizes and morphologies were visualized and characterized with scanning and transmission electron microscopy. Previous studies show a size and concentration-dependent toxicity. However, in the current studies, the coated Ag NPs were in considerably less toxic than the uncoated Ag NPs. The MTT assay of cell viability shows that surface coated functionalized particles are not toxic while unfunctionalized particles are toxic at the exposure levels and time course studied. The initiating, irritation inflammatory response using IL-2 and TNF-a production showed significant increase in non-functionalized silver particles while only marginal induction in functional particles. The results indicate that toxicity depends on the surface based on coating deactivation rather than nominal size of the nanomaterial. Other characteristics including overall dimension, surface dissolution, etc. require further studies.

1393 MANUFACTURED NANO-SIZED ALUMINA PARTICLES INDUCE ENDOTHELIAL CELL DYSFUNCTION: IMPLICATIONS IN VASCULAR DISEASE.

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Manufactured nanoparticles (MNP) display unique physicochemical characteristics due in part to their small size and large surface area that also make them highly desirable for a number of applications. Alumina or aluminum oxide is the most abundantly produced nanosized particle. Due to the extreme potential of MNP and their increased usage, occupational and public exposure will dramatically increase in the future. Human exposure via inhalation and ingestion can lead to increased blood concentrations. The vascular endothelium is uniquely susceptible to such xenobiotics circulating through the bloodstream. Inflammation or dysfunction of the endothelial layer has been shown to be an initiating event for the development of vascular diseases. It is hypothesized that MNP will lead to increased endothelial cell dysfunction, evidenced by increased inflammatory processes. Human umbilical vein endothelial cells and primary porcine pulmonary artery endothelial cells were treated with nano-sized (~10 nm) alpha-gamma alumina particles (10-100 μg/mL). It was found that alumina significantly increased mRNA expression of vascular cellular adhesion molecule-1 (VCAM-1) and E-selectin (ELAM-1). Alumina treatment also increased VCAM-1, ELAM-1, and intracellular adhesion molecule-1 (ICAM-1) protein determined by Western blot and immunofluorescence analysis. The protein induction of VCAM-1 was inhibited by co-treatment with an NF-κB inhibitor (BAY 11-7085), suggesting that the NF-κB signaling pathway may be responsible for VCAM-1 induction. These results suggest that nano-alumina particles can lead to endothelial cell activation and dysfunction by the induction of a number of pro-atherogenic inflammatory events and that these events may be modulated through the NF-κB pathway.

1394 THE PREFERENTIAL BINDING OF HUMAN SERUM PROTEINS TO NI, AL AND DIAMOND NANOPARTICLES.

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In a physiological environment, proteins rapidly accumulate on particulate material that has a charged or hydrophobic surface. A growing body of research has demonstrated that these surface-bound proteins facilitate the detection of particulate material by phagocytic cells and help determine the distribution and clearance of these materials as well as the severity of secondary immune or inflammatory responses. Identifying these bound proteins and understanding how surface properties control protein binding is essential for predicting particle induced toxicity. As a first step in this process, the identity and relative proportion of proteins bound to the surface of nickel (nominal size 50 nm), aluminum (nominal size 51 nm) and diamond (nominal size 75 nm) nanoparticles following their exposure to human serum were determined. Particle bound proteins were isolated, assayed for total protein and labeled with ^{13}C containing tags using an Applied Biosystems ICAT system. Each bound protein sample was combined with an equal amount of free serum proteins that had been labeled with analogous ^{12}C containing tags and these combined samples were separated on a 1-D SDS PAGE gel. Protein bands were excised, subjected to in-gel trypsin digestion and analyzed by LC MS/MS following avidin purification. By quantifying the number of equivalent peptide sequences containing ^{13}C and ^{12}C tags, the relative proportion of proteins bound to each particle and present in free serum was determined. Although some serum proteins such as β-2-glycoprotein and α-2-HS-glycoprotein readily accumulated on all particles, each mate-

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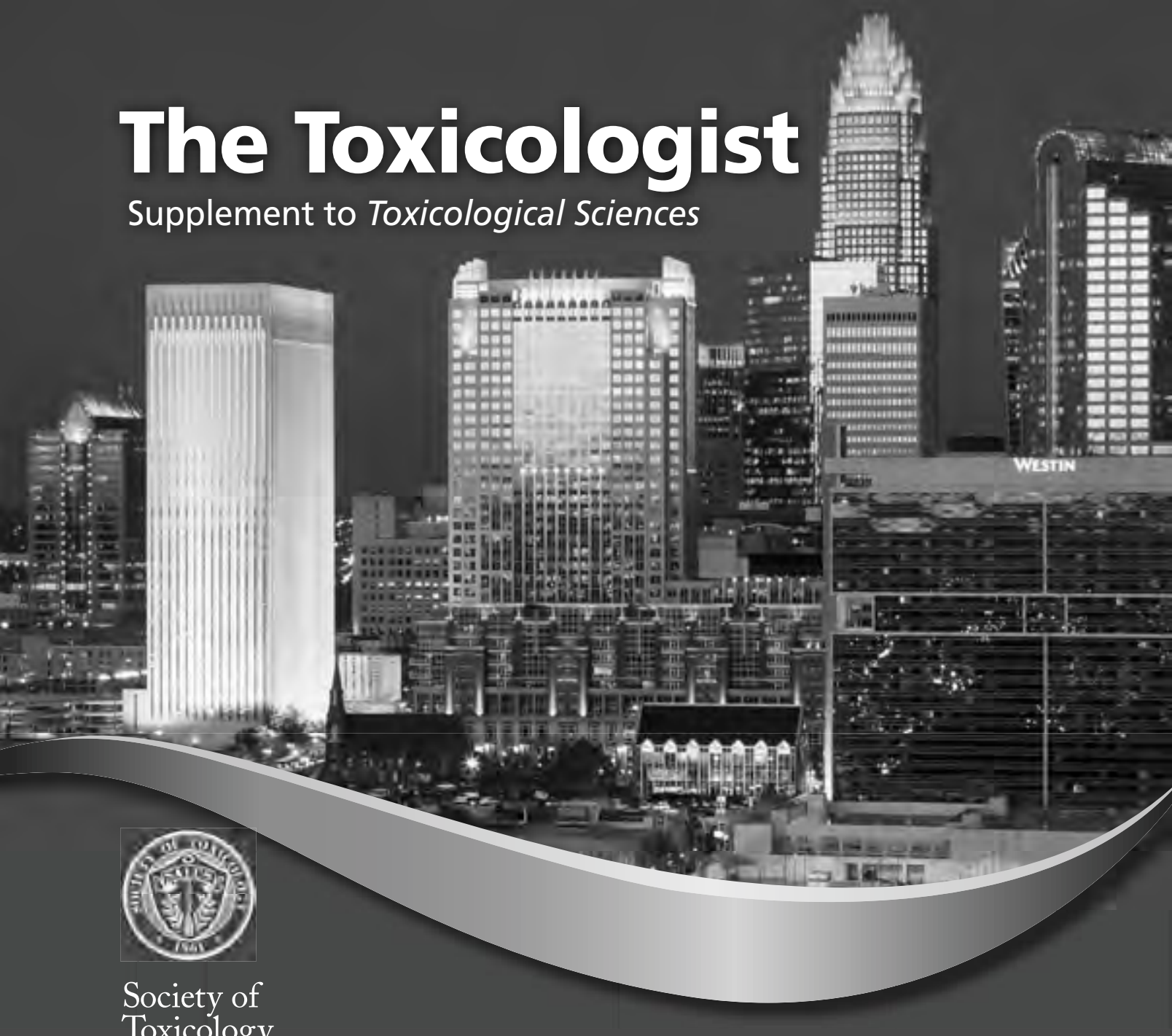

Society of Toxicology

46th Annual Meeting and ToxExpo™

Charlotte, North Carolina

An Official Journal of the Society of Toxicology

www.toxsci.oxfordjournals.org

OXFORD UNIVERSITY PRESS

ISSN 1096-6080
Volume 96, Number 1, March 2007

Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, and poster sessions of the 46th Annual Meeting of the Society of Toxicology, held at the Charlotte Convention Center, Charlotte, March 25–29, 2007.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 449.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 480.

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