in the lung recovered cells of pristine nano-C60 exposed rats at the 1 day time point, but decreased over time. However, no increases in lung cell inflammatory responses, i.e. % neutrophils, were measured between the two forms of C60 at any of the postexposure time points evaluated. We show that under ambient conditions in water, fullerenes can generate carbon centered radicals detected by electron spin resonance spectroscopy. These oxygen radicals may be responsible for increased lipid peroxidation at the 1 day time point. This work demonstrates both the difficulty in interpreting/extrapolating in vitro toxicity measurements and highlights the complexities associated with probing the toxicological response of nanoparticle systems.

1118 NANO-PARTICLES - A SHORT-TERM INHALATION TEST WITH TIO2 IN RATS LINKED TO *IN VITRO* SYSTEMS.

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Inhalation exposure is the route of most concern for nano-particles. There is that nano-particles in aerosols agglomerate to larger clusters affecting their deposition, distribution and effects in the lung.
Various testing methods are currently used to estimate the effects of nano-scaled materials in the lung, i.e. inhalation, intra-tracheal instillation and various cell culture systems. Compared to inhalation studies, these systems are relatively simple but the exposure is, considering the complex processes in nano-particle aerosols. Alternative exposure routes will need validation by inhalation studies covering the appropriate endpoints.
Therefore an inhalation study with rats was performed with exposure to 50, 10 and 2 mg/m3 nano-TiO2 for 6 hours on 5 days. At the end of the exposure, and two and twelve days thereafter, animals were examined for an extensive set of parameters: Organ burdens were estimated in 7 tissues and electron microscopy was used to characterize the particles deposited in the tissues.
The particles in the atmosphere had a median diameter of 2 µm and less then 1% were actually in the nano-range (<100 nm), indicating agglomeration. Agglomerates in airways and alveoli (extra-cellularly and within activated macrophages) had a similar size distribution. 10 organs were examined by histopathology. S-phase response and apoptosis was examined in the lung.
Cytokine profiles, indicators of oxidative stress (malondialdehyde, carboxymethyllysin, 8OHdG) and indicators of complement activation, as well as standard clinical pathology parameters were analyzed in lung lavage fluid and blood.
Signs of inflammatory response were observed in the lung and the results correlated well with results from a previous subchronic inhalation study. However, the wide range of examined parameters in this study, revealed a much more differentiated picture of the effects of nano-TiO2 in the lung. The results will be discussed in detail and compared to intra-tracheal instillation studies as well as tests with cell cultures.

1119 ROLE OF PARTICLE AGGLOMERATION IN NANOPARTICLE TOXICITY.

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Particle agglomeration can affect the physical characteristics of airborne particles and influence deposition and toxicity. We hypothesized that there will be a difference in the toxicity of fresh (predominantly singlet) vs. aged (predominantly agglomerated) carbon nanoparticles. We measured the agglomeration rate of freshly generated carbon nanoparticles and determined whether agglomeration is affected by residence time, particle charge, or humidity. To examine the role of these parameters on carbon nanoparticle toxicity, we exposed BALB/C mice for 5 hrs to filtered air or carbon nanoparticles generated by spark discharge and examined lung injury and inflammation 24 hrs after exposure. Freshly generated carbon nanoparticles (60 nm, count median diameter, CMD, with a minor peak around 10 nm) produced significantly greater lung inflammation compared to nanoparticles aged approximately 3 minutes (260 nm CMD). This fresh nanoparticle-induced inflammation was concentration dependent with lavage fluid neutrophils at 2%, 4%, 14%, and 35% for 0, 1, 2.5, and 5 mg/m^3 nanoparticle concentrations, respectively. There was little difference, however, in total protein concentrations in the lavage fluid of mice exposed to fresh vs. aged nanoparticles. Moreover, despite the role of particle charge in the physics of agglomeration processes, there was no significant difference in the response of mice exposed to charged nanoparticles vs. nanoparticles that were brought to charge equilibrium with a Kr source. Thus, the aging of freshly generated carbon nanoparticles has a profound effect on toxicity but it is unclear if this decrease in toxicity is due solely to particle agglomeration or changes in surface chemistry of the carbon nanoparticles. Ongoing studies are examining the effect of: 1) particle agglomeration on the toxicity of nanoparticles generated from metals and 2) low and high humidity on the pulmonary toxicity of freshly generated carbon nanoparticles.

1120 AN IMPROVED METHOD TO PREPARE SUSPENSIONS OF NANOPARTICLES FOR TREATMENT OF LUNG CELLS IN CULTURE OR *IN VIVO* EXPOSURE BY PHARYNGEAL ASPIRATION OR INTRATRACHEAL INSTILLATION.

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Occupational health risks associated with the production and use of nanomaterials are at this time undefined. Therefore, a need to conduct studies examining the health of effects of nanoparticle exposure is of great importance. However, nanoparticles agglomerate and clump in solution, making it difficult to accurately deliver nano-sized particles in an in vivo or in vitro experimental procedure. Therefore, a dispersal method which does not alter the biological activity of the particles surface and is not toxic to the lungs was developed. Experiments were conducted to determine the best method to suspend nanosized particles. Ultrafine and fine carbon black and titanium dioxide were suspended in a variety of suspension medias including phosphate buffered saline (PBS), rat and mouse bronchoalveolar lavage fluid (BALF), and dipalmitoyl phosphatidylcholine (DPPC). To assess and compare how the various suspension medias dispersed the particles, images were taken using light microscopy, scanning electron microscopy (SEM), and transmission electron microscopy (TEM). The results of this study show that PBS is not a satisfactory media to prepare particle suspensions of nanosized particles. However, BALF is an excellent vehicle in which to suspend ultrafine particles. The use of protein alone or DPPC alone, in concentrations found in BALF, did not result in satisfactory dispersions. However, the combinations of protein plus DPPC are a satisfactory, although slightly less effective, substitute for BALF.
The findings and conclusions in this abstract have not been formally disseminated by the National Institute for Occupational Safety and Health and should not be construed to represent any agency determination or policy.

1121 ARE POLY(ETHYLENE GLYCOL)-FUNCTIONALIZED NANOPARTICLES BIOCOMPATIBLE?

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Nanoparticles engineered for biomedical application need to be biocompatible to avoid adverse health effects. Surface-coating with poly(ethylene glycol) (PEG) is being used for this purpose. Since pulmonary delivery of nanoparticles is of great interest for therapeutic treatments targeting both pulmonary and extrapulmonary tissues, we sought to evaluate in the respiratory tract the biocompatibility of different nanoparticle coatings. We looked at the effect of two commonly used coatings, PEG (Mw = 5 kg/mol) and serum albumin (SA, Mw= 66 kg/mol), on pulmonary inflammation, cytotoxicity, and particle translocation. Single doses of saline and citrate-stabilized-, PEG-coated- or SA-coated- 50nm Au particles were intratracheally microsprayed into male F-344 rats. 24-hours after delivery, Au from all particle-exposed groups was detected in all regions of the lung analyzed, with the smallest amount being found in regional lymph nodes and the highest amount being found in lung tissue and cells of the bronchoalveolar lavage fluid (BALF). Rats exposed to SA- and PEG-coated Au, relative to citrate-stabilized Au, showed higher Au concentration in the BALF supernatant ($p<0.05$). This indicates that surface coatings prevent particle uptake by mononuclear phagocytic cells. Surprisingly, PEG-, but not SA-coated Au particles induced large increases in biochemical markers of cell toxicity (2-fold, $p<0.05$), polymorphonuclear neutrophils (60-fold, $p<0.0001$), and lymphocytes (10-fold, $p<0.01$), as measured in the BALF one day after exposure. These findings of severe pulmonary inflammation due to PEGylation differ with the generally held view of PEG biocompatibility. Future studies with different PEG-nanoparticle formulations will determine the mechanism of this unexpectedly high inflammatory response.

1122 COMPARATIVE SOLUBILITY OF NANOPARTICLES AND BULK OXIDES OF MAGNESIUM IN LUNG SIMULANT FLUIDS.

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Nanoparticles (NP), with > 1 dimension < 100 nanometers (nm) can clear airborne smoke particles. NP deposit in the deep lung, evade phagocytosis (< 1,000 nm diameter) and enter the lung interstitial space; if dissolved rapidly, we predict minimal health effects. We compared the solubility of Nanoactive [NA] ™ MgO Plus

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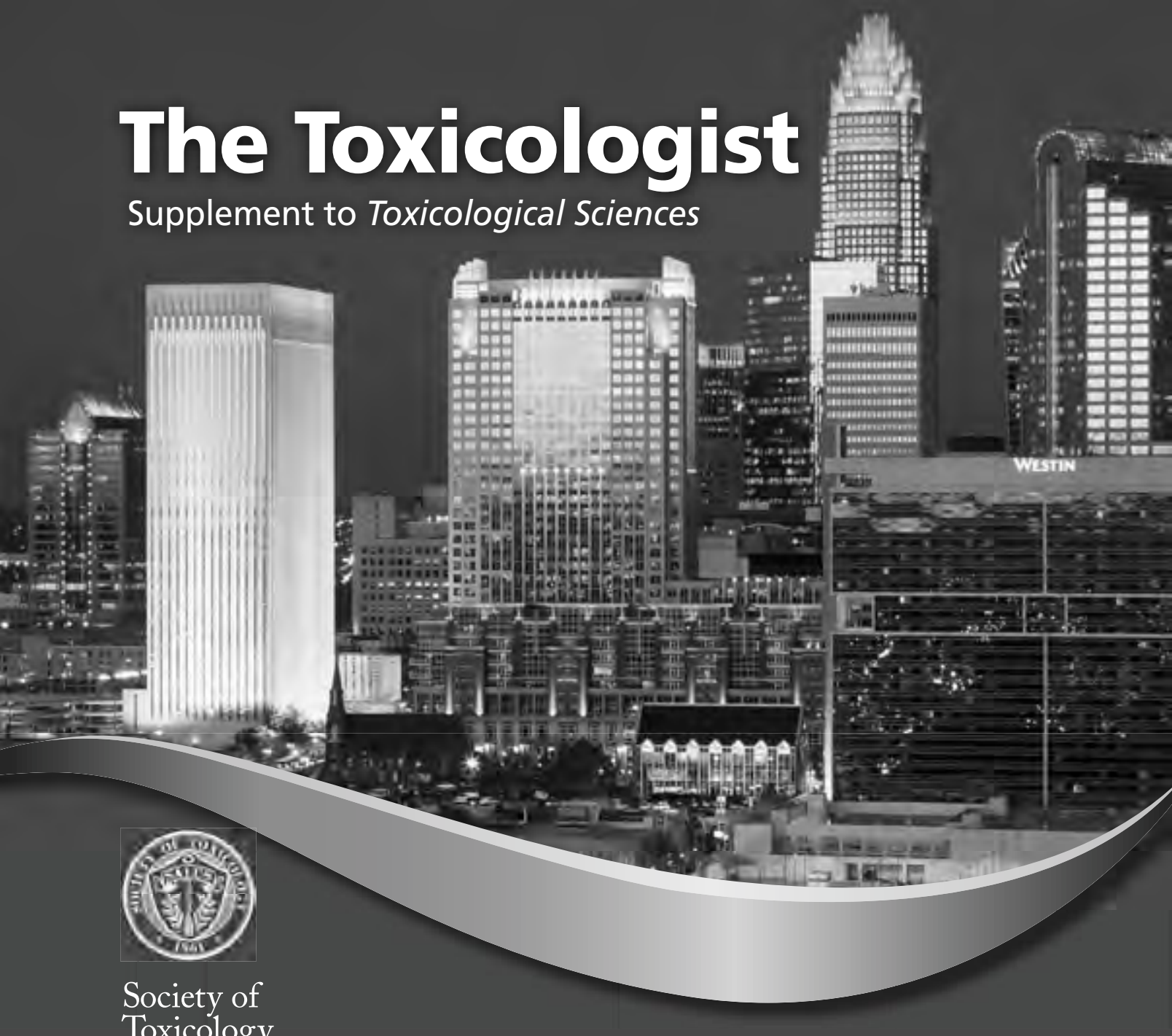

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Preface

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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