PS 2192 USE OF LABELED SINGLE WALLED CARBON NANOTUBES TO STUDY TRANSLOCATION FROM THE LUNGS.

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Colloidal gold nanoparticles (10nm) were used to label single walled carbon nanotubes (SWCNT) in studies aimed at determining how SWCNT clear from the lungs. Gold labeled SWCNT were delivered to the lungs by pharyngeal aspiration to C57BL/6 mice. Neutron activation analysis (NAA) of lung, blood and other organs was carried out at various time points after aspiration to determine if the gold labeled SWCNT translocated out of the lungs. Five mice per group were studied at 1 hour, 1 day, 3, 7 and 28 days after exposure to a single dose (40ug) of gold labeled SWCNT. A phosphate buffered saline (PBS) aspiration group served as the negative control. At sacrifice, the lungs, GI tract, heart, brain, liver, kidneys, right cranial mediastinal lymph node and a blood sample were taken for analysis of gold content by NAA. Lungs from additional mice were fixed and sectioned for study of the gross distribution of gold labeled SWCNT in the lungs. Gold content of the PBS aspiration group was negligible. For labeled SWCNT, blood gold content was below detectable levels for all time points. Lymph node gold content was not significantly different from the PBS group at any time point. Only lung and GI tract had significant labeled SWCNT at any time point. Lung gold content was 0.181±.008, 0.13±0.006, 0.089±.014, 0.096±.006 and 0.049±.007 ug (mean±SE) at 1 hr, 1 day, 3, 7 and 28 days, respectively. Initially there was a rapid decline of burden from the lungs due to mucociliary clearance which was correlated with GI tract content. Lung burden decreased by 49% between 7 and 28 days. Histological examination demonstrated significant gold labeled SWCNT still present in the airways at 7 and 28 days. While it is uncertain as to the mechanism of the slower phase clearance of lung burden between 7 and 28 days it does not appear to be due to transport to major organs.

PS 2193 PERSISTENT PULMONARY INFLAMMATION, AIRWAY MUCOUS METAPLASIA AND MIGRATION OF MULTI-WALLED CARBON NANOTUBES FROM THE LUNG AFTER SUBCHRONIC EXPOSURE.

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Multi-walled carbon nanotubes (MWCNTs) are manufactured carbon compounds with many commercial applications. The fiber-like dimensions of MWCNTs, their durability, and ability to cause peritoneal inflammation are reminiscent of asbestos, but their toxicity is incompletely investigated. To address the hypothesis that MWCNTs cause persistent morphologic changes and migrate beyond the lung, C57BL/6J mice were exposed by pharyngeal aspiration to 20 or 80 μg MWCNTs (mean dimensions of 4.2 μm x 49 nm) or vehicle. Lung and tracheobronchial lymph node were collected for histopathology 7 and 56 days after exposure. MWCNTs principally accumulated in macrophages and caused granulomatous inflammation. Inflammation extended to the pleura in 7/8 and 4/8 MWCNT-exposed mice at 7 and 56 days, respectively. Both short and long MWCNTs projected beyond the cytoplasmic margins of some macrophages, indicating incomplete phagocytosis or cytoplasmic penetration after phagocytosis. Airway epithelial changes included hypertrophy, cellular atypia and mucous metaplasia. Sirius Red staining demonstrated fibrosis of granulomas and alveolar septa by 7 days post-exposure. Activated caspase-3 and TUNEL assays of the 80 μg exposure group at 7 days post-exposure demonstrated increased apoptosis in alveolar macrophages. MWCNTs accumulated in the draining tracheobronchial lymph nodes and were principally intracellular. At 56 days post-exposure, subpleural lymphatics were focally dilated in one mouse and peribronchiolar lymphatics were dilated in all 4 mice in the 80 μg exposure. Subpleural lymphatics were also dilated in one mouse at 7 days post-exposure. In 4 mice, including both mice with subpleural lympangiectasia, MWCNTs appeared to penetrate the pleura. These findings demonstrate that MWCNTs cause persistent pulmonary inflammation, can be translocated within the lung by alveolar macrophages, can migrate from the lung to the regional lymph node and can penetrate the cytoplasm of macrophages.

PS 2194 CARBON NANOTUBES TESTED IN 5- AND 90-DAY INHALATION STUDIES IN RATS.

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Carbon nanotubes (CNT) are nanomaterials with outstanding characteristics. Using CNT in various applications can free inhalable CNT. First concerns occurred when epithelioid granulomas and interstitial inflammation in the mouse lung were reported after intratracheal instillation of single-wall CNTs. Similar findings were also reported for multi-wall CNT after i.p. injection and instillation in rats. As these represent non-physiologic exposures, we performed specially designed 5- and 90-day-inhalation studies. Aerosols of multi-wall CNT were generated by a brush generator and well characterized. In the 5-day study, concentrations of 2.5, 10 and 30 mg/m3 were tested. Multifocal granulomatous inflammation accompanied by diffuse histiocytosis, hyperplasia/-trophy of the bronchial epithelium and granulocytic infiltration was noted in the lungs. Moreover, multi-focal degeneration of the olfactory epithelium was observed in the nasal cavity at the high concentration. A strong increase of biochemical and cytological parameters in the broncho-alveolar lavage fluid was consistent with the histological findings. Some effects at the low concentration were reversible, whereas others, such as PMN count, did not fully recover within 21 days. In the 90 day study, concentrations of 0.1, 0.5 and 2.5 mg/m3 caused effects comparable to those described above. At the low concentration granulomatous inflammation of minimal grade without neutrophilic infiltration and lipoproteinosis was observed in a few animals; more pronounced effects were seen at the higher concentrations. The mediastinal lymph nodes of all animals contained macrophages with black matter, forming small granulomas within the lymph nodes.
This is (one of) the first subchronic inhalation study with multi-wall CNT. Using actual aerosols we could give accurate concentration-effect data and define a LOAEC of 0.1 mg/m3. This can be the basis for further risk assessments of multi-wall CNT production, handling and use.

PS 2195 PULMONARY TOXICITY OF INHALED MULTI-WALLED CARBON NANOTUBES.

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The large scale manufacture of multi-walled carbon nanotubes (MWCNT) suggests occupational exposures may occur. In order to investigate the pulmonary toxicity of MWCNT, male C57BL6/J mice (6 weeks old) were exposed to aerosolized MWCNT (10 mg/m^3, 5 hours per day; mass mode aerodynamic diameter 1.3 μm, count mode aerodynamic diameter 0.4 μm) for 2, 4, and 8 days. All mice were sacrificed at one day post-exposure. In bronchoalveolar lavage (BAL) studies, polymorphonuclear leukocytes (PMNs) were assessed to index pulmonary inflammation, BAL fluid lactate dehydrogenase (LDH) activity was measured as a marker of cytotoxicity, and BAL fluid albumin was determined as a marker of the lung air-blood barrier integrity. Air-exposed controls had 0.2 ± 0.1 (x 10^3) PMNs/mouse. MWCNT exposure increased PMNs levels to 153.7 ± 26.6 and 125.2 ± 26.2 (x 10^3) PMNs/mouse after 2 and 4 days exposure, respectively. After 8 days exposure, PMNs increased further to 1,151.7 ± 124.2 (x 10^3) PMNs/mouse. In air-exposed controls, BAL fluid LDH activity was 58 ± 3 (units/l), and MWCNT exposure induced significant increases to 131 ± 6, 159 ± 9, and 252 ± 10 (units/l) after 2, 4 and 8 days exposure, respectively. Air-exposed control BAL fluid albumin was 0.13 ± 0.01 (mg/ml), and MWCNT exposure induced significant increases to 0.19 ± 0.01, 0.28 ± 0.02, and 0.37 ± 0.02 (mg/ml) after 2, 4 and 8 days exposure, respectively. Histopathological evaluation of lungs after 4 and 8 days of exposure confirmed pulmonary inflammation. After 8 days of MWCNT exposure, some mice had histopathological evidence of fibrosis at sites of MWCNT deposition. In summary, these data indicate that exposure to aerosolized MWCNTs results in dose-dependent increases in pulmonary inflammation and damage, suggesting that aerosolized MWCNT may pose an occupational health hazard. However, additional dose-response and time course studies are necessary to fully evaluate the potential health risks posed by exposure to aerosolized MWCNT.

PS 2196 PULMONARY TOXICITY OF MULTI-WALLED CARBON NANOTUBES.

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Occupational exposures may occur due to the large scale manufacture of multi-walled carbon nanotubes (MWCNT). Because the toxicity of carbon nanotubes can be influenced by the presence of metal contaminants, bulk MWCNT were examined for their metal content. These analyses determined MWCNT had 0.78% metal contamination, with Fe (0.32%) being a major constitutent. Acellular electron spin resonance studies determined that MWCNT do not generate ROS, despite the presence of trace iron in the MWCNT. In order to investigate the pulmonary toxicity of MWCNT, male C57BL6/J mice (6 weeks old) were exposed by pharyngeal aspiration to MWCNT (0-40 μg/mouse) and mice were sacrificed at 1,

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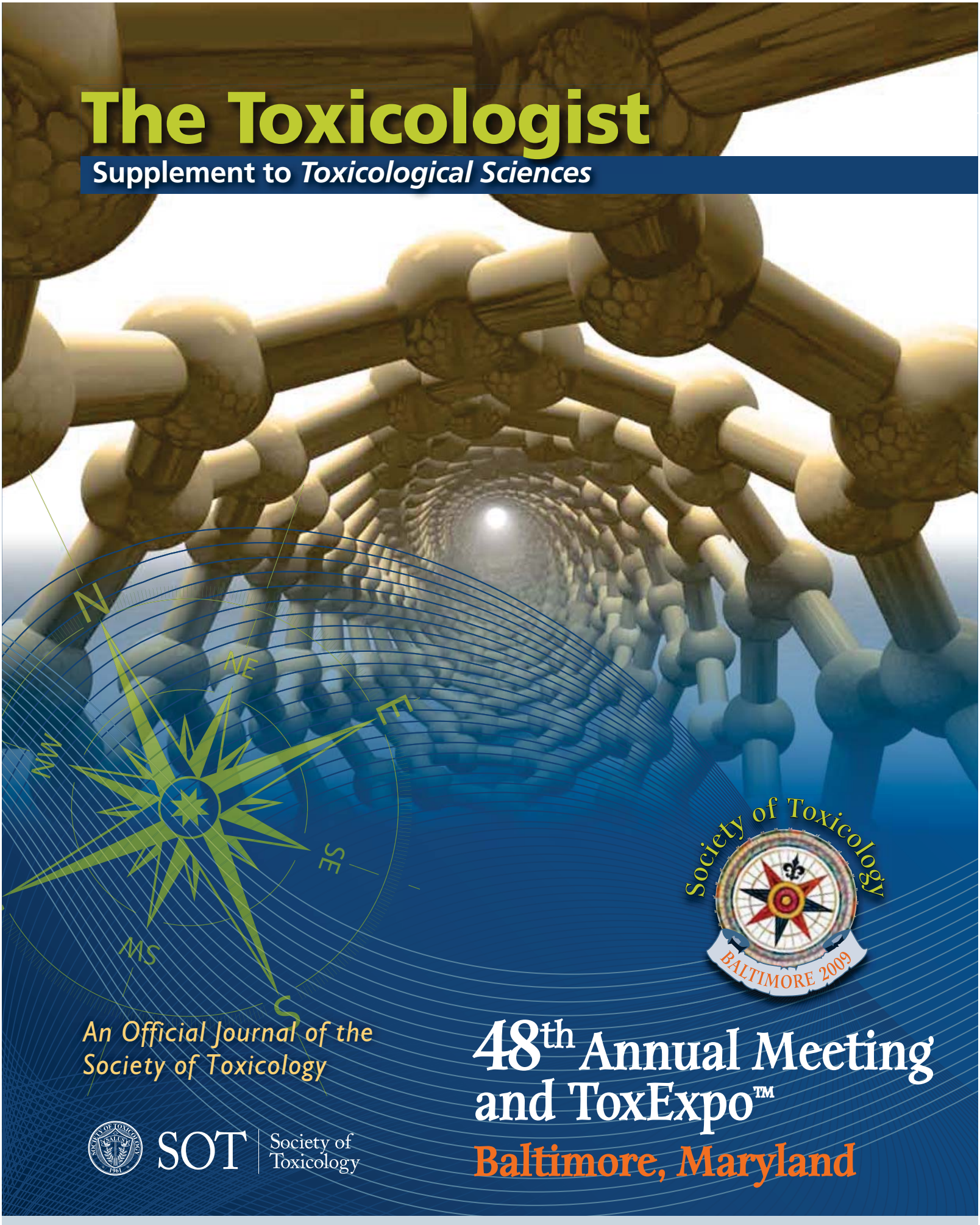

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WHY SUBMIT A PROPOSAL?

1. To present new developments in toxicology.
2. To provide attendees an opportunity to learn about state-of-the-art technology and how it applies to toxicological research.
3. To provide attendees an opportunity to learn about the emerging fields and how they apply to toxicology.

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Continuing Education—Emphasis on quality presentations of generally accepted, state-of-the-art knowledge in toxicology

Note: CE Courses will be held on Sunday.

Symposia—"Cutting-edge" science; new areas, concepts, or data

Workshops—State-of-the-art knowledge in toxicology

Roundtables—Controversial subjects

Historical Highlights—Review of a historical body of science that has impacted toxicology

Informational Sessions—Scientific planning or membership development

Education-Career Development Sessions—Sessions that provide the tools and resources to toxicologists that will enhance their professional and scientific development

2010 Thematic Approach

The Scientific Program Committee will continue the thematic approach for the 2010 Annual Meeting. All proposal submissions will be reviewed for their relevance under the following themes—***Cell Signaling, Gene-Environment Interactions, Metabolic Disease, Mitochondrial Basis of Disease, Toxicity Testing in the 21st Century,*** and ***Translational Toxicology*** for the 2010 meeting. Please note that while we are actively soliciting proposals for the themes listed above, all proposal submissions will be reviewed under the current criteria for their timeliness and relevance to the field of toxicology.

Please refer to the SOT 2009 *Program,* Scientific Program Overview on the fold-out cover for a list of 2009 sessions highlighted under the thematic approach.

You can now submit your proposal on-line at www.toxicology.org

Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the continuing education, symposia, workshop, roundtable, platform, and poster discussion sessions of the 48th Annual Meeting of the Society of Toxicology, held at the Baltimore Convention Center, March 15–19, 2009.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 469.

The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 487.

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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