PS 793 PULMONARY RESPONSE, OXIDATIVE STRESS AND GENOTOXICITY INDUCED BY CARBON NANOFIBERS.

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Carbon-based nanomaterials are considered to be one of the key elements in nanotechnology. Their structure gives an unusual combination of properties that are highly desirable for many industrial products. High aspect ratio makes them an attractive structural material, but their nanometer-scale diameter and needle-like shape have drawn comparisons with asbestos. It is known that inhaled asbestos fibers induce proliferation of connective tissue (fibrogenic response) and increase the risk of acquiring pulmonary carcinoma. We have previously reported that exposure to fibrous single walled carbon nanotubes (SWCNT) caused a robust, acute inflammation with early onset of interstitial fibrosis, formation of granulomas, K-*ras* mutations found in mouse lungs and DNA damage observed in V79 cells. In the current study, we compared effects of carbon-based nanofibers (Pyrograf-III) with asbestos fibers (crocidolite) or SWCNT *in vivo* and *in vitro*. We found that *in vitro* exposure of RAW264.7 macrophages to nanofibers caused cytotoxicity and ROS production. Additionally, treatment of V79 cells with nanofibers caused adverse effects examined by two different genotoxicity assays (comet and micronucleus tests). Pulmonary exposure to nanofibers resulted in an augmentation of biomarkers of cell injury and oxidative stress, strong acute inflammation, as well as interstitial fibrosis and increased collagen deposition in mouse lungs. Mice exposed to an equal dose of nanofibers or asbestos induced less collagen deposition as compared to that seen after exposure to SWCNT. Our current results strongly indicate the need for further assessments on the health effects of nanofibers.
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PS 794 CHARACTERIZATION OF MULTI-WALLED CARBON NANOTUBES (MWNTS).

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The production of engineered multi-walled carbon nanotubes (MWNTs) has increased significantly in recent years. MWNTs exhibit unique physical, chemical, optical, and electrical properties that have made them very attractive candidates for use in composite materials, energy conversion, packaging, consumer healthcare and medical applications. However, there are very limited data available on human exposure to MWNT and the potential health effects associated with exposure. Many of the unique physicochemical properties of MWNTs are known to influence biological activity and may play a significant role in their assessment of toxicity.
Six different types of MWNTs were selected for use in the study based on their specified length and diameter. Each MWNT type was obtained from 3-5 sources, which resulted in 24 different samples. Carbon nanotube purity was determined for all samples by TGA. Purity for the samples was 86.1-98.9%, precision for duplicate analyses was ≤0.78%. Metal content was determined by XRF. The analysis targeted a number of metals, (Fe, Co, Ni, Mo, and Y), that have a potential to be present as contaminants because of their use in synthesis and cleaning processes for MWNT. Total metal content in all samples was 0.94-19.8% on weight basis. Fe, Co, Ni, and Mo were found in significant concentration whereas Y was not detected in any of the samples.
The diameter and length were determined for samples using HR-TEM and SEM, respectively. Many of the small diameter nanotubes met their vendor provided specifications whereas majority of the medium and large diameter tubes did not. The length of the 2 shortest nanotubes was within their vendor provided specifications whereas all longer-tubes did not meet their vendor-supplied specifications.

PS 795 MULTI-WALLED CARBON NANOTUBE EXPOSURE INDUCES MAST CELL ACTIVATION AND ALTERS AORTIC VASCULAR REACTIVITY.

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Due to their unique physical and chemical characteristics, the use of nanomaterials has increased dramatically in recent years leading to a growing need for research examining their potential impact on the environment and human health. Multi-walled carbon nanotubes (MWCNT) represent an important nanomaterial with wide ranging applications. Mast cells are well recognized for their role in allergy, asthma and cardiovascular disease. The aim of this study was to examine the activation of mast cells in the pulmonary and cardiovascular systems following exposure to MWCNTs. We examined the ability of MWCNTs to activate bone marrow-derived mast cells (BMMCs) as measured by degranulation and cytokine production. Additionally, we compared the development of pulmonary inflammation and changes in aortic vascular reactivity between C57BL/6 and B6.Cg-*Kit*$^{W\text{-}sh}$ mast cell deficient mice following MWCNT instillation. MWCNT exposure (10-100 μg/ml) did not alter BMMC degranulation in vitro, however, MWCNTs stimulated production of several pro-inflammatory cytokines including osteopontin. C57BL/6 mice instilled with 100 μg MWCNTs developed pulmonary inflammation including increased numbers of macrophages, neutrophils and eosinophils which were associated with increased osteopontin levels. Further, C57BL/6 mice exposed to MWCNTs exhibited impaired aortic vascular relaxation to forskolin and altered constrictor responses to norepinephrine. These changes in vascular reactivity were not present in B6.Cg-*Kit*$^{W\text{-}sh}$. These findings demonstrate that MWCNT can direct mast cell production of pro-inflammatory mediators that may potentially contribute to impaired vascular relaxation and adverse health effects in vivo.
This work supported by NIH RO1ES5016246 and East Carolina University.

PS 796 NEUROTOXICITY AND CELLULAR DISTRIBUTION OF SINGLE-WALLED CARBON NANOTUBES.

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Single-walled carbon nanotubes (SWCNT) exhibit unique chemical and physical properties that are attractive for many potential biomedical applications. The evaluation of neurotoxicity of SWCNT is important for realizing these practical applications. However, no neurotoxicity studies of the functionalized materials have been reported. We investigated and compared the concentration-dependent cytotoxicity of SWCNT and fuctionalized SWCNT with polyethylene glycol (SWCNT-PEG) in PC12 cells using the MTT and LDH assay. SWCNT elicited cytotoxicity in a concentration-dependent manner, and SWCNT-PEG exhibited less potency than SWCNT. Lesser cytotoxicity of SWCNT-PEG suggested that surface properties of carbon nanotubes may contribute to their cytotoxicity. Moreover, reactive oxygen species (ROS) were generated in a concentration-dependent manner after exposure to these nanomaterials, indicating an oxidative stress mechanism. Furthermore, nuclear condensation with Hoechst33342 staining and time-dependent caspase 3 activation after exposure to SWCNT (10 μg/ml) shows evidence of apopotosis. Interestingly, more apoptotic PC12 cells appear and there is a higher activity of caspase 3 after exposure to SWCNT-PEG, suggesting that surface conjugated PEG may help to trigger apoptosis signaling. The uptake of these carbon materials by PC12 cells were demonstrated using Raman Microscopy. However, dopamine levels in the cells were not significantly altered at 24 hours as measured by HPLC/EC. These studies provide a framework for further characterizing the neurtoxic potential of different types of SWCNT and suggest that the nervous system may be targeted by single-walled carbon nanotubes under some conditions.
Support by NCTR E7282 and ORISE.

PS 797 DISPERSION STATUS OF SINGLE WALLED CARBON NANOTUBES IS A KEY DETERMINANT OF THEIR BIOLOGICAL ACTIVITIES.

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Single walled carbon nanotubes (SWCNT) have wide applications, but raise an urgent concern regarding their potential toxicities. A major obstacle to the biological and toxicological evaluation of nanoparticles is their dispersion in biological samples or buffers. SWCNT tend to form large agglomerates in solutions which affect

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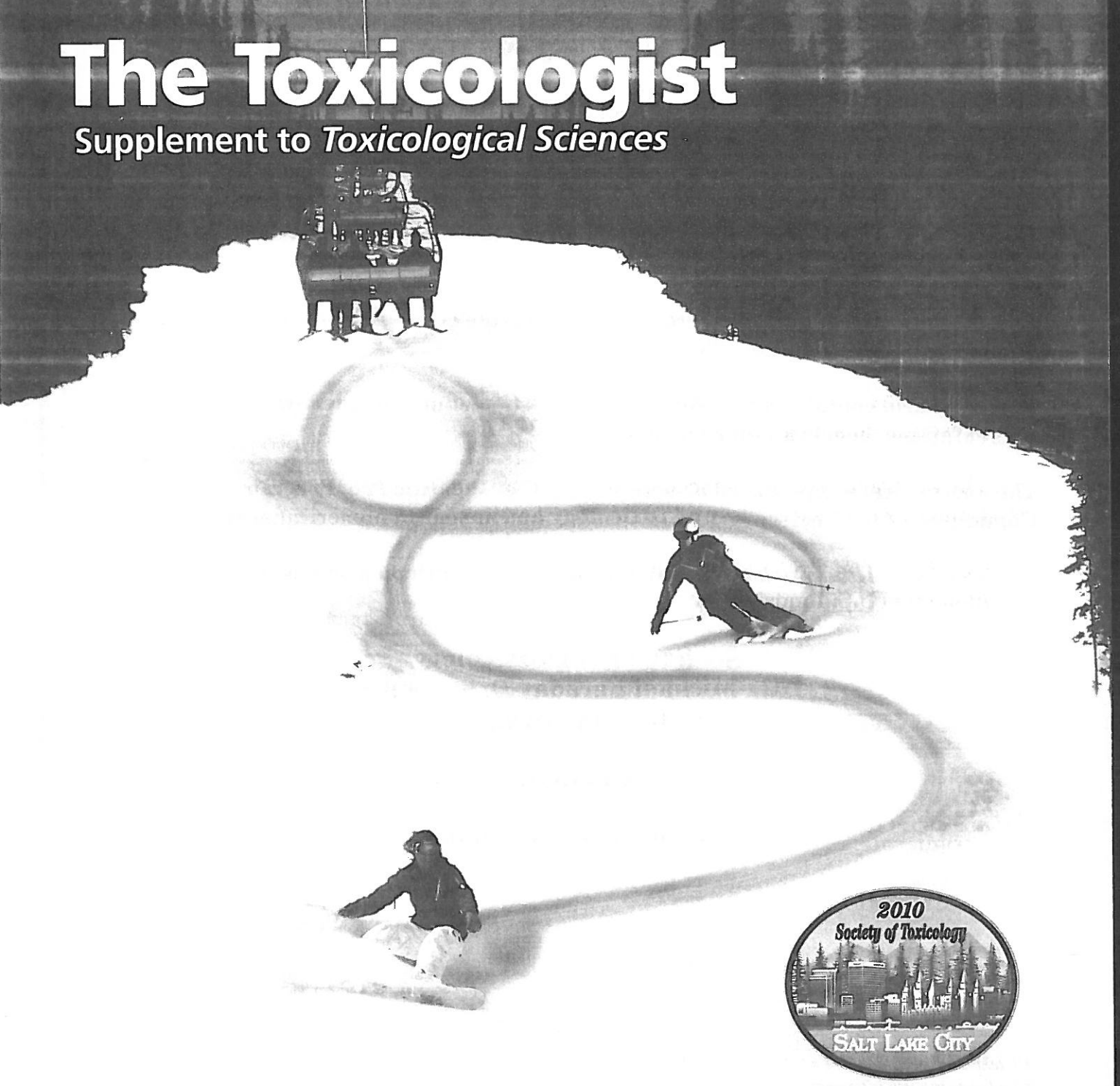

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 49th Annual Meeting of the Society of Toxicology, held at the Salt Palace Convention Center, March 7–11, 2010.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 473.

The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 496.

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