significantly greater in differentiated cells, showing that activation of THP-1 cells increases their response to MWCNT stimulation. Cells co-exposed to IL-4 or IL-13 showed a significant decrease in MWCNT-induced IL-1β levels. Western blotting showed that IL-13, but not MWCNT, activated STAT-6 in THP-1 cells. Conclusions: IL-4 and IL-13 suppress MWCNT-induced expression of IL-1β in macrophages via STAT-6 phosphorylation. Our data suggest that Th2 cytokines up-regulated in asthma inhibit the innate immune response of macrophages to carbon nanotubes. (Funded by NIEHS RC2 ES018772 and R01 ES020897)

PS 439 Zinc Oxide Surface Modification of Multiwalled Carbon Nanotubes Enhances Chemokine and Growth Factor Production in Human Monocytes and Lung Fibroblasts *In Vitro.*

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Carbon nanotubes, a product of emerging nanotechnologies, are gaining increasing attention due to possible health risks from occupational and environmental exposures. Previous studies with rodents have shown that MWCNTs stimulate the production of pro-fibrogenic growth factors such as transforming growth factor-β1 (TGF-β1) & platelet-derived growth factor (PDGF) in vivo. Thin-film coating of MWCNT with metal oxides by a process called atomic layer deposition (ALD) modifies and enhances the functionality of MWCNTs in electronics and engineering. We hypothesize that metal oxide surface coating of MWCNT with zinc oxide (ZnO) alters the production of pro-inflammatory cytokines & chemokines as well as pro-fibrogenic growth factors by human monocytes (THP-1) and human lung fibroblasts (HLF-16Lu). To test our hypothesis MWCNTs were coated with ZnO via ALD. THP-1 and HLF-16Lu were exposed to coated or uncoated MWCNT for 24 hr and then we measured mRNAs levels (via RT-PCR) of the growth factors PDGF and TGF-β1, the pro-inflammatory cytokine IL-1β, and the mononuclear cell chemokine CXCL10. THP-1 cells exposed to ZnO-coated MWCNTs showed a 6-fold increase in IL-1β mRNA expression, and ~2-fold increase in TGF-β1 mRNA and PDGF mRNA levels. In the HLF-16Lu fibroblasts, ZnO-coated MWCNTs increased the mRNA expression of TGF-β1 3-fold and CXCL10 6-fold but proved to be cytotoxic at higher doses. Uncoated MWCNTs had no effect on any of the target mediators in either cell line. Our findings indicate that surface modification of MWCNTs with ZnO enhances the production of pro-fibrogenic proteins by macrophages and fibroblasts in vitro. These findings suggest that MWCNT modified by ALD coating with ZnO could increase the toxicity and pathogenicity of MWCNT in the lung.
(Funded by: NIEHS Grants R01ES020897 & RC2-ES018772)

PS 440 Metabolomic Analysis of Liver Cells Exposed to Carbon Nanotubes and Graphene Oxide.

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Carbon nanotubes (CNTs) and other graphenic nanomaterials are being used extensively in industrial, consumer, and mechanical applications based in part on their unique structural, optical and electronic properties. Due to the widespread use of these nanoparticles (NPs), human and ecological exposure is probable and inevitable. To determine the effects CNTs and graphene oxide (GO) have on biochemical processes, metabolomics-based profiling of human (C3A) and zebrafish (ZFL) liver cells was utilized. Cell cultures were exposed to 0, 10, or 100 ng/mL of covalently or non-covalently modified nanomaterial for 24 and 48 hrs while particle size distribution, charge, and aggregation kinetics were monitored concurrent with exposure studies. Following NP exposure, metabolites were extracted and derivatized prior to GC/MS analysis or lyophilized and buffered for 1H NMR analysis. Acquired spectra and chromatograms were subjected to multivariate analysis to determine the consequence of NP exposure on the metabolite profile of C3A and ZFL cells. The resulting scores plots illustrated temporal and dose dependent responses to all classes of NPs tested. Loadings plots coupled with univariate analysis were then used to identify metabolites of interest. Preliminary data suggest that CNT and GO exposure causes perturbations in processes involved in cellular oxidation as well as fluxes in lipid metabolism and fatty acid synthesis. Dose-response trajectories are apparent for each nanomaterial tested and spectral components related to both dose and NP modifications were determined. Correlations of the significant changes in metabolites will aid in identifying potential biomarkers associated with carbonaceous nanoparticle exposure in both humans and ecologically relevant species.

PS 441 Physical Characterization of Multiwalled Carbon Nanotubes for Inhalation Studies.

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Animal inhalation studies have reported that adverse pulmonary, cardiovascular, and immune reactions may result from exposure to multi-walled carbon nanotubes (MWCNTs). At the present time, however, there is little guidance for adequate sampling and characterization of MWCNT aerosols for evaluating exposures and obtaining an applicable dose metric for risk assessment. This is mainly because MWCNTs tend to agglomerate and form complex structures making them difficult to characterize. To address this problem, we conducted detailed sampling and characterization studies of MWCNTs that had similar particle morphologies to those found in the workplace. Representative samples were collected using filters, a cascade impactor, and direct reading instruments, and they were used for microscopic observation, gravimetric analysis, and real-time monitoring. Particle number distributions on a filter (0.008–0.10 particles/μm^2), and mass distributions using an impactor (0.1–0.3 mg on peak stages) were determined. Microscopic analyses indicated that MWCNTs can be classified into three shape categories: irregular, isometric, and fibrous particle structures. Each particle structure contained a mean of 18 nanotubes, and 1 μg of MWCNTs contained 2.7×10^6 particle structures composed of 4.9×10^7 individual nanotubes. Impactor measurements showed that the mass median aerodynamic diameter of the aerosol was 1.5 μm with a geometric standard deviation of 1.67. The shape factor of individual fibers was 1.94–2.71, and the isometric particles had an effective density of 0.71–0.88 g/cm^3. Results also indicated that real-time particle number counts were realistic, but without an index of agglomeration, they were insufficient for adequate risk assessment. Information from this study can be used to estimate initial lung burden and to design an improved lung deposition model that considers three individual MWCNT particle shapes. The described methods can be used as guidance for sampling and characterizing other engineered nanoparticles.

PS 442 Cellular Responses Induced by Single-Wall Carbon Nanotubes with Varying Physical Properties in Alveolar Epithelial Cells.

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Concern over the influence of carbon nanotubes (CNTs) on human health has risen due to advances in the development of nanotechnology. Some studies have shown that unpurified CNTs induced high levels of cellular responses than those of purified CNTs. They suggest that the residual metals involved in CNTs attribute to induction of oxidative stress. Here, we examine our hypothesis that the physicochemical properties of single-wall carbon nanotubes (SWCNTs) may have important implications for biological responses. We have developed novel dispersion procedure of CNTs with their different physical properties in culture medium. In vitro cytotoxicity assays were performed on human alveolar epithelial cell lines (A549) using impurity-free SWCNTs with varying physical properties and commercial SWCNTs with residual metals as a reference. Cell viability, apoptosis, intracellular reactive oxygen species (ROS) generation, cell cycle distribution, and cellular uptake of SWCNTs were investigated. Impurity-free SWCNTs with their different physical properties (CNT-1, CNT-2) and SWCNTs containing trace amounts of metals (CNT-3) did not cause significant inhibition of cell proliferation, induction of apoptosis and arresting cell cycle progression. On the other hand, all samples significantly increased level of the intracellular ROS production after 24h incubation. These results show that residual metals involved in SWCNTs may not be a definitive parameter for induction of oxidative stress. The relatively short line shape of SWCNTs small bundles were observed in the vacuoles of cells exposed to CNT-1. The relatively long line shape of SWCNTs large bundles were observed in the cytoplasm and vacuoles of cells exposed to CNT-2. A large number of aggregated SWCNTs with punctate structures were observed in the cytoplasm and vacuoles of cells exposed to CNT-3. We suggest that the physical properties of SWCNTs are closely related to the cellular uptake and induction of oxidative stress.

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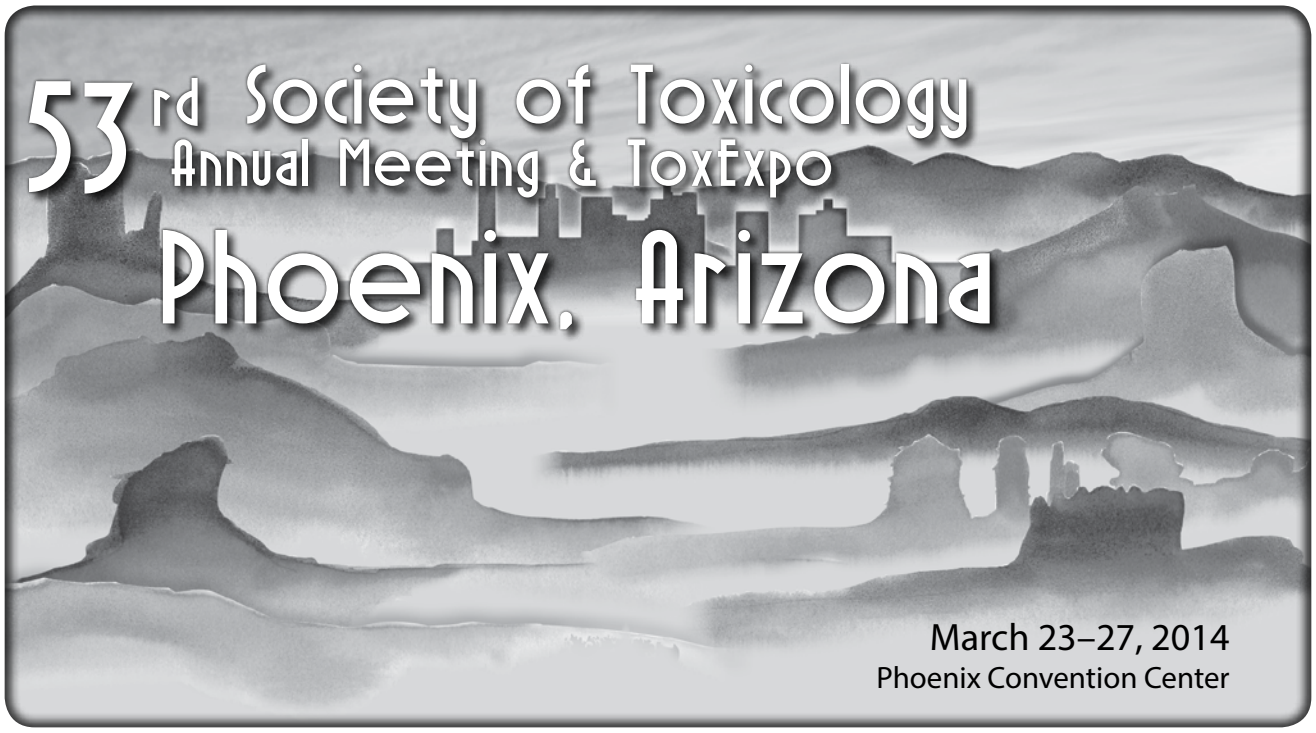

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Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 52nd Annual Meeting of the Society of Toxicology, held at the Henry B. Gonzalez Convention Center, March 10–14, 2013.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 536.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 561.

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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