ventilation. Two independent methods were used to characterize the asthma-like response at the last challenge, the analysis of pulmonary inflammatory by bronchoalveolar lavage (BAL) and physiologic endpoints showing changes in respiration delayed in onset. The most distinct outcomes characterizing the asthmatic response in this bioassay were increased neutrophils in BAL and the delayed respiratory response. These data demonstrated further that the vigor of asthma-like response after challenge is clearly dependent on the inhalation elicitation dose (C x t) of prechallenged rats to attain the asthmatic state. This relationship of the elicitation response served as basis for the dose-response analysis and estimation of the benchmark NOAEL. After adjustments accounting for differences exposure durations, in the rat-to-human pulmonary doses, and the intra-human variability, the resultant threshold Cxt of asthmatic rats and humans converged into the same threshold limit value.

PS 426 Identification of Novel Exposure and Lung Cancer Gene Markers in Carbon Nanotube-Exposed Human Lung Epithelial Cells.

T. A. Stueckle[1], A. Mishra[1], R. Derk[1], T. Meighan[1], V. Castranova[1], Y. Rojanasakul[2] and L. Wang[1]. *[1]NIOSH, Morgantown, WV; [2]West Viriginia University, Morgantown, WV.*

Concern for increased risk of CNT-induced lung cancer has arisen due to asbestos-like high aspect ratio, pulmonary persistence and fibrosis. Our previous study found that chronic in vitro exposure to dispersed single (D-SWCNT) and multi wall CNT (D-MWCNT) resulted in neoplastic transformation in human small airway epithelial cells (SAEC). Genome profiling identified oncogene signaling mechanisms in CNT SAECs that were quite different from asbestos-exposed (ASB) SAEC. Few in vivo studies identified whole lung gene markers associated with MWCNT exposure, but did not compare CNT vs. asbestos genetic response. Here, toxicogenomic profiling with correlation feature selection strategies identified particle-specific, key gene markers from our previous study. D-SWCNT, D-MWCNT, ASB, ultrafine carbon black (UFCB) and control SAEC genome profiles were subjected to comparative marker and class neighbor analyses followed by multistep cross validation to identify genes with highly correlated expression for each treatment. Specific treatment markers and genome profiles were subjected to Ingenuity Pathway and Biomarker Analysis to determine both specific markers performance and identify disease markers. Gene marker subsets and disease markers were validated using rtPCR and protein expression. Here, we present robust SWCNT, MWCNT, ASB and UFCB specific gene marker sets for in vitro chronically exposed SAEC. Matching our original analysis, both D-MWCNT and D-SWCNT markers were associated with lipid metabolism and cancer while ASB and UFCB centered on inflammatory response and senescence, respectively. Biomarker Analysis identified known lung and other cancer markers (MYC, PPARG) in CNT SAECs which differed from inflammation-associated cancer markers (IL-1B) in ASB SAECs. In conclusion, toxicogenomic profiling in a chronic in vitro exposure model identified particle-specific gene markers and known lung cancer markers which can potentially aid in assessing CNT exposure and detection of early disease markers.

PS 427 ROS Evaluation for Series of CNTs Using ESR Method and Its CNT Concentration Effects.

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Carbon nanotubes (CNTs) are becoming important materials in industries. It is a concern that CNTs may induce carcinogenic responses through pulmonary exposure. It has been recently reported that CNTs scavenge ROS, which is utilized for toxicological evaluations. Although the electron charge transfer seems the noticeable phenomena of toxicological chemical reactions, any comprehensive evaluation of ROS scavenging capabilities using a variety of CNTs has not been demonstrated well. The present work specifically investigates ROS scavenging capabilities using the series of CNTs and their derivatives: more than 15 kinds of CNTs. Those ROS scavenging properties were measured by ESR with DMPO. Highly crystallized, mechanically chopped, mechanically de-bulked, and metal doped CNTs were evaluated (Group A). Furthermore, several of commercially available CNTs (Group B) were compared with Group A. Interestingly the ROS scavenging rate was not significantly influenced by mechanical treatments, but depended on crystallization at high temperature. Very thin DWCNTs showed elimination of OH radical almost, implying existence of diameter threshold. The ratio of CNTs to DMPO influenced the scavenging rate of CNTs buy not titanium dioxide, as a higher concentration of CNTs showed the lower scavenging rate, this suggests that DMPO is partly adsorbed on the CNT surface and decreases the activity. The results suggest that the electron transfer on the CNT surface is the fundamental mechanism of ROS scavenging. Dangling bonds are not a key factor for scavenging, though. ROS is affected by CNT/DMPO ratio.

PS 428 The Biological Response to Carbon Nanotubes in the BEAS-2B Cell Line Is Affected by Medium Conditions.

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There are many reports on the use of an SV-40/adenovirus-transformed normal human bronchial epithelial cell line (BEAS-2B) to evaluate nanomaterials, especially multi-walled carbon nanotubes (MWCNT). However, the results have been controversial; one explanation is that while some experimental culture media contained serum, others did not. Here, we clarified the influence of serum on the BEAS-2B response to MWCNT compared with that on normal human bronchial epithelial cells (NHBEC; Cell application) and studied its effect on MWCNT endocytosis. Cytotoxicity and cytokine secretion profiles of MWCNT on BEAS-2B cells or NHBEC were examined in media with or without serum (Ham's F12 containing 10% fetal bovine serum [Ham's F12] and serum free growth medium [SFGM]). Cellular uptake of MWCNT was observed by fluorescence microscopy and analyzed by flow cytometry. We also examined if MWCNT uptake was suppressed by two kinds of endocytosis inhibitors. BEAS-2B cells cultured in Ham's F12 and NHBEC cultured in SFGM exhibited similar biological responses to internalized MWCNT in terms of cell growth inhibition and cytokine secretion. BEAS-2B cells cultured in SFGM did not internalize MWCNT, and the IC_{50} value of this cell line was 10 times higher than that in Ham's F12. MWCNT uptake was suppressed both by clathrin- and caveolae-mediated endocytosis inhibitors for BEAS-2B cells cultured in Ham's F12 and NHBEC in SFGM. We conclude that the BEAS-2B cell line in serum-containing medium exhibits clathrin- and caveolae-mediated endocytosis of MWCNT, and displays the biological responses suitable for safety assessment of nanomaterials as a model of NHBEC.

PS 429 Evaluation of the Effect of Carbon Nanotubes on the Expressions of Endothelial Genes Implicated in Different Pathways of Cellular Death.

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Carbon nanotubes (CNTs) are attractive for various nanomedicine applications including their intravascular use. Therefore, the vascular biocompatibility of CNTs is a critical safety issue. Here we investigate the effect of carboxylated multi-walled CNTs (M60COOH) and their pristine counterparts (M60) on cultured human umbilical vein endothelial cells (HUVECs) by evaluating the changes in the expression of selected genes with known involvement in autophagy, apoptosis or necrosis. We have utilized Death PathwayFinder RT^2 Profiler PCR Array (Qiagen), to monitor expression of 84 selected genes. HUVECs were treated for 24 h with 100μg/ml of M60 or M60COOH. Controls included HUVECs with serum starvation, or treatment with 1μM camptothecin for 24h, or incubation with 1mM H_2O_2 for 2h. The cDNA was constructed from isolated RNA and the level of gene expression was analyzed by real time PCR using the PCR Array Data Analysis software (Qiagen).

Out of 84 monitored genes just 40 genes changed the expression significantly ($P<0.05$) often only after one or two treatments. The Bonferroni correction reduced the number of significantly changed genes to 14. Expression profiles after treatment with M60 and M60COOH differed ($P<0.05$). Both nanomaterials upregulated different proapoptotic genes. In contrast to M60, only M60COOH upregulated autophagy related genes for NFKB1, SQSTM1, and INS. Comparably, these gene array results complement our previous finding of a significant acumulation of the autophagosome protein marker LC3B in M60COOH but not in M60 treated HUVECs.

Our study suggests that the screening of mRNA levels of cell death pathway genes may be a valuable complementary tool in the testing of cellular toxicity of nanomaterials. However, further gene selection, standardization and validation of assays are required.

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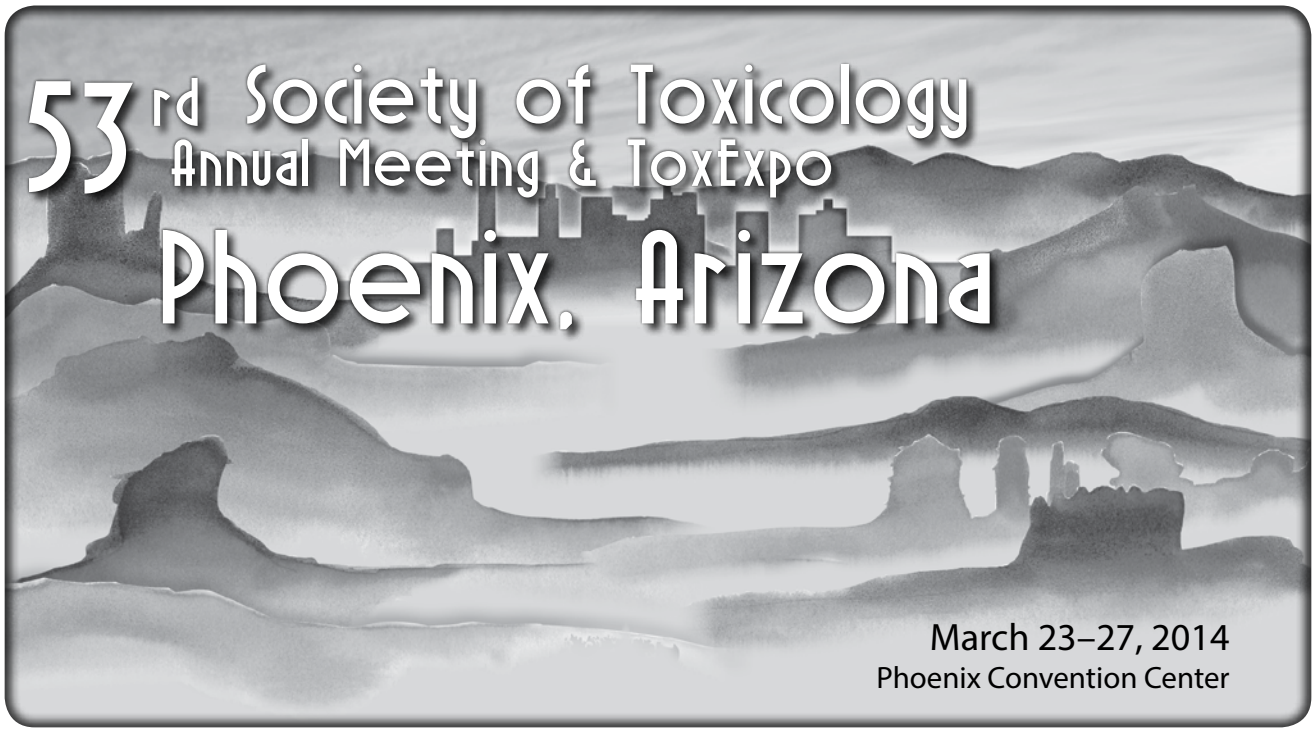

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Preface

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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