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Usual and Unusual Features of Pulmonary Responses to Carbon Nanotubes. V. E. Kagan, A. A. Shevednova. University of Pittsburgh and National Institute for Occupational Safety and Health, Pittsburgh, PA, USA.

Single walled carbon nanotubes (SWCNT) are new materials of emerging technological importance. As SWCNT are introduced into the life cycle of commercial products, their effects on human health and environment should be addressed. Pharyngeal aspiration of SWCNT elicited unusual pulmonary effects in C57BL/6 mice that combined a robust but acute inflammation with early onset yet progressive fibrosis and granulomas. A dose-dependent increase in the protein, lactate dehydrogenase (LDH), and g-glutamyl transferase (GGT) activities in BAL were found along with accumulation of 4-hydroxynonenal (oxidative biomarker), and depletion of glutathione in lungs. An early neutrophils accumulation, followed by macrophage influx were accompanied by early elevation of pro-inflammatory cytokines. Early release of fibrogenic TGF-b1 was associated with a rapid progressive fibrosis found in mice exhibited two distinct morphologies: (1) SWCNT-induced granulomas mainly associated with hypertrophied epithelial cells surrounding SWCNT aggregates and (2) diffuse interstitial fibrosis and alveolar wall thickening likely associated with dispersed SWCNT. In vitro exposure of murine RAW264.7 macrophages to SWCNT triggered TGF-b1 production similarly to zymosan but generated less TNF-a and IL-1b. SWCNT did not cause superoxide or NO€ production, active SWCNT engulfment, or apoptosis in RAW264.7 macrophages. Equal doses of ultrafine carbon black particles or fine crystalline silica did not induce granulomas, alveolar walls thickening, and caused a significantly weaker pulmonary inflammation and damage. Based on our results, mechanism-based interventions may be developed to decrease toxicity of SWCNT.

Disclosures: ***V.E. Kagan****, None.*

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Nanoparticles - Toxicological Approaches . P. Simeonova, A. Shvedova, M. I. luster, Z. Li. National Institute for Occupational Safety and Health, Morgantown, WV, USA.

Nanotechnologies will revolutionise our life including medicine, but they also pose important toxicological questions that are related to the unique nature of materials and processes at the nanometer scale. Human contact with nanomaterials can be related to targeted exposure through therapeutics and cosmetiscs or untargeted exposure through occupational and environmental contamination. The accumulation of toxicological data on engineered nanomaterials will allow for development of adequate risk assessment and regulations. One direction of the nanomaterial industries is production of new carbon nanomaterials. Graphite sheets are rolled-up, usually in the presence of metal catalyst, to form long single wall carbon nanotubes which are about 1 nm in diameter. Since the discovery of their one-dimensional electronic band structure, the carbon nanotubes (CNT) have emerged as leading candidates for nanodevice applications. Recently, it has been demonstrated that respiratory exposure to CNT, in contrast to the exposure to ultrafine carbon black, is associated with increased oxidative stress, inflammation, and fibrosis in the lung. The unique physical characteristics of CNT raise concerns that they may have not only more pulmonary toxicity but might be associated with systemic effects. We hypothesized that CNT respiratory exposure is related to oxidative and inflammatory responses in the vascular system, which might be a prerequisite of atherogenesis. C57BL/6 mice were exposed to CNT in doses (0.5; 1; 2 mg/kg) by single intra-pharyngeal installation and the mice were sacrificed at different time points (1; 7; 28; 56; and 180 days) after the exposure (the experimental settings have been related to pulmonary toxicity including development of granulomas). By extra long quantitative PCR of mitochondrial (mt) DNA, we found that CNT exposure induced a dose-dependent aortic mtDNA damage, an oxidative stress dependable parameter, at day 7, 28, 56, and 180 days after exposure. These responses were accompanied by increase production of reactive oxygen species in the aortic tissue, measured by an electron spin resonance assay. Similar oxidative modifications were observed in the aortic tissue of ApoE-/- mice, a model of human atherosclerosis. Consistent with these results, we demonstrated that the acute pharyngeal aspiration of CNT exposure induces activation of the oxidative sensitive gene, heme-oxygenase (HO-1) in the lung, heart, and aorta in transgenic mice which carries a mouse HO-1-luc construct. Overall, these initial studies demonstrated that the respiratory exposure to CNT provokes dose-dependent severe lung toxicity and vascular effects related to oxidative stress. The role of these effects in atheroma formation or acceleration will be evaluated in the next sets of experiments.
Disclaimer
The findings and conclusions in this abstract are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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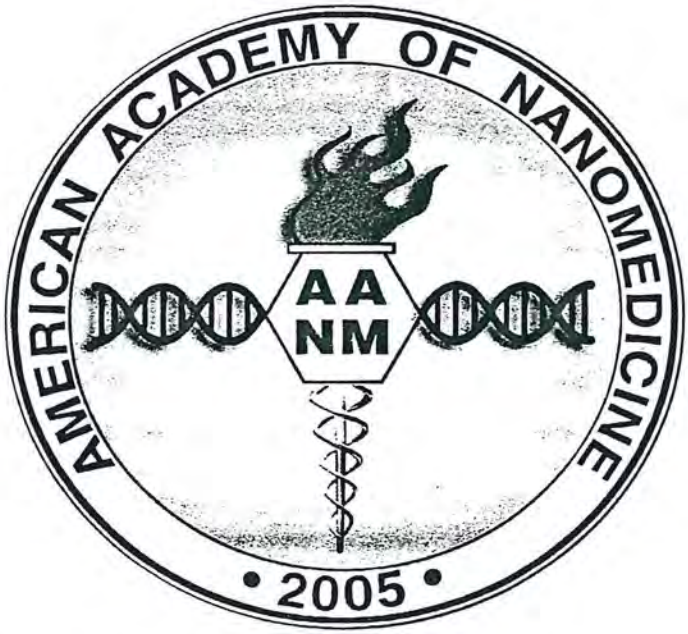

PROGRAM AND ABSTRACTS

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