SPIO is not strongly pro-inflammatory. The bioavailability of aspirated SPIO (by ICP-MS) was <0.1% and was cleared from the lung with a half-time of 7-8 days indicating that the lung retained a significant amount of SPIO at the time of bacterial instillation (24 hr post-dosing). Finally, mice were administered 0, 5, 30, or 100 μg SPIO by OPA 24 hr prior to intra-nasal instillation of 50k colony forming units (CFU) of S. pneumoniae. The SPIO doses were selected to represent the mouse equivalents of human occupational exposure for 1, 5, and 20 d at the Permissible Exposure Limit. The low pyrogenic/inflammatory potential of these exposures was confirmed by the absence of changes in surface body temperature. However, mice pretreated with 30 or 100 μg SPIO exhibited a 3.6- and 7.0-fold increase, respectively, in CFU recovered from the lung, indicating mice exposed to SPIO had reduced lung clearance of S. pneumoniae. These studies suggest that the direct toxicity of SPIO may be less important than those effects elicited by SPIO interaction with other stressors. Supported by NIEHS NCNHIR Consortium ES019544

PS 1981 A Comparative *In Vivo* Screening of Nine Classes of Multiwalled Carbon Nanotubes for Acute Lung Toxicity in Mice

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Multi-walled carbon nanotubes (MWCNTs) present potential health risks during their manufacture and handling in the electronics and medical industries. To improve understanding of MWCNT behavior following inhalation, we are investigating how aggregative characteristics, aspect ratio, surface carboxylation, and purity from trace metals affect MWCNT pulmonary toxicity in vivo. To characterize aggregative behavior, we used dynamic light scattering to assess the hydrodynamic radii and zeta potentials of nine classes of MWCNTs in dispersion medium (DM). In order to assess pulmonary toxicity, we exposed eight-week-old male A/J mice via oropharyngeal aspiration to DM vehicle or a single MWCNT class at 40 μg/mouse, and sacrificed the mice after 24 hours. Treatment with unpurified and carboxylated MWCNTs was associated with lung inflammation as indicated by flow cytometric and cytospin analyses of neutrophil influx into bronchoalveolar lavage fluid (BALF). Across all MWCNT classes, we found no evidence of alveolar/capillary barrier dysfunction or frank cellular damage as indicated by BALF supernatant total protein or lactate dehydrogenase activity. Similarly, no evidence of severe oxidative stress was detected in lung tissue as indicated by total glutathione levels. Our results indicate that high-dose exposure to unpurified and carboxylated MWCNTs causes acute lung inflammation but not frank cellular toxicity in the short term. This work was supported by NIH Grants U19ES019545 and P30ES007033, and NSF grants CBET-0932885 and DGE-0718124.

PS 1982 Inhalation of Nanosized Titanium Dioxide Alters Cardiovascular Autonomic Function

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Nanotechnology is a rapidly growing field with the potential to influence all aspects of modern life. However, the cardiovascular toxicity of nanomaterials is not well understood. We have previously demonstrated a disruption in normal microvascular function following nanomaterial exposure via alterations in autonomic control. Presently, using a telemetry and a baroreflex function model, we show changes in autonomic control following inhalation exposure to nanosized titanium dioxide (nano-TiO_2) for 4 hours for 2 days at 6 mg/m^3. Telemeterized rats were acclimatized and exposed to sham (day 0), then nano-TiO_2 or sham on 2 consecutive days (days 1, and 2). Renal sympathetic nerve activity (rSNA), mean arterial pressure (MAP) and heart rate (HR) were continuously monitored. 24 h after the last exposure, baroreflex sensitivity was measured with phenylephrine (PE; 1-8 μg/kg) or sodium nitroprusside (SNP; 5-20 μg/kg). MAP increased during nano-TiO_2 relative to day 0 and sham (max ΔMAP sham -8.1±4.3 mm Hg, nano-TiO_2 3.0±2.1 mm Hg). The nano-TiO_2-induced MAP increases were largely driven by diastolic blood pressure (DBP) increases (day 1: sham DBP 98±3.5 mm Hg, nano-TiO_2 110±2.3 mm Hg), suggesting an enhanced peripheral resistance. Overnight, rSNA and HR were significantly elevated following exposure, suggesting an augmentation in the normal sympathetic nerve diurnal pattern (max; ΔHR sham 3±5 BPM, nano-TiO_2 14±1 BPM: ΔSNA sham -2.2±0.9 μV, nano-TiO_2 0.84±0.6). PE infusion enhanced and prolonged the depression in HR following nano-TiO_2 exposure compared to sham (max ΔHR - sham 13±1 BPM, nano-TiO_2 -15±1), suggesting increased parasympathetic signaling, which could be mitigated with hexamethonium or atropine. Nano-TiO_2 exposure significantly enhanced MAP depression by SNP (max ΔMAP -34±1.5 mm Hg sham, -41±1.3 mm Hg nano-TiO_2), though the mechanism unclear. Considered together, engineered nanomaterial exposure may alter cardiovascular function through autonomic signaling that is not obvious under resting conditions. (Funding NIH ES015022, TRN)

PS 1983 Endothelial Cells As Biosensors to Assess the Vascular Inflammatory Potential of Serum following Nanomaterial Exposure

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Assessing mechanisms underlying the adverse vascular health effects of systemic inflammation induced by inhaled toxins presents a substantial research challenge. We have developed an ex vivo model that allows for a realistic exposure method to better elucidate the mechanisms involved in a living system. This approach applies serum from exposed animals to cultured primary endothelial cells, as this is the component in direct contact with the vascular endothelium. Here, we apply this assay paradigm to assess the impact of pulmonary exposures to multi-walled carbon nanotubes (MWCNT) or graphene. Mice were exposed to varying doses (4, 10 or 40 μg) of MWCNT, various types of graphene, or carbon black via pharyngeal aspiration, and serum was collected at 4 and 24 h post-exposure. Serum collected from 19 d inhalation exposures to 0.5 or 5.0 mg/m3 MWCNT was also assayed for endothelial activation. Serum from exposed mice induced an up-regulation of endothelial cell surface VCAM and ICAM expression, along with elevations in mRNA at the 4 h time point. Multiple sizes of graphene were tested; the smallest sizes (<2 μm x <2 μm x 1-2 nm and 5 μm x 5 μm x 7 nm) induced up-regulation of surface VCAM, but were overall less potent than carbon black, used as a control particle. Furthermore, we assessed nitric oxide (NO) generation by endothelial cells using electron paramagnetic resonance (EPR) methods, and found that NO was decreased via treatment with serum from MWCNT-exposed mice following stimulation with 2 mM ATP. Microarray analysis of endothelial cell response to serum from the inhalation and instillation exposures revealed a common set of response elements. In conclusion, pulmonary exposure to carbon-based nanomaterials alters circulating factors which promote endothelial cell activation and decreased NO bioavailability.

PS 1984 Surface Amination Enhances the Toxicity of Silica-Coated Silver Nanoparticles

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Surface charge can greatly influence the toxicity and bioavailability of engineered nanoparticles (NPs). Positively charged NPs generally elicit greater toxicity than comparable negative or neutrally charged particles. The effect of amination on NP toxicity was investigated in embryonic zebrafish, a model vertebrate. Embryos were exposed to 0.5-100ppm suspensions of 80nm silica (Si) or 70nm silver with 20nm Si-coating (AgSi), or aminated NPs of like size and composition. Surface amination significantly increased the toxicity of the NPs. Si NPs did not induce mortality or morbidity at the tested concentrations, whereas aminated Si induced 58% mortality at 100ppm. Both AgSi NPs were significantly more toxic to embryos than Si NPs. AgSi NPs significantly delayed development at 24 hours post fertilization in 25 (50%), 50 (64%) and 100 (75%) ppm treatments, and caused significant mortality beginning at 10ppm. In comparison, aminated AgSi NPs delayed development significantly as low as 1 ppm and induced significant mortality at 5ppm, with 100% mortality above 50ppm. Both AgSi NPs induced significant sublethal effects, including craniofacial and fin malformations, edemas, and body curvatures. When similar silica coated Ag NPs with varied surface amination levels (0.5x, 1x, and 2x) were tested at the same concentrations, the AgSi-1x was significantly more toxic than the 0.5 or 2x AgSi NPs, inducing mortality at 100 (95%) ppm. In contrast, AgSi-2x only induced 38% mortality at 100 ppm, and AgSi-0.5x NPs did not cause toxicity at any concentration tested. Increased amination was observed to alter the stability of the aminated NP dispersions in the exposure media, with the 2x NPs being the least stable in suspension. Our results suggest that increasing surface amination only leads to increased toxicity when bioavailability is held constant, highlighting the importance of understanding NP stability and bioavailability during exposure.

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