Höchberg, Germany). The particle size-number distribution of ultrafine particles (PM0.1) were assessed NanoSight LM10 HS system (Nanosight Ltd., Salisbury, UK) using the Nanoparticle Tracking Analysis (NTA). The biomarkers measured for each aspect of toxic endpoints include: 1. Inflammation and oxidative damage markers, such as Clara cell protein (CC16), nitric oxide (FeNO), and 8-hydroxydeoxyguanosine (8-OHdG). 2. Cardiovascular biomarkers, such as fibrinogen, vascular cell adhesion molecule (VCAM), intercellular adhesion molecule-1 (ICAM-1), high-sensitivity C-reactive protein (hsCRP), and heart rate variability (HRV). 3. Lung function test. We found plasma GPx (glutathione peroxidase) level was significantly higher in high particles concentration workers (log conoentration≧8.1) than low particles concentration workers (log conoentration<8.1). 8-isoPGF2alpha in EBC was not correlated with concentration (x10^8 #particles/mL), % of UFP and particles number of UFP. Particles concentration (x10^8 #particles/mL) was also not associated with 8-OHdG in urine, plasma and WBC as well as SOD in plasma. The possible reason for no association between effect biomarkers and particle concentration in EBC may be due to storage of EBC in -80°C refrigerator for a period of time which may misclassify the exposure concentration. Further study is required.

2730 Surface Area- and Mass-Based Comparison of Lung Toxicity and Allergic Exacerbation in an Ovalbumin Asthma Model following Pulmonary Exposure to Fine and Ultrafine Nickel Oxide

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The correlation of specific nanomaterial physico-chemical properties with toxicological responses is an area of growing interest with implications for the selection of appropriate dose metrics in nanotoxicity studies. In this study, the role of nickel oxide mass and surface area in the induction of pulmonary inflammation and exacerbation of respiratory allergy was explored. To address this concept, 181 nm fine (NiO) and 42 nm ultrafine (NiONP) particles were characterized and incorporated into an *in vivo* time course study and ovalbumin (OVA) asthma model. Particle toxicity was compared at equal masses of 40 micrograms and at equal surface areas of 1.92 mm^2. For the time course study, female BALB/c mice were exposed once to particles or vehicle control by oropharygenal aspiration and euthanized 1, 10, 19, or 29 d post-exposure, which represent critical time points in the OVA model. For the OVA model, mice were aspirated with particles on d 0, sensitized to OVA via IP injection on d 1 and 10, challenged with OVA by aspiration on d 19 and 28, and euthanized on d 29. In the time course study, exposure to mass-normalized doses of particles resulted in significantly elevated lactate dehydrogenase levels, lung neutrophil number, and mediastinal lymph node size in mice exposed to NiONP, which persisted to 29 d post-exposure. However, normalization of doses for surface area mitigated all differences between particles, suggesting that NiO surface area drives pulmonary inflammation. In the OVA model, exposure to equal masses of NiO and NiONP induced differential mechanisms of immune augmentation. Exposure to NiO caused increased penh over allergy controls and higher levels of Th2 cytokines in the lavage fluid. Exposure to NiONP resulted in significantly increased lymph node size over all other groups and elevated levels of both Th1 and Th2 cytokines over control animals, but reduced serum OVA IgE levels. Interestingly, normalization of doses for surface area in the OVA model mitigated differences in serum IgE and Th2 cytokine levels, but not eosinophil influx to the lung and Th1 cytokines. Overall, findings suggest that although surface area of NiO dictates pulmonary injury and inflammation, it may not be the only physico-chemical property responsible for modulation of immune responses in the lung.

2731 Comparative Mouse Pulmonary Toxicity of Nickel Nanoparticles with Different Surface Modification

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With the development of nanotechnology, a large amount of nanoparticles are being produced or will be produced. Due to their specific physical and chemical properties, nanoparticles have been increasingly used in the fields of engineering, information technology and biomedicine. Nickel nanoparticles, because of their low melting point, high magnetism, high surface area, and high reactivity, have found applications in various areas including industry, environment, and biomedicine. Thus occupational and non-occupational exposure to nickel nanoparticles are increasing. It is necessary and urgent to study the adverse effects of nickel nanoparticles on individuals as well as to find ways to alleviate their toxicity. In this study, we examined and compared the short-term and long-term effects of three kinds of nickel nanoparticles with different surface modification on mouse lungs. Mice were intratracheally instilled with nickel nanoparticles without surface modification (Nano-Ni), nickel nanoparticles partially passivated with oxygen (Nano-Ni-P), or nickel nanoparticles coated with a thin layer of carbon (Nano-Ni-C). Control mice were instilled with normal saline. Our results showed that Nano-Ni exposure caused severe acute lung inflammation at day 3 after exposure, which was reflected by increased number of neutrophils and increased levels of CXCL1/KC, LDH and protein in the BALF. The lung inflammation induced by Nano-Ni was confirmed by histological examination, which showed infiltration of a large amount of polymorphonuclear (PMN) cells and macrophages in the alveolar space, alveolar septa, perivascular area, and peribronchial and peribronchiolar areas. Nano-Ni also caused increased MMP-2/9 protein levels and activity in the BALF. By six weeks after exposure, Nano-Ni-exposed mice developed chronic lung inflammation as evidenced by infiltration of neutrophils and enlarged foamy macrophages and extensive pulmonary fibrosis. Nano-Ni-P exposure caused similar acute and chronic lung inflammation to Nano-Ni, but at a much lesser degree. Nano-Ni-P caused a moderate acute neutrophilic inflammation, but mostly resolved by six weeks. Nano-Ni-C only caused mild acute and chronic inflammation. Our results suggest that Nano-Ni exposure can cause severe acute and chronic lung inflammation and injury while surface modification such as carbon coating can alleviate Nano-Ni-induced lung injury.

2732 Lung Deposition and Retention of Multi-Walled Carbon Nanotubes after 28-Day Inhalation and 28-Day Post Exposure in SD Rats

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The newly revised OECD inhalation toxicity testing guidelines 412 and 413 require measurement of lung deposition and retention of poorly soluble nanomaterials in order to evaluate their clearance and biopersistence. With this aim, male SD rats were exposed to MWCNT at 0, 0.257, 1.439 and 4.253 mg/m^3 for 28 days (6h/day, 5day/week, 4week). After 28 days of exposure, the rats were sacrificed at post-1, 7, and 28 days and bronchoalveolar lavage (BAL) fluids were obtained to evaluate changes in inflammatory cells and markers. Blood biochemistry, hematology and histopathology examinations of the lungs were also conducted. The lung deposition and retention of MWCNT were evaluated by elemental carbon (EC) content in the lungs after digestion. Polymorphonuclear cells (PMN) and LDH in the BAL fluids increased in a significant concentration-dependent manner after 28 days of MWCNT exposure and at 7 and 28 days post exposure compared with the controls. Lung deposition and retention of MWCNT in the lungs showed concentration and time dependency after 28 days of MWCNT exposure and post-exposure 7 and 28 days. Based on these endpoints examined a NOAEL was identified at 0.257 mg/m^3 for 28 day subacute inhalation of MWCNT. (1159).

2733 Role of Toll-Like Receptor 5 in Multi-Walled Carbon Nanotube-Induced Lung Injury

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Innate immune responses play a significant role in mediating environmental lung injury. Toll-like receptors (TLRs) recognize exogenous (pathogen-associated) or endogenous (danger-associated) molecular patterns and shape innate immune responses. Bacterial Flagellin is the only known ligand for TLR5. However, we have recently demonstrated a significant contribution of TLR5 in sterile lung injury induced by either ozone or short fragment hyaluronan, suggesting that TLR5 may be involved in lung injury responses. The contribution of TLR5 in nanomaterial induced lung injury is completely unknown. We aimed at investigating the role of TLR5 in multi-walled carbon nanotube (MWCNTs) induced lung injury. We exposed wild type and TLR5 KO mice to well characterized tangled or rod-like MWCNTs (single oropharyngeal aspiration of 2 mg/kg) and studied lung injury at days 1 and day 21 post exposure. Lung lavage analyses and histology were employed to assessed lung injury and inflammation. Measurement of total lung collagen and morphometry was used to evaluate pulmonary fibrosis. Both forms of MWCNT induced significant lactate dehydrogenase and cytokine release in bronchoalveolar lavage fluid at day 1 and day 21. Lavage fluid from TLR5 KO mice had higher amounts of total proteins and LDH at day 21 post exposure. Inflammatory and fibrotic mediators such as (osteopontin, platelet derived growth factor-aa and transforming growth factor-beta were elevated at days 1 and 21 after both forms of nanotube

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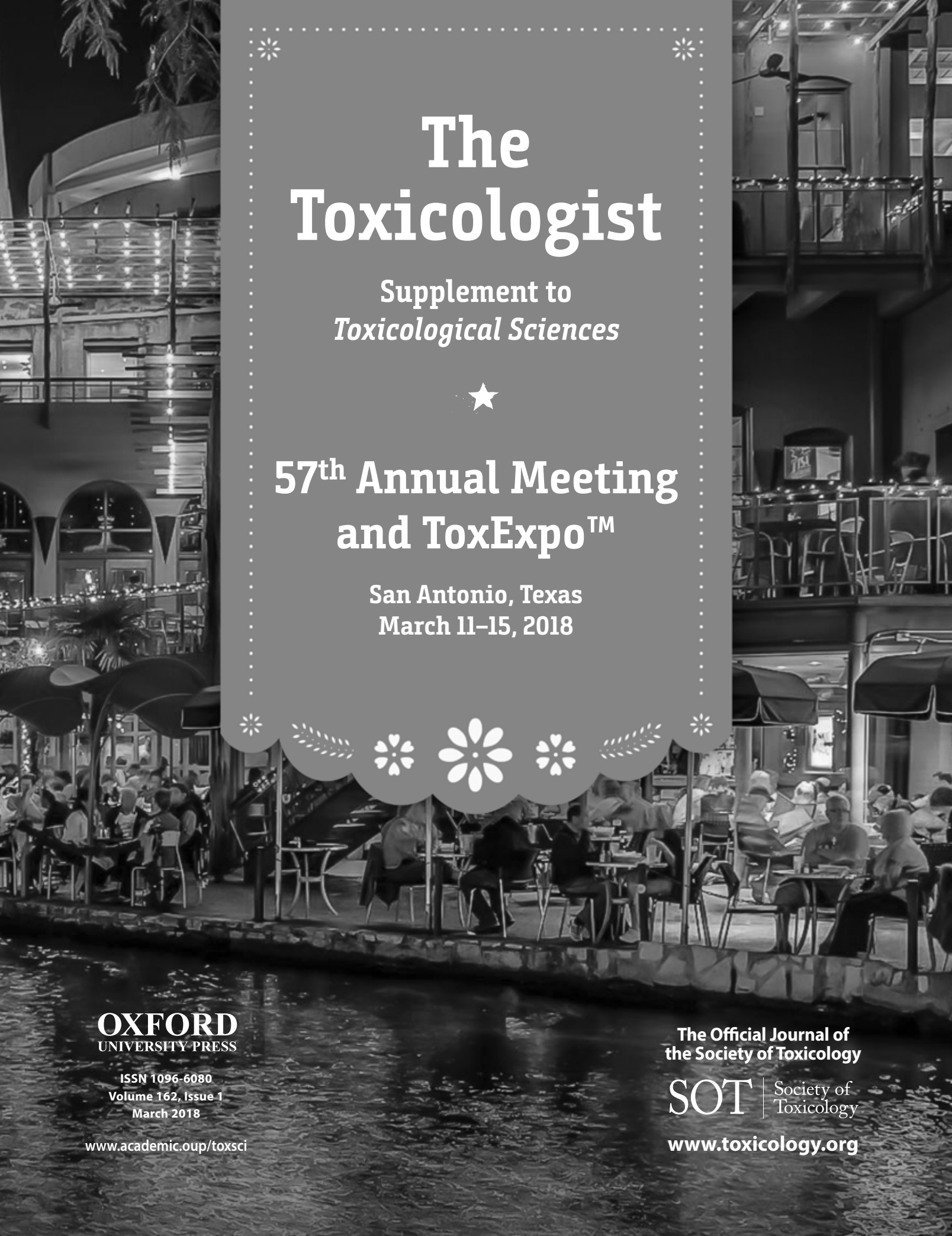

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