In recent work we have classified several NM on their ability to generate Reactive Oxygen Species (ROS) in a macrophage cell line using air pollutant particles as a positive control. Interestingly, TiO2, Carbon Black and Fullerol were void of toxicity while the NH2 modified polystyrene NP tested positive in cytotoxicity as compared to the COOH or unmodified versions. The mechanism for this toxic outcome has been correlated to its small size and positive charge. Furthermore, this nano/bio interaction is cell specific when tested in 5 different cell lines and can be related to its mechanisms of cellular uptake. Taken together these data have helped establish a method of toxic detection utilizing the Hierarchical Oxidative Stress model for future NM. I will further use this system to categorize a set of Fullerene derivatives which is a good candidate due to their high volume of production and conflicting literature data about the potential toxicity. As nanotechnology develops, it is essential that the toxicological approach also evolves and stays up to date. This will provide an important safeguard for the continued expansion of the nanotechnology industry.

438 NANOMATERIALS TOXICITY: CLASSIFICATION USING MULTI-CRITERIA DECISION ANALYSIS.

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Potential toxicity of nanomaterials and resulting risks at different stages of product life cycle (e.g., development, production, use and disposal) are widely unknown and may depend on last minute changes in engineering design and functionalization. To guide nanomaterial research and applications, as well as its safe use, we developed a decision support system for classifying nanomaterials into different risk categories. The classification system is based on a comprehensive set of performance metrics that measure both the toxicity of nanomaterials and the expected environmental and human health impacts through product life cycle. The stochastic multicriteria acceptability analysis (SMAA-TRI) sorting method, a formal decision analysis tool, was used as the foundation for this classification system. It allows incorporating expert estimates with experimental and modeling data on nanomaterial physico-chemical characteristics, associated uncertainties and life-cycle impacts. SMAA-TRI expedites analysis of uncertainty by using Monte Carlo simulation to explore the spaces of feasible values for expert-assigned criteria weights, experimental measurements and modeling results. The results provide decision makers with a probabilistic characterization of nanomaterial properties for risk management purposes. The application of this classification system is illustrated for several nanomaterial classes, including titanium dioxide (TiO2), nC60 (a fullerene), single-walled carbon nanotube (SWNT), single-walled carbon nanotube-by product (SWNT-BP), and Quantum Dot (CdSe Core).

439 ANALYSIS OF SIZE-DEPENDENT CELLULAR RESPONSES TO SILICA NANOPARTICLES FROM INTEGRATED GENOMIC AND PROTEOMIC DATA.

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Identifying the biological pathways activated by nanomaterials using unbiased and comprehensive approaches has become a subject of increasing importance for the safe advancement of nanotechnology. A fundamental question is whether the biological responses to an engineered material changes significantly as the material approaches the nano-scale. To address this we are using integrated global genomic and proteomic analyses to define and compare the signaling networks induced in RAW 264.7 macrophages by different diameters of amorphous silica. We find that the ability of unopsonized silica particles to induce overt cell death in macrophages over 24 hr follows a predictable relationship with the total administered particle surface area across a wide range of particle diameters (7-300 nm). Quantitative analysis by protein microarray ELISA show a similar relationship with total administered surface area for several secreted proteins, including TNF, VEGF and G-CSF in response to particles ranging from 10-300 nm. Dose-response studies comparing transcriptional profiles after acute (2 hr) exposure to 10 nm or 500 nm silica were also conducted using whole genome microarray. Pearson correlation analysis indicates that overall there is a high degree of similarity in the genes altered by both particle sizes when compared using similar surface area dose metrics. Pathway enrichment analysis using the integrated data also demonstrated a high degree of similarity in the major cell processes activated by small (10nm) and large (500 nm) particles. However, for a significant fraction of the genes that are induced by both sizes of particles, dose-response patterns based on particle mass dose were identified which do not follow a clear relationship with total particle surface area. These results suggest that for different subsets of biological responses, there are size-dependent modes of action which may reflect differential mechanisms of particle uptake or localization of action.

440 ENHANCED CYTO- AND GENOTOXIC EFFECTS OF FE(III) NANOPARTICLES COMPARED TO FE(III) FINE PARTICLES IN HUMAN LUNG CELLS.

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In a comparative study the toxicity of nano- (<100 nm) and fine (<5 μm) hematite, arsenopyrite (<5 μm), TiO2 (<50 nm), and quartz (<5μm) particles were investigated. The physico-chemical analysis of the particles revealed a high content of Fe2O3 in hematite and arsenopyrite samples. DQ12 and TiO2 did not contain any iron. The arsenic content in the arsenopyrite sample was 16 ng/mg as measured by HPLC-ICP-MS. Uptake studies by transmission electron microscopy in human lung cells (BEAS-2B) showed that all particles were located close to the nuclear membrane and to mitochondria. No particles were found within the nucleus or mitochondria. Cyto- and genotoxicity studies in primary human lung fibroblasts (IMR-90) revealed that the hematite nanoparticles were most cyto- and genotoxic as assessed by trypan blue and comet assay. Arsenopyrite was negative in both of these test systems up to a tested concentration of 50 μg/cm2. Measurement of acellular radical generation by electron spin resonance indicated that fine hematite particles generated the highest amount of hydroxyl radicals in the presence of H2O2 compared to the hematite nanoparticles and TiO2. Treatment with the reducing agent ascorbic acid or cell lysates resulted in a high radical generation from the nanoparticles as compared to the fine particles. Intracellular formation of reactive oxygen species was measured by H2DCFDA staining and was found to be highest for fine hematite and lowest for hematite nanoparticles, arsenopyrite and TiO2. We conclude from our study that hematite nanoparticles may elicit DNA damage via a mechanism that involves a reduction and mobilisation of Fe(III) in the cytoplasm after cellular uptake. A direct interaction of Fe(II)/Fe(III) ions with DNA might also be a possible mechanism for induction of particle-induced genomic damage.

441 SINGLE-WALLED CARBON NANOTUBES: GENO- AND CYTO-TOXIC EFFECTS IN LUNG FIBROBLAST V79 CELLS.

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With the development of nanotechnology, there is a tremendous growth of the application of nanomaterials, which increases the risk of human exposure to these nanomaterials through inhalation, ingestion and dermal penetration. Among different types of nanoparticles, single walled carbon nanotubes (SWCNT) with extremely small size (1 nm in diameter) exhibit extraordinary properties and offer possibilities to create materials with astounding features. Since the release of nanoparticles in an enclosed environment is of great concern, a study of possible genotoxic effects is important. Our previous data showed that pharyngeal aspiration of SWCNT elicited pulmonary effects in C57BL/6 mice that were characterized by a robust, acute inflammatory reaction with an early onset and resulting in progressive interstitial fibrogenic response, and the formation of granulomas. In the present study, the genotoxic potential of SWCNT was evaluated *in vitro*. The genotoxic effects of nanoparticles were examined using three different test systems: the comet assay and micronucleus (MN) test in a lung fibroblast (V79) cell line, and the *Salmonella* gene mutation assay in strains YG1024/YG1029. Cytotoxicity tests showed loss of viability in a concentration- and time-dependent manner after exposure of cells to SWCNT. Results from the comet assay demonstrated the induction of DNA damage after only 3 hr incubation with 96 $\mu g/cm^2$ of SWCNT. The MN test indicated some but not significant micronucleus induction by SWCNT in the V79 cell line at the highest concentrations tested. With two different strains of *Salmonella typhimurium*, no mutations were found following SWCNT exposure.

442 A 28-DAYS REPEATED DOSE AND GENOTOXICTY STUDY OF SILVER NANOPARTICLES.

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Silver nanoparticle is one of the most controversial research areas regarding toxicity relative to biological systems. To evaluate the toxicity of silver nanoparticles, the rats (4 group, 20/group, male and female) were orally administrated once a day, for 28days at dosage level of 0, 30, 300 and 1,000 mg/kg/day. Mortality, clinical obser-

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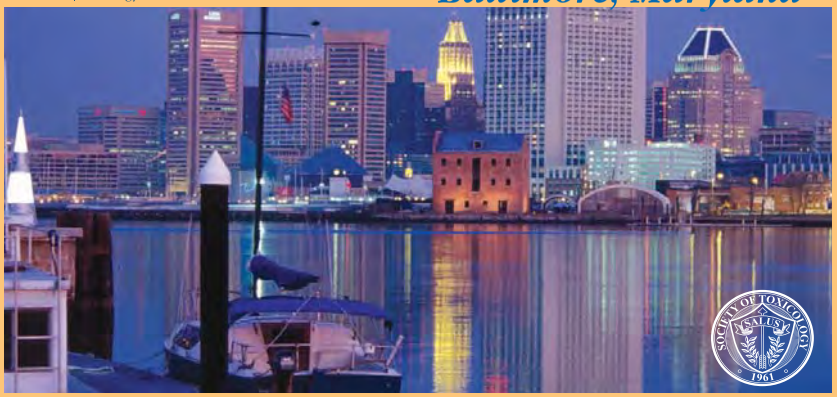

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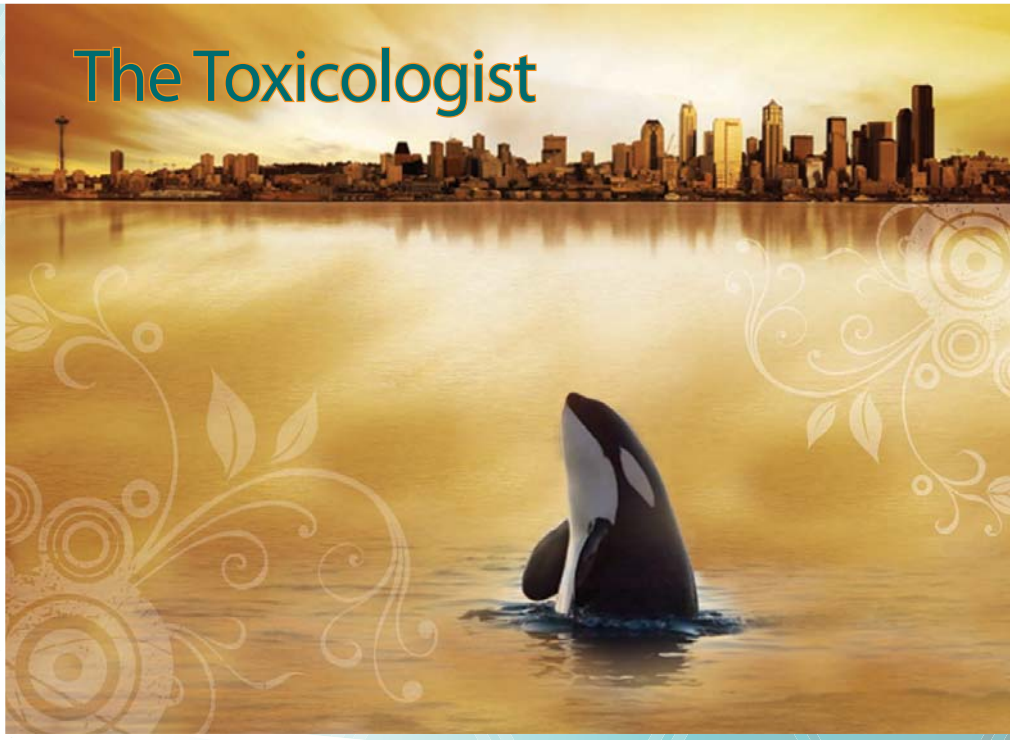

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