

**PS 2070 THE TOXICITY OF SILVER AND SILICA NANOPARTICLES IN COMPARABLE HUMAN AND MOUSE CELL LINES.**

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The toxicity of silica (SiO<sub>2</sub>) and PVP-coated silver (Ag) nanoparticles (NPs) was investigated in two pairs of human or mouse cell lines originating from lung epithelium (A549 and ASB-XIV) and macrophages (THP-1 and J744A.1). Both NPs were characterized in H<sub>2</sub>O and cell media. The primary sizes were 69 nm (Ag) and 27 nm (SiO<sub>2</sub>) as determined by TEM. Cytotoxicity was tested after 24 h in terms of viability by dehydrogenase activity (WST-8), apoptosis (Annexin V/PI) and the formation of ROS (DCF). Murine cells are more sensitive to NPs than human cells and the toxic response depends on both the NP type and the cell type. The EC50 was significantly higher for SiO<sub>2</sub> compared to Ag NP. Significant increases in ROS generally occurred at doses close to EC50 or higher leaving the question whether increased ROS were caused by the NPs or as a consequence of cell death. Induction of ROS was also assessed by the comet assay and modifications of DNA. In both human and murine epithelial lung cells, the EC50 NP concentrations from the WST-8 assay correlated well with results from the annexin V/PI assay. Death at EC50 in the lung cells was equally due to apoptosis and necrosis after exposure to either NP. However, large discrepancies were found when comparing EC50 values from the WST-8 assay in macrophages to results from the Annexin V/PI assay. The WST-8 assay appeared to overestimate cell death caused by Ag NPs in J774A.1 cells and by SiO<sub>2</sub> NPs in THP-1 cells, whereas the assay underestimated the EC50 values of SiO<sub>2</sub> NPs in J774A.1 cells and Ag NPs in THP-1 cells. These discrepancies suggest that the WST-8 assay should be confirmed by additional assays e.g. annexin V/PI. Our preliminary data suggest that NP mediated toxicity can be higher in murine cell lines compared to their human counterparts. This information could be of importance if risk assessment will be based upon animal experimentation. This association will be the subject of investigation in our future work.

**PS 2071 AN *IN VITRO* INVESTIGATION OF THE TOXICITY OF SILVER NANOPARTICLES.**

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During the last decade the public has become increasingly exposed to engineered nanoparticles (NPs), including silver NPs used as anti-microbials, although there is little data on their toxicity or long-term impact on human health. We determined cytotoxicity, genotoxicity and epigenetic changes by silver NPs administered to HL60 and Jurkat cells, which are both derived from human lymphocytes. The cells were selected to investigate the mechanisms of uptake of the NPs since HL60 cells can carry out phagocytosis while Jurkats cannot. HL60 or Jurkat cells were incubated with two types of silver NPs (Nanocompositix) (0.01, 0.1, 0.5, 1 µg/ml) in RPMI medium for 4h, 24h, 48h at 37°C with controls. The silver NPs (10nm diameter) had either positive or negative charges. Cytotoxicity was determined using the MTT assay and DNA damage by the Comet assay. Comet Assay IV software defined the Olive Tail Moment (OTM) of 200 cells. DNA was also extracted from cells exposed to the silver NPs (1µg/ml) to determine global methylation within CpG islands of long interspersed nuclear elements-1 (LINE-1) using pyrosequencing. At minimal levels of cytotoxicity (≤20% loss of cell viability) there were dose related increases in DNA damage by both forms of silver NPs. The profiles of damage with time were generally similar for Jurkat and HL60 cells. There was no significant difference in methylation of LINE-1. These studies show that silver NPs were genotoxic to the cells at concentrations producing low levels of cytotoxicity. However, neither the ability of the cell to carry out phagocytosis nor changes in methylation status influenced the DNA damage seen. Although the underlying mechanisms for the damage are still unclear, the initial charge on the NP when the cells were first dosed did not influence the toxicity. Currently we are investigating whether the charge on the NPs changes during time in culture since preliminary data has indicated that both forms of particles aggregated with time in RPMI.

**PS 2072 IRON OXIDE NANOPARTICLES CAUSE OXIDATIVE STRESS AND DERMAL TOXICITY.**

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A number of commercially available metal/metal oxide nanoparticles (NP) such as superparamagnetic iron oxide (SPION) are utilized by the medical field for a variety of applications. We hypothesize that SPION may be toxic to skin via the ability of particles to be internalized and thereby initiate oxidative stress, inducing redox-sensitive transcription factors leading to inflammation. Due to the skin's susceptibility to UV radiation, it is also important to address the combined effect of UVB and NP co-exposure. To test this hypothesis, the effects of dextran-coated-SPION of different sizes (15-50 nm) and manufacturers (MicroMod (MM), Germany and Royal Institute of Technology, Sweden) were evaluated in 2 cell lines: human epidermal keratinocytes (HEK) and murine epidermal cells (JB6 P+). HEK cells exposed to 20 nm (KTH and MM) had a decrease in viability while the 15 and 50 nm particles were not cytotoxic. HEK cells were also capable of internalizing the KTH particles (15 and 20 nm) but not the MM SPION (20 and 50 nm). IL-8 and IL-6 were elevated in HEK cells following exposure to SPION. Exposure of JB6 P+ cells to all SPIONs evaluated resulted in activation of AP-1; however, only UVB plus SPION (15 and 20 nm KTH and 50 nm MM) resulted in significant NF-κB induction in cells. Pre-exposure of JB6 P+ cells to UVB followed by NPs induced a significant depletion of glutathione, release of cytokines, and cell damage as assessed by release of lactate dehydrogenase. These data indicate that co-exposure to UVB and SPIONs was associated with induction of oxidative stress and release of inflammatory mediators. These results verify the need to thoroughly evaluate the adverse effects of UVB when evaluating dermal toxicity of engineered NPs on skin. Supported by NIOSH [OH008282](#), NORA 927Z1LU and EC-FP-7-NANOMMUNE-214281.

**PS 2073 A TOXICOGENOMIC ANALYSIS OF GENE EXPRESSION CHANGES IN TiO<sub>2</sub> NANOPARTICLE-TREATED MICE.**

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There is a growing concern over the potential toxicity resulting from nanoparticle (NP) exposure. TiO<sub>2</sub> NPs, which are widely used in many consumer products, can be absorbed into the body through oral or inhalation exposure. Although TiO<sub>2</sub> NPs appear to be relatively safe, recent studies have reported genotoxicity in mice orally exposed to TiO<sub>2</sub> NPs. It is believed that inflammation and oxidative stress are the most likely mechanisms underlying NP-induced toxicity; however, the precise molecular responses to TiO<sub>2</sub> NP exposure in various tissues remain poorly defined. The aim of the present study was to identify early molecular markers for TiO<sub>2</sub> NP exposure and/or toxicity in various mouse tissues, through the use of a toxicogenomics approach, with an ultimate goal of facilitating risk assessment in humans. Adult male and female C57BL/6 mice were exposed to TiO<sub>2</sub> NP (<25 nm) in water at a single dose of 500 mg/kg, by oral gavage; control mice received vehicle only. At 24 h post treatment, the mice were sacrificed, and various tissues were collected for analysis. Real-time RNA-PCR quantification of hepatic mRNA expression was performed for a total of 242 genes related to inflammation, oxidative stress, and DNA damage, using a pathway-focused gene expression profiling PCR array (SABiosciences), for detection of early toxicity markers. No histological or functional changes were observed in the liver or other major organs of the treated mice. Interestingly, at least 17 genes were found to be up- or down-regulated in the liver of TiO<sub>2</sub> NP-treated mice (with a criterion of >2-fold change, compared to control), including a cytochrome P450 gene (Cyp), which was upregulated by 40-fold at the mRNA level and by 3-fold at the protein level. Furthermore, the upregulation of this Cyp gene appeared to be gender-specific. Additional studies are underway to examine the mechanisms for, and toxicological implications of, the TiO<sub>2</sub> NP-induced gene expression changes.

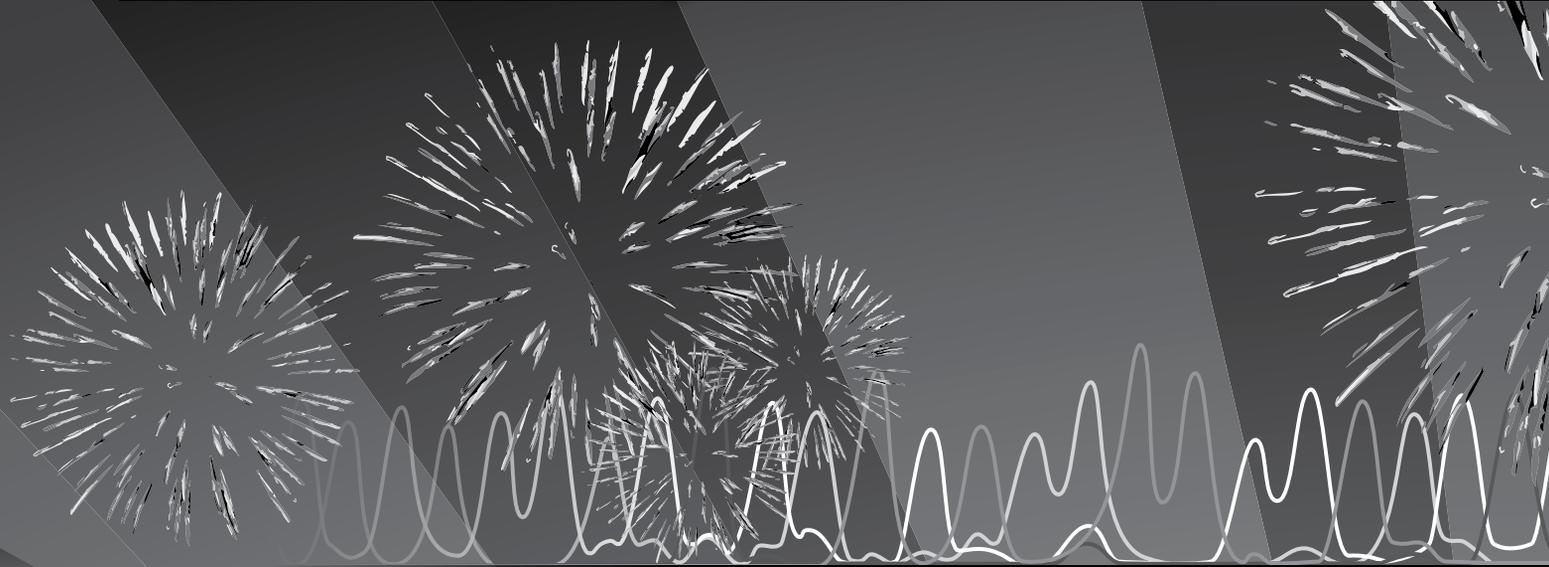
**PS 2074 GOLD NANOPARTICLES INCREASE THE LIVER TOXICITY OF ACETAMINOPHEN.**

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Much research has focused on assessing the potential toxicity of nanoparticles when administered alone in various test systems. However, the possibility that nanoparticles may enhance the toxicity of other agents when given simultaneously has not

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# Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 50th Annual Meeting of the Society of Toxicology, held at the Walter E. Washington Convention Center, March 6–10, 2011.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 578.

The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 606.

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