2692 The Synthesis of Gum Arabic-Modified CdTe Quantum Dots with Low-Cytotoxicity for *In Vivo* Applications

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Gum Arabic(GA) is a natural glycoprotein polymer with low cytotoxicity and is often used in the food and pharmaceutical industries. Polymers are often used as capping agents in nanoparticles synthesis to prevent nanoparticle aggregation and to reduce nanoparticle toxicity. CdTe quantum dots (QDs) have potential applications as probes for *in vivo* diagnostics. However, these nanoparticles have significant cytotoxicity. In this study we aimed to synthesise CdTe QDs with high luminescent properties for applications in *in vivo* bio-imaging. Two different synthesis methods were used. We capped the QDs with GA to reduce the cytotoxicity and improve the solubility of the nanoparticles. These QD-GA nanoparticles were characterized using Ultraviolet-visible (UV–vis) spectroscopy, Photoluminescence (PL) spectroscopy, High-Resolution Transmission Electron Microscopy (HRTEM) and Fourier Transform InfraRed spectroscopy (FTIR). Also, the hydrodynamic particle size, polydispersity index (PDI) and Zeta potential of GA capped QDs were also evaluated to ascertain their colloid stability. The cytotoxicity of the QDs were evaluated on two human cancer cell lines, namely HeLa and PC-3 using the WST-1 assay. The PL intensity of the QDs synthesised using the two methods were 678nm and 675nm, respectively. HRTEM analysis showed that the average particle size were 3.45nm and 3.9nm, respectively. The average PDI were 0.27±0.02 and 0.35±0.02. The cytotoxicity assays showed that GA capping reduced the cytoxicity and improved the stability of the QDs. These nanoparticles can potentially be used for *in vivo* applications.

2693 Involvement of ROS Generation in Copper Oxide Nanoparticles-Induced AP-1 Activation

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Occupational exposures to copper dusts or fumes have been reported to be harmful to human health, with possible risk of cancer among copper smelter workers. Copper (II) oxide (CuO) nanoparticles have not, to our knowledge, been extensively examined for potential carcinogenic or genotoxic effects. To investigate the mechanisms of CuO-induced pathogenesis, the effect of CuO on AP-1-MAPKs and ROS generation were investigated. The results indicated CuO caused a 2-fold increase in AP-1 activity in JB6 cells. The induction of AP-1 activity in cultured cell lines was time and dose-dependent. The signal transduction pathways for AP-1 activation were also investigated. Western Blot analysis demonstrate that CuO stimulates phosphorylation of p38 MAPK and ERKs. CuO also generated ROS when incubated with the cells as measured by electron spin resonance (ESR). Nano-sized CuO generated more ROS than the fine sized particles when incubated with the cells. Finally, co-incubation of the cells with free radical scavenger N-acetylcysteine or PVPNO decreased AP-1 activation and phosphorylation of MAPKs, thus suggesting that oxidative stress is involved in WC-Co-induced toxicity and AP-1-MAPKs activation.

2694 Bismuth Sulfide Nanoparticle-Induced Nephrotoxicity and Autophagy-Associated Mechanisms

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Bismuth compounds have been widely used in electronics industry, alloy manufacture, cosmetics and medicine. Recently bismuth nanomaterials (BiNP) were synthesized for imaging and diagnostic purpose, while safety concern of bismuth cannot be ignored. Here, we prepared ultrasmall BiNP and showed an enhanced tumor CT imaging, but BiNP revealed a moderate nephrotoxicity in mice, including the elevated amounts of creatinine and blood urea nitrogen (BUN) in blood and urea. Pathologically, we found the increased amount of apoptosis in proximal tube cells, indicating the injury of BiNP. In the meanwhile, the autophagy marker LC3II significantly increased in the kidney of the BiNP treated mice. The autophagy inducer rampamycin can alleviate the kidney injury by BiNP, while chloroquine deteriorated the BiNP induced nephrotoxicity, as indicated by the creatinine, BUN, the kidney injury marker KIM-1, and pathological observations for the number of apoptotic cells. *In vitro* studies showed the cytotoxicity of BiNP on human embryonic kidney 293 cells (HEK293) compared to other cell types. The occurrence of monodansylcadaverine fluorescence staining and the amount of LC3II that can be inhibited by 3-MA indicated autophagy induced by BiNP. BiNP were capable of entering cells and localized in the cytoplasm observed by transmission electron microscopy with bismuth element confirmed by energy dispersive X-ray analysis. Mechanistically, we found that BiNP induced autophagy was through AMPK pathway but not PI3K and MAPK pathway, followed by the inhibition of mTOR activity, with further increase of downstream protein expressions such as Beclin1, Atg12, and p62. With our novel finding of bismuth induced autophagy, potential approaches may be applied to reduce the nephrotoxicity by bismuth.

2695 Alterations in Metabolite Profiles of Macrophages Exposed to Graphene Nanoplatelets

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Graphene nanoplatelets (GNPs) are novel 2D nanoparticles consisting of planar stacks of graphene with thickness of only 2-12 nm but width and length dimensions up to microns. GNPs are widely applicable due to their conductivity of electricity and heat, and their abundant surface area for drug delivery systems. Although human exposures are increasing, our knowledge regarding immune-specific responses to GNPs and mechanisms of interactions is lacking. Our current study utilized a metabolomic profiling approach to evaluate macrophage responses to GNPs. Further we assessed the potential role of the scavenger receptor CD36 in mediating these GNPs-induced responses. RAW264.7 macrophages were exposed to GNPs without functionalization or functionalized by carboxylation or amineylation at concentrations of 0, 25, 50, or 100 µg/ml for 1, 3, and 24h. Following exposure, no cytotoxicity was observed. Concentration-dependent changes in internalization were determined by alterations in side-scatter using flow cytometry. Non-functionalized GNPs were internalized more than functionalized GNPs. Following incubation with a CD36 competitive ligand sulfo-N-succinimidyl oleate (SSO) or a CD36-specific antibody, uptake of GNPs was reduced. GNP exposure also induced mitochondrial membrane potential while pretreatment with the CD36 antibody attenuated these changes. In addition, macrophages exposed to non-functionalized GNPs at concentrations of 0, 50, or 100 µ /ml for 1 or 3h, or SSO for 1h were harvested for metabolomic profiling and both metabolite and lipid fractions were examined. Principal component analysis showed all groups to be different from the control and one another. The number of compounds changed following exposure appeared to be both concentration- and time-dependent. Specifically, a total of 481 compounds were altered following the exposure to 100 µg/ml of GNPs, whereas 291 compounds were altered following exposure to 50 µg/ml (Fold Change > 2; p<0.01). Compounds were associated with pathways such as spingolipid and cholesterol metabolism, glutathione synthesis, energy metabolism, inflammatory signaling and others. Lastly, a number of metabolites were found in common between cells exposed to the CD36 receptor ligand and GNPs suggesting CD36-dependent and independent responses. Together our data demonstrates the influence of functionalization on GNP-macrophage interactions, the role of CD36 in the cellular response, and metabolic pathways disrupted due to exposure. *NIEHS ES024392.*

2696 Cytotoxicity of Copper (II) Oxide Nanoparticles in Rat Intestinal Cells: Effect of Simulated Gastrointestinal Fluids and Generation of Oxidative Stress

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Metallic oxide nanoparticles (NPs) have applications in industry, medicine and commercial products. Exposure to NPs can occur by inhalation, dermal contact and oral ingestion. We have previously reported on the dose- and time-dependent cytotoxicity of CuO NPs (size < 50 nm) in rat intestinal cells (IEC-6) from the aspect of oral ingestion. This study assessed the effect of pretreating CuO NPs (1 mg/ml) with simulated gastrointestinal (GI) fluids (pepsin at pH 2 to 6, pancreatin at pH 7, bile salts at pH 7; incubated sequentially) on cytotoxicity in IEC-6 cells. The treated NPs were isolated by ultracentrifugation, suspended in media and probe sonicated before dosing the cells. Cells were exposed for 24 hr with the treated NPs (0.1 - 100 ug/ml) and cytotoxicity was assessed using a colorimetric method that measures mitochondrial activity. The zeta potential (ZP) and hydrodynamic diameter (HD) of similarly treated CuO NPs were measured after each incubation step. The ability of non-treated or pristine CuO NPs to generate oxidative stress in the cells was also assessed. Following a 4-hr exposure to CuO NPs (0.1 - 100 ug/ml), H_2O_2 and glutathione (GSH) were quantitated in the cells by a biolu-

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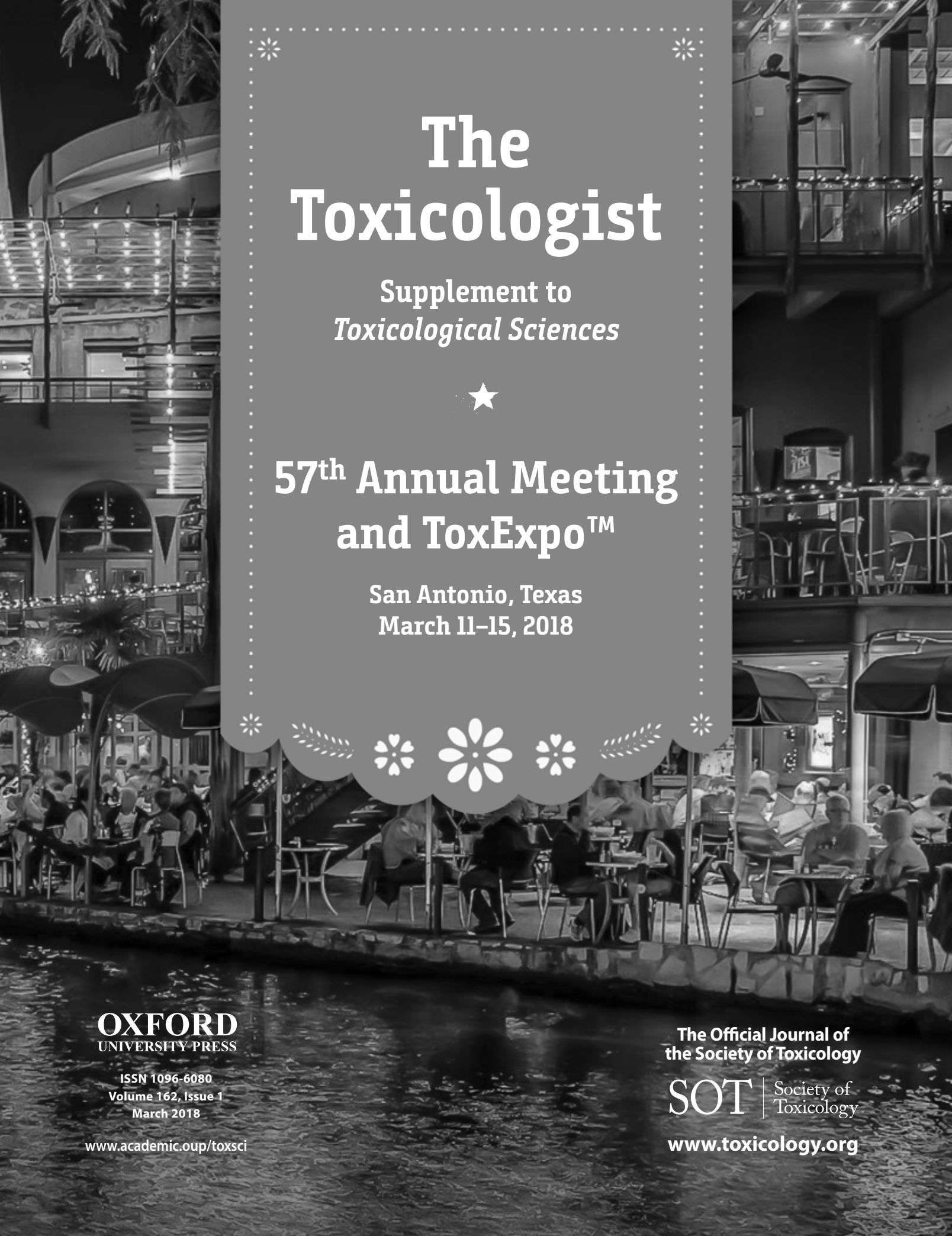

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