nanoparticles (such as nano-size nickel, cobalt and titanium dioxide) is limited but suggests that metal nanoparticles may exert more adverse effects than standard-sized particles. This study addresses the overall hypothesis that transition metal nanoparticles exert genotoxic effects via alternation of cell homeostasis through a mechanism mediated by oxidative stress. In this study, we used an intratracheal instillation mouse model, and in vitro system, to study the potential genotoxic effects of transition metal nanoparticles. Our results show that exposure to Nano-Co and Nano-Ni caused reactive species species (ROS) generation in vitro and in vivo. Exposure of lung epithelial A549 cells to Nano-Co or Nano-Ni resulted in p53 protein expression, modification and down-regulation of Rad-51 protein expression, and increased formation of γH2AX foci which were abolished by pretreatment of cells with ROS scavangers or inhibitors. The results were further confirmed by in vivo studies; the concentration of 8-OHdG in mouse lungs exposed to Nano-Co and Nano-Ni significantly increased over time after exposure. Furthermore, proliferating cell nuclear antigen (PCNA) staining in mice lungs exposed to Nano-Co and Nano-Ni significantly increased over time and were greater than that caused by Nano-TiO2. Our results suggest that metal nanoparticles cause oxidative stress which is involved in nanoparticle-induced DNA damage and genotoxic effects. These findings have important implications for understanding the potential health effects of nanoparticle exposure.

PL 1979 INDUCTION OF ANEUPLOIDY BY SINGLE WALLED CARBON NANOTUBES.

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Engineered carbon nanoparticles are newly emerging manufactured particles with potential applications in multiple fields, including electronics, computers, and aerospace. The low density and small size of these persistent particles makes respiratory exposures to workers likely during the production or use of various commercial products. To examine the potential of nanotubes to induce genetic damage in normal lung cells, primary and immortalized human small airway epithelial cells were cultured and then exposed to single walled carbon nanotubes (SWCNTs) or a positive control vanadium pentoxide. The nanotubes had an average diameter of 1.1 nanometer and a length of 50-100 microns. Cellular tubulin, mitotic spindle integrity and centriole number were determined by immunofluorescence for beta-tubulin and centrin and photographed using fluorescent and confocal laser scanning microscopy. The chromosome number was examined by fluorescent in situ hybridization. After 24 hours of exposure to either SWCNT or vanadium pentoxide, binucleate cells, bundled tubulin and fragmented centrosomes were present. Abnormalities included changes in mitotic spindles, including multiple poles that resulted in aneuploid chromosome number. Confocal microscopy demonstrated nanotubes within the nucleus that were in association with cellular and mitotic tubulin as well as the chromatin. These findings indicate that these SWCNTs can enter the nucleus, inducing mitotic spindle disruption and abnormal chromosome number. Thus, our study indicates that direct interaction between chromatin and SWCNTs may contribute to genetic changes in somatic cells. Exposure to agents that interfere with the formation and movement of the mitotic spindle apparatus and cause abnormalities in chromosome number result in a greater risk of cancer.

PL 1980 QUANTITATIVE STRUCTURE ACTIVITY MODELING OF GOLD NANOPARTICLE TOXICITY IN A ZEBRAFISH DEVELOPMENTAL SYSTEM.

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Understanding how the surface physiochemical properties of nanomaterials dictate biocompatibility and potential toxicity is a central challenge in the emerging field of nanotoxicology. Although Quantitative Structure Activity Relationship (QSAR) modeling has been useful for deriving predictive relationships between the properties of chemicals and their biological effects, there has been little effort to evaluate the accuracy of QSAR methods in predicting biological response from nanomaterials. In this work, experimental results were employed to develop a generalized linear model to predict the probability of developmental toxicity in zebrafish embryos 24 hours post-fertilization. The experiment consisted of exposing zebrafish embryos to eight different concentrations of gold nanoparticles, with three different core sizes and four different surface modifications with chemical ligands. The toxicity model was statistically developed using physical and structural characteristics of the gold nanoparticles, including nine different chemical property descriptors as predictor variables. Beyond particle size and concentration, two of the QSAR variables investigated (polar surface and solvent accessible surface area) were found to be statistically significant predictors of toxicity. The model exhibits good performance and, because all the predictor variables are continuous, it can be used to point to regions in the experimental space with reduced toxicity and aid to further the understanding of the mechanisms that influence it.

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PL 1981 THE EFFECT OF CADMIUM EXPOSURE ON CALCIUM HOMEOSTASIS AND SIGNALING PATHWAYS.

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Cadmium constitutes a threat to human health. Yet the exact molecular mechanisms involved in mediating transcriptional responses to cadmium remain unresolved. Cadmium has been shown to elevate intracellular calcium levels, which could activate multiple signaling cascades. Here we report the functional analysis of two cadmium responsive genes in the nematode Caenorhabditis elegans, numr-1 and numr-2, whose expression, in part, is regulated by alterations in intracellular calcium ([Ca2+]i) levels. In the absence of metal, constitutive expression of numr-1/-2 is developmentally regulated with maximal expression in intestinal cells during the L1 larval stage and minimal expression in adults. When adult nematodes are exposed to metal, numr-1/-2 expression increases dramatically in intestinal cells. In C. elegans the intestinal cells experience endogenous endoplasmic reticulum (ER) stress during development and cadmium is a toxicant that induces ER stress. It has been proposed that cadmium can increase intracellular calcium levels through the release of calcium from ER stores. We found that when adult nematodes carrying a NUMR-1::GFP translational fusion are exposed to thapsigargin or a calcium ionophore, numr-1 expression dramatically increases throughout the intestine, suggesting alterations in [Ca2+]i levels may regulate numr-1/-2 expression. To gain a better understanding of the effects of cadmium on [Ca2+]i we used a protein based calcium ion sensor, cameleon YC 3.60, expressed in HEK 293 cells. We found that exposing HEK 293 cells to 30uM cadmium decreased the release of intracellular calcium ions by treatment with ionomycin; suggesting that ER calcium stores had been depleted. Taken together, our data suggests that cadmium affects intracellular calcium levels, which may ultimately regulate the transcriptional response of cadmium inducible genes. These results offer insights into the effect of cadmium exposure on calcium homeostasis and signaling pathways.

PL 1982 MANGANESE TOXICITY IN CELLS THAT HYPER-ACCUMULATE PHOSPHATE INVOLVES PROTEIN TURNOVER EFFECTS OF THE PROTEOSOME.

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Manganese ions are known to form tight complexes with phosphate *in vitro*, and we have investigated the effects of intracellular phosphate on manganese using the bakers yeast *S. cereviae*. Phosphate accumulation and metabolism in *Saccharomyces cerevisiae* is regulated by the cyclin dependent kinase Pho85 and the cyclin Pho80. When phosphate is abundant, they negatively regulate the transcription of phosphate uptake and metabolism genes. Cells with a genetic deletion of *pho80* accumulate increased amounts of multiple species of phosphate. The *pho80Δ* genetic deletion strain also accumulates increased levels of manganese when exposed to high manganese and is very sensitive to manganese toxicity. To investigate the mechanism of manganese sensitivity in the *pho80Δ* strain, we compared the transcriptional profile of *pho80Δ* vs WT strains exposed to manganese. As expected, a number of phosphate metabolism genes were up-regulated, including the metal-phosphate transporter *PHO84*. However, up-regulation of the metal-phosphate transporter only partially explains the sensitivity towards manganese and both *PHO84*-dependent and –independent pathways are responsible for manganese sensitivity. In a screen for multi-copy suppressors of the *pho80Δ* manganese sensitivity, we isolated *RAD23*, which encodes a proteasome-associated protein. *RAD23* does not act at the level of transcription and instead works downstream in a *PHO84*-independent fashion to reverse manganese toxicity. The reduction in manganese sensitivity is dependent on the N-terminal UbL ("ubiquitin-like") domain of Rad23p that interacts with the proteasome. We conclude that manganese toxicity in cells that hyperaccumulate phosphate involves protein turnover effects of the proteosome.

PL 1983 BIS(MALTOLATO)OXOVANADIUM ACTIVATES STAT-1 IN HUMAN LUNG FIBROBLASTS AND ANTAGONIZES IL-13-INDUCED STAT-6 SIGNALING.

P. C. Bost and J. C. Bonner. *Toxicology, North Carolina State University, Raleigh, NC.*

Bis(maltolato)oxovanadium(IV) (BMOV) is a bioavailable vanadium-based compound that has potential therapeutic value for the treatment of diabetes. We have previously shown that vanadium analogs activate signal transducer and activator of

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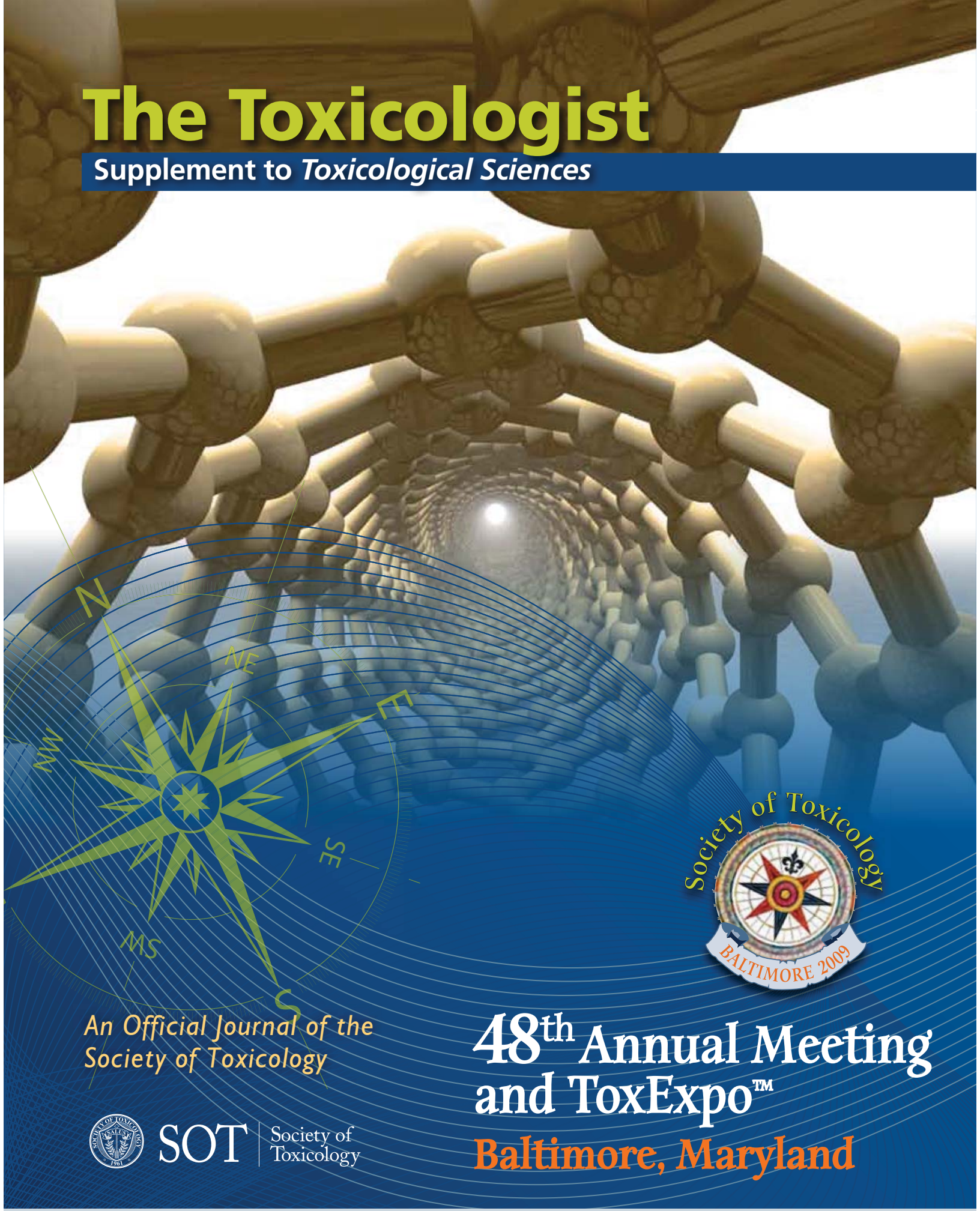

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