Chondrocytes show a statistically significant increase in the production of reactive oxygen species after exposure to lead. Singlet oxygen and superoxide radicals as well as hydrogen peroxide levels were all increased in a time and dose dependent fashion. This was accompanied by an increase in DCFDA conversion. These effects happened within minutes of lead addition. GPX and catalase were inhibited by lead at low concentrations (0.4 micromolar). The resultant increase in oxidative stress induces a phenotypic change in the articular chondrocytes characterized by large increases in type X collagen and the caspases. Interestingly, prolonged exposure of the chondrocytes to lead (24 hours) induced a six fold increase in SOD-1 expression. We interpret this observation as an attempt by the cells to resist the change in the oxidative milieu.
Articular chondrocytes that are exposed to lead alter their redox environment, tipping the balance toward oxidative stress. This induces specific phenotypic changes characteristic of cartilage breakdown that will progress to OA.

635 PARTICULATE CR(VI)-INDUCED DNA DOUBLE STRAND BREAK MISREPAIR LEADS TO NEOPLASTIC TRANSFORMATION.

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DNA double strand breaks (DSBs) are one of the most dangerous types of DNA damage. Defects in DSB repair can cause the loss or amplification of chromosomal material and tumorigenesis. Hexavalent chromium (Cr(VI)) is a potent respiratory toxicant and carcinogen with widespread human exposure. The most toxic and carcinogenic form of Cr(VI) is the particulate such as lead chromate (LC), which deposits and persists in the respiratory tract after inhalation. LC particles induce DSBs in human lung cells. The hMRE11-RAD50-NBS1 protein complex has emerged as a central player in the human cellular DNA-damage response, and recent observations suggest that these proteins are at least partially responsible for linking DSB damage detection to DSB-repair and cell cycle-checkpoint functions. Using the comet assay, we found that LC induced concentration-dependent increases in DSBs in cultured human lung cells with 0.1, 0.5, 1, and 5 µg/cm2 LC inducing 1.5, 2, 4.9 and 10.2 percent increase in tail DNA relative to control, respectively. The repair of LC-induced DSBs occurred within 24 h. This repair required MRE11 as reducing Mre11 expression by siRNA inhibited repair. We confirmed these observations by treating MRE11 deficient skin cells with LC and found that the repair of these lesions was greatly reduced in these cells as well. To link the DSB to carcinogenesis, we developed a model of neoplastic transformation using MRE11 deficient cells. A 5 day exposure to LC induced loss of cell contact inhibition in a concentration-dependent manner with 0, 0.1, 0.5 and 1 µg/cm2 lead chromate inducing 1, 78, 44, 103 growth foci in 20 dishes, respectively. The transformed cells developed through a series of sequential steps, including altered cell morphology and anchorage-independent growth. These data indicate that MRE11 protects cells from LC-induced DNA DSBs and neoplastic transformation. This work was supported by NIEHS grant ES10838 (J.P.W.)

636 MANGANESE INDUCES RAPID AND SELECTIVE LYSOSOME TRAFFICKING AND DEGRADATION OF THE GOLGI MEMBRANE PROTEIN GPP130.

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We used rat neuronally derived GABAergic (AF5) cell and HeLa cell models to investigate the effect of Mn exposure on intracellular trafficking. Cross-reactivity in an immunoblot analysis of AF5 cells revealed that Mn exposure (100 – 150µM) caused the rapid (within 4 hr) depletion of an initially unknown protein with an apparent MW of ~95kDa. Mass spectroscopy identified this protein as Golgi Phosphoprotein 4 (GPP130). GPP130 is a Golgi-localized integral membrane protein that cycles to endosomes where it may mediate endosome-to-Golgi retrieval of other cycling Golgi proteins (Natarajan and Linstedt, 2004). Mn-induced GPP130 degradation was neither recapitulated by the protein synthesis inhibitor cyclohexamide nor blocked by the proteasome inhibitor PSI suggesting a post-translational and proteasome-independent mechanism. After exposure to Mn, GPP130 underwent a dramatic redistribution from its normal Golgi localization to endosomal and lysosomal structures and then, by 2-4 h, was significantly depleted from all cellular structures. In support of the model that Mn had induced trafficking of GPP130 to lysosomes where GPP130 was then degraded the degradation was blocked by the lysosome hydrolase inhibitor chloroquine. Importantly, the normal localization and abundance of endosome and Golgi markers, including the GPP130-related protein GP73 whose Golgi localization depends on endosome-to-Golgi retrieval, indicated that Mn specifically affected GPP130 and did not generally disrupt membrane trafficking. Thus, cellular toxicity resulting from Mn exposure involves, in part, induced trafficking and degradation of the Golgi protein GPP130.

637 CADMIUM INDUCES STAT3 ACTIVATION BY A MECHANISM DEPENDENT ON NADPH OXIDASE ACTIVITY.

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Oxidative stress elicited by Cd is a likely contributor to hepatotoxicity. Cd can activate some oxidative stress-sensitive transcription factors that are responsible for regulating gene expression such as AP-1 or Nrf2, however STAT3 is not fully characterized. The aims of this study were to determine the activation of STAT3 pathway induced by Cd-oxidative stress and to address the participation of STAT3 in Hsp70 production in HepG2 cells. Cells were treated with 5 µM CdCl2 for 0.25, 0.5, 1, 2, 3, 4 or 5 h. Cadmium induced 4-fold Stat3 activation after 1 h treatment, determined by nuclear protein Western blot. To explore the ROS source for Cd-induced STAT3 activation, inhibitors for different ROS generating systems were used. Only DPI, an inhibitor of NADPH oxidase, decreased STAT3 activation. NADPH oxidase activity, was then determined. Cd induced 3-fold the activity of this enzyme. To confirm if NADPH oxidase-derived ROS were involved in STAT3 activation, SOD-peg and Catalase-peg were added as antioxidants. Treatment with Catalase-peg reduced significantly STAT3 activation. MAPK pathway is activated by oxidative stress. In order to explore if MAPK pathway is involve in STAT3 activation, we pretreated HepG2 cells with 20µM of PD98059 (Erk inhibitor), SB203580 (p38 inhibitor) or SP600125 (JNK inhibitor). Only Erk and JNK inhibitors abrogated Cd-induced STAT3 activation. Finally, in order to figure out some physiologic relevance in Cd-induced STAT3 activation, we explored Hsp70 expression, a Cd-induced protein. Pretreatment with a specific STAT3 peptide inhibitor, abrogated Cd-induced Hsp70 expression. Our data suggest that Cd activates NADPH oxidase activity which induces ROS production leading Erk and JNK activation, these MAPK promote STAT3 phosphorylation that can induce a protective mechanism against Cd toxicity.
CONACYT P 39618-M.

638 GENE EXPRESSION PROFILE IN RESPONSE TO POTASSIUM DICHROMATE-INDUCED TOXICITY IN HUMAN DERMAL FIBROBLASTS.

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Several adverse health effects including irritant and allergic contact dermatitis have been reported among workers following occupational exposure to chromium containing compounds. To understand the molecular mechanisms responsible for the dermal toxicity of chromium, a differential gene expression profile of human skin fibroblasts exposed to a cytotoxic concentration of hexavalent potassium dichromate [Cr(VI)] was studied. Skin fibroblasts were exposed to 5 micromolar Cr(VI) for time intervals up to 24-hours and a differential gene expression profile was studied using the human Toxicology and Drug Resistance Microarray (Super Array Inc.). Of the 280 genes represented on the array, 32 were found differentially expressed in the fibroblasts exposed to Cr(VI). In general, genes involved in stress response, cell cycle control, drug metabolism, apoptosis and growth were found differentially expressed in the Cr(VI) exposed fibroblasts. The molecular mechanisms responsible for the Cr(VI)-induced differential gene expression were investigated using heme oxygenase 1 (HO-1) as the model gene. HO-1 gene expression was significantly higher in the Cr(VI) exposed cells compared with the control cells. Pre-exposure of dermal fibroblasts to actinomycin D (inhibitor of transcription) and N-acetyl cysteine (scavenger of reactive oxygen species) blocked the Cr(VI)-induced overexpression of the HO-1 gene. Similarly, modulating the intracellular glutathione level by pre-treating cells with either BSO or glutathione significantly influenced the potential of Cr(VI) to induce the expression of the HO-1 gene. Similar results were obtained when experiments were conducted using a luciferase reporter gene expression system containing the HO-1 gene promoter. In conclusion, our results demonstrate that the cellular glutathione level may be an important determining factor in the dermal toxicity induced by hexavalent chromium.

639 DEVELOPMENT OF A BASE SET OF TOXICITY TESTS AS A COMPONENT OF A NANOPARTICLE RISK MANAGEMENT FRAMEWORK.

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The development of a risk management framework for nano or ultrafine particle-types requires a base set of hazard data. Previously, we have suggested "parallel tracks" as a strategy for conducting nanoparticle research. Mechanistic studies on "representative" nanoparticles could be supported by governmental agencies. Alternatively, for commercial nanoparticles, the EHS framework would include a minimum base set of toxicity studies, supported by the companies that are develop-

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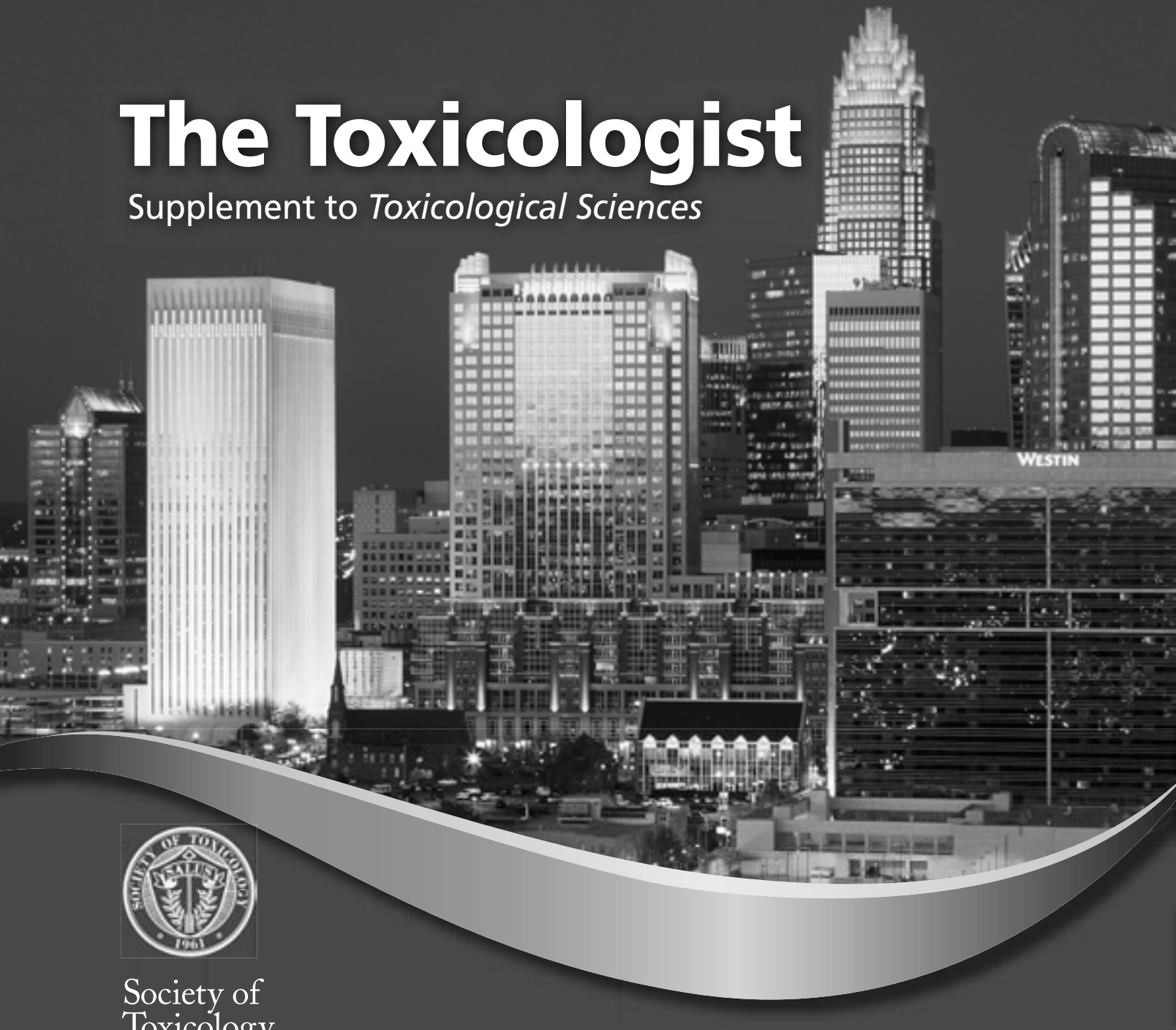

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, and poster sessions of the 46th Annual Meeting of the Society of Toxicology, held at the Charlotte Convention Center, Charlotte, March 25–29, 2007.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 449.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 480.

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