known as to the molecular mechanisms involved with mercury intoxication at very low levels, it is clear that mercury targets the immune system. It has been known for some time that inorganic mercury ($Hg^{+2}$)at non-toxic levels disrupts immune system homeostasis, in that genetically susceptible rodents develop idiosyncratic autoimmune disease. More recently it has been shown in several different model systems that mercury exposure of mice that are not susceptible to frank $Hg^{+2}$-induced autoimmune disease nevertheless leads to exacerbation of autoimmune disease. Multiple studies have suggested that autoimmune disease can often be associated with the inability of antigen receptors to properly trigger activation of the ERK signal transduction pathway in lymphocytes. We show that in the presence of non-toxic concentrations of $Hg,^{+2}$ the T cell receptor (TCR) fails to properly activate the ERK signal transduction pathway. Similarly, in B cells exposed to low concentrations of inorganic mercury, the B cell receptor (BCR) also fails to properly activate ERK. In both instances it is unlikely that $Hg^{+2}$ targets ERK directly, but rather that it compromises the function of upstream signal transduction elements including LAT, Syk, and Zap-70. We speculate that other environmental agents besides mercury may also have the ability to interfere with antigen receptor mediated signal transduction in lymphoid cells, and so disrupt immune system homeostasis in a similar manner. Supported by NIEHS grants RO1ES11000, RO1ES12403 and P3ES01247.

## 1177 GENOTOXICITY OF SOLUBLE AND PARTICULATE CADMIUM COMPOUNDS

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The present study aims to compare direct and indirect genotoxicity of particulate CdO and soluble CdCl2 in human lung cells as primary targets of metal induced carcinogenicity. As a model for nucleotide excision repair (NER) the removal of benzo[a]pyrene-induced DNA adducts was measured by a highly sensitive HPLC/fluorescence assay. Both CdCl2 and CdO inhibited the repair of the induced adducts in a dose-dependent manner at non-cytotoxic, environmentally relevant concentrations up to about 40 and 60 %, respectively. This repair inhibition started at 10 µM CdCl2 and 0.2 µg/cm2 CdO, concentrations, where both compounds showed no induction of oxidative DNA damage after 24 h incubation. As potential molecular targets for the observed repair inhibition proteins with zinc binding motifs like the NER zinc finger protein XPA and p53 have been identified. Thus cadmium efficiently substituted zinc in the zinc finger domain of XPA, as demonstrated by a 1000 fold higher binding constant, and subsequently deformed the zinc finger structure. Furthermore in cultured human cells both CdCl2 (≥ 25 µM) and even more pronounced CdO (≥ 0.2 µg/cm2) converted the correctly folded "wild type" p53 conformation into a so-called "mutant" form with an unfolded zinc binding domain. Further experiments demonstrated changes in p53 downstream events such as diminished transcription of p48 and XPC as well as altered cell cycle control in response to UVC irradiation and benzo[a]pyrene.
Taken together our results indicate a general NER inhibition by cadmium compounds, with XPA and p53 being potential molecular targets. Comparing soluble and particulate cadmium compounds, in most test systems particulate CdO showed stronger effects. As the general population is frequently co-exposed to particulate cadmium compounds and mutagens, this aspect may be significant with respect to cadmium-induced carcinogenicity.

## 1178 CHANGES IN GENE EXPRESSION ASSOCIATED WITH EXPOSURE TO ENVIRONMENTAL TOXICANTS

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When organisms are exposed to toxicants, they defend themselves against intracellular damage by activating the transcription of genes that encode proteins that defend the host, repair the damage, or remove/metabolize the toxicant. Since many of these "stress-response" proteins and the signal transduction cascades that regulate the stress-response are evolutionarily conserved, we hypothesize that exposure to environmental toxicants modulates the transcription of an evolutionarily conserved set of genes from yeast to mammals. To investigate this hypothesis we are comparing the expression profiles from yeast and C. elegans that were exposed to archetypical toxicants. In the present study we examined the responses to the carcinogenic transition metal cadmium and the DNA alkylating agent N-methyl-N'-nitro-nitrosoguanidine (MNNG). Toxicological studies for both cadmium and MNNG were performed to identify equivelent exposure times and toxicant concentrations. Transcriptomes for cadmium- and MNNG-exposed nematodes and yeast were obtained using Agilent oligonucleotide microarray analysis. Current analysis indicates that > 100genes genes are differential expressed after cadmium exposure, (fold change≥2, p<0.01) and >400 genes were differentially expressed following MNNG exposure. Subsequently the functions of these genes will be identified and compared to identify conserved and divergent Gene Ontology's, pathways, and interactomes nodes among the gene whose levels of expression affected by cadmium and MNNG. The result will help us to discover not only expression profiles associated with specific toxicants, but also common "stress-response" genes regulated by different environmental toxicants. Moreover, this result will be incorporated into a larger study to compare the expression profiles from four species (yeast, C. elegans, zebrafish embryos and mice) exposed to different classes of toxicants in order to define evolutionarily conserved regulatory pathways that control the stress response.

## 1179 GENE EXPRESSION PROFILE IN HUMAN SKIN FIBROBLASTS EXPOSED TO POTASSIUM DICHROMATE

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Chromium containing compounds are extensively used in various applications resulting in significant human exposure. Several adverse health effects, including irritant and allergic contact dermatitis, have been reported among workers following occupational exposure to chromium containing compounds. In order to better understand the molecular mechanisms responsible for the dermal toxicity of chromium, differential gene expression profiles of human skin fibroblasts exposed to a cytotoxic concentration of hexavalent potassium dichromate [Cr(VI)] were studied. Skin fibroblasts were exposed to 5 µM Cr(VI) for time intervals up to 24-hr and their differential gene expression profile was studied using the Toxicology and Drug Resistance Microarray (Super Array Inc.). Of the 280 genes represented on the array, the expression levels of 32 genes were found to be differentially affected in the fibroblasts exposed to Cr(VI). In general, genes involved in stress response, cell cycle control, drug metabolism, apoptosis and growth were differentially expressed in response to Cr(VI) exposure. The role of intracellular glutathione on the Cr(VI)-induced alterations in the expression of genes was further investigated using heme oxygenase 1 (HO-1) as the model gene. Modulating the intracellular glutathione level by pre-treating the cells with either BSO (buthionine-Sulfoximine) or glutathione significantly influenced the potential of Cr(VI) to induce expression of the HO-1 gene. Pre-treating the cells with BSO resulted in a significant reduction in glutathione levels. The Cr-induced overexpression of the HO-1 gene in the BSO-treated cells was significantly higher than in those cells without BSO treatment. On the other hand, pre-treating the cells with glutathione partially blocked the Cr(VI)-induced overexpression of the HO-1 gene. In conclusion, our results demonstrate that Cr(VI) exerts its toxic effects in human skin fibroblasts by multiple mechanisms involved in various cellular functions; and the cellular glutathione level appears to be an important factor influencing Cr(VI)'s effects on the expression of genes.

## 1180 DIVALENT METAL TRANSPORTER-1 REGULATION BY IRON AND VANADIUM MODULATES HYDROGEN PEROXIDE-INDUCED DNA DAMAGE IN LUNG CELLS

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The divalent metal transporter-1 (DMT1) participates in the detoxification of metals that can damage lung epithelium. Elevated extracellular iron levels in vitro increase the expression of DMT1 in bronchial epithelial cells stimulating iron uptake and storage in ferritin, which may make iron unavailable to participate in the generation of extracellular reactive oxygen species (ROS). To further test whether increased DMT1 expression is protective against ROS formation and subsequent cellular damage, we exposed human bronchial epithelial cells (BEAS-2B) to 100 µM ferric ammonium citrate (FAC) or 50 µM vanadium sulfate (which downregulates DMT1 expression) for 4 h. Cells were then washed and incubated for 20 h in media. The cells were then washed and exposed to 100 µM FAC with or without 20 µM $H_2O_2$ (an endogenously produced oxidant) for 30 min. After the exposure the comet assay was used to assess cell DNA single strand breaks (SSBs). Cells pre-treated with $VOSO_4$ and subsequently exposed to FAC + $H_2O_2$ had a statistically significant ($p < 0.05$) increase in DNA SSBs (i.e., comet area > 1250 $\mu m^2$) when compared to control cells pre-treated with cell media alone (~546 $\mu m^2$). Cells that were pre-treated with FAC had a non-significant decrease in DNA SSBs (~419 $\mu m^2$) compared to the control cells. Among cell groups that were incubated with FAC without $H_2O_2$, there were no increased SSBs (i.e., comet areas of 350 – 440 $\mu m^2$). These results provide further evidence that increased DMT1 expression serves as a protective mechanism in the lungs by stimulating cells to intracellularly transport and bind iron, thus making it unavailable to participate in ROS generation and increased DNA SSBs. [This abstract may not reflect official EPA policy. AM supported by EPA/UNC T829472].


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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 45th Annual Meeting of the Society of Toxicology, held at the San Diego Convention Center, San Diego, March 5–9, 2006.**

**An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 500.**

**The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 534.**

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