the chronic exposure group, Calm1, Calm2, Atp5o, Ppp3ca, Mapk1 were all down-regulated except Calm2 in the 50 ppm treatment group, relative to controls. Similarly, Alas1 was negatively regulated in all treatment groups except the 90d 50 ppm group. Cyp3a13 was negatively regulated in all treatment groups during all time points. Confirming microarray results are the down-regulation of Calm2 -3.886, Alas1 -1.616, Atp5o -2.706 and Cyp3a13 -1.79 genes in the long term exposure group

**1079** ASSOCIATIONS BETWEEN LONGITUDINAL MEASURES OF OCCUPATIONAL LEAD DOSE AND RENAL FUNCTION.

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Introduction: The exposure range associated with lead-related nephrotoxicity in the occupational setting has not been clearly established. With the exception of two small studies, prior research has been cross-sectional thus limiting inferences regarding causality.
Methods: We evaluated associations between lead dose and serum creatinine from three annual evaluations in a cohort of 803 Korean lead workers. Blood lead was measured via atomic absorption spectrophotometry; tibia lead was measured via $^{109}$Cd X-ray fluorescence. Generalized estimating equations were used to evaluate annual change in serum creatinine in relation to tibia lead concentration at the beginning of each follow-up period and concurrent change in blood lead. Models were adjusted for age, sex, body mass index, hypertension, days between evaluations, current/former lead worker status, time since retirement, plant of employment, and baseline blood and tibia lead.
Results: 75.5% of the 575 participants who completed all three evaluations were male. At baseline, 7.7 % and 0.5 % reported diagnoses of hypertension and diabetes, respectively. Mean (SD) age and lead job duration were 41.4 (9.5) and 8.5 (6.3) years, respectively. Mean (SD) blood and tibia lead levels were 31.3 (14.1) μg/dL and 35.1 (32.6) μg/g bone mineral, respectively. Concurrent change in blood lead was associated with an annual increase in serum creatinine of 0.012 (95% confidence interval, 0.003, 0.020) mg/dL for each 10 μg/dL increase in blood lead per year. In contrast, tibia lead was not significantly associated with change in serum creatinine.
Conclusions: These results support the inference that occupational lead exposure contributes to renal function decline.

**1080** ACUTE LUNG INFLAMMATORY RESPONSE FOLLOWING PHARYNGEAL ASPIRATION OF STAINLESS STEEL WELDING FUME OR SOLUBLE CHROMIUM IN A/J AND C57BL/6J MICE.

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Previous data from our laboratory showed a greater lung inflammatory response in tumor susceptible (A/J) versus resistant (C57BL/6J) mice to aspirated chromium-containing manual metal arc-stainless steel welding fume (WF) at 7 and 28 days post-exposure. To gain further insight into the mechanisms and time course underlying this inflammatory response to WF, an acute time point was completed. Mice were exposed by pharyngeal aspiration to four doses (one dose every three days), of 5mg/kg WF, 1.5mg/kg soluble chromium (S-Cr), or saline vehicle. Bronchoalveolar lavage (BAL) and histopathology were done 2 days after the fourth dose. Lung injury (lactate dehydrogenase [LDH] and albumin), cytokines (IFN-γ, IL-6, MCP-1, and TNF-α), inflammatory cell influx (% polymorphonuclear leukocytes [PMN] and lymphocytes), and nitric oxide (NO) were measured in the BAL. At 2 days, both strains had increased lung injury, cytokines, and % PMN following exposure to WF or S-Cr but only the WF-exposed A/J mice had significantly increased NO levels. The C57BL/6J had equal degrees of inflammatory cell influx, lung injury, and cytokines following exposure to either WF or S-Cr. In contrast, the A/J mice exhibited a more heightened response to WF than to S-Cr, which was significantly higher than the C57BL/6J. Lung lesions, observed by histopathology, ranging from multifocal, minimal to moderate in severity, were found to be similar between the two strains and the exposure groups. It was also observed that the exposed C57BL/6J mice had higher lymphocyte numbers compared to the susceptible A/J strain. In conclusion, the mechanisms responsible for the lung inflammatory response to WF versus S-Cr appear to differ in the A/J but not in the C57BL/6J mice. These data suggest components, other than chromium, in the stainless steel WF exert additional toxicological effects in the A/J strain.

**1081** CHROMIUM(VI) INDUCES GENES THROUGH STAT1 TRANSACTIVATION OF INTERFERON-STIMULATED RESPONSE ELEMENTS.

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There is a traditional view that Cr(VI) suppresses inducible gene expression. However, recent evidence has shown that Cr(VI) stimulates cell signaling that activates nuclear translocation and DNA binding of the members of the STAT family of transcription factors. To investigate whether this binding leads to acute induction of STAT-driven genes, human airway epithelial (BEAS-2B) cells were transiently transfected with luciferase reporter constructs driven by STAT1 responsive ISRE or gamma interferon activated sites (GAS). Addition of 5 μM Cr(VI) stimulated only the ISRE reporter, suggesting that Cr(VI) mimics the action of interferon α/β. This was confirmed by demonstrating that Cr(VI) only induces the endogenous, ISRE driven gene, IRF7, but not IRF1, which is predominantly GAS site-driven. Induction of IRF7 mRNA levels occurred within 2 h of Cr(VI) exposure and Western analysis of nuclear proteins correlated this induction with a rapid increase in tyrosine phosphorylated STAT1. Cr(VI)-stimulated IRF7 mRNA expression was blocked in cells expressing STAT1 siRNA, but was not blocked in cells incubated with a neutralizing antibody to interferon α/β receptor (CD118). Cr(VI) inhibits certain gene induction by retaining histone deacetylase-1 (HDAC) activity in their proximal promoters (Wei,Y.D., et al. J.Biol Chem. 279:4110-4119 2004). In contrast, Cr(VI)-stimulated transactivation of the ISRE reporter and induction of endogenous IRF-7 mRNA and was inhibited in cells previously incubated with the HDAC inhibitor sodium butyrate. These data demonstrate that Cr(VI) does induce acute phase genes and present a novel mechanism in which Cr(VI) acts at the level of cell signaling to activate STAT1 to induce interferon (IFN)-stimulated genes through a HDAC-dependent mechanism. *Supported by NIEHS grant ES10638.*

**1082** MICROARRAY ANALYSIS OF PARTICULATE CHROMATE-INDUCED GENE CHANGES IN HUMAN LUNG CELLS.

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Hexavalent chromium (Cr(VI)) is a widespread environmental contaminant and a well- established human lung carcinogen with solubility playing an important role in its carcinogenicity. However, the carcinogenic mechanism remains unknown. Our study showed that particulate Cr(VI) is cytotoxic and genotoxic to human lung cells. Functional changes within the cell are believed to depend on the number of gene expression differences and the actual functional relationships between them. To identify genes that are induced by particulate Cr(VI) in human lung cells, microarray analysis was used allowing the measurement of the expression level of thousands of genes simultaneously. We treated the cells with lead chromate (0, 0.5 μg/cm2) for 24 hours and hybridized RNA onto oligo microarrays. After normalizing and filtering the data from two color oligo microarray scans, we found that 515 of a total of 887 genes have changed expression including 24 genes that are significantly up-regulated (fold change greater than or equal to 1.5), and 97 genes are significantly down-regulated (fold change less than or equal to 0.67). In addition, we identified a list of particulate Cr(VI) inducible genes which plays important role in cell cycling pathways. This work was supported by NIEHS grant ES10838 (J.P.W.)

**1083** PARTICULATE HEXAVALENT CHROMIUM INDUCES CHROMOSOME INSTABILITY AND DECREASED EXPRESSION OF SPINDLE ASSEMBLY CHECKPOINT PROTEINS.

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The spindle assembly checkpoint (SAC) pathway ensures cells do not prematurely enter anaphase causing the formation of aneuploid cells. Aneuploidy is a type of chromosome instability (CIN) involving the loss or gain of chromosomes. CIN is a hallmark of lung cancer with 70-80% of lung tumors having severe aneuploidy including triploid and tetraploid complements and is proposed as an early event in carcinogenesis. Hexavalent chromium (Cr(VI)) is a known lung carcinogen. Cr(VI)-induced tumors exhibit chromosome instability (CIN), but the mechanisms underlying these effects are unknown. We have found chronic, low doses of lead chromate, a particulate Cr(VI) compound, causes increased aneuploidy with many aneuploid cells being able to continue to grow and persist. Specifically, after 120 h treatment of 5 μg/cm2 lead chromate, 55% of the cells were aneuploid. Additionally, this treatment caused an increase in anaphase, often disorganized

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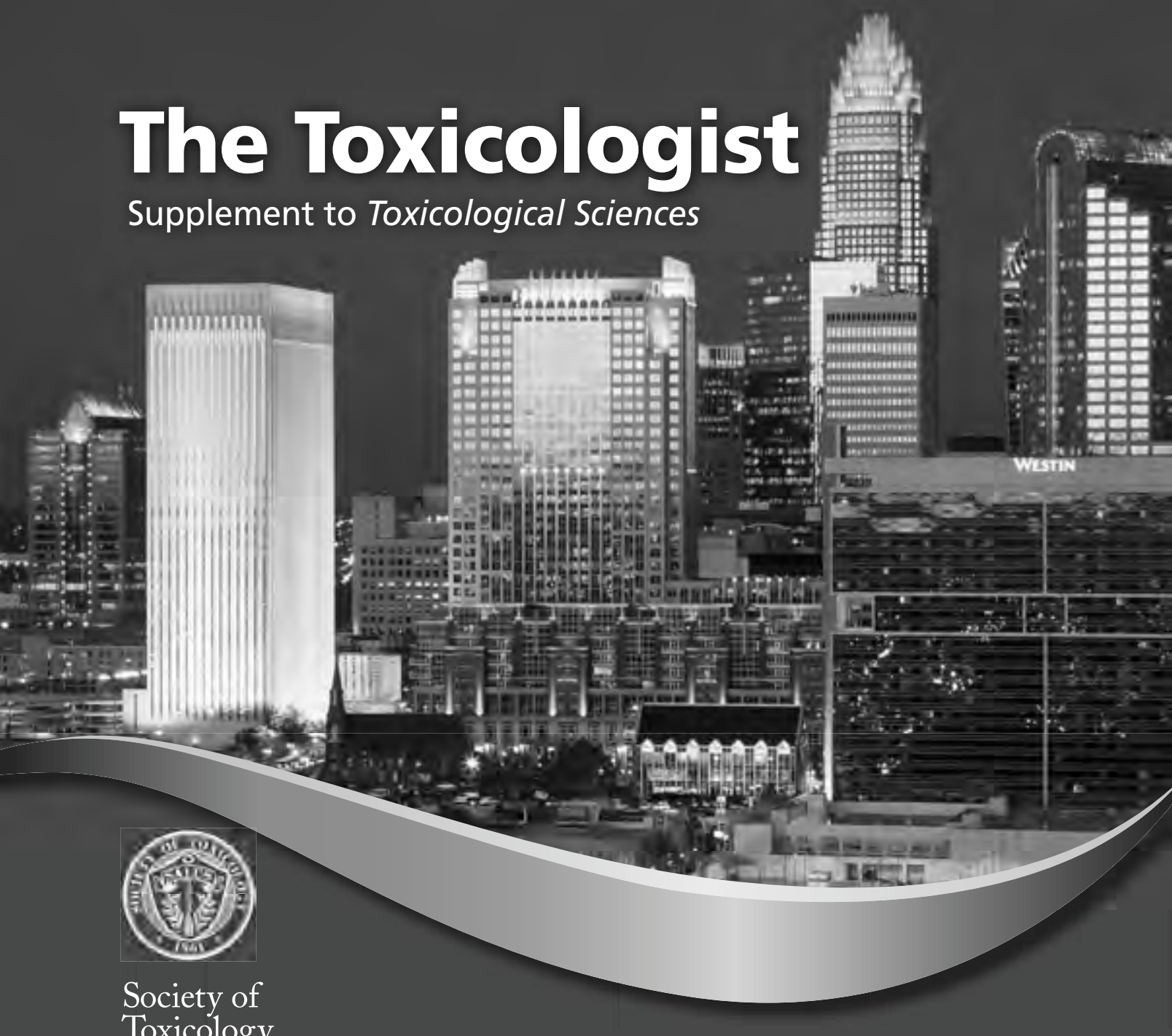


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# Preface

**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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