peroxidation. Exposure to CdCl2 also resulted in a significant decrease in RUNX2 mRNA expression, about 40% at 6 and 12 hours, compared to untreated controls. To show that cadmium-induced oxidative damage occurs upstream from changes in RUNX2 expression, cells will be pretreated with antioxidants to control the level of oxidative stress. We predict antioxidants will prevent cadmium-induced decrease in RUNX2 expression. This study will provide insight into the mechanisms underlying cadmium-induced alterations in bone function.

1939 A N-TERMINAL MUTANT FORM OF MT-3 AFFECTS THE GROWTH RATE, VECTORIAL ACTIVE TRANSPORT AND EXPRESSION OF CADHERIN MOLECULES IN MCF-7 BREAST CANCER CELLS.

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The metallothioneins (MT) are well-known for their role as metal-binding proteins and for their protective affects against heavy metal induced toxicity. MT-3 possesses neuronal growth inhibitory activity, a characteristic feature not shared by any other member of the MT family. Previous studies from this laboratory have shown that MT-3 can inhibit the growth of the PC-3 prostate cancer cell line or the MCF-7 and Hs578T breast cancer cell lines. Furthermore, studies from this laboratory also suggested that MT-3 might have a role in cell differentiation. This was suggested by studies which demonstrated that the stable expression of MT-3 restored active vectorial ion transport to a proximal tubule cell line that had lost this differentiated function. Active vectorial ion transport was monitored by the formation of out-of-focus areas of the cell monolayer known as domes, a hallmark of cultured renal epithelial cells that retain the in situ property of vectorial active transport. In the present study, a site directed mutant of MT-3 was generated in an attempt to determine which epitope of the MT-3 protein was responsible for the growth inhibition noted when MCF-7 cells were stably transfected with the MT-3 gene. The MT-3 mutant possessed alteration in the beta domain of the protein, specifically, proline 7 and 9 were mutated to threonines. Transfection of the MT-3 mutant into MCF-7 cells abolished the growth inhibitory activity of the protein. Furthermore, the cells formed domes in culture indicating a gain-of-function for the differentiated property of vectorial active ion transport. It was also demonstrated that these cells expressed high levels of E-cadherin compared to the parent MCF cells as well as the MCF cells expressing the MT-3 gene, suggesting that MT-3 may be involved in the regulation of junctional molecules.

1940 MOLECULAR AND TOXICOLOGICAL RESPONSES TO MERCURIALS IN C. ELEGANS.

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Humans are typically exposed to three different species of mercury: inorganic, methyl and the mercury-containing compound thimerosal. While these compounds are toxic, their mechanisms of toxicity are poorly understood. We hypothesize that different mercurial species modulate the activity of unique and overlapping intracellular signal transduction pathways to affect transcription. Using the nematode C. elegans, we have investigated the mechanisms of toxicity of these compounds. After determining an equitoxic dose for each compound, microarrays were run to determine changes in gene expression resulting from mercury exposure. Bioinformatics analysis was then used to predict which signaling pathways are affected by the different mercury species. To assess the potential roles of these pathways, siRNA used to knock-down genes of interest, and C. elegans was subsequently exposed to the different mercurials to test for a mercury-sensitive or mercury-resistant phenotype. The localization and induction of novel genes will be investigated by integrating GFP-tagged genes into C. elegans. Through this combination of toxicology, bioinformatics and molecular biology techniques, we hope to elucidate the mechanisms by which the different mercurials exert their respective toxicities.

1941 DOSE RESPONSE EFFECTS OF MUTANT KI-RASG12C IN MOUSE LUNG.

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Our laboratory has developed a bitransgenic mouse lung tumor model that, upon treatment with 500ug/ml of doxycycline (DOX) for 12 months, allows for the maximal expression of the human Ki-rasG12C allele in the lung, resulting in the development of benign focal hyperplasias and adenomas. We determined if different levels of mutant RAS expression would influence the phenotype of the lung lesions. Treatment with 25 and 100ug/ml of DOX resulted in dose-dependent increases in tumor multiplicity. At the 500ug/ml dose, all of the lesions were <1mm; however, in mice that received the lower doses of DOX, there was a significant number of lung lesions that were ≥1mm, with some reaching up to 4mm in size. Interestingly, there was a dose-dependent difference in the morphology of the proliferative lesions. The 25 and 500ug/ml treated bitransgenic mice exhibited hyperplasias and relatively benign adenomas, whereas the 100ug/ml treated mice also exhibited more severe, high grade adenomas with atypic features of AC. Immunohistochemical analysis of signaling pathways suggested similarities and differences in the expression and/or phosphorylation of specific signaling molecules. Increased expression of p19ARF, along with the concomitant activation of the p53 pathway, was only seen at the 500ug/ml dose. Elevated levels of Ki-67 staining were found at all 3 levels of transgene expression. Interestingly, increased caspase-3 activity was noted at the 25 and 100, but not the 500ug/ml, dose. Increased expression of survivin was seen at the 100ug/ml and 500ug/ml doses but not at the 25ug/ml dose. Using a phospho-specific antibody, we found an increase in phosphorylated JNK at the 25ug/ml dose, but not at the two higher doses. Our results suggest that the molecular alterations driving tumorigenesis may differ at different levels of transgene expression, and this should be taken into consideration when inducible transgene systems are utilized to promote tumorigenesis in mouse models.
(Supported by NCI grant CA91909)

1942 SILICA CARCINOGENICITY IN A SUSCEPTIBLE MOUSE MODEL.

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In 1997 IARC classified crystalline silica as a Group I human carcinogen despite disagreements in the scientific community related to the lack of a mouse model for silica-induced carcinogenicity. Since mutations of the p53 tumor suppressor gene are the most frequently observed genetic changes in human and animal cancers, this study was designed with mice deficient in p53 to evaluate the potential carcinogenicity of crystalline silica. Specifically, these experiments examined the effects of pharyngeal aspiration of freshly fractured silica (0 or 2mg) on various biochemical, molecular and genomic changes and incidence of preneoplastic lesions in the lungs of wildtype, heterozygous and homozygous mice after 2 and 6 months. Analysis performed on bronchoalveolar lavage fluid markers (albumin, lactate dehydrogenase), cells (differential cell counts, apoptosis, cell cycle analysis), and lung tissue (microarray, DNA damage) have shown differences related to exposure in various markers of toxicology and oxidative stress. Histopathologic alterations associated with silica exposure included alveolar epithelial cell hyperplasia, peribronchiolar bronchiolization and lipoproteinosis in the lungs of silica-exposed animals. Microarray analysis demonstrated alterations in genes related to cell cycle control, DNA damage repair and apoptosis, consistent with alterations seen in the cellular analysis. Preliminary microarray analysis also suggests a variation in activated signaling pathways in the wild-type animals as compared to the heterozygous animals. The data described here shows an effect of p53 status on response to silica exposure as early as 2 months following the initial exposure. This susceptible mouse model may provide insights into the critical role of p53 in silica-induced lung injury.
The findings and conclusions of this abstract are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

1943 USE OF GENETICALLY MODIFIED C3B6F1 TRP53(+/-) P53 HAPLOINSUFFICIENT MICE FOR SHORT-TERM CANCER BIOASSAYS OF ANTIRETROVIRAL (ARV) DRUGS.

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The advent of ARV drugs revolutionized the treatment of HIV/AIDS and has allowed pregnant HIV-positive women to give birth to uninfected babies. However, ARV therapy is not without side-effects and as new ARV drugs become available it is necessary to test them in combination with existing drugs. The ARV, zidovudine (AZT) is genotoxic in fetal mice and monkeys and carcinogenic in mice. We assessed a new C3B6F1 trp53(+/-) (designated C3B6-trp53tm1Brd[N12]F1) p53 haploinsufficient, genetically modified mouse model for use in short-term cancer bioassays. These mice are produced by mating Taconic C3H females with C57Bl6(N12)trp53(-/-) males. They were dosed with 0, 80, 160, 240 mg/kg/day AZT, by gavage in aqueous methylcellulose/ polysorbate 80 (0.2/0.1%), transplacentally (via maternal gavage) from GD12 to GD18 then postnatally from PND1 until 45 weeks old. The dose and dose volume was reduced to 50% from PND1-10 to reduce acute toxicity. During the initial postnatal period (PND1- PND28), survival was >95% and >82% for the control and dosed groups respectively. The AZT treatment produced only small (<10%) reductions in body weight gain. AZT at all 3 concentrations increased blood reticulocyte micronuclei formation at PND1, 10 and 28. AZT treatment did not significantly reduce hepatic mitochondrial gene ex-

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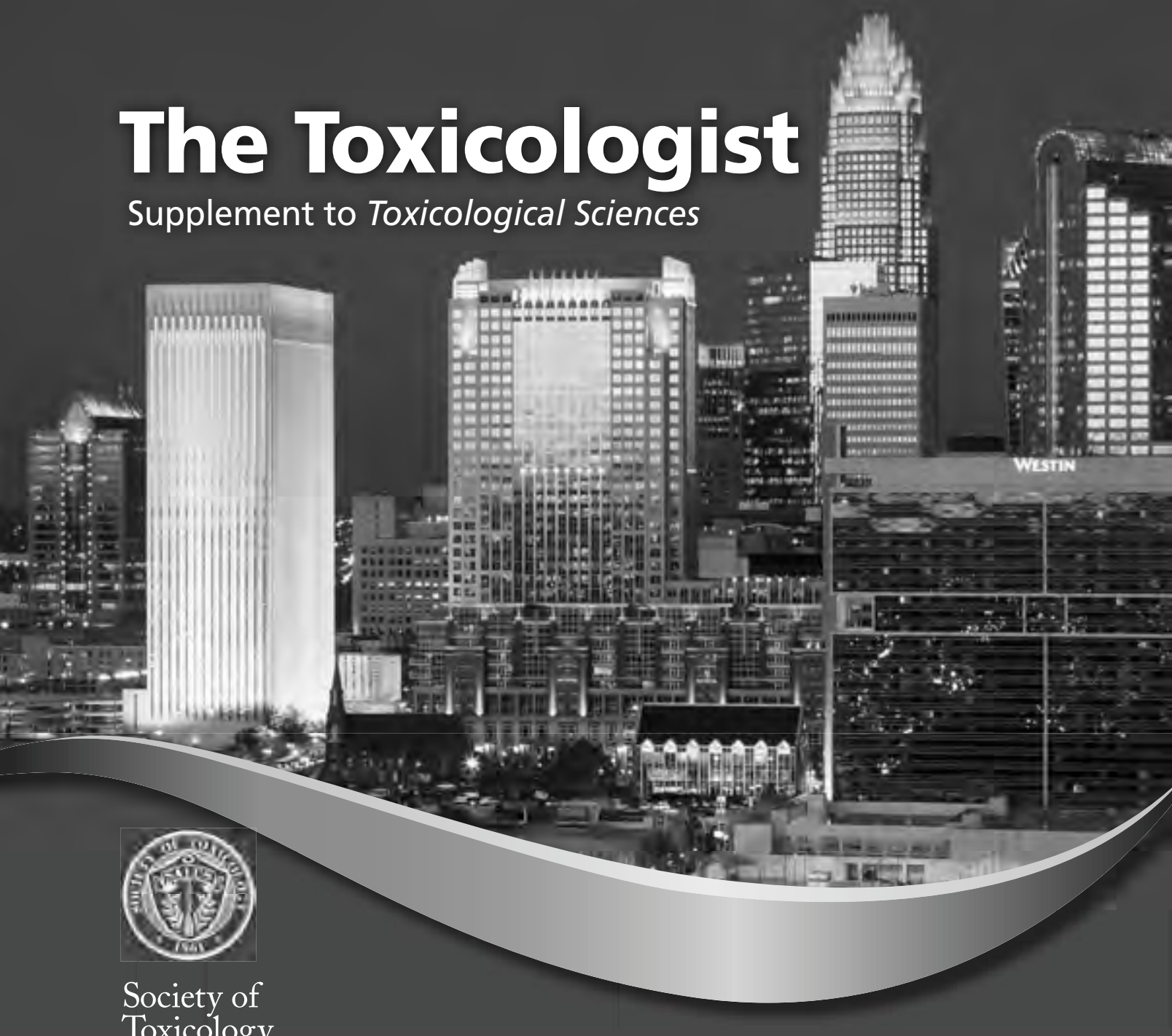

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Preface

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.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

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