groups, increases in kidney carbonyls were lowest among the PbxCdxAs group at all three timepoints. Cellular adaptation to trace element-induced oxidative stress is suggested by the attenuation of increases in kidney carbonyls at the 90 and 180 day timepoints. Statistically significant increases in kidney glutathione levels (measured as nonprotein thiols) were measured after 30 and 180 days of exposure among most treatment groups, with some of the greatest increases measured among the four combination groups at the 30 day timepoint (96%-145% increase) and the 180 day timepoint (20%-70% increase). In contrast, kidney non-protein thiols were statistically significantly decreased in 4 of 7 treatment groups after 90 days of exposure (28%-33% decrease). These data demonstrate that low-level exposure to trace elements or their mixtures results in measurable increases in oxidative stress and upregulation of cellular defensive mechanisms [Supported by USEPA Star Grant R827161-01-0].

1160 CHANGING METAL ACCUMULATION IN NEW ORLEANS: DIFFERENCES BETWEEN SURVEY I (1992) AND SURVEY II (2000).

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New Orleans soils have been surveyed and mapped twice. Survey I was completed in 1992 and Survey II was completed in 2000. This study evaluates the possibility for change between the two surveys. All samples were collected in residential neighborhoods at least one block from a busy street. The Survey I collection had 4, 026 samples stratified by 283 census tracts and Survey II had 4, 389 samples stratified by 286 census tracts. The extraction methods used the same protocol for pH (1 M Nitric acid), room temperature and 2 hour shaker time. They differed in amount of sample extracted, 4.0 g (Survey I) compared with 0.4 g (Survey II). ICP-AES techniques were used to measure 8 metals. The analytical results of the extraction methods were evaluated with homogenized soil samples from the Wageningen Evaluating Programs for Analytical Laboratories, International Soil-analytical Exchange (WEPAL; ISE). All correlation results were linear and the Survey I results were converted to make them equivalent with the Survey II results. Geographic Information Science (GIS) evaluation was done by assigning a median soil metal result to the centroid of each census tract; Kriging interpolation of the above data with Surfer; Importing ASCII grids into ArcView GIS using the grid machine extension; Forming a new grid by Survey II divided by Survey I grid cells. Changes in metals were observed. Most prominent were increases in the inner city Pb, Zn, Cu. Amounts of Cr, Cd and Mn appear to be about the same, and V, and Ni decreased. Reasons for increases of Pb and Zn include: Power sanding of New Orleans old wood homes with Pb-based paint; Zn is a constituent of tires and paints. The suburb lacks similar metal sources and new soils are commonly added for landscaping purposes. Overall, residential soil metals appear to undergo a relatively high rate of change. Pb, Zn and Cu appear to continue accumulating in the inner-city.

1161 TOXICOGENOMICAL STUDY ON HUMAN BLADDER EPITHELIUM EXPOSED TO ARSENIC.

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In this study, human urothelium (UROtsa) cells were exposed to arsenite [As(III)-30 μM], monomethylarsenous acid [MMA(III)1-5 μM], or buthionine sulfoximine [BSO-25 μM] followed by [As(III)-1μ M] for up to 18 hr and the changes in gene expression determined by using a human oligonucleotide chip (18, 861 genes). The hybridizations were performed at least three times using independent total RNA preparations to ensure reproducibility. Differentially expressed genes were identified based on 2-fold cut off and gene significantly different from the control cells (t-test analysis, $p<0.05$). Only up-regulated genes have been assessed. Both As(III) and MMA(III) treatments produce an oxidative stress response. Interestingly, MMA(III) exposure for 6 hr did not induce any metallothionein genes but induced numerous unique genes [such as dual specificity phosphatase (DUSP1, DUSP2); CDC like kinase (CLK1); DNA damage inducible transcript (DD1T3)] and even caused greater increases in stress genes [e.g. heat shock protein (HSPA6, HSPA1A); DnaJ(HSP40)]. Reduction in cellular GSH content via BSO treatment followed by As(III) exposure for 6 hr exacerbrate the gene expression-modifying effects of arsenite on UROtsa cells. The induction of heat shock protein (HSPA1A, HSPA6); metallothionein (MT1G); and solute carrier family (SLC30A) genes revealed synergistic effects of cytotoxicity for both AsIII and BSO. These results indicate that oxidative stress must be a common pathway in cellular response to exposure to different arsenicals. Furthermore, As(III) and MMA(III) induce genes involved in similar but different pathways. The absence of metallothionein gene induction by MMA (III) exposure may demonstrate different mechanism of recognition by the UROtsa cells or mechanism of toxicity (NIEHS 04940, SWEHSC 06694 and NCI 023074).

1162 DIFFERENTIAL EFFECTS OF CHRONIC LOW LEVEL ARSENIC EXPOSURES ON TRANSCRIPTION FACTOR BINDING IN CARDIOVASCULAR TISSUES.

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Chronic exposure to low levels of trivalent arsenic in drinking water promotes differential induction of cardiovascular genes, vascular remodeling, and vascular disease. To resolve the signaling pathways involved in arsenic-induced phenotypic change, proteomic analysis of transcription factor DNA binding arrays in nuclear extracts from mouse hearts or cultured porcine vascular smooth muscle cells were examined. *In vivo*, mice fed 10-50 ppb of sodium arsenite (AsIII) in their drinking water for 5 weeks had increases in nuclear proteins binding to AP-1, Ets, FKHR, GATA, HIF and Stat consensus DNA cis elements. Nuclear extracts from smooth muscle cells had similar, but more limited increases in the binding of these transcription factors. In contrast to previous reports for higher levels of exposure, there were no significant increases in stress response factors, NF-κB, or p53 DNA binding in either model with these AsIII exposures. AsIII exposures also decreased nuclear levels of a significant number of transcription factors. Gel mobility shift assays and western analysis of proteins from multiple animals and cell cultures were used to confirm increases seen in the array analyses. Genes induced by these AsIII exposures include vascular endothelial cell growth factor, plasminogen activator inhibitor-1, endothelin-1. These data demonstrate that chronic, low dose AsIII exposures activate multiple interacting signaling cascades to transcriptionally promote cardiovascular vascular remodeling and response genes. Supported by NIEHS SBRP grant ES07373

1163 EUKARYOTIC TRANSLATION INITIATION FACTOR 4E IS A CELLULAR TARGET FOR ARSENIC BUT NOT CHROMIUM TOXICITY.

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The mRNA cap binding translation factor, eukaryotic translation initiation factor 4E (eIF4E), was studied as a potential cellular target for the toxicity and cell death induced by arsenic and chromium. Human cell lines HCT15, PLC/PR/5, HeLa and Chang, were treated with sodium arsenite (As) and potassium dichromate (Cr). Exposure to both As and Cr resulted in significant cytotoxicity and cell death in all four cell lines. In all the cell lines treated with As and Cr, the transcript for eIF4E did not exhibit any change compared with the corresponding control cells. However, in the cells treated with As alone, the cellular expression level of eIF4E protein was significantly lower compared to the corresponding control cells. Further studies revealed that exposure of cells to As, but not to Cr, resulted in significant induction of ubiquitination of eIF4E protein. Results of the experiments involving inhibitors for the cellular proteasome pathway confirmed that the exposure of As but not Cr activated the proteolysis of eIF4E mediated through the ubiquitin/proteasome pathway. Whether the As-induced cytotoxicity and cell death were due to the inhibition of eIF4E was studied by specifically silencing the expression of eIF4E gene using a small interfering RNA (SiRNA) targeting eIF4E gene expression. The SiRNA-mediated silencing of eIF4E gene resulted in cytotoxicity and cell death suggesting that eIF4E is a potential cellular target for cytotoxicity and cell death due to exposure to As.

1164 EFFECT OF ARSENITE ON PU.1, C/EBPS, AND NFKB ACTIVATION IN U937 PROMONOCYTIC LEUKEMIA CELLS.

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Arsenite has been reported to exert dose-dependent dual effect; triggering apoptosis at relatively high concentration, whereas it induces partial differentiation at low concentration in leukemia cells. However its bilateral character regarding the molecular mechanisms remains to be clearly defined. We examined the effect of arsenite on key transcription factors for macrophage differentiation such as PU.1 and C/EBPs to find out how arsenite interacts with the signaling pathways for differentiation in U937 promonocytic leukemia cells. Electrophoretic mobility shift assays were used to analyze the interaction between arsenite induced signaling and these transcription factors. In addition the phorbol ester TPA which activates PKCs was compared with arsenite as a second type of differentiation inducer for leukemia cells. The PU.1 activation was not changed in the presence of 1 μM or 10 μM arsenite for 3, 6, or 24-hrs exposure. On the other hand, activation pattern of PU.1

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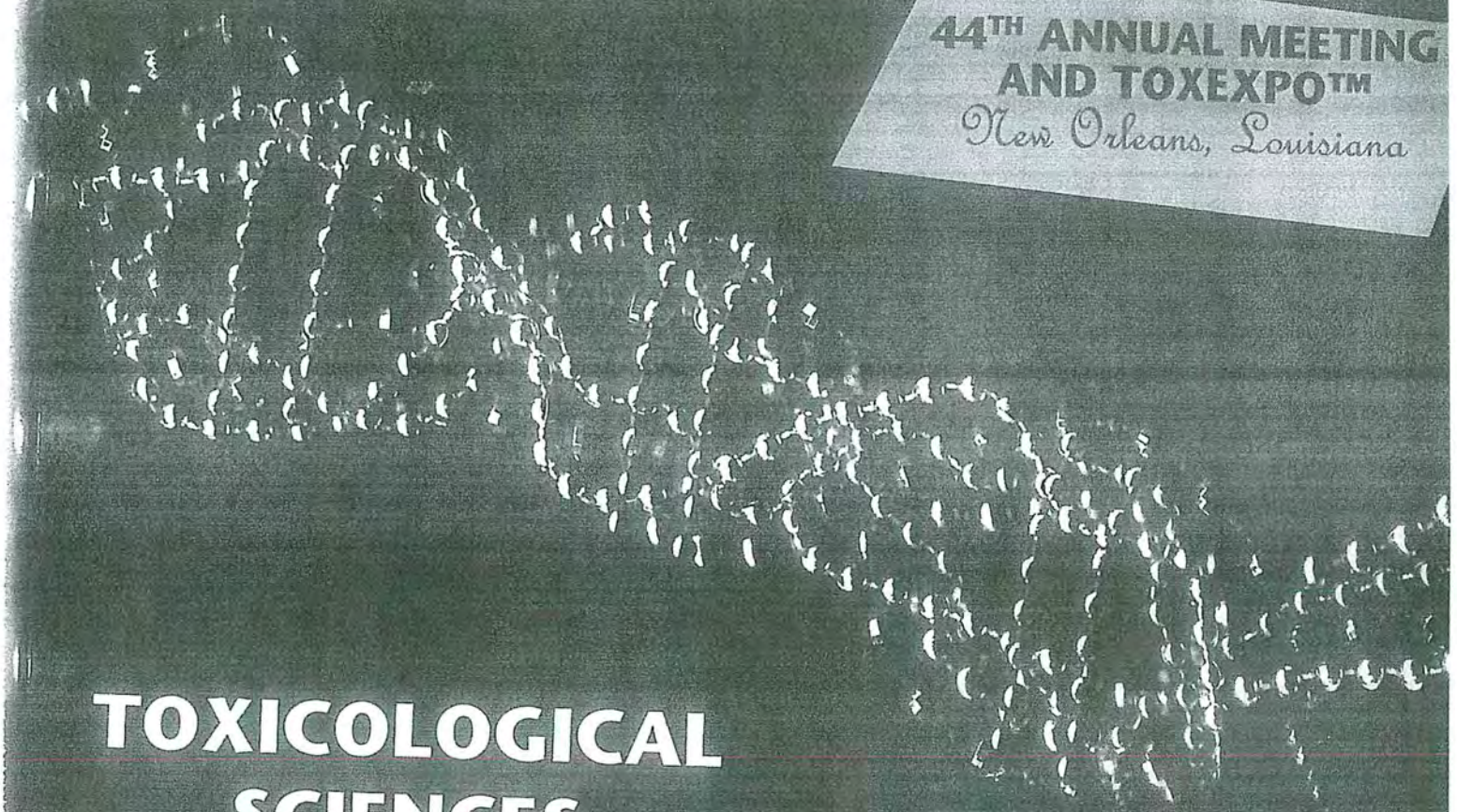

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