levels significantly increased in the nails, as well as in striatum and midbrain, potential targets of Mn neurotoxicity, for the MMA-HS group compared to the GMA-MS group and controls. Our results demonstrate nail Mn to be a potentially viable and sensitive biomarker for welding fume exposure. The ease with which nails can be harvested, transported, and stored makes them an attractive surrogate for monitoring exposures in occupational settings.

PS 2318 PERIPHERAL BLOOD GENE EXPRESSION PROFILING REVEALS SILICA-INDUCED PULMONARY TOXICITY.

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The present research aimed to investigate peripheral blood gene expression profiling as a minimally invasive surrogate approach to study silica-induced pulmonary toxicity. Rats were exposed to crystalline silica by inhalation (15 mg/m3, 6 hours/day, 5 days). Pulmonary damage and blood gene expression profiles were determined at various latency periods (0 - 16 weeks). Silica exposure resulted in pulmonary toxicity in the rats as evidenced by histological changes in the lungs and elevation of LDH activity in the bronchoalveolar lavage fluid (BALF). Analysis of global gene expression profiles in the blood of the rats identified genes that were differentially expressed in response to silica exposure. The differential blood gene expression profiles correlated with the pulmonary toxicity parameters in the silica exposed rats. Genes involved in biological functions such as inflammatory response, cancer, pulmonary damage, oxidative stress, energy metabolism, fibrosis, etc, were found differentially expressed in the blood of the silica exposed rats compared with the controls. Induction of pulmonary inflammation in the silica exposed rats, as suggested by differential expression of inflammatory response genes in the blood, was supported by significant increases in the number of neutrophils and macrophages as well as the activity of pro-inflammatory chemokines – MCP1 and MIP2, observed in the BALF of the silica exposed rats. A silica-responsive blood gene expression signature developed using the gene expression data predicted with significant accuracy the exposure of rats to lower concentrations (1 and 2 mg/m3) of silica. Taken together our findings suggest the potential application of peripheral blood gene expression profiling as an efficient surrogate approach to study silica-induced pulmonary toxicity.
Disclaimer: The findings and conclusions in this abstract have not been formally disseminated by NIOSH and should not be constructed to represent any agency determination or policy.

PS 2319 BIOACTIVATION OF THE NASAL TOXICANT 2, 6-DICHLOROBENZONITRILE: AN ASSESSMENT OF METABOLIC ACTIVITY IN HUMAN NASAL MUCOSA AND IDENTIFICATION OF BIOMARKERS OF EXPOSURE AND POTENTIAL TOXICITY.

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The herbicide 2,6-dichlorobenzonitrile (DCBN) is a potent nasal toxicant in rodents. However, it remains unknown whether DCBN causes nasal toxicity in humans. CYP2A5, a P450 enzyme predominantly expressed in mouse nasal mucosa, is largely responsible for converting DCBN into electrophilic intermediates, which, through formation of glutathione conjugates (DCBN-GS) and protein adducts, cause tissue damage. The human orthologs of CYP2A5, CYP2A6 and CYP2A13, are both expressed in the nasal mucosa, and are capable of activating DCBN. Therefore, we hypothesized that 1) human nasal tissues can activate DCBN; and 2) DCBN-GS or its derivatives can serve as biomarkers of potential DCBN exposure and toxicity. To test these hypotheses, we first established a sensitive LC-MS/MS method for detection and quantification of DCBN-GS in biological matrices. We then demonstrated that human fetal nasal mucosa microsomes catalyzed the formation of DCBN-GS *in vitro*, with a Km value comparable to that for DCBN-GS formation in adult mouse nasal microsomes. The involvement of CYP2A enzymes in this bioactivation in human nasal microsomes was confirmed by the finding of an inhibition of the activity by 8-methoxyporsalen, a known CYP2A inhibitor. Furthermore, DCBN-GS was detected in the nasal mucosa and nasal-wash fluid obtained from DCBN-exposed mice; the detected amounts of DCBN-GS increased, with increases in DCBN dose, and the conjugate was detectable at as early as 30 min after DCBN exposure. Moreover, metabolites of DCBN-GS, including DCBN-Cys, which may serve as alternative biomarkers, were also detected in the nasal mucosa and nasal-wash fluid. Thus, our data indicate that DCBN is potentially toxic to human nasal tissues, and that DCBN-GS (or its derivatives) in nasal-wash fluid may serve as biomarkers of DCBN exposure and potential nasal toxicity in humans. (Supported in part by NIH grant ES007462)

PS 2320 SYSTEMIC UPTAKE OF ^{14}C 2, 3-BUTANEDIONE ADMINISTERED BY INTRATRACHEAL INSTILLATION IN MALE SPRAGUE-DAWLEY RATS AND OROPHARYNGEAL ASPIRATION IN MALE B6C3F1 MICE.

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2,3-Butanedione (BD) is a reactive diketone that is found in butter and has been used in artificial butter flavor, and is thought to cause bronchiolitis obliterans in popcorn workers. The extent of uptake of BD from inhalation exposure is a concern. The objective of this study was to evaluate the ability of BD to be taken up in the lung, enter the systemic circulation, and bind to hemoglobin and albumin. [1-^{14}C] BD was administered to male Sprague Dawley rats (100 mg/kg) by intratracheal instillation (ITI), and to male B6C3F1 mice (200 mg/kg) by oropharyngeal aspiration (OPA). After 24 h, animals were euthanized and blood collected. Blood and plasma were analyzed for ^{14}C to estimate the systemic dose at 24h. Binding to plasma albumin was assessed following isolation by trichloroacetic acid precipitation, and ultrafiltration, or by ammonium sulfate precipitation. Binding to hemoglobin was assessed by dialysis of hemolysate followed by size exclusion HPLC, or by precipitation of globin from hemolysate with acidic acetone. At 24 h, 1.2 ± 0.1 % of the dose was found in rat blood, 0.66 ± 0.06 % in rat plasma, 0.35 ± 0.12 % in mouse blood and 0.17 ± 0.05 % in mouse plasma. Albumin binding in rats was 3.12 ± 0.28 nmol equiv/mg albumin, with 38% of the radioactivity in plasma bound to albumin. In mice, binding was 0.99 ± 0.26 nmol equiv./mg albumin, with 45% of the radioactivity in mouse plasma bound to albumin. The extent of binding to hemoglobin in the rat was 0.44 ± 0.20 nmol equiv/mg hemoglobin, and 0.31 ± 0.05 nmol/mg globin. In mice, the extent of binding to hemoglobin was 0.19 ± 0.10 nmol/mg. This study demonstrated that BD, following administration by ITI in rats or by OPA in mice, can enter the systemic circulation and react with hemoglobin and albumin. This shows the promise for evaluating hemoglobin and albumin adducts as biomarkers of exposure in humans.

PS 2321 RESVERATROL, AN AHR LIGAND, ALLEVIATES BACTERIAL ENTEROTOXIN-INDUCED ACUTE LUNG INJURY *VIA* UPREGULATION OF MIRNA 155 AND SUBSEQUENT INCREASE IN MYELOID-DERIVED SUPPRESSOR CELLS.

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Acute lung injury (ALI) has many etiologies such as inhalation of a toxic substance, pneumonia, surgery and sepsis. The treatment options for ALI are very limited, and better therapeutic options are urgently needed. We administered Staphylococcal enterotoxin B (SEB, 50μg/mouse) through the intranasal route in order to induce ALI, and treated mice with resveratrol (RES), a natural plant product and an AhR ligand. We demonstrated that pre-treatment with 100 mg/kg bodyweight oral RES alleviated vascular leak and edema induced by SEB. SEB inhalation resulted in a significant increase in the percentage and absolute cell numbers of Gr-1+CD11b+ Myeloid Derived Suppressor Cells (MDSCs) in the lungs. Moreover, resveratrol pre-treatment further increased the percentage and absolute number of MDSCs. Arginase expression, a hallmark of MDSCs, was significantly increased in RES-treated mice when compared to vehicle controls. While SEB activation in vitro resulted in extensive T cell proliferation, addition of sorted MDSCs, particularly those from RES-treated groups, caused significant suppression of T cell expansion. Next, we carried out an affymetrix survey of 600 different miRNAs in lung infiltrating lymphocytes. Ingenuity pathway software analysis revealed 11 important miRNAs that were differentially regulated in SEB-administered mice versus RES-treated groups. Interestingly, miRNA 155 exhibited 18.764 fold change in expression in SEB+vehicle-administered group when compared to 46.474 fold change in SEB+RES-treated group. We also studied the target genes of miRNA 155, and found that IL-1β and NOS-2 were highly upregulated in SEB-administered group compared to the control. RES treatment further increased the expression of these

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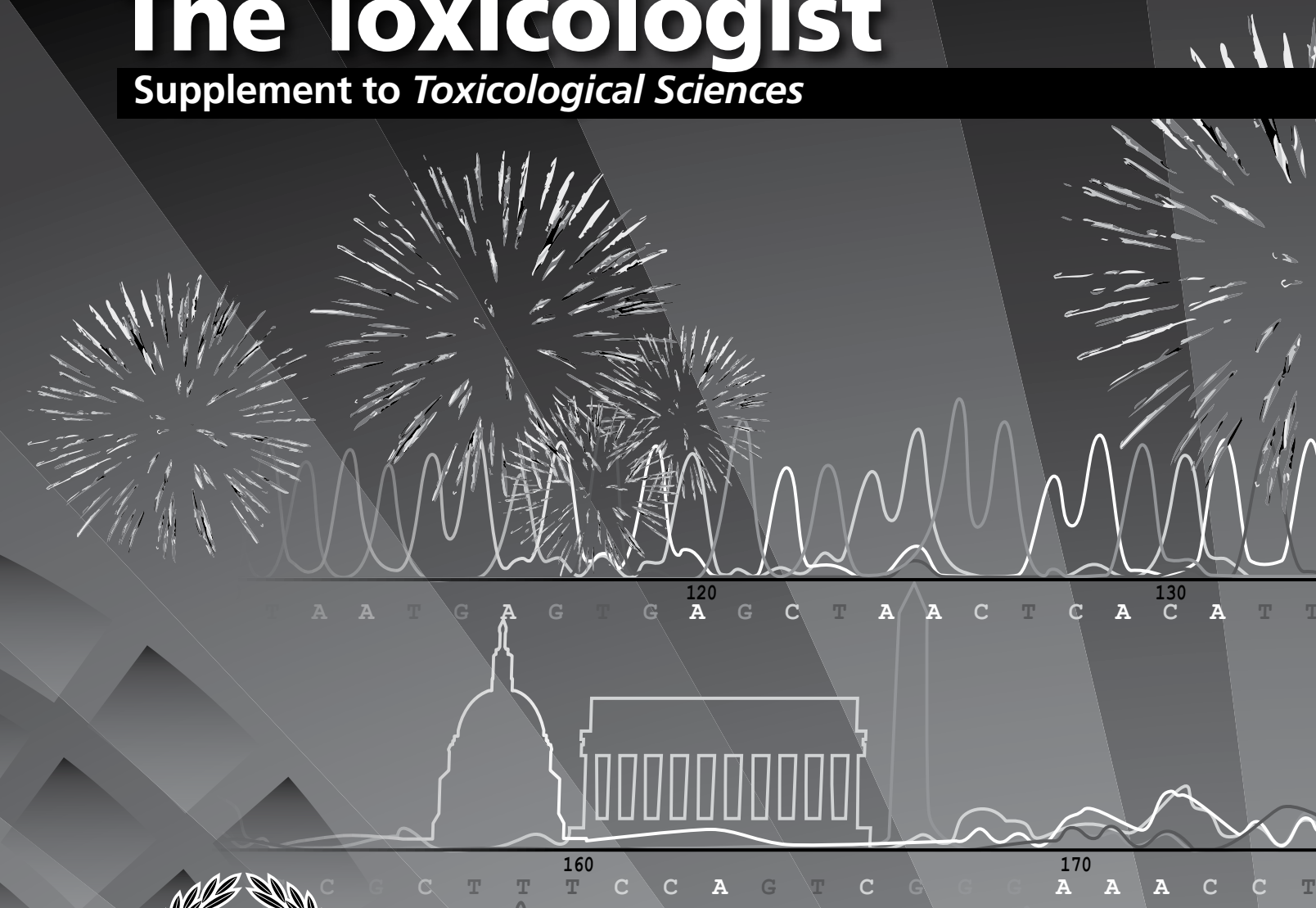

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 50th Annual Meeting of the Society of Toxicology, held at the Walter E. Washington Convention Center, March 6–10, 2011.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 578.

The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 606.

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

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