was collected prior to dosing and at 12 hour intervals for a total of 168 hours. Urine samples were assayed by ELISA for clusterin, retinol binding protein (RBP) 4, heme oxygenase (HO)-1, osteopontin (OPN), Yb1 (mu) glutathione S-transferase (GST), α glutathione S-transferase (αGST), metalloproteinase tissue inhibitor (TIMP)-1 and $\beta_2$-microglobulin. Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (Kim-1) were assayed by Meso Scale Discovery (MSD) Multi-Spot® Assay. Biomarker levels remained constant for control animals throughout the time course. However, for animals dosed with 200 and 500 mg/kg D-serine, significant increases were observed with peaks at 12 hours post-dose (HO-1, Yb1 GST and αGST), 24 hours post-dose (clusterin, RBP4, TIMP-1 and β2-microglobulin), 96 hours post-dose (Kim-1 and NGAL) or 120 hours post-dose (OPN). Biomarkers returned to baseline levels at 36 hours (Yb1 GST and αGST), ≥ 48 hours (HO-1, $\beta_2$-microglobulin, TIMP-1, clusterin and RBP4) or ≥ 168 hours (NGAL, Kim-1 and OPN). Gene expression studies were also conducted in control and dosed kidney tissue, and significant increases in transcription were seen in most biomarkers examined. RBP4, however, demonstrated significantly lower expression upon nephrotoxin exposure. Expression profiles indicate that this protein set differed in maximal response times. Their collective detection in urine is a potential noninvasive strategy to determine early onset of low level subclinical kidney damage in response to toxin exposures, ultimately leading to development of rapid field monitoring for the prediction of health hazards associated with chemical exposure.

## PS 1879 TRANSPLACENTAL DISTRIBUTION OF METALS AND THEIR INTERACTIONS ASSESSED BY BIOMONITORING IN MOTHER/CHILD PAIRS.

H. Käfferlein[1], R. Kopp[1, 2], E. Gutwinski[1], M. Kumbartski[2] and T. Brüning[1].
*[1]BGFA - Ruhr University, Bochum, Germany and [2]University of Duisburg-Essen, Essen, Germany.*

Exposure of the fetus to (heavy) metals has been associated with adverse health outcomes including developmental toxicity. However, few data exist on the transplacental passage of metals and their interaction with each other in the maternal-fetal unit. In our study, venous and umbilical cord blood samples from 50 mother/child pairs were studied for exposure to multiple heavy metals, essential minerals and trace elements. Smoking status was assessed by cotinine in urine. Lead (Pb) showed the highest median concentration of heavy metals in maternal samples (11.5 µg/L) followed by nearly equal concentrations of mercury (Hg, 0.44 µg/L) and cadmium (Cd, 0.34 µg/L). Smokers showed higher Cd levels than non-smokes (0.73 vs. 0.29 µg/L, P<0.001). Slightly but significantly lower levels of Pb were observed in fetal blood (10.3 µg/L, P<0.004), whereas Cd was strongly reduced (0.05 µg/L). In contrast, higher concentrations of Hg were detected in fetal samples (1.48 µg/L, P<0.0001). Selenium (Se) and iron (Fe) showed a similar distribution in the maternal/fetal unit as observed for Pb, whereas the distribution of manganese (Mn) was similar to Hg. Copper (Cu) and Zn were strongly reduced in the fetus and distribution was more similar to Cd. Linear regression analysis revealed positive associations between maternal and fetal concentrations for Pb, Mn and Hg (P≤0.014). No associations between maternal and fetal blood were found for Cd, Cu, Fe and Zn. Exposure to heavy metals (single or in combination) did not influence the levels of essential minerals such as Zn. In conclusion, the placenta provides a barrier for Cd, Cu and Zn, whereas Fe, Pb and Se enter the fetal environment unaffected. Mn and Hg are unequivocally transported to the fetus resulting in increased exposures compared to the mother. However, homeostasis of essential elements remains unaffected by exposure to heavy metals at low exposures. Overall, our results contribute to the risk assessment of heavy metals and adverse health outcome in the most vulnerable population, the fetus.

## PS 1880 SURVEILLANCE FOR SYSTEMIC EFFECTS OF METALS AND OTHER MATERIALS RELEASED FROM RETAINED EMBEDDED FRAGMENTS IN U.S. SOLDIERS.

K. S. Squibb[1], J. Gaitens[1], C. Dorsey[1], J. Centeno[2] and M. McDiarmid[1].
*[1]University of Maryland School of Medicine, Baltimore, MD and [2]Division of Biophysical Toxicology, Armed Forces Institute of Pathology, Washington, DC.*

Concern has heightened regarding long term health effects associated with embedded fragments in soldiers. In the past, fragments embedded in muscle tissue were thought to be relatively inert, however recent work has shown that veterans with embedded depleted uranium (DU) fragments have elevated blood and urine uranium levels more than 18 years after injury involving DU munitions during the first Gulf War. This finding is supported by studies showing release of metals from certain types of medical implants. To better understand and prevent health problems resulting from retained metal and non-metal fragments in soldiers, the Department of Veterans Affairs has established a program charged with developing clinical management guidelines for embedded fragments. These will be based on results from analysis of fragment content, health surveillance and biomonitoring of veterans with prolonged systemic exposure to chemicals released from fragment material over time. Chemical characterization of over 400 removed fragments has shown that most are metal alloys (83%) while others are different types of organic material, plastics, wood and stones. Based on this information and knowledge of the toxicity of metals, a biomonitoring protocol utilizing primarily urine has been developed to characterize systemic exposure to the following carcinogenic and cytotoxic metals: Al, As, Cd, Cr, Co, Cu, Fe, Mn, Ni, Pb, U, W and Zn. Customized health surveillance and management guidelines will be developed for veterans with chronically elevated excretion of specific metals using biomarkers of potential effects of the metal(s) of concern. Biomonitoring protocols for compounds released from non-metallic fragment materials, such as isocyanate, phthalates and acrylics, will continue to be developed as our knowledge of the breakdown of fragments embedded in muscle tissue increases. *Supported by Department of Veterans Affairs and the Armed Forces Institute of Pathology*

## PS 1881 DOD IMPACT ASSESSMENT AND MANAGEMENT OF NAPHTHALENE-RELATED RISKS.

J. Hulla[1], J. E. Snawder[2], S. P. Proctor[3] and G. D. Chapman[4]. *[1]SPK-ED-EC, U.S. Army Corps of Engineers, Sacramento, CA, CA, [2]Biomonitoring Team, National Institute for Occupational Safety and Health, Cincinnati, OH, [3]Military Performance Division, U.S. Army Research Institute of Environmental Medicine, Natick, ME and [4]Military Infectious Disease Research Program, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD.*

The Department of Defense Chemical and Materials Risk Management Directorate is using a scan-watch-action process to identify, rank and manage risks associated with emerging contaminants. Naphthalene is characterized as a likely human carcinogen by the NTP and in the EPA's most recent draft health risk assessment. Thus, naphthalene-related environmental health regulations are evolving. The potential impacts have been assessed, using multi-criteria decision analysis, for five of the Department's functional areas. One of the areas of concern is exposure to naphthalene among fuel handlers. To determine whether these exposures present unacceptable risk, the Army Research Office awarded a Small Business Innovative Research Project for the development of a miniature real-time naphthalene sensor. NIOSH's Biomoniting Team and Investigators from the Army Research Institute for Environmental Medicine, UC-Davis and the Army Corps of Engineers are collaborating on a second DOD-funded project. This project will validate the prototype sensor as a dosimeter by defining correlations between measured exposures and biomarkers of exposures to-be-collected from military fuel handlers. To date, naphthalene specificity with sensitivity of 0.5 mg/m3 has been demonstrated and definition of the firmware chemometrics is underway. Implementation of the human subjects research protocol is pending institutional review boards' approval.

## PS 1882 EFFECTS OF STYRENE CO-EXPOSURE ON FORMATION OF 1, 3-BUTADIENE DERIVED N7-GUANINE ADDUCTS.

M. T. Thompson[1], S. Goel[1], L. M. Hallberg[2], J. B. Ward[2], J. A. Swenberg[3] and G. Boysen[1]. *[1]Environmental and Occupational Health, University of Arkansas for Medical Sciences, Little Rock, AR, [2]Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston, TX and [3]Environmental Sciences & Engineering, University of North Carolina at Chapel Hill, Chapel Hill, NC.*

Protein and DNA adducts have been widely applied for monitoring the internal dose of reactive compounds and metabolites after environmental or occupational exposures. Formation of DNA and protein adducts correlate well with external exposures in rodents and human studies. A recent study in butadiene (BD) exposed workers demonstrated that BD-specific protein adducts correlate with external BD exposure (R2 = 0.6) in BD monomer workers and not in BD-styrene polymer workers (R2= 0.08), despite the fact that the BD exposures were 3-fold higher in the polymer workers. Styrene co-exposure was 14-fold higher in the polymer workers than in the monomer workers. It is suggested that styrene co-exposure effects BD metabolism, since both are metabolized by P450 2e1 to DNA reactive epoxides. Subsequent in vitro studies showed inhibition of P450 2e1 activity by styrene oxide. We report herein the effects of styrene co-exposures on the formation of N7-guanine adducts in vivo. Female B6C3F1 mice were exposed to filtered air, 20 ppm BD, 250 ppm styrene or 20 ppm BD plus 250 ppm styrene for 6 h /day, 5 days/week for 2 weeks. A method was developed for simultaneous quantitation of the isomeric N7-hydroxybuten-guanine (N7-HB-Gua), N7-trihydroxybutan-gua-

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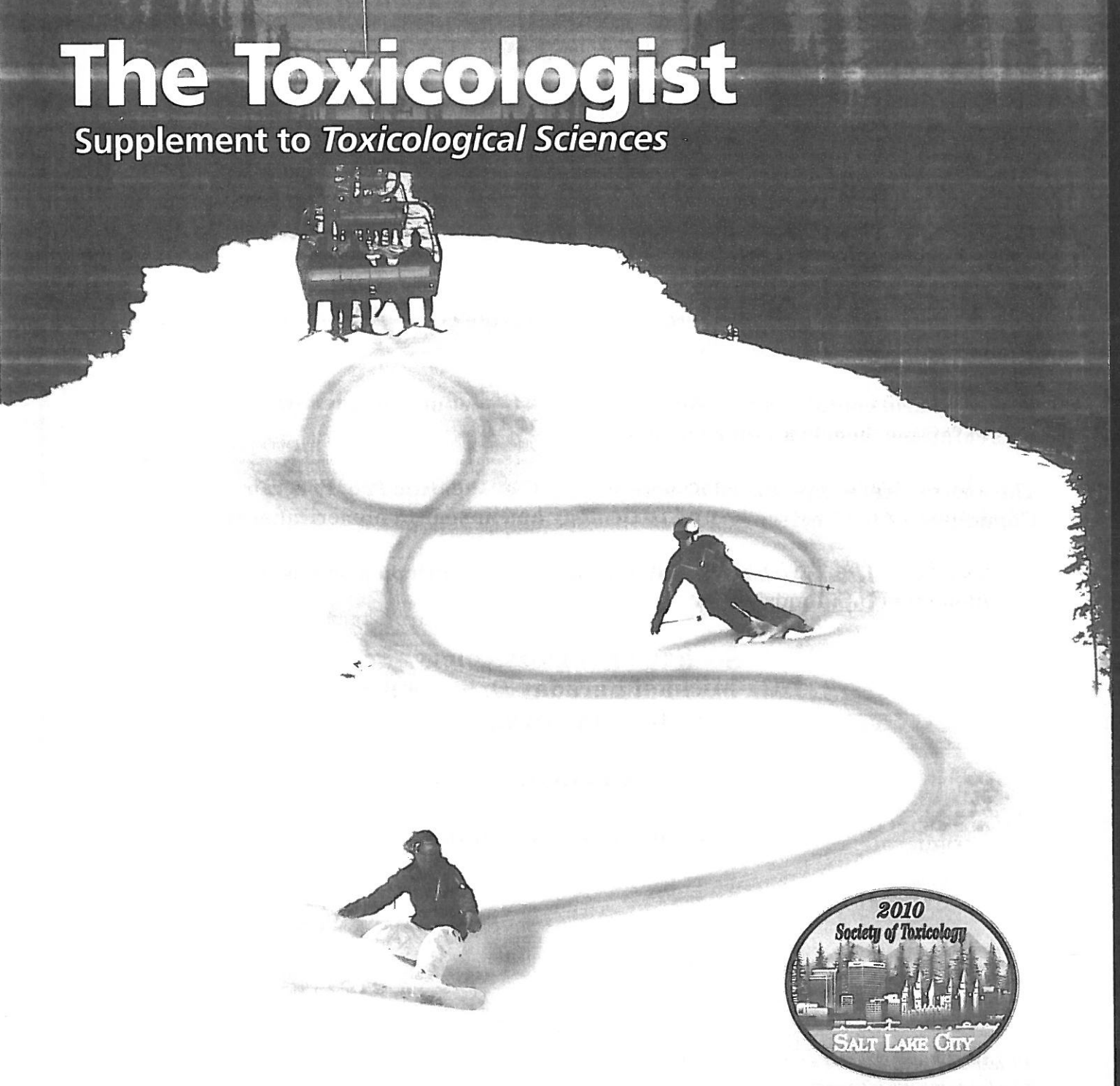


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# Preface

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**An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 473.**

**The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 496.**

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