fect of endophyte toxins on hepatic gene expression under thermoneutral (TN) and HS conditions. Core temperature (Tc) was monitored continuously in rats (n=24) implanted with telemetric transmitters. Rats were fed ad libitum either endophyte-infected (E+) or uninfected (E-) diets and maintained under Tn conditions (21C) for five days, followed by TN or HS conditions (31C) for three days. Feed intake (FI) and body weight (BW) were measured daily; selected visceral organ weights and serum chemistry were evaluated at the end. Liver sections were either fixed in 10% formalin or frozen at –80C. Protein expression of hepatic CYP3A4 was evaluated using immunohistochemistry. Hepatic enzyme activities of antioxidants, superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) were determined spectrophotometrically. Hepatic apoptosis rates were determined using TUNEL assay. Both E+ and HS induced alterations in liver-specific genes were evaluated using DNA microarrays. Intake of E+ reduced FI and BW under TN and HS conditions. Core temperature at TN decreased from pretreatment level, but increased during HS. Serum prolactin decreased with E+ treatment at TN, and increased during HS. Heat stress, E+, and the combination reduced liver weight relative to BW. Protein level of CYP3A4 was greater in E+ liver compared to E-. In addition, rats exposed to E+ and HS had less amounts of SOD, CAT and GPx; and greater apoptosis rates. Microarray analysis is being used to evaluate genes associated with antioxidant, detoxification and immune functions. Present findings suggest that rats respond to E+ and HS by inducing CYP3A4 expression and suppressing hepatic antioxidant enzymes, which could ultimately increase oxidative stress and damage.

177 EFFECTS OF MIXTURES OF THE CHLOROACETATES ON TEH INDUCTION OF OXIDATIVE STRESS IN HEPATIC TISSUES OF MICE.

E. A. Hassoun and B. Dougan. *Pharmacology, The University of Toledo, Toledo, OH.*

Dichloroacetate (DCA) and tricholoroacetate (TCA) are byproducts produced during the process of chlorination of the drinking water. The two compounds were found to be hepatotoxic and hepatocarcinogenic in rodents, with oxidative stress considered as one of the possible mechanisms of toxicity. Since the compounds always exist in the water as mixtures, rather than individual, it is very important to determine the interactivities between the two compounds. To achieve that, the compounds were administered to groups of male B6C3F1 mice, p.o, at doses of 150 and 300 mg/kg and in two mixtures, DCA+TCA 150, and DCA+TCA 300, that correspond, respectively to 75 and 150 mg/kg of each of the two compounds. The animals were sacrificed 8 h later, and changes in the biomarkers of oxidative stress, including production of superoxide anion (SA) and lipid peroxidation (LP), as well as activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) were determined in hepatic tissues. The compounds caused significant production of SA and LP, with Potentiation/ synergestic effects observed with the mixtures. Also, the compounds and the mixtures caused dose-dependent suppression of SOD and GSH-Px activities, and had slightly smaller effects on CAT activity. The results suggest that oxidative stress play an important role in the hepatotoxicity of the chloroacetates, with more effects produced when the compounds exist in mixtures.

178 ATP SYNTHASE AND UBIQUINONE ARE TARGETS FOR TCDD MITOCHONDRIAL TOXICITY.

H. Shertzer, M. Genter, D. Shen, D. W. Nebert, Y. Chen and T. P. Dalton. *Environmental Genetics & Molecular Toxicology, Department of Environmental Health, University of Cincinnati Medical Center, Cincinnati, OH.*

Mitochondria generate ATP and participate in signal transduction and cellular pathology and/or cell death. TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) decreases hepatic ATP levels and generates mitochondrial oxidative DNA damage, which is exacerbated by increasing mitochondrial glutathione redox state and by inner-membrane hyperpolarization. This study identifies mitochondrial targets of TCDD that initiate and sustain reactive oxygen production and decrease ATP levels. One week after treating mice with TCDD, liver ubiquinone (Q) levels were significantly decreased, while rates of succinoxidase and Q-cytochrome c oxidoreductase activities were increased. However, the expected increase in Q reduction state following TCDD treatment did not occur; instead, Q was more oxidized. These results could be explained by an ATP synthase defect, a premise supported by the unusual finding that TCDD lowers ATP/O ratios without concomitant changes in respiratory control ratios. Such results suggest either a futile cycle in ATP synthesis, or hydrolysis of newly-synthesized ATP prior to release. The TCDD-mediated decrease in Q, concomitant with an increase in respiration, increases complex 3 redox-cycling. This acts in concert with glutathione to increase membrane potential and reactive oxygen production. The proposed defect in ATP synthase explains both the greater respiratory rates and the lower tissue ATP levels.

179 VITAMIN E DEFICIENCY ENHANCES PULMONARY INFLAMMATORY RESPONSE AND OXIDATIVE STRESS INDUCED BY SINGLE WALLED CARBON NANOTUBES IN C57BL/6 MICE.

A. A. Shvedova[1], E. R. Kisin[1], A. R. Murray[1], O. Gorelik[2], S. Arepalli[2], V. Castranova[1], S. H. Young[1], F. Gao[3], Y. Y. Tyurina[4], T. Oury[3] and V. E. Kagan[4,5]. *[1]PPRB, NIOSH, Morgantown, WV, [2]GBTech, Inc., NASA-JSC, Houston, TX, [3]Pathology, University of Pittsburgh, Pittsburgh, PA, [4]CFRAH, University of Pittsburgh, Pittsburgh, PA and [5]GSPH, University of Pittsburgh, Pittsburgh, PA.*

Exposure of mice to single walled carbon nanotubes (SWCNT) induces an unusually robust pulmonary inflammatory response with a very early onset of fibrosis, which is accompanied by a significant oxidative stress and antioxidant depletion. The role of specific components of the antioxidant protective system, specifically vitamin E, the major lipid-soluble antioxidant of membranes and lipoproteins, in the SWCNT induced reactions required further investigation. We used C57BL/6 mice, maintained on a vitamin E-sufficient diet as well as on a vitamin E-deficient diet, to explore and compare the pulmonary inflammatory reactions to aspired SWCNTs. The induced vitamin E-deficiency (a 90-fold depletion of α-tocopherol in the lung) resulted in a significant decline of other antioxidants as well as in accumulation of lipid peroxidation products. A more severe decrease of pulmonary antioxidants was detected in SWCNT treated vitamin E-deficient mice as compared to controls. Exposure of vitamin E-sufficient mice to SWCNTs markedly shifted the ratio of low to high molecular weight forms of extra-cellular SOD (EC-SOD) such that approximately 3-4 times greater amounts of this neutrophil-associated enzyme were present. This effect was enhanced in vitamin E-deficient animals. Lowered levels of antioxidants in vitamin E-deficient mice were associated with a higher sensitivity to SWCNT-induced acute inflammation (PMNs number, released LDH, protein content, pro-inflammatory cytokines level) as well as pro-fibrotic pathways (TGF-β elevation and collagen deposition). Given that pulmonary levels of vitamin E can be manipulated through diet, its effects on SWCNT responses may be of practical importance in optimizing protective anti-inflammatory strategies.

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180 LUNG EXTRACELLULAR THIOCYANATE LEVELS ARE MODULATED BY CFTR AND CAN AMELIORATE MYLEOPEROXIDASE-MEDIATED INJURY.

L. W. Velsor[2], C. T. Kariya[1,2], S. Gauthier[2] and B. J. Day[1,2,3]. *[1]Molecular Toxicology and Environmental Health Sciences, University of Colorado HSC, Denver, CO, [2]Medicine, National Jewish Medical & Research Center, Denver, CO and [3]Immunology, National Jewish Medical Research Center, Denver, CO.*

The cystic fibrosis transmembrane conductance regulator (CFTR) has been shown to transport a wide variety of anions into the lung epithelial lining fluid (ELF). We wanted to examine the effect of defective CFTR on thiocyanate levels in the lung ELF and adaptive responses to Pseudomonas aeruginosa (PA) challenge. Wild type and CFTR KO mice were challenged intratracheally with PA, and on the 3rd day of infection bronchoalveolar lavage fluid was obtained and analyzed for thiocyanate levels using a colorimetric assay. Basal levels of lung ELF thiocyanate were similar in both wild type and CFTR KO mice. PA infection increased the levels of lung ELF thiocyanate 4-fold in the wild type but only 2-fold in the CFTR KO mice. In separate studies, we measured the basal thiocyanate levels in human lung epithelial cell lines sufficient (C38) and deficient (IB3) in CFTR grown in transwells. CFTR sufficient cells had significantly higher basal levels of thiocyanate in apical compartment as compared to CFTR deficient cells. To test for the functional importance of thiocyanate, we exposed human lung epithelial (A549) cells to a MPO system that generates hypochlorous acid in presence of different concentrations of thiocyanate. Thiocyanate significantly decreased the MPO-induced cytotoxicity in dose-depended manner. These data suggest that CFTR is partially responsible for thiocyanate transport in the apical compartment. Furthermore, our data also indicates that the lung adapts to infectious agents with elevated ELF thiocyanate levels which may protect the lung against MPO released from activated neutrophils. Individuals with cystic fibrosis may lack the ability to adequately adapt to lung infections resulting excessive injury. (This work was supported in part through funding by NIH HL75523).

181 A ROLE FOR GLUTATHIONE TRANSPORT IN THE ATTENUATION OF OXIDATIVE INJURY BY HYPERTONIC SALINE.

B. J. Day[1,2], J. Huang[1,2] and C. T. Kariya[2]. *[1]Molecular Toxicology and Environmental Health Sciences, UCHSC, denver, CO and [2]Medicine & Immunology, National Jewish Medical & Research Center, Denver, CO.*

The lung is continually exposed to environmental agents and pathogens. The lung epithelial lining fluid (ELF) is first to encounter these agents and GSH is a major antioxidant found in this apical fluid. The cystic fibrosis transmembrane conductance regulator protein (CFTR) is the only known GSH transporter that maintains

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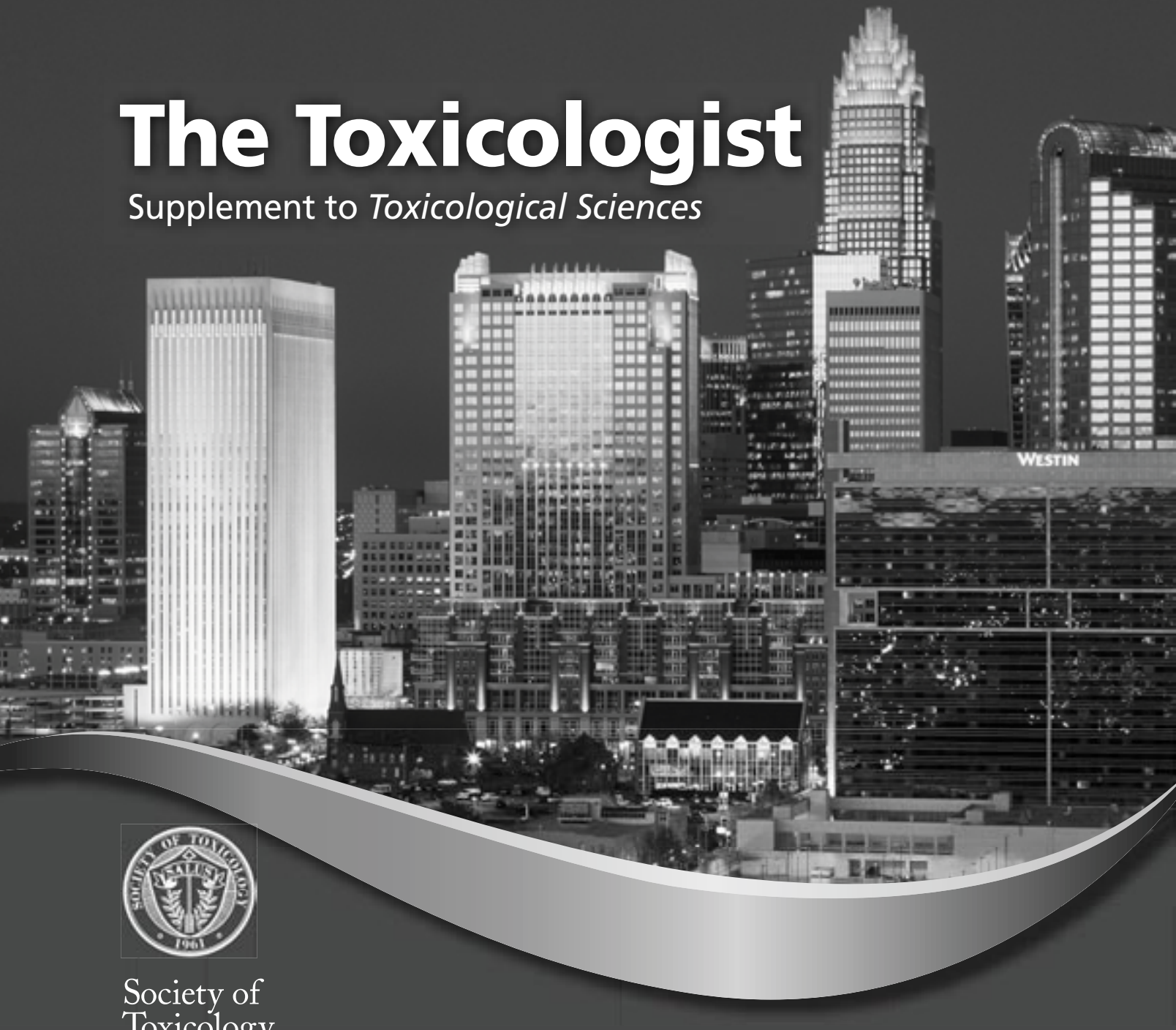

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Preface

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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