receive the priming dose of $H_2O_2$ prior to exposure to 0.1–100 μM $H_2O_2$. Clonogenicity analyses revealed that the priming dose of $H_2O_2$ increased the percentages of reproductively active cells in populations that were subsequently treated with the 0.1, 0.2 and 0.4 μM concentrations of $H_2O_2$. This effect, however, was not observed at the higher concentrations of $H_2O_2$. The results from this study suggest that low concentrations of $H_2O_2$ may be mitogenic for BEC and/or stimulation with low concentrations of $H_2O_2$ may induce an adaptive response in BEC that protects them from the otherwise cell cycle arresting effects of ROS. [Funded by the U.S. DOE]

**1711** THIOL DEPLETION OF HUMAN BRONCHIAL EPITHELIAL (HBE) CELLS FOLLOWING EXPOSURE TO TOLUENE DIISOCYANATE (TDI) VAPORS.

M H Karol, V A Tyurin, R W Lange, D L Wilson, B W Day and V E Kagan. *Department of Environmental and Occupational Health, University of Pittsburgh, Pittsburgh, PA.*

Toluene diisocyanate (TDI), a synthetic, highly reactive organic chemical, is recognized as the most frequent cause of occupational asthma in the western world. Yet, the mechanism underlying TDI asthma remains unclear. Previous studies performed in the laboratory indicate that TDI forms adducts with bronchoalveolar lavage proteins and glutathione. This implies that TDI—by virtue of depletion of endogenous thiols—may induce oxidative stress. To test the hypothesis we compared the response to oxidative stress, induced by phenoxyl radicals of etoposide, of pulmonary tissue from TDI-treated animals and TDI-treated HBE cells with those from control samples. The etoposide phenoxyl radicals (generated by tyrosinase-catalyzed oxidation of etoposide) specifically interact with thiols and this reaction can be monitored by disappearance of a characteristic signal in the ESR spectra. We found that in lungs of mice and in HBE cells, exposure to TDI (0.5 and 1.0 ppm for 30 min) causes oxidative stress detectable as significantly decreased (>50%) ability to reduce the phenoxyl radical. Expanded, submerged cultures of HBE cells were transferred to transwell membranes at passage 2 or 3. Upon reaching confluence the apical medium was removed from HBE cultures and henceforth fed from the basal compartment. Following 10–21 days of air/liquid interface culture HBE cells underwent mucociliary differentiation as well as alignment into a properly oriented, columnar morphology. H+E stained sections revealed goblet-type secretory cells, lucent columnar cells and developed ciliated cells. Studies are underway to characterize intracellular adducts and to analyze the involvement of glutathione and perturbations in its regulation following exposure to TDI vapor in differentiated HBE cell cultures. Supported by NIEHS # 05651.

**1712** FRESHLY GENERATED STAINLESS STEEL WELDING FUME INDUCES GREATER LUNG INFLAMMATION IN RATS AS COMPARED TO AGED FUME.

J M Antonini[1,2], R W Clarke[2], G G Krishna Murthy[2], P Sreekanthan[3], T W Eagar[3], and J D Brain[2]. [1]*NIOSH/HELD, Morgantown, WV;* [2]*Harvard School of Public Health, Boston, MA;* [3]*MIT, Cambridge, MA.*

It has been previously reported that long-lived radicals are present on the surface of freshly generated fumes. The objective of this study was to determine if freshly formed welding fume induces greater lung inflammation and injury in rats due to the presence of reactive oxygen species than aged welding fume. Fume was collected during gas metal arc welding using a stainless steel consumable electrode and found to be of respirable size with a mean diameter of < 2 μ. Male CD/VAF rats were dosed intratracheally with the welding fume 30 min (FRESH) and 1 and 7 days (AGED) after fume collection at a dose of 1.0 mg/100 g b wt. Bronchoalveolarlavage (BAL) was performed 24 hr post-instillation. Lung injury and inflammation were assessed by measuring the concentration of neutrophils, albumin, lactate dehydrogenase (LDH), and glucosaminidase (GLU) in the recovered BAL fluid. More neutrophils and enhanced GLU activity were observed for the FRESH group as compared to both AGED groups ($p<0.05$). Slight, but not significant, elevations were seen in albumin content and LDH activity for the FRESH group as compared to the AGED groups. No significant differences were observed for any of the parameters when fume aged 1 vs. 7 days were compared. When the FRESH and AGED fumes (12.5, 25, and 50 μg/ml) were suspended in dichlorofluorescin (15 μM), a probe which becomes fluorescent when oxidized, the concentration-dependent increases in fluorescence were greater for the FRESH fume vs. the AGED fumes. We have demonstrated that freshly generated welding fume induces greater lung inflammation than AGED fume. This is likely due to increased reactive oxygen species on fresh fume surfaces. (Supported by NIOSH#109979)

**1713** STIMULATION OF CELL DIVISION AND TISSUE REPAIR MAY EXPLAIN α-NAPHTHYLTHIOUREA RESISTANCE.

C C Barton, T J Bucci, L G Lomax, A Warbritton, and H M Mehendale. *Division of Toxicology and Louisiana Institute of Toxicology, College of Pharmacy and Health Sciences, Northeast Louisiana University, Monroe, LA.*

In the 1940s, it was discovered that rats quickly developed tolerance to the pulmonary toxicant α-naphthylthiourea (ANTU) when exposed to low doses in the form of poison baits. Thus far, differences in bioactivation, detoxification, distribution and excretion have not been able to explain this phenomenon. To test the hypothesis that stimulated cell division and tissue repair underlie ANTU resistance, an ANTU autoprotection model was developed: 5 mg ANTU/kg, po was given to male Sprague-Dawley rats (175–225 g) followed by 70 mg ANTU/kg, po 24 hr later. The low non-lethal dose provided 100 % protection against the normally 100 % lethal dose. Injury was assessed over a time-course through estimation of vascular permeability and histopathological examination. Autoprotected rats had less injury as compared to the unprotected rats after challenge with the lethal dose, indicating that their survival was due to lack of alveolar flooding. Cell division and tissue repair, dynamic and opposite responses to injury, were assessed through $^3$H-thymidine and bromodeoxyuridine incorporation assays. There was a significant increase in cells (endothelial and epithelial) undergoing S-phase of the cell cycle in the autoprotection model indicative of repair. Administration of the antimitotic agent colchicine (1 and 0.5 mg/kg, ip) abolished autoprotection indicating that the protective mechanism requires cell division. Furthermore, the protective dose of ANTU was found to decrease TGF-β mRNA as determined through quantitative RT-PCR. A decrease in this cell cycle inhibitor could play a role in allowing cells to escape out of G0 and enter the cell cycle. These studies suggest that the protective dose of ANTU stimulates cell division and tissue repair processes which are able to block the progression of injury upon challenge with a normally lethal dose.

**1714** ANTIOXIDANT STATUS OF BRONCHOALVEOLAR LAVAGE FLUID AND LUNGS FROM RATS SUBJECTED TO BURN AND/OR SMOKE INHALATION.

M A Dubick[1], B S Jordan[1], S C Carden[1], K Crissman[2], G E Hatch[2], P Langlinais[1] and D W Mozingo[1]. [1]*US Army Inst Surg Res, San Antonio, TX, and* [2]*US EPA, NHEERL, Research Triangle Park, NC.*

The present study investigated antioxidants in lavage fluid and lung in a rat model to simulate an injury encountered by firefighters and soldiers. Anesthetized rats (n = 5/group) received 20% full thickness skin burns. After a 5 hr recovery period, half the animals in the burn or sham burn groups were exposed to cooled western bark (fir and pine) smoke for 16.25 min. At 1, 12, 24, 48 and 96 hr after exposure to the smoke, rats were euthanitized and lungs were lavaged by infusing three 5 ml aliquots of normal saline. Smoke exposure resulted in plasma carboxyhemoglobin of 19 ±2% and produced areas of erosion of the tracheal surface, resulting in loss of epithelium and exposed basement membrane. In lavage fluid collected 1 hr after smoke exposure, concentrations of ascorbic acid were 30% and 46% lower ($p<0.05$) in the burned/smoked and smoked rats, respectively, than in controls. In contrast, uric acid concentrations in lavage fluid were markedly elevated in these groups when compared with controls. In addition, lung malondialdehyde concentrations were 100% and 45% higher at 12 hr and 24 hr in both smoke-exposed groups compared with controls. These data suggest that smoke inhalation, independent of burn injury, induces an oxidant stress that persists for at least the first 24 hr after smoke exposure. (This abstract does not represent Army, DoD or EPA policy).

**1715** PULMONARY AND LIVER CYTOKINE mRNA LEVELS AFTER INTRAPERITONEAL INJECTION, INTRATRACHEAL INSTILLATION OR INHALATION OF LPS IN C57BL/6 MICE.

C J Johnston, J N Finkelstein, R Gelein, P Mercer, N Corson and G Oberdörster. *University of Rochester, Depts. of Environmental Medicine and Pediatrics, Rochester, NY.*

Endotoxin (lipopolysaccharide; LPS) can induce systemic effects as well as acute lung injury often leading to respiratory distress syndrome. Using a mouse model of acute lung inflammation induced by intratracheal instillation (IT) intraperitoneal injection (IP) or inhalation (INH) of LPS, we compared the kinetics of mRNA expression. Eight-week old C57BL/6 mice were dosed with either 5 mg/kg body wt. (IP), 5 μg/mouse (IT) or 12 min. (INH) of 0.023 μg/mouse (LPS) and sacrificed 2 hrs. post-exposure. At 2 hrs. post

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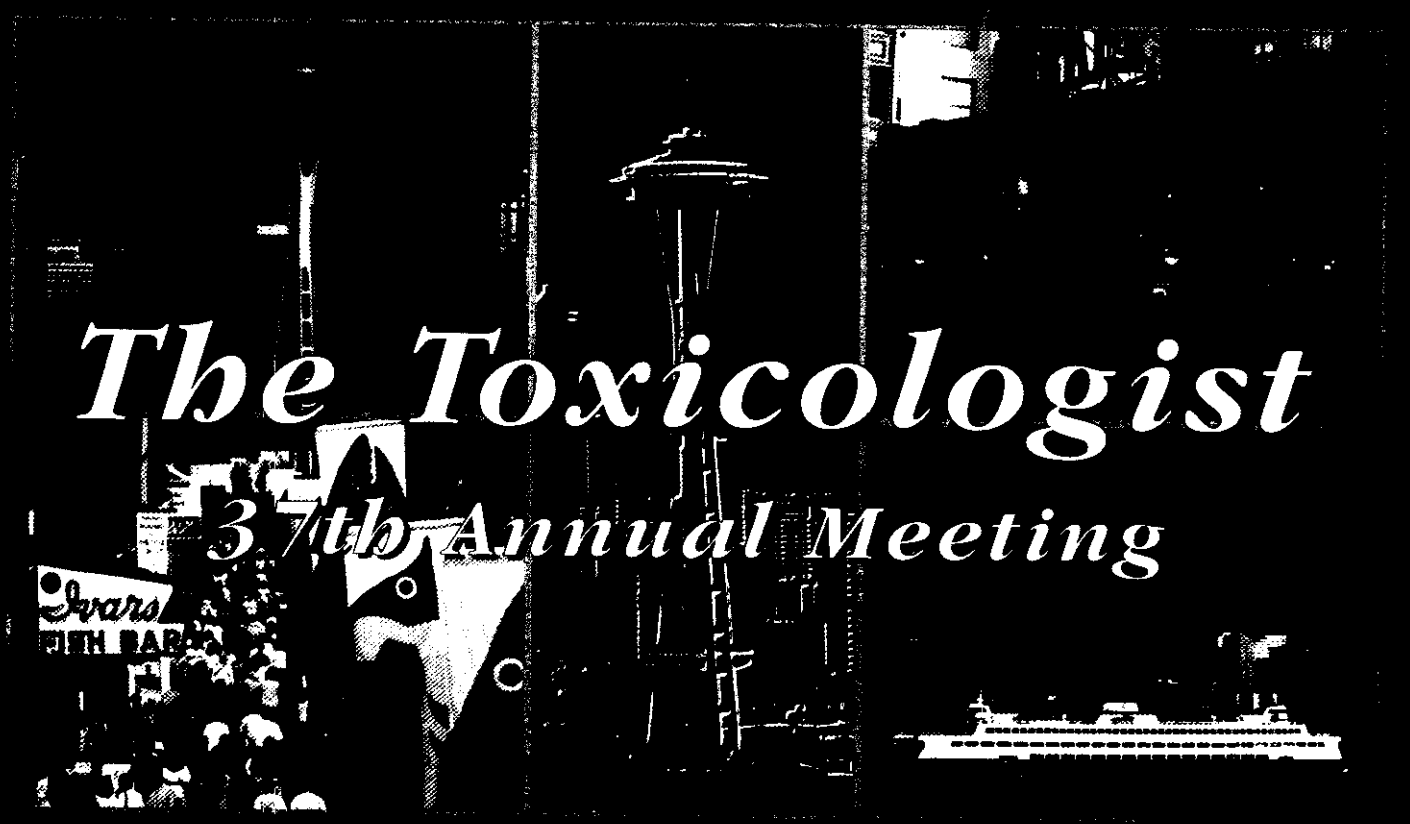


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# Preface

**This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster / discussion, workshop, roundtable, and poster sessions of the 37th Annual Meeting of the Society of Toxicology, held at the Washington State Convention Center, Seattle, Washington, March 1-5, 1998.**

**An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 407.**

**The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 433.**

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