2129 Multi System Injury Following Whole Body Exposure to Sulfur Mustard and Potential Treatments

S. Dachir, I. Rabinovitz, G. Yacov, M. Cohen, L. Cohen, H. Gutman, R. Gez, S. Chapman, V. Horwitz and T. Kadar. *Pharmacology, The Hebrew University, Jerusalem, Israel.*

Whole body exposure to sulfur mustard (HD) may be devastating resulting in multi system injuries. HD was used in many conflicts around the world and it is still a major threat for both, army troops and civilians. The aim of this study was to demonstrate the effects of HD on the eyes, skin and the respiratory system, in a most realistic scenario, using whole body exposure to HD vapor. Rats were exposed to HD vapor (LCt10-30) for duration of 10 min. Air containing HD flowed through the chamber in a constant current and the concentration was continuously monitored using FTIR. Clinical evaluation including clinical severity score and blood counts and histological evaluation were performed up to four weeks post-exposure. The potential of steroids treatment to ameliorate the HD effects was tested by betamethasone administration starting five minutes following exposure up to two weeks. Rats developed typical HD intoxication symptoms following a latency period of several hours demonstrating at first swollen and erythematic nose. This was followed by excessive rhinorrhea, eye closure, lacrimation, ronchi and wheezing, breathing difficulties, weight loss and leukopenia. Histological evaluation revealed a long lasting damage to the trachea, lungs and eyes. Treatment with steroids significantly improved clinical signs during the first week post-exposure. Later, a gradual improvement was observed in all animals. This model, of whole body exposure to HD, was found to closely mimic the deleterious effects of HD on the respiratory system and on the eyes, as was described in human victims during WWI and the Iran-Iraq war. Preliminary results indicate that steroids ameliorate part of HD effects, yet, the treatment was not sufficient to overcome the long term damages. Further research is needed to test additional combinations.

2130 A Multidisciplinary Approach for Inhalation Phosphine Poisoning

B. Wong, R. Lewandowski, H. Hoard-Fruchey, M. Martens, M. W. Perkins, T. Hamilton, J. Devorak, J. Simons, C. Rothwell, K. P. Sherman, A. M. Rodriguez, J. Tressler and A. M. Sciuto. *USAMRICD, Gunpowder, MD.*

Phosphine gas (PH3) is an extensively used reactive intermediate in the chemical industry and also a rodenticide and fumigant. National concern over phosphine's potential as a terrorist threat has increased because of its widespread use in pest control, ease of retail access, and absence of comprehensive treatment strategies. Although the exact mechanism of PH3 toxicity is poorly understood, it is thought to inhibit mitochondrial cytochromes while also causing a host of target organ and systemic effects, including oxidative stress, cardio-pulmonary toxicity, and overall metabolic disturbance. An improved understanding of the mechanisms of PH3 toxicity is central to evaluating potential therapeutic compounds and requires a multidisciplinary approach. A custom inhalation gas exposure system was designed for the whole-body exposure of conscious male rats to phosphine and coupled with real-time physiological monitoring. After PH3 exposure at concentration-time products ranging from 16500 to 21250 ppm×min, rats were euthanized at 1, 3, 6 and 24 hr post-exposure. The heart, brain, lungs, liver, kidneys, and blood were removed and analyzed using various toxicological, biochemical, genomic, and histopathologic methods to assess target organ and systemic effects. PH3 exposure induces real-time changes in pulmonary and cardiac function. ECG data from telemetry-implanted rats matched data from case studies of human PH3 exposure. Histopathological examination indicated little to no observable pathologic changes in the lung or heart, but transmission electron microscopy indicated ultrastructural damage to the cardiac tissue and mitochondria. Biochemical and genomic analysis of various tissues indicated alterations in metabolic, immune, and inflammatory cellular processes, as well as reductions in mitochondrial function. Our data suggest that PH3-induced death is due to acute cardio-pulmonary crisis and that concentration and time are not the only determinants of dose-dependent lethality. The elucidation of many aspects of PH3 poisoning has been achieved with our multidisciplinary approach, and continued use of this flexible approach will permit more effective identification of therapeutic windows and development of rational medical countermeasures and countermeasure strategies.

2131 Comparative Pulmonary Toxicity of Inhaled Metalworking Fluids in Rats and Mice

K. R. Ryan[1], M. Toraason[4], M. Cesta[1], R. Herbert[1], A. Brix[2], M. Cora[1], K. Janardhan[3], K. Witt[1], G. Kissling[1] and D. L. Morgan[1]. *[1]Division of the National Toxicology Program, NIEHS, Research Triangle Park, NC; [2]EPL Inc, Research Triangle Park, NC; [3]ILS Inc, Research Triangle Park, NC and [4]NIOSH, Cincinnati, OH.*

Metalworking fluids (MWFs) are complex formulations designed for effective machining operations. Adverse health effects (respiratory symptoms, dermatitis, cancer) have been reported in exposed workers. While known carcinogens have been removed from newer MWFs, recent studies in experimental animals indicate a continued health risk. This study examines the hypothesis that unrecognized health hazards exist in marketed MWFs presumed safe based on hazard assessments of individual ingredients. Subchronic inhalation studies were designed to characterize and compare the potential toxicity of four unique MWFs: Trim VX, Cimstar 3800, Trim SC210, and Syntilo 1023. These MWFs were devoid of potentially toxic contaminants present in previously used MWFs. Male and female Wistar Han or Fischer 344N/Tac rats and B6C3F1/N mice were exposed to 0, 25, 50, 100, 200, or 400 mg/m3 of MWF for 13-weeks, after which survival, body and organ weights, hematology and clinical chemistry, histopathology, and genotoxicity were assessed. Survival was not affected and toxicity was primarily limited to the respiratory tract of rats and mice. Toxicity was similar in rats and mice and gender differences were not observed. Increased lung weights (rats: 15-20%; mice: 12-50%) were associated with significant histological changes in the lung following exposure to all four MWFs. Pulmonary fibrosis was the most significant lesion caused by MWF exposure; concentration-related increases in severity and a statistically significant increase in the incidence of fibrosis were present only in rats and mice exposed to Trim VX. All four MWFs also caused lesions in the nasal cavity and larynx of rats and mice. Differences in toxicity between the MWFs were attributed to differences in chemical components (e.g., % water, biocides, hexane-extractable components, oil). These data confirm that newer MWFs have the potential to cause respiratory toxicity in workers repeatedly exposed via inhalation.

2132 Acrolein Toxicity on Larynx: Damage on Vocal Fold Epithelial Barrier Function

X. Liu, W. Zheng and M. P. Sivasankar. *Department of Speech, Language, and Hearing Sciences, Purdue University, West Lafayette, IN; School of Health Sciences, Purdue University, West Lafayette, IN.*

Acrolein is formed by combustion of fossil fuels, woods, plastics, and animal fats and also exists in tobacco smoke; chemically it is highly reactive. The vocal folds play an essential role in respiration and voice production and are at risk of acrolein exposure from inhaling polluted air. The outermost surface of vocal folds consists of epithelial cells with tight junctions serving the purpose to protect the underlying connective and muscle tissues. Our recent data suggest that acrolein has an acute toxic effect on ion transport across the vocal fold epithelial barrier. However, its influence on the protective function of the epithelial barrier has never been investigated. This study was designed to investigate the barrier integrity of vocal fold epithelia following acrolein exposure *in vitro*. The barrier integrity was evaluated for transepithelial resistance (TEER), sodium fluorescein (NaFl) permeability, and the tight junctional protein expression. Freshly isolated vocal fold epithelia from porcine larynges were exposed to acrolein (50-1300 μM) or Hanks' Balanced Salt Solution (HBSS) as controls for 3 hr. Cell viability studies using MTT assay revealed that the cell viability became significantly reduced by 27.2% when acrolein concentration reached 500 μM compared with controls ($p \leq 0.001$). Incubating vocal folds with 100 μM acrolein for 3 hr resulted in 11.35% reduction of TEER ($p<0.05$). NaFl assay further indicated a 130.5% increase in barrier permeability ($p<0.05$) following treatment with 100 μM acrolein compared with controls. The qPCR analyses showed that exposure with 100 μM acrolein for 3 hr did not cause any significant changes in expression of mRNAs encoding the tight junctional protein occludin and claudin3 ($p=0.235$; $p=0.58$); though the mRNA levels revealed the increasing trend by 102.5% and 21.6%. These findings suggest that acrolein exposure damages the vocal fold epithelial integrity and compromises its protective barrier function. Reduced TEER and increased permeability seem unlikely to be caused by altered gene expression of tight junction proteins. This study has a significant public health importance, because it has laid the groundwork for further mechanistic investigation of acrolein toxicity on larynx structure and function that are essential to people's daily voice production. (Supported by NIH/NIDCD R01DC011759).

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Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 55th Annual Meeting of the Society of Toxicology, held at the New Orleans Ernest N. Morial Convention Center, March 13–17, 2016.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 603.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 629.

The abstracts are reproduced as accepted by the Scientific Program Committee of the Society of Toxicology and appear in numerical sequence. Author names which are underlined in the author block indicate the author is a member of the Society of Toxicology. For example, J. Smith.

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