technology can serve as a tool for assessing chemical irritancy potential. To determine the transcriptional response to dermal irritants, male Fisher 344 rat skins were exposed to 10% sodium lauryl sulfate (SLS, a model skin irritant) for 1 h *in vivo*. Skin total RNA was isolated at 0 h (control), and 1 and 4 hrs following the beginning of the exposure to monitor transciptomic profiles using the Affymetrix RatTox U34 array. Our results indicated that dermal exposure to SLS resulted in a significant change of gene expressions: more than 20 genes (ie., inflammatory, Bcl-2-related, oncogenes) were increased >2-fold, whereas more than 24 genes (ie., cytochrome P450-related, tumor suppressor) showed a >2-fold decrease (1h vs 0 h controls). By 4 hr, more than 60 genes (ie., inflammatory, oxidative and cellular stress, cell cycle, transcription factors, Bcl-2-related) were up-regulated and more than 10 genes (transcription factors, junctional proteins) were down-regulated by a factor >2-fold when compared to the 0 h controls. A strong temporal change of gene expression was observed in the skin following exposure to SLS. Characterization and analysis of the transcriptomic response of skin to SLS can enhance the risk assessment of dermal irritants.

786 *IN VITRO* ASSESSMENT OF OXIDATIVE STRESS AND CYTOTOXICITY IN LIVING DERMAL EQUIVALENTS EXPOSED TO M-XYLENE.

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Dermal exposure to volatile organic chemicals (VOCs) can lead to irritation, inflammation, and cytotoxicity *in vivo*. Using an improved *in vitro* exposure method for VOCs, we wanted to assess oxidative stress and cytotoxicity in dermal fibroblasts exposed to m-xylene. Dermal equivalents containing $2.5x10^5$ cells were incubated for 1 or 4 hr in a m-xylene/culture medium mixture (range=0.5 to 11.5 µg/ml m-xylene). Following exposure, cell viability (MTT assay and cellular LDH activity), cellular thiol levels, and endogenous catalase activity were measured. At 1 and 4 hr, cell viability decreased with increasing m-xylene concentration. The EC_{50} calculated using the MTT assay were 8.33 ± 0.26 and 6.85 ± 0.33 µg m-xylene/g tissue at 1 and 4 hr, respectively. The EC_{50} at 4 hr was significantly lower ($P<0.05$) compared to the EC_{50} calculated from the 1 hr exposures. At 1 hr, the EC_{50} determined from measuring cellular LDH activity was 23.7 ± 0.88 µg m-xylene/g tissue. By 4 hr, the EC_{50} had decreased significantly ($P<0.05$) to 9.24 ± 0.05 µg m-xylene/g tissue. A temporal decrease in the levels of endogenous antioxidants (catalase and thiols) was also observed with increasing m-xylene concentration. Pretreatment of dermal equivalents with the antioxidant N-acetylcysteine significantly increased ($P<0.05$) cell viability. These results suggest oxidative stress may promote m-xylene-induced cytotoxicity in living dermal equivalents. Moreover, these VOC-induced cellular responses could ultimately be related to actual dermal exposure scenarios. (Supported by NIOSH/CDC and AFOSR/NL)

787 PREDICTION OF MOLECULAR MECHANISM OF SKIN IRRITATION AFTER ACUTE EXPOSURE TO SODIUM LAURYL SULFATE.

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Sodium lauryl sulfate (SLS) is an anionic surfactant, causing irritant contact dermatitis. Skin irritation by this detergent is not well understood due to the complex molecular interactions. Knowledge of molecular mechanisms and the relationship between duration of surfactant exposures on the skin and the degree of irritation is limited. Here we measured an early inflammatory mediators, interleukin 1-alpha (IL-1α), inducible nitric oxide synthase (iNOS), nitric oxide (NO) and ROS in response to two different concentrations of SLS (1% and 10%)-induced irritation.The dorsal thoracic aspects of male F-344 rats were exposed to SLS for 1 hr using Hill Top Chambers. At 0, 1, 2, 4 and 6 hours after exposure, skin samples were processed for analysis. Western blot of 1% SLS exposed skin samples showed an increase in IL-1α protein levels from 13-37% over controls at various time points, while IL-1α in 10% SLS samples only increased by 10%. This protein induction reached a maximum at 2 hr. The change in iNOS levels in 1% SLS skin over the respective controls was comparable to change in 10% SLS exposed skin samples but occurred at 4 hours. However, NO levels showed a different response. Like NOS protein level in 1% SLS exposed samples, NO level increases peaked at 4 hr after beginning of exposure. In 10% exposed samples NO level peaked at 1 hr after exposure and gradually decreased. There was a significant generation of ROS seen in 1% SLS exposed skin, which reflects the damaging effects on the skin. The reduced level of thiol further strengthens the potential association of oxidative stress and skin damage during SLS exposures. These results suggest that the change in the levels of skin's molecular and biological response to SLS exposure explained the biochemical mechanisms associated with SLS-induced irritation (Supported by CDC/NIOSH RO1 OH03654-03).

788 HISTOPATHOLOGIC ASSESSMENT OF ACUTE DERMAL EXPOSURE TO *M*-XYLENE, *D*-LIMONENE AND SODIUM LAURYL SULFATE IN RATS.

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Skin exposure to organic chemicals and solvents may cause skin irritation and generate proinflammatory mediators that initiate an irritant response. Histopathology can serve as a fixed reference point in a changing microenvironment for explanation of concurrent cellular responses. Changes in the levels of selected proteins in the irritant cascade were quantified after an exposure and compared to visible tissue changes. Here we describe the dermal pathology of male F-344 rats exposed to meta-xylene, *d*-limonene and sodium lauryl sulfate for one hour using Hill Top Chambers®. Skin samples were collected at zero, one, two, four and six hours after the end of the exposure. Light microscopic evaluation was performed on formalin-fixed and paraffin embedded skin sections. Hematoxylin and eosin stained sections were assessed and scored. A single topical exposure to meta-xylene, *d*-limonene, and sodium lauryl sulfate resulted in granulocyte infiltration in rats as early as 2 hours. Segmental detachment of the epidermis from the dermal interface occurred in prolonged exposures of meta-xylene and *d*-limonene compared to the control groups. These findings were interpreted to be the consequences of potential up-regulation of inflammatory mediators that result in skin damage. (Supported by CDC/NIOSH RO1 OH03654-03)

789 PYRIDOSTIGMINE BROMIDE SUPPRESSES IL-8 IN HUMAN EPIDERMAL KERATINOCYTES AND IN ISOLATED PERFUSED PORCINE SKIN EXPOSED TO DEET AND PERMETHRIN.

N. A. Monteiro-Riviere, A. O. Inman, R. E. Baynes and J. E. Riviere. *Center for Cutaneous Toxicology and Residue Pharmacology, North Carolina State University, Raleigh, NC.*

Gulf War personnel were given pyridostigmine bromide (PB) as a prophylactic treatment against possible organophosphate exposure and then exposed to the insecticide permethrin (Pe) and the insect repellent DEET. Simultaneous exposure and the interaction of these compounds could contribute to the ill health effects in the Gulf War veterans. The purpose of this study was to assess the effects of DEET and /or systemic PB on permethrin absorption. A large combination of topical mixtures of permethrin and/or DEET in various vehicles were applied to isolated perfused porcine skin flaps (IPPSFs). The absorption data has been reported elsewhere. Concentrations of interleukin-8 (IL-8) and TNF-α were assayed in the absorption studies to probe for a potential inflammatory effects after complex mixture application. IPPSF's (n=4/treatment) were topically dosed with mixtures of Pe, DEET, Pe/DEET, and ethanol (EtOH). Each treatment was repeated with perfusate spiked with 50 ng/ml of PB. Timed IPPSF venous effluent samples (0, 0.5, 1, 2, 4, and 8 hrs) were assayed by ELISA for IL-8 and TNF-α and by EIA for PGE_2. Surprisingly, across most topical mixture combinations, release of IL-8 and TNF-α were significantly suppressed when PB was infused into the IPPSFs. To probe the potential mechanism of this PB effect, human epidermal keratinocyte (HEK) cell cultures were exposed to Pe, DEET, Pe/DEET, with and without PB in DMSO vehicle. IL-8 was assayed at 1, 2, 4, 8, 12, and 24hrs. PB suppressed IL-8 in permethrin treatments from 4 to 24 hrs supporting the IPPSF results. In conclusion, these studies clearly demonstrate that systemic exposure to PB suppressed the cytokine IL-8 release from keratinocytes. The relation of this finding to PB-induced changes in permethrin absorption and/or other factors in the pathogenesis of Gulf War illness deserves further attention. (Supported by USAMRMC Grant DAMD-17-99C-9047)

790 LACK OF EFFECTS OF SULFUR MUSTARD AND JP-8 JET FUEL ON PERCUTANEOUS ABSORPTION OF SIMULTANEOUSLY ADMINISTERED TOPICAL PERMETHRIN AND DEET.

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Systemic absorption of topically-applied permethrin and/or DEET have often been cited as potential toxicants involved in the etiology of the Gulf War illness. Previous studies in our laboratory have implicated pyridostigmine bromide (PB) as a potential modulating factor on permethrin dermal absorption. Others have postulated a toxicodynamic interaction with systemically absorbed permethrin and DEET. The purpose of the present study was to assess the effects of simultaneously administered JP-8 jet fuel or low-level (sub-blistering) sulfur mustard (HD) on permethrin

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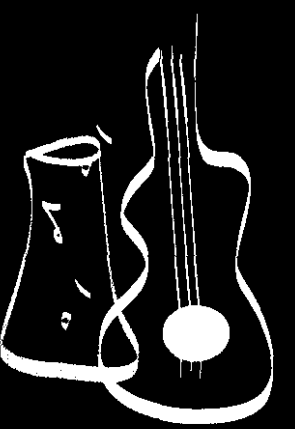

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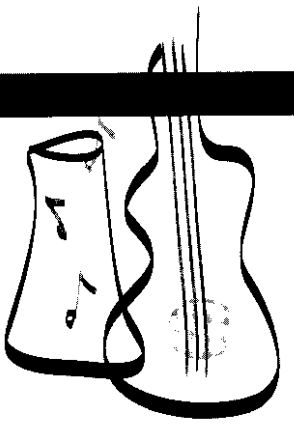

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Preface

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 41st Annual Meeting of the Society of Toxicology, held at the Opryland Hotel and Convention Center, Nashville, Tennessee, March 17–21, 2002.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 385.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 411.

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

Additional Late-Breaking Abstracts are issued in a supplement to this publication and are available at the 41st Annual Meeting and through the Society of Toxicology Headquarters office.

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