and aliphatic components, naphthalene and dodecane. Porcine skin sections and silastic membranes in an *in vitro* system were used to characterize chemical-biological interactions that modulate diffusion of jet fuel components in membranes. Isolated perfused porcine skin flaps (IPPSFs) were used to evaluate diffusion in a viable skin model with intact microvasculature. In these 5-hour studies, Jet A, JetA+DIEGME, JetA+8Q21, and JetA+Stadis 450, JetA+DIEGME+8Q21, JetA+DIEGME+Stadis 450, JetA+8Q21+Stadis 450, and JP-8 mixtures were tested. Naphthalene absorption (0.76 - 2.39% dose) was greater than dodecane absorption (0.1 - 0.84% dose), while the IPPSFs demonstrated that dodecane absorption was significantly greater in JP-8 than in JetA. DIEGME+Stadis 450 significantly increased naphthalene (1.88% dose) and dodecane (2.02% dose) penetration into the skin and fat tissues of IPPSFs. These findings were supported by the fact that DIEGME and Stadis 450 significantly increased naphthalene and dodecane absorption, respectively, in skin sections *in vitro*. The effects of the fuel additives were not as evident in the artificial membrane suggesting that fuel additives may alter diffusional pathways unique to the skin. Data also demonstrated that more dodecane than naphthalene remained in the stratum corneum (SC) and skin surface and DIEGME+Stadis 450 significantly increased SC deposition of naphthalene but not dodecane. These data suggest that various combinations of the fuel additives can potentially alter transdermal diffusion of aliphatic and aromatic components of jet fuels. (Supported by USAFOSR#FQ8671.)

277 CYCLOSPORIN A EXACERBATES SKIN IRRITATION INDUCED BY TRIBUTYLTIN THROUGH INCREASED NF-κB ACTIVATION.

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Skin irritation is a complex phenomenon that involves resident epidermal cells, fibroblasts of dermis, and endothelial cells as well as invading leukocytes interacting with each other under the control of a network of cytokines and lipid mediators. Searching for pharmacological agents able to modulate xenobiotic-induced skin irritation, we found that cyclosporin A (CyA), a potent immunosuppressant, exacerbates the skin irritation induced by tributyltin (TBT) rather than preventing it. We have previously demonstrated in the mouse the involvement of interleukin-1a and tumor necrosis factor-a (TNF) in TBT-induced skin irritation. Here, we show that CyA (28 mg/kg), at a concentration that results in systemic immunosuppression as assessed by lymphoproliferative response, potentiates TBT-induced skin irritation through increased TNF production, associated with increased TBT-induced transcription factor NF-kB activation in CyA treated mice. Using a murine keratinocyte cell line (HEL30), we were able to demonstrate, *in vitro* as well, that the CyA potentiates TBT-induced activation of NF-kB and cytokine production, this was preceded by a dose (0.1-10 uM) and time dependent increase in cellular oxidative activity, essential for NF-kB activation. This effect was not exclusive to TBT but could be extended to other mitochondrial poisons such as sodium arsenate. The increased cellular oxidative activity, NF-kB activation and cytokine production induced by CyA may offer an explanation at the molecular level of the adverse skin reactions sometimes associated with CyA treatment in human skin diseases.

278 IODINE PROTECTS SKIN AGAINST CHEMICAL AND THERMAL BURNS.

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Sulfur mustard (SM) is a powerful vesicant employed as a chemical warfare. The currently available pharmacological antidotes against this blisterogen are of limited use. We have shown that post-exposure treatment with iodine protected against SM-induced skin lesions in the fur-covered guinea pig model. The iodine formulation was efficacious at intervals of 15 and 30 min between SM (neat 1.27 mg) exposure and treatment. Longer intervals of 45 and 60 min were also beneficial but to a lesser extent than the short ones. In order to verify the mechanism of the protective activity of iodine, we examined whether iodine oxidizes SM to form an inactive vesicant. Gas chromatography/mass spectrometry analysis of SM extracted from skin treated with iodine or its vehicle revealed that iodine did not chemically inactivate SM. Furthermore, iodine treatment immediately after exposure to hot water (75 Celsius) for 10 sec significantly reduced the ulceration area by 74%. Prophylactic treatment with iodine reduced the ulceration area by 98%. The present findings indicate that iodine-induced protection stems presumably from epidermal-dermal reactions with iodine leading to prevention of inflammatory and necrotic processes. Whatever the mechanism is, the iodine preparation is suggested as a potential antidote against skin lesions induced by chemical and thermal stimuli. (This work was supported by the U.S. Army Medical Research and Material Command under Cooperative Agreement No. DAMD17-98-2-8009.)

279 ETHYOL® (AMIFOSTINE) REDUCTION OF PALMAR-PLANTAR ERYTHRODYSESTHESIA (PPE) IN RATS TREATED WITH DOXIL® (DOXORUBICIN HCL LIPOSOME INJECTION).

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Palmar-plantar erythrodysesthesia (PPE) is reported in approximately 15% of cancer patients receiving Doxil®. PPE starts as a burning/tingling sensation in the extremities, and can eventually progress into subdermal lesions. PPE is currently managed by dose reduction or an increased treatment interval. Another approach is to identify agents that minimize PPE but allow dose-intensive treatment with Doxil. A nonclinical model of PPE was developed in rats. Rats treated with Doxil (2.5 mg/kg IV 1/week for 5 weeks) develop PPE histologically similar to the lesion in patients after 4 to 6 weeks of treatment. PPE lesions were scored weekly by size and severity using a five-point scale for each body region; overall score was the sum for all region scores. Results are presented as mean total score for each treatment group. Rats were treated concurrently with Doxil and potential therapies. Retinol palmitate and 2-mercaptoethane sulfonate (Mesna®) reduced PPE severity slightly, but not significantly. DMSO, alpha-tocopherol and pentoxifylline had no apparent effect on PPE. Pyridoxine (500 mg/kg SC 2/week, $p<0.02$) and ergotamine (3.5 mg/kg IM 1/week, $p<0.01$) significantly reduced PPE. Weekly treatment with Ethyol® (150 or 200 mg/kg, IV) prior to Doxil administration virtually eliminated the most severe PPE. Severity scores were reduced from 15.8 (Doxil only) to 7.2 and 4.3 for the two Ethyol groups, respectively ($p<0.02$). Antitumor efficacy of Doxil (4-10 mg/kg IV, 1-3 treatments) was not decreased when cotreated with Ethyol (50-200 mg/kg IV, 1-4 treatments) in four mouse-tumor models: C26 colon, Lewis lung, M109 lung, and J-6456 lymphoma. Thus, Ethyol is effective in reducing the severity and incidence of PPE induced by Doxil without altering its antitumor efficacy. These studies suggest that evaluation of potential therapies in appropriate preclinical models may lead to effective anti-PPE treatments that can be used in the clinic.

280 HISTOPATHOLOGIC ASSESSMENT OF ACUTE DERMAL EXPOSURE TO *meta*-XYLENE IN RATS AND GUINEA PIGS.

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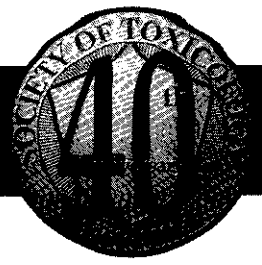
Irritation by organic chemicals and solvents is not well understood due to the complex interplay of multiple, simultaneous molecular interactions leading to acute change. Histopathology provides a valid and verifiable reference point in this changing microenvironment. Rats are often used as experimental animals for the study of toxic mechanisms and guinea pigs are a common species for toxicology tests, which are used to categorize chemicals as skin irritants. The purpose of our study was to compare the time course and severity of the histopathological responses in rats and guinea pigs, so that this could be factored into our choice of species for mechanistic studies. A single topical exposure to xylene resulted in acute dermal inflammation in rats and guinea pigs as early as 2 hours. The dorsal thoracic aspect of male F-344 rats and Hartley Guinea Pigs were exposed to xylene for one hour using Hill Top Chambers®. At zero, one, two, four and six hours after exposure skin samples were collected. Light microscopic evaluation was performed on formalin-fixed, routinely processed and paraffin embedded skin sections. Histopathology provides a visual foundation in a changing microenvironment and serves as an anchor for sound explanation of concurrent molecular data. In our acute dermal exposures with xylene, inflammation was more pronounced in guinea pigs than rats. In addition, after one-hour topical xylene exposure, severity in rats and guinea pigs progressively increased in dermal tissues at two, four and six hours. When evaluating granulocyte infiltration, guinea pigs exposed to this irritating solvent respond more rapidly and with greater severity than rats. For selecting a single species for further molecular evaluation however, availability or specificity of antibodies may be a consideration. (Supported by CDC/NIOSH RO1 OH03654-03.)



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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 40th Annual Meeting of the Society of Toxicology, held at the Moscone Convention Center, San Francisco, California, March 25–29, 2001.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 451.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 479.

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

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