blood in hairless rats. Methods: Occlusive dermal exposure (2h) was done with 230 µl of the chemicals (JP-8, xylene, tetradecane) using Hill top chambers®. Linear microdialysis probes (10 mm) were inserted in the dermis under urethane anesthesia. The dialysis fluid was pumped at a flow rate of 2 µl/min and the dialysate was collected for 7h following probe insertion. The expression of substance P(SP), calcitonin gene related peptide (CGRP) and prostaglandin E2(PGE2) in the skin was measured by enzyme immunoassay(EIA). The effect of Celecoxib(500 µl, 10 mg/ml) pretreatment,6 &18 h before the application of test chemicals was assessed. Separate experiments with similar skin exposures were conducted and TEWL, erythema and expression of IL-1α & TNF α in the skin & blood was measured. Results: The mean concentrations of SP & PGE2 after the application of chemical (55.7 ± 14.8 & 298.6 ± 30.2 pg/ml) and 3h after its removal (38.2 ± 15.5 & 132.2 ± 10.1 pg/ml) indicated that JP-8 induced significantly higher release of SP & PGE2 as compared to baseline value ($P < 0.05$). Similar results were obtained with xylene exposure ($P > 0.05$). Tetradecane however, demonstrated significantly lower expression of SP & PGE2 compared to JP-8 ($P > 0.05$). CGRP was not detected in any of the samples. Pretreatment with Celecoxib showed a significant decline ($P < 0.05$) in SP & PGE2 release induced by JP-8 and xylene. The skin irritation as shown by increase in TEWL and erythema levels was in the order of JP-8 ≈ xylene > tetradecane. JP-8 and xylene significantly increased the expression of IL-1α and TNFα in skin and blood as compared to control ($P < 0.05$). Conclusion: Dermal microdialysis data correlated with TEWL and cytokine data and thus can be used to quantify skin irritation potential of JP-8 and related chemicals.

841 EVALUATION OF SKIN BARRIER CREAMS TO JP-8 IRRITATION IN NEW ZEALAND WHITE RABBITS *(ORTYCTOLAGUS CUNICULI)*

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Skin Irritation, as well as skin and systemic toxicity due to accidental JP-8 jet fuel exposure remains a concern for the US Air Force and their fuel handling personnel. Personal protection equipment and clothing (PPEC) is a necessity under normal operations but requirements to meet workload goals can lengthen individual exposure causing PPEC failure, especially during extended operations. To ensure work conditions result in the lowest JP-8 exposure, our goal was to add a skin-enhancement barrier cream to the PPEC armament. Initially we needed an over-the-counter (OTC) product or cream claiming to have skin enhancement and/or barrier properties, which could be quickly fielded. To determine the best OTC creams, a number of creams were tested *In Vitro* on both silastic membrane and dermatomed pig skin. The five best creams were selected for *In Vivo* testing on New Zealand White Rabbits to determine the degree of protection against JP-8 irritation. The barrier creams were applied to the skin of shaved rabbits then exposed to 0.5ml of JP-8 for four hours at selected sites using a 2cm Hilltop Chamber. The eleven sites included one negative control site (skin and hilltop chamber only), one control site (barrier cream and hilltop chamber only), three positive controls (JP-8 and hilltop chamber only), and three sample sites (JP-8, hilltop chamber and barrier cream applied). Also included on each rabbit were three sites of unexposed bare skin. Readings were taken both with a colorimeter and visually according to the Draize Irritation Scale. These sites were evaluated at eleven time points over 72 hours. Two creams have shown protection against JP-8 irritation, while other creams that protected against JP-8 penetration *In Vitro*, do not provide sufficient protection for JP-8 irritation on rabbit skin *In Vivo*.

842 PARTITIONING BEHAVIOR OF SELECTIVE AROMATIC AND ALIPHATIC JET FUEL COMPONENTS ACROSS MEMBRANES

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Jet fuel components are known to partition into skin and cause occupational irritant contact dermatitis (OICD) as well as systemic effects following dermal absorption. The purpose of this study was to experimentally determine how these jet fuel components partition from (1) solvent mixtures into diverse membrane-coated fibers (MCFs) to predict dermal absorption and (2) biological media into MCFs to predict tissue distribution. Three diverse MCFs, polydimethylsiloxane (PDMS, lipophilic), polyacrylate (PA, polarizable), and carbowax (Wax, polar) were selected to simulate the physicochemical properties of skin *in vivo*. When MCFs were exposed to solutions containing the jet fuel components, these components partitioned into the MCF materials depending on the strengths of the molecular interactions. Following an appropriate equilibrium time between the MCF and dosing solutions, the MCF was injected directly into a GC-MSD to quantify the amount that partitioned into the membrane. Three vehicles (water, 50% ethanol-water and 4%BSA solution) were studied for selected jet fuel components. Preliminary data suggest that as the aromatic components become more hydrophobic, the greater the partitioning into the membrane irrespective of MCF at 100% water. This relationship is less clear once ethanol is introduced. Interestingly, in media, the aliphatics showed a reversed trend when partitioning from the BSA solution. This infers that plasma protein binding and not only molecular weight may limit tissue distribution of these aliphatic components. These preliminary observations strongly suggest that these diverse membranes can be used to quantify partitioning behavior of jet fuel components during dermal absorption and tissue distribution. This information can be incorporated into PBPK models to provide a more accurate assessment of tissue dosimetry of related toxicants (Supported by USAFOSR FA 9550-04-1-0376).

843 INERT MULTIPLE MEMBRANE-COATED FIBERS PREDICT DERMAL ABSORPTION OF CHEMICALS FROM MIXTURES

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Skin absorption of compounds from chemical mixtures is affected by many factors including chemical-chemical, chemical-vehicle, chemical-skin and vehicle-skin interactions; with the rate-limiting process primarily being interactions with the stratum corneum. To address this, we have developed a multiple membrane-coated fiber (MCF) approach that unlike *in vitro* skin systems, has the advantages of relatively high throughput. Three diverse MCFs [polydimethylsiloxane (PDMS, lipophilic), polyacrylate (PA, polarizable) and CarboWax (wax, polar)] were selected to simulate the array of molecular interactions existing in the skin/chemical mixture systems. Skin permeability coefficient (log k_p) of a set of 16 diverse compounds from chemical mixtures (water, water-ethanol, water surfactant) were measured by *in vitro* flow through diffusion experiments and membrane/chemical mixture partition coefficients (log $K_{MCF/Mix}$) were determined. Concentrations of all chemicals were assayed using GC-MS. Multiple regression analysis was used to define equations linking log k_p to log $K_{MCF/Mix}$ for the three MCFs across the three vehicle systems. Significant correlation equations were defined for each vehicle exposure: water - R^2=0.96; 50% ethanol - R^2=0.91; and 1% SLS - R^2=0.86. Differences in equations across vehicles probably reflect mixture-skin interactions. These studies demonstrate that dermal absorption of a diverse series of compounds can be estimated from data collected in three inert fibers which reflect the physicochemical diversity of interactions seen when chemicals partition into the stratum corneum. (Supported by NIOSH OH-07555 and USAFOSR FA 9550-04-1-0376).

844 EFFECTS OF A TOPICAL HEDGEHOG ANTAGONIST ON NORMAL SKIN

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Hedgehog (Hh) signaling is an important regulator of normal development and tissue homeostasis. The majority of human basal cell carcinomas (BCC) have mutations in the Hh pathway, resulting in pathway activation and uncontrolled basal cell proliferation. A topical Hh pathway antagonist, THA, is being investigated for the treatment of BCC. To evaluate the effects of dermal exposure, vehicle cream or 0.4%, 1.8%, or 3.1% THA cream were topically administered twice daily to Hanford mini-pigs for 2 months followed by a 1 month recovery period. Drug-related effects were minimal, limited to the skin, and included a few incidences of desquamation, very slight erythema, mild infiltration of mononuclear cells and/or multifocal parakeratotic crusting observed in some animals given 1.8% and/or 3.1% THA. No dermal changes were noted in animals receiving 0.4% THA or after a 1 month recovery period in any animals given THA. In addition, no drug-related signs of systemic toxicity were observed. Plasma concentrations of THA were low and variable. No gender differences were noted and bioavailability was estimated to be 0.8% in mini-pigs. To estimate the absorption of THA through human skin, various formulations of ^{14}C-labeled THA were topically applied in vitro to excised human skin samples and the amount of radioactivity was measured in epidermal and dermal layers and receptor fluid. The percentage of radioactivity in epidermal (without stratum corneum) and dermal levels ranged from 4.3% to 11% and 1.7% to 7.9%, respectively. Of the applied radioactive dose, 1.8% to 2.9% was measured in the receptor fluid. As a result, bioavailability following topical treatment of THA was estimated to be approximately 2%. In summary, topical application of THA twice daily for 2 months resulted in minimal systemic exposure and was well tolerated in mini-pigs. Since bioavailability was estimated to be approximately 2%, systemic exposure following topical administration of THA in humans is expected to be low.

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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 45th Annual Meeting of the Society of Toxicology, held at the San Diego Convention Center, San Diego, March 5–9, 2006.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 500.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 534.

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

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