donor. The experiments were performed as finite dose studies with radio-labeled Testosterone, Caffeine, (4-Chloro-2-methylphenoxy)acetic acid (MCPA) and Mannitol in modified Franz type diffusion cells. 10 µl of the test substance preparation were applied on 1 square cm of the skin preparation. The exposure time was 6 h and after a first skin wash, the post observation period was 18 h. Penetrated test substances were quantified by liquid scintillation counting and were used to calculate the maximal penetration rate, the lag time and the permeability constant (Kp). Moreover the absorbed dose was calculated from the amount of test substance in the receptor fluid and the skin. Testosterone absorption was 20 ± 5 and 12 ± 1% for FTS and DMS, respectively. For Mannitol it was 27 ± 15 and 13 ± 7%, respectively and for MCPA 17 ± 3 and 12 ± 2%, respectively. For Caffeine the absorption was 47 ± 14% in both skin preparations. Generally, Kp was higher in DMS compared to FTS (e.g. for Testosterone 21x and 90x 10-5cm/h, respectively). Moreover, FTS had higher amounts of test substance remaining in the skin and often lower amounts in the receptor fluid compared to DMS and the lag time was longer. The absorbed doses were, however, assessed to be comparable for FTS and DMS within the variability of this study.

PS 641 ANTI-INFLAMMATORY DRUG EFFICACY FOR TREATING SULFUR MUSTARD INDUCED CUTANEOUS LESIONS.

J. L. Plahovinsak[1], M. D. Etheridge[1], J. Rhone[1], F. M. Reid[1], J. F. Dillman[2] and J. S. Graham[2]. *[1]Battelle, Columbus, OH and [2]U.S. Army Medical Research Institute of Chemical Defense, Aberdeen, MD.*

Battelle's Biomedical Research Center and the U.S. Army Medical Research Institute of Chemical Defense have aligned research efforts for efficacy testing of candidate drugs to promote wound healing of sulfur mustard (SM)-induced injuries. Using an established SM dermal weanling swine model, this GLP-compliant study evaluated the efficacy of a non-steroidal anti-inflammatory drug, diclofenac sodium with the steroid, clobetasol propionate. Sites on the ventral abdomen of each female Yorkshire-cross pig were exposed to 400 µL of neat SM. Two sites on one side of the ventral midline were superficial dermal injuries (SD, 8 min) and two sites on the opposite side were deep dermal injuries (DD, 30 min). Treatments were applied to one site per depth at 2 hours post-exposure, twice daily, for 5 days. Parameters measured on Study Days 0 (transepidermal water loss and infrared imagery), 2, 3, 7, and 14 included digital photos, wound size measurements, modified Draize Scoring, and non-invasive bioengineering methods (transepidermal water loss, reflectance colorimetry, and infrared imagery). Tissues were collected on Day 14 and processed for histopathology and immunohistochemistry. At 14 d, treatment of SD injuries with diclofenac sodium and clobetasol did not significantly influence healing, as the untreated sites were nearly healed. However, treatment of DD injuries enhanced healing as evidenced through increased re-epithelialization and epidermal hyperplasia. Decreased severity of dermal, follicular, sweat gland, and smooth muscle necrosis was observed in the treated DD lesions. Immunohistochemical localization of collagen type VII and CD49f (alpha 6) was observed in SD sites. Untreated SD sites showed decreased immunospecificity for CD49f compared to the treated sites. For DD injuries, equivalent immunospecificity for collagen type VII between treated and untreated sites was observed. This work was supported by the U.S. Army Medical Research and Materiel Command under Contract W81XWH-05-D-0001, Task Order 10.

PS 642 DERMAL ABSORPTION OF DICYCLOHEXYLAMINE (DCHA) IN METAL WORKING FLUID FORMULATIONS.

R. Baynes, A. Linthicum, J. Yeatts, J. Brooks and E. Koivisto. *North Carolina State University, Raleigh, NC.*

Dicyclohexylamine (DCHA) is commonly used in the metal working industry to prevent corrosion of fabricated materials. In the last decade there has been increased use of DCHA as a biocide in metal-working fluids (MWFs); although it is not registered by the U.S. EPA for this purpose. There is no published information describing the dermal absorption of DCHA in spite of the fact that machine workers are most likely to be exposed by the dermal route than any other route and DCHA is a known dermal irritant. The objective of this research was to quantify the dermal absorption of DCHA in vitro using pig skin because pig skin is similar to human skin anatomically and biochemically. DCHA was applied to pig skin in 3 generic MWF formulations commonly used in industry: soluble oil (SO), synthetic (SYN), and semi-synthetic (SS). Dermatomed pig skin (n = 5-6) was loaded in a flow-through diffusion cell system with the dermal surface perfused for an 8-hr exposure to mimic occupational exposures. Dosing solutions containing MWFs or water were prepared below or near the saturated solutions for DCHA to provide finite or infinite dosing conditions. There was an initial 1.0 hr lag period and peak fluxes occurring at 2.0 to 3.0 hrs for all of the formulations tested. Dermal absorption of DCHA was greatest from SS (12.5%), but significantly less from SO (4.6%) and SYN (5.9%) formulations. Surprisingly, 81% DCHA was absorbed from water mixtures. These preliminary results suggest that DCHA can more readily diffuse across pig skin from aqueous solutions than from complex MWF formulations. This may be due to differential partitioning behavior within the formulations. In conclusion, there are significant differences in absorption of DCHA across the various MWF formulations, thus it is imperative to consider such differences in dermal risk assessments involving this widely used additive in the metal machining industry. This work was supported by NIOSH grant R01-01-03669.

PS 643 INTERLEUKIN 6 EXPRESSION MODULATES IRRITANT DERMATITIS SEVERITY.

E. G. Lee, B. M. Mickle and R. Gallucci. *Pharmaceutical Sciences, Oklahoma State University Health Sciences Center College of Pharmacy, Oklahoma City, OK.*

Of reported occupational injury associated with workman's compensation, contact dermatitis ranks second most prevalent over all. Inflammatory cytokines are known to be closely involved in dermatitis, and modulation of various cytokines by specific irritants could exacerbate skin damage contributing to increased irritancy. If specific cytokines can be associated with irritancy, this may be of significant predictive value when judging the irritancy potential of a chemical, or the response of an individual to irritant exposure. Interestingly JP-8 jet fuel, which is non-corrosive yet causes severe irritant dermatitis, decreases the expression of the inflammatory cytokine IL-6 in exposed skin. Because IL-6 is paradoxically associated with both skin healing and inflammation, it may be that chemically induced, or genetically associated modulation of skin IL-6 levels contributes to severity of dermatitis. To investigate this, the skin of IL-6 deficient (KO), IL-6 over-expressing transgenic (Tg), and wild type (WT) mice was exposed to the irritants JP8 jet fuel, benzalkonium chloride, and acetone as a control. Skin samples were collected after up to 7 days of exposure and were assessed for inflammation by visualization of dermatoses, histopathology, and inflammatory cytokine expression. It was found that KO mice displayed significantly greater levels of inflammation as compared to WT and Tg mice. By 7 days, there is a nearly six-fold increase in inflammatory M1 macrophages in JP8 treated IL-6KO skin, while no increase was apparent in Tg skin. Similarly, the expression of the inflammatory cytokines IL-1, CCL3, CCL11, and CCL20 was increased 4-6 fold after seven days of JP8 treatment in KO skin, where very small changes were apparent in Tg skin. These data indicate that IL-6 is indeed not pro-inflammatory in skin, but rather is associated with resistance to irritancy. Thus, IL-6 could prove to be a useful marker in determining irritancy potential of a chemical or susceptibility of an individual to irritant dermatitis. Supported by NIOSH grant 5R03OH009662.

PS 644 THE EPIOCULAR™ ASSAY FOR TESTING EYE IRRITATION *IN VITRO* : IN HOUSE VALIDATION WITH 60 TEST SUBSTANCE IN A ROUTINE LAB OF THE CHEMICAL INDUSTRY.

A. Schrage[1], S. Kolle[1], B. Wareing[1], R. B. Tacou[1, 2], B. van Ravenzwaay[1], H. Kanderova[3] and R. Landsiedel[1]. *[1]Experimental Toxicology and Ecology, BASF SE, Ludwigshafen am Rhein, Germany, [2]Master Program in Toxicology, Technical University of Kaiserslautern, Kaiserslautern, Germany and [3]MatTek Corporation, Ashland, MA.*

The bovine corneal opacity and permeability (BCOP) test was regulatorily accepted for the identification of corrosive and severe ocular irritants (GHS category 1) in 2009. But no in vitro test has been regulatorily accepted for the differentiation of ocular irritants and non-irritants (GHS category 2). Human reconstructed tissue models have been suggested for incorporation in a tiered test strategy to ultimately replace the Draize eye irritation test (OECD405). These models use cell death as an indicator of ocular irritation. We established and evaluated the EpiOcular assay to discriminate irritants from non-irritants. Test substances that decreased viability to ≤ 60% (compared to control) are considered eye irritants (GHS cat 1 or cat 2) and test substances with less effect are considered non-irritants. In addition to the EpiOcular Test we performed the BCOP assay (OECD437) and the direct peptide reactivity assay (DPRA, Gerberick). The tests were performed with 60 test substances including a broad variety of chemicals and formulations for which in vivo data (Draize test) were available: 18 severe irritants/corrosives (GHS category 1), 21 irritants (GHS category 2), and 21 non irritants. For the assessed data set the EpiOcular assay had a sensitivity of 90%, a specificity of 73% and an overall accuracy of 81%. Applying a lower viability threshold (50% instead of 60%) resulted in 82, 82 and 82%, respectively. The DPRA assay was not useful for prediction of eye irritation potential of the 60 compounds. Whereas the BCOP assay was – as expected – useful in further differentiating strong irritation effects. We will use the EpiOcular assay and the BCOP assay in a testing strategy to identify strong eye irritation, eye irritation and no eye irritation effects of test substances in routine testing of industrial chemicals and agrochemical formulations.

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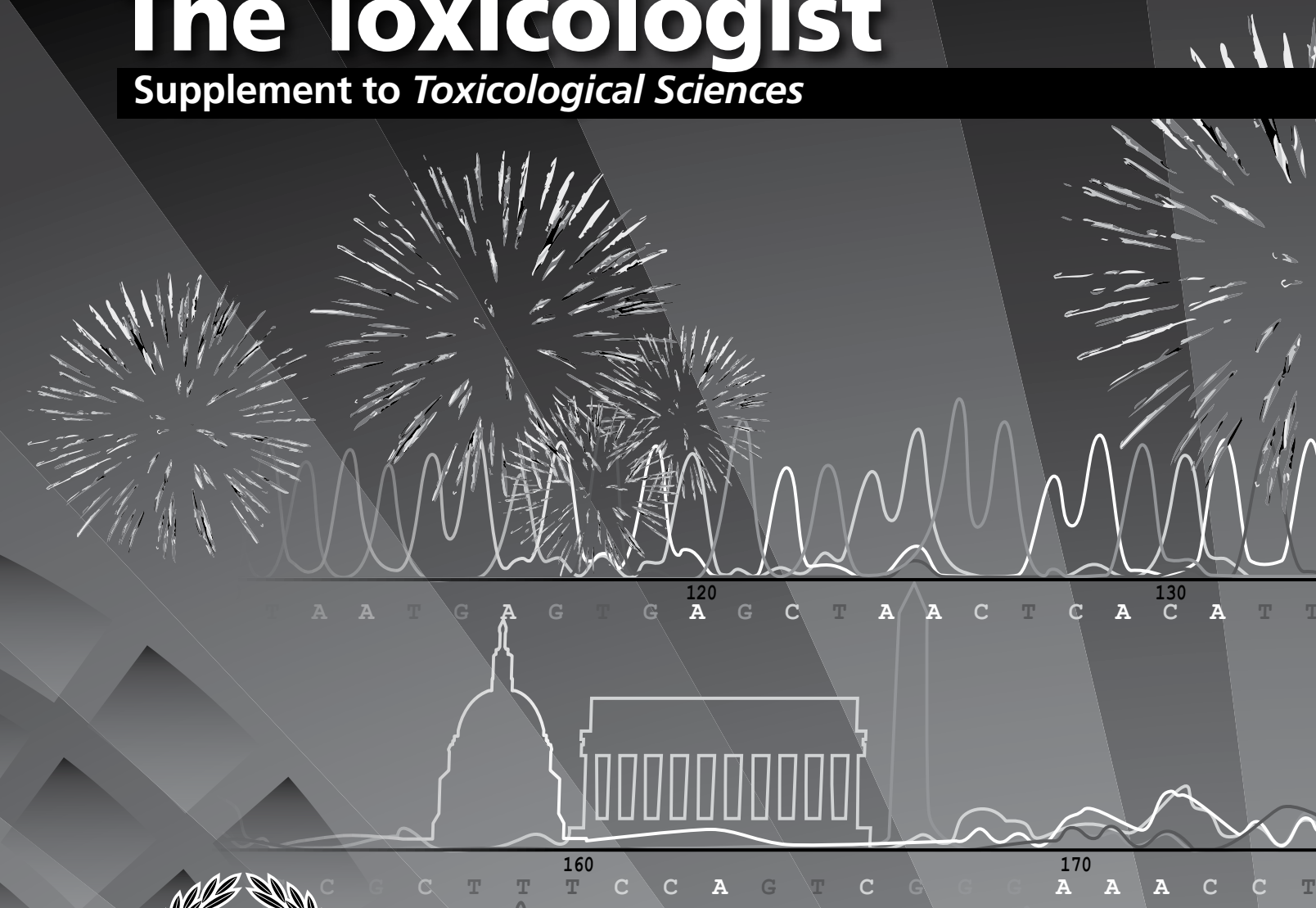

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 50th Annual Meeting of the Society of Toxicology, held at the Walter E. Washington Convention Center, March 6–10, 2011.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 578.

The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 606.

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

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