methyl N- methylanthranilate to naive sites on the back followed by immediate exposure of the test sites to UVB and UVA from a Solar Simulator. Phototoxic effects were observed in 14/35 female volunteers with 1% methyl N-methylanthranilate in 75% ethanol/25% diethyl phthalate; no phototoxic effects were observed in 29 volunteers with 0.1%, 0.3% or 0.5% in 75% ethanol/25% diethyl phthalate. A study to determine the photoallergic potential of methyl N-methylanthranilate was conducted in 26 female volunteers using a modified human photomaximization procedure (six 24-hour occluded induction applications with each application followed immediately by UVB/UVA exposure from a Solar Simulator; after a 2-week rest period, a 24-hour occluded challenge application was immediately followed by exposure to UVA/UVB); phototoxicity was also evaluated during the induction phase of this study. No photoallergic or phototoxic reactions were observed with 0.5% in 75% ethanol/25% diethyl phthalate. Based on the findings in these studies, it can be concluded that the NOEL for methyl N-methylanthranilate for phototoxic effects in humans is 0.5%; and under the conditions of the above study, methyl N-methylanthranilate is not photoallergic in humans at a concentration of 0.5%.

1838 GENE EXPRESSION IN RAT SKIN FOLLOWING CUTANEOUS EXPOSURE TO XYLENE, SODIUM LAURYL SULFATE AND LIMONENE.

J. N. McDougal[1], C. M. Garrett[2] and J. V. Rogers[2,1]. *[1]Pharmacology and Toxicology, Wright State University School of Medicine, Dayton, OH and [2]GeoCenters Inc., Air Force Research Laboratory, Wright-Patterson AFB, OH.*

In the US, occupational skin disease is the second most significant cause of occupational disease, after accidents. Some of this disease is due to exposures to occupational chemicals such as solvents, fuels and surfactants. Understanding the mechanisms of acute irritation will assist in assessing risks to exposures as well as potential therapy and prophylaxis. Gene expression studies may provide useful information about normal processes in the skin and the responses of the skin to exogenous chemicals. We exposed rats, cutaneously, to m-xylene (pure liquid), sodium lauryl sulfate (1% & 10% aqueous solution) and d-limonene (pure liquid) for one hour and measured transcriptional responses at the end of the exposure and three hours later for comparison with untreated skin samples. Total skin RNA was isolated and analyzed using the Affymetrix RatTox U34 array. We found that 120 of approximately 850 genes were detected as present with Affymetrix software. The largest number of these genes was in the metabolism (19) and oxidative/cellular stress responsive (9) categories. Other transcripts present in untreated skin were categorized as cellular structure, signaling, hormones, extracellular matrix, differentiation/cell division, transporters/ligands and a receptor. We found that limonene treatment caused the largest change in mRNA levels with a total of 34 transcripts increased and 4 transcripts decreased at one or four hours. 10 % sodium lauryl sulfate caused 5 transcripts to increase and 17 to decrease at one or four hours. Xylene treatment resulted in 6 increased transcripts and 14 decreased transcripts at one or four hours. Differences in the skin responses to these 3 treatments may reflect different mechanisms of irritation. These changes in gene expression suggest some proteins that should be quantified as we investigate the time course of the irritant cascade. (supported by CDC/NIOSH R01 OH03654)

1839 VEHICLE COMPOSITION INFLUENCES THE PHARMACOLOGIC EFFECTS AND KINETICS OF CAPSAICIN IN HUMAN SKIN.

L. K. Pershing[1], C. A. Reilly[2] and D. J. Crouch[2]. *[1]Dermatology, University of Utah, Salt Lake City, UT and [2]Center for Human Toxicology, University of Utah, Salt Lake City, UT.* Sponsor: G. Yost.

Less-than-lethal pepper spray products are prepared by solubilizing capsaicinoids in various solvents, including alcohols and propylene glycol. Previous studies showed that capsaicin activity in human skin (erythema) was 3X greater in propylene glycol than isopropyl alcohol. This study investigated the uptake and elimination of capsaicinoids in human skin as a possible kinetic basis for the responses. Twelve sites on the volar forearms of twelve human subjects were exposed for 1, 5, 10 and 15 min to a single, nonoccluded 150 mcg dose of capsaicin prepared in either 70/30 (v/v) isopropyl alcohol/water (IPA), 80/20 (v/v) mineral oil/isopropyl alcohol (MO) and 80/20 (v/v) propylene glycol/isopropyl alcohol (PG). Skin capsaicinoid concentrations were quantified in stratum corneum harvested with ten 1.3 diameter adhesive discs applied and removed from each skin site either immediately after exposure (1, 5, 10 or 15 min) or 3, 6, 11 or 24 hrs after removal of a 15 min exposure. The samples from each skin site were combined, extracted and analyzed for capsaicin and dihydrocapsaicin concentration by LC-MS and the kinetic parameters Cmax, Tmax, AUC and Thalf determined. Both capsaicinoids were detected in stratum corneum within 1 min of exposure. Cmax for capsaicin in PG (5.6 mcg) was similar to MO (6.6 mcg), but 3X less than IPA (16.1 mcg). Differences in AUC between the vehicles reflected the rank order of Cmax. Dihydrocapsaicin concentrations were ~60% of capsaicin in all solutions and all skin samples at all time points, independent of vehicle. Tmax and Thalf of the capsaicinoids were similar in PG, MO and IPA. Thalf of capsaicin and dihydrocapsaicin in human stratum corneum was ~24 hrs. Thus, alcohols influenced the extent of capsaicinoid uptake, but not the rate of uptake or elimination kinetics in human skin *in vivo.* Therefore, the elevated potency of capsaicin in PG is likely due to a vehicle influence on the receptor-mediated pharmacologic effects of capsaicin.

1840 EVALUATION OF DERMAL ABSORPTION OF AQUEOUS TOLUENE IN F344 RATS USING REAL-TIME BREATH ANALYSIS AND PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING.

A. D. Woodstock and K. D. Thrall. *Battelle, Pacific Northwest Laboratory, Richland, WA.*

Toluene is a ubiquitous chemical commonly used for its solvent properties in industry and manufacturing, and is a component of many paint products. Because of its widespread use, there is potential for both occupational and non-occupational dermal exposure to toluene. To understand the significance of these exposures, the dermal bioavailability of toluene was assessed in F344 male rats using a combination of real-time exhaled breath analysis and physiologically based pharmacokinetic (PBPK) modeling. Animals were exposed to toluene at a 0.5 or 0.2 mg/ml aqueous concentration using a 2.5-cm diameter occluded glass patch attached to a clipper-shaved area on the back of the rat. Immediately following exposure, individual animals were placed in a glass off-gassing chamber and exhaled breath was monitored as chamber concentration in real time using an ion trap mass spectrometer. The exhaled breath profile clearly demonstrated the rapid absorption of toluene, with peak chamber concentrations observed within 1 hr from the start of exposure. The PBPK model describing the exposure and off-gassing chamber was used to estimate a dermal permeability coefficient (Kp) to describe each set of exhaled breath data. Regardless of exposure level, a single Kp value of 0.074 +/- 0.005 cm/hr provided a good fit to all data sets. These rat studies using aqueous toluene will form the basis for comparing the dermal bioavailability of toluene in various paint products and may ultimately aid in understanding human health risk under a variety of exposure scenarios. (Supported by NIOSH grant 1-RO1-OH03658-01A2).

1841 A MATHEMATICAL MODEL OF THE PERMEATION KINETICS OF THE MEMBRANE-COATED FIBER TECHNIQUE ACCOUNTING FOR PARTITION, DIFFUSION AND BOUNDARY LAYER FACTORS.

X. R. Xia, R. E. Baynes, N. A. Monteiro-Riviere and J. E. Riviere. *Center for Cutaneous Toxicology and Research Pharmacokinetics, North Carolina State University, Raleigh, NC.*

A mathematical model was developed to describe the permeation kinetics of the membrane-coated fiber (MCF) technique, which is used for *in vitro* assessment of dermal absorption of chemical mixtures. In addition to the basic percutaneous absorption factors, partition coefficient and membrane diffusivity, a boundary layer adjacent to the membrane was considered in the model. The cumulative amount permeated into the membrane was expressed as a function of permeation time in an exponential equation. The two constants introduced into the model, clearly defined with the physiochemical parameters of the system, can be obtained by regression of the experimental data sampled over a limited time. The partition and diffusion coefficients, as well as, the thickness of the boundary layer were calculated from the two constants. The mathematical model adequately described the permeation kinetics of the MCF technique. All of the theoretical predictions were supported by the experimental results. The measured partition coefficients were correlated well with the published octanol/water partition coefficient (R2=0.88). The thickness of the boundary layer was 5.2μm in a donor solution stirred at 400 rpm. The contribution of the boundary layer to the permeation kinetics is 2K times larger than that of the membrane, where K is the partition coefficient of a given compound. These results suggest that the permeation rate of a hydrophobic compound could be controlled by the boundary layer even though the diffusivity of the compound in the membrane is lower than that in the donor solution. Supported by NIOSH R01-OH 03669 and 07555.

1842 PHYSIOLOGICAL MODELING OF THE DERMAL ABSORPTION OF OCTAMETHYLCYCLOTETRASILOXANE (D4).

M. B. Reddy[1], R. J. Looney[2], M. J. Utell[2], M. L. Jovanovic[3], J. M. McMahon[3], D. A. McNett[3], I. D. Dobrev[1], K. P. Plotzke[3] and M. E. Andersen[4]. *[1]Quantitative and Computational Toxicology Group, Center for Environmental Toxicology and Technology, Colorado State University, Fort Collins, CO, [2]University of Rochester School of Medicine, Rochester, NY, [3]Toxicology, Health and Environmental Sciences, Dow Corning Corporation, Midland, MI and [4]CIIT Centers for Health Research, Research Triangle Park, NC.*

Studies on human dermal absorption of octamethylcyclotetrasiloxane, D4, through axilla skin *in vivo* and through abdominal skin *in vitro* recently have been completed. A mathematical model describing the dermal absorption of D4 was developed and combined with an inhalation PBPK model for this material. The model