811 EVALUATION OF THE DERMAL ABSORPTION OF METHYL ETHYL KETONE IN F344 RATS USING REAL-TIME BREATH ANALYSIS AND PBPK MODELING.

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Methyl ethyl ketone (MEK) is an industrial solvent found as a component of a variety of paints and coatings. Dermal exposure to MEK can result from the occupational or household use of paints and other commercial products. To understand the significance of these exposures, the dermal bioavailability of MEK 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 MEK at a 5 mg/ml aqueous concentration using a 2.5-cm diameter occluded glass patch system attached to a clipper-shaved area on the back of the rat. Immediately following exposure the animal was placed in a glass off-gassing chamber and exhaled breath was monitored as chamber concentration in real time using an ion trap mass spectrometer (MS/MS). This real-time methodology was able to discern the uptake, peak concentration and clearance phases associated with the dermal exposure. For example, the exhaled breath profile clearly demonstrated the rapid absorption of MEK, with peak chamber concentrations ranging from 20 to 25 ppm observed within 30-60 minutes from the start of exposure. The PBPK model describing the exposure and off-gassing system was used to estimate a single dermal permeability coefficient to describe all the sets of exhaled breath data from n=6 animals. These rat studies using aqueous MEK will form the basis for comparing the dermal bioavailability of MEK in various paint products and may ultimately aid in understanding human health risk under a variety of exposure scenarios. (Supported by NIOSH 1-RO1-OH03658-01A2).

812 ASSESSMENT OF DERMAL IRRITATION OF THREE BENZENE SULFONATE COMPOUNDS.

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Three benzene sulfonate compounds are present in groundwater near a former disposal site at concentrations ranging from <1 mg/L to <500 mg/L. Dermal irritation studies were performed for each of the three sulfonate compounds to determine if they would cause irritation to the skin of persons using water containing the compounds for bathing, showering, or other uses where skin would be exposed. The three compounds are: (1) benzene sulfonate; (2) benzene meta-disulfonate; and (3) para-hydroxybenzene sulfonate. The studies were performed in accordance with USEPA's Health Effects Test Guidelines: OPPTS 870.2500, Acute Dermal Irritation, 1998. At the highest dose tested (5, 000 mg/L), all three sulfonate compounds were considered to be slight irritants, producing very slight to mild erythema. In all cases, the reactions were reversible. At the second highest dose tested (2, 000 mg/L), benzene meta-disulfonate and para-hydroxybenzene sulfonate caused no irritation and were considered not to be irritants. At the second highest dose only benzene sulfonate is considered a slight irritant, producing a mild erythema that was completely reversible within 24 hours. Benzene sulfonate is not considered an irritant at 1, 000 mg/L or at 500 mg/L. It is important to note that all three sulfonate compounds produced only a slight irritation at the highest dose tested. No compound produced edema or a severe irritation (i.e., severe erythema). Furthermore, all irritation responses at the highest dose tested were reversible within 72 hours, and the only irritation response observed at the second highest dose (2000 mg/l of benzene sulfonate) was reversible in less than 24 hours.

813 ASSESSMENT OF DERMAL PENETRATION OF THREE BENZENE SULFONATE COMPOUNDS.

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Three benzene sulfonate compounds are present in groundwater near a former disposal site at concentrations ranging from <1 mg/L to <500 mg/L. Dermal penetration studies were performed for each of the three sulfonate compounds to determine if they would be systemically absorbed by persons using water containing the compounds for bathing, showering, or other uses where skin would be exposed. The three compounds are: (1) benzene sulfonate (BSA); (2) benzene meta-disulfonate (BDSA); and (3) para-hydroxybenzene sulfonate (HBSA). The dermal penetration studies with infinite doses of 2, 000 mg/L aqueous solutions were performed *in vitro* for 24 hours with human abdominal skin using Franz diffusion cells with 0.9% saline solution as receptor fluid. Each compound was tested with six skin samples from a minimum of three donors. The integrity of human skin was tested with 3H-water before use. Aliquots of receptor fluid were analyzed for the presence of the test compounds using ion-pairing reverse phase high performance liquid chromatography (HPLC) and ultraviolet absorption. HPLC conditions were 53:47, 25 mM tetrabutylammonium bromide:methanol (isocratic). Analytical wavelengths were 263, 267 and 271 nanometers for BSA, BDSA and HBSA, respectively. No sulfonate compounds were detected in the receptor fluid at 24 hours in any of the test cells. The Estimated Quantitation Limit (EQL) for all compounds was determined to be 0.5 ng/ul. Assuming that the compounds were present at one-half the EQL, the permeability constants, Kp, were 2E-05 cm/hour. The results of this study confirm the results of a pilot study performed using the same methods but different chromatographic conditions.

814 MECHANISMS OF UVB LIGHT-INDUCED SUPPRESSION OF NITRIC OXIDE PRODUCTION IN MURINE KERATINOCYTES.

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Ultraviolet light of high energy and shorter wavelengths (UVB, 290-320 nm) is utilized therapeutically to reduce irritation in inflammatory dermatosis. The mechanisms underlying the actions of UVB are unknown. We hypothesize that the UVB light suppresses oxidant generation in the skin. Nitric oxide is a highly reactive oxidant generated by keratinocytes by an inducible form of nitric oxide synthase (NOS2) in response to the inflammatory cytokine, gamma interferon. In the present studies we examined the effects of UVB light on NOS2 activity in keratinocytes. We found that UVB light suppresses gamma-interferon-induced nitric oxide production in these cells. This effect was dose-dependent in the range of 2.5-25 mJ/cm^2. This was found to be due to inhibition of NOS2 mRNA and protein expression in the cells, as determined by RT-PCR and western blotting, respectively. Two transcription factors known to be important in regulating expression of NOS2 are signal transducer and activator of transcription-1 (STAT-1) and nuclear factor κB (NF-κB). Using electrophoretic mobility shift assays, we found that gamma interferon readily induced STAT-1 activity while NF-κB was constitutively expressed in the cells. UVB light (25 mJ/cm^2) was found to cause a 30-40% reduction in the activation of these transcription factors. Nuclear translocation of the p50 and p65 subunits of NF-κB was also marked reduced by UVB light. Taken together, our data suggest that UVB light functions to suppress expression of NOS2 by inhibiting activation of key transcription factors important in regulating expression of the NOS2 gene. Decreased expression of NOS2 and subsequent nitric oxide production in keratinocytes may be an important mechanism for the anti-inflammatory and therapeutic actions of UVB light. Supported by NIH grant ES 06897.

815 THE EFFECTS OF CHRONIC ALCOHOL CONSUMPTION ON DERMAL PENETRATION OF PESTICIDES.

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The skin is the major source of xenobiotic exposure in occupational settings. Topically applied ethanol is commonly used as a dermal penetration enhancer. The hypothesis of this work is that ethanol, consumed orally, will also behave as a dermal penetration enhancer. A series of four pesticides, paraquat (MW = 257, log K_{ow} = -4.5), 2, 4 D (MW = 221, log K_{ow} = 2.8), atrazine (MW = 216, log K_{ow} = 2.3) and trifluralin (MW = 335, log K_{ow} = 5.1) were selected as model compounds to test this hypothesis. These compounds were chosen for their diverse octanol water partition coefficients (K_{ow}), a factor known to influence percutaneous penetration. Male Wistar rats were fed a diet of 36% ETOH (25 mM in blood) or control in a liquid diet for 4-8 weeks. The animals were then sacrificed, their skin shaved, removed and placed in an *in vitro* Bronaugh Style flow through diffusion chamber. The test compound was spiked with ^{14}C labeled pesticide and placed on the epidermis for 24 hours. Buffer flowing past the dermal side of the skin was collected in 90-minute fractions and counted *via* liquid scintillation. Chronic ethanol consumption significantly enhanced dermal penetration for the three most hydrophilic compounds tested ($p<0.05$). The penetration of trifluralin, the most hydrophobic pesticide, was inhibited by chronic ethanol consumption ($p<0.05$). A regression analysis demonstrates a correlation between hydropholicity and enhancement of transdermal penetration by chronic ethanol consumption. Chronic ethanol consumption, therefore, leads to compromised dermal barrier in rats resulting in increased penetration of pesticides. These studies imply that alcoholic workers have greater dermal exposure of chemicals than previously estimated.

816 TRANSCRIPT PROFILING OF MURINE LYMPH NODE CELLS : ALLERGEN-INDUCED EARLY GENE CHANGES.

C. J. Betts[1], J. G. Moggs[1], H. Caddick[1], M. Cumberbatch[1], G. Orphanides[1], R. J. Dearman[1], G. F. Gerberick[2], C. A. Ryan[2] and I. Kimber[1]. *[1]Syngenta Central Toxicology Laboratory, Macclesfield, United Kingdom and [2]The Procter & Gamble Company, Cincinnati, OH.*

In order to identify early events induced in lymphoid tissue following topical treatment of mice with contact allergen, gene expression changes in draining lymph node cells (LNC) have been profiled using DNA microarrays. BALB/c strain mice

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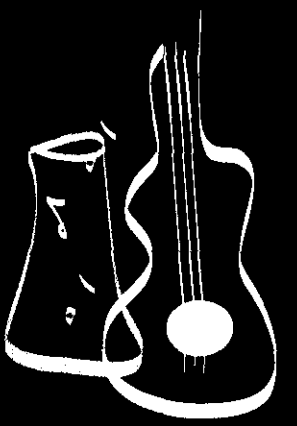

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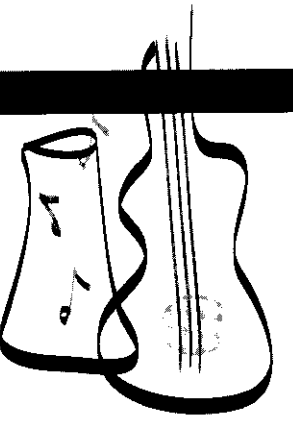

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Preface

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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