286 ENHANCED OXIDATIVE STRESS IN THE SKIN OF VITAMIN E DEFICIENT MICE EXPOSED TO METAL WORKING FLUID.

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Metal working fluids (MWFs) are widely used in industry for metal cutting, drillings, shaping, lubricating, and milling. Many occupational health concerns have arisen for workers exposed to MWFs. It has been reported earlier that occupational exposure to MWFs causes allergic and irritant contact dermatitis. Previously, we have shown that dermal exposure of female and male B6C3F1 mice to 5% MWFs for 3 months resulted in accumulation of mast cells and elevation of histamine in the skin. Topical exposure to MWFs also resulted in elevated oxidative stress in the liver of both sexes and the testes in males. The goal of this study was to evaluate whether oxidative stress in the skin exacerbated mast cell influx after MWF treatment. Oxidative stress in skin of B6C3F1 mice was generated by vitamin E deprivation. Mice were given vitamin E deficient or basal diets for 34 weeks. Topical treatment with MWFs (100 µl, 30%) started after 18 weeks of alimentary vitamin E deprivation. Microscopic alterations in the skin 16 weeks after exposure to MWFs included a very mild increase in the thickness of squamous epithelium of the epidermis with mild enlargement of sebaceous glands, and a 46% increase in mast cell accumulation in mice receiving vitamin E deficient diets. Total antioxidant reserve in skin of vitamin E deprived mice treated with MWFs was decreased by 71% compared to those mice given a vitamin E sufficient diet. Depletion of GSH and protein thiols in the dermis of vitamin E deprived mice exposed to MWFs was 39% and 42% respectively, compared to mice given a basal diet. Further study is necessary to delineate the role of oxidative stress in the enhancement of mast cell accumulation caused by topical exposure to MWFs.

287 SIGNIFICANT EFFECTS OF APPLICATION VEHICLE, SKIN OCCLUSION, CUTANEOUS CYP450 INDUCTION, AND AMBIENT TEMPERATURE ON DERMAL ABSORPTION AND CUTANEOUS DISPOSITION OF PENTACHLOROPHENOL (PCP).

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To assess the impacts of skin exposure variables on dermal absorption and cutaneous disposition of PCP, one of the most highly detected environmental contaminants, ^{14}C-PCP was dosed in ethanol, acetone, a water-ethanol mixture, or a soil-based mixture in a porcine skin flap model (40 µg/cm^2, n=3-4/treatment). Effects of vehicle composition, skin occlusion, skin pre-exposure to a CYP_{450} inducer (benzo[a]pyrene, B[a]P), and ambient temperature change were examined. Significant exposure-dependency in PCP dermal absorption and tissue disposition were determined. The *ex vivo* 8-hr dermal absorption varied from 0.2 to 26% under different exposure scenarios. Ethanol and acetone vehicles yielded identical total absorption of 1.1%, but very different absorption profiles. Water addition to the ethanol vehicle dramatically enhanced PCP dermal uptake from 1.1 to 14.1% (14-fold, $P<0.05$). Mixing soil dust into the liquid water-ethanol vehicle significantly decreased dermal absorption (14.1 → 3.4%, $P<0.05$). Occlusion of the dosed skin markedly enhanced dermal absorption (3.4 → 26%) and cutaneous tissue penetration from the soil matrix. An air temperature drop from 37 to 25 °C decreased PCP absorption by 6-fold (ethanol, 1.1% → 0.2%, $P<0.05$). Cutaneous CYP_{450} induction by B[a]P pre-exposure tripled the dermal absorption (1.1 → 3.2%, $P<0.05$) and decreased the absorption/penetration ratio. In conclusion, organic vehicle selection, water-organic solvent mixing, soil dust mixing, skin occlusion, cutaneous CYP_{450} status, and ambient temperature variation can dramatically change dermal absorption and cutaneous disposition, and thus alter local vs systemic risk from occupational and environmental exposures to toxicants similar to PCP. (Supported by EPA-CR 824007 and NIOSH/CDC.)

288 *IN VITRO* PERCUTANEOUS ABSORPTION OF NONYLPHENOL (NP) AND NONYLPHENOL ETHOXYLATES NPE-4 AND NPE-9 IN ISOLATED PERFUSED SKIN.

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The purpose of this study was to assess the percutaneous absorption of (1%) ring-labeled 14C-NP (n=4), 14C NPE-4 (n=4), and 14C NPE-9 (n=4) in the isolated perfused porcine skin flap (IPPSF) model and compare it to *in vitro* pig skin flow through (PSFT) diffusion studies. Previous published data (Monteiro-Riviere *et al.*, 2000) suggest that NP, NPE-4 and NPE-9 were minimally absorbed across the skin of rat, human, and porcine skin diffusion cells. Studies were conducted in an *ex vivo* perfused porcine skin model that has been shown to predict human exposure. The IPPSF was dosed with either 100 µl of 1% radiolabeled NPE, NPE-4 or NPE-9 in polyethylene glycol (PEG-400) vehicle and water solution and perfused for 8 hr. There was no significant difference between the NP, NPE-4 and NPE-9 absorption, surface, and stratum corneum residues between porcine diffusion cells or isolated perfused porcine skin. The only significant differences within models is that NP had higher dosed skin concentrations in the IPPSF than NPE-9. NPE-4 and NPE-9 had significantly higher skin concentrations in the PSFT than in the IPPSF, possibly reflecting the lack of dermal tissue perfusion in diffusion cell model systems. These studies concur with previous research that these compounds are minimally absorbed through skin. Lower skin penetration in the IPPSF is probably more predictive of in vivo absorption where dermal perfusion reduces this artifactual accumulation seen in diffusion cell systems. (Supported by the Alkyphenols and Ethoxylates Research Council.)

289 MODELING PERCUTANEOUS ABSORPTION FROM COMPLEX CHEMICAL MIXTURES.

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The process by which a chemical is absorbed through the skin is highly complex. When absorption of a chemical present in a mixture is considered, the situation becomes considerably more complex. In theory, a complete mathematical description of the absorption process can be made using coupled partial differential equations. However, it is difficult, if not technically impossible to obtain the measurements necessary to parameterize the model. Our approach is to use a simple non-linear model that represents the mean profiles from absorption experiments carried out in the isolated perfused porcine skin flap (IPPSF) and porcine skin flow through (PSFT) *in vitro* systems using pentachlorophenol (PCP) in mixtures containing water, ethanol, sodium lauryl sulfate, and methyl nicotinate. The parameters in the model reflect underlying biological and biophysical processes that influence the rate at which a compound in a mixture is absorbed. The model is used to differentiate between mixture treatment effects, as well as to ascribe statistical significance to changes in various profile properties as a function of mixture composition. Since the data are in the form of repeated measurements, longitudinal data analysis techniques are used, thereby making the best use of the experimental arrangement. This method makes few assumptions concerning the actual mechanism of percutaneous absorption, while still retaining enough flexibility to capture the complexity of the underlying physical processes governing the absorption of chemicals from complex mixtures. (Supported by ATSDR U61/ATU484504 and EPA OW 0043 NTTA.)

290 INTRA-INDIVIDUAL VARIATIONS IN SKIN IRRITATION RESPONSES.

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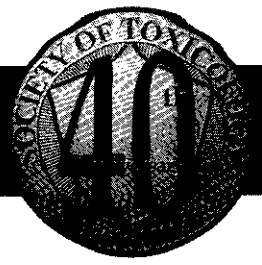
Understanding variations in skin irritation response patterns is fundamental to predicting those responses and to defining unique susceptibilities that might exist among human subpopulations. Variation in irritation responses between human subjects and between different skin sites within subjects has been reported. What has not been well described is the simple variation that might exist within individual subjects in general; *i.e.*, how well does a subject's response to one irritant challenge predict their response to another, even when the challenges are concurrent. To address this question, a study was conducted to examine individual response patterns to concurrent acute and cumulative irritation patch test exposures. A population of Caucasian and Asian test subjects was patch tested for acute irritation to 20% sodium dodecyl sulfate (SDS), 100% octanoic acid, 100% decanol, 10% acetic acid and water using a human 4 hr patch test. They were concurrently patch tested with 0.025%, 0.05%, 0.1%, and 0.3% SDS in a 14-day repeat 24 hr exposure patch test (cumulative irritation test). Individual subject's responses were compiled for each test method, test material, and test material concentration and compared (across the entire population) in 3 ways: 1) acute response to two chemicals with similar overall irritation potentials, 2) cumulative response to various SDS concentrations, and 3) acute/high concentration *vs.* cumulative/low concentration SDS exposures. Using regression analysis, positive and significant (albeit moderate) correlations were observed in the acute chemical comparisons and in the cumulative response comparisons. There was no correlation between acute and cumulative irritation response patterns to SDS. In spite of the overall correlations, many variant responses were seen among individual test subjects. This is a finding that needs



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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.

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