of a decrease of the proliferation rate. Although changes of the medium osmolarity played a role in these effects, their contribution was only minor. In conclusion, $CaCl_2$ modulates the proliferation rate and the cell cycle distribution of cultured human keratinocytes.

358 BIOTRANSFORMATION AND CYTOTOXICITY OF SULFAMETHOXAZOLE (SMX) AND DAPSONE (DDS) IN NORMAL HUMAN-NEONATAL EPIDERMAL KERATINOCYTES (NHEK).

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SMX and DDS are both associated with a high incidence of cutaneous drug reactions (CDR), though SMX causes a significantly greater frequency of adverse effects. Proposed mechanisms for the pathogenesis of these CDR suggest that bioactivation to a hydroxylamine metabolite is a critical initiating step. However, conventional metabolism studies demonstrating the bioactivation of SMX or DDS to systemically available hydroxylamine species have failed to adequately explain how these toxic metabolites may elicit the site-specific reactions observed clinically. Because the skin possesses substantial metabolic capacity, we hypothesized that local bioactivation of SMX and/or DDS by keratinocytes may be a contributing factor in the development of CDR. NHEK suspensions ($7x10^5$/mL) derived from cultures grown in high Ca^{+2} (2mM) media for 48 hr were able to metabolize 1mM SMX and DDS to N-acetyl and hydroxylamine derivatives, albeit at low levels. Greater amounts of N-acetyl-SMX were formed than monoacetyl-DDS (3.6 vs. 2.0 nmoles, respectively, at 12 hr), though hydroxylamine formation was more comparable (0.9 vs. 1.2 nmoles). Metabolite formation occurred in a time- dependent manner from 0.5 to 24 hr. A similar metabolic profile was also observed for SMX using NHEK cultured in low Ca^{+2} (0.15mM) media. Despite this bioactivating capability, however, evaluation of the effect of SMX and DDS (31.3µM-4mM) on NHEK viability failed to demonstrate a significant increase in cell death above controls, even after 24 hr exposure. Comparison of the cytotoxic effects of synthetic hydroxylamines toward NHEK showed that 3 hr exposure to DDS-hydroxylamine caused a concentration-dependent increase in cell death (LC_{50}=281±80µM). In contrast, NHEK demonstrated no increase in cell death when incubated with SMX-hydroxylamine (31.3µM-4mM). Considering the predominance of keratinocytes in normal human skin, local formation and release of hydroxylamine metabolites into the micro-environment of the skin may play a role in the development of CDR. (Supported by NIH Grant AI41395.)

359 COMPARISON OF DERMAL CORROSION VALUES FOR SELECTED INDUSTRIAL CHEMICALS USING CORROSITEX.

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Skin irritation is the most frequently reported occupational hazard for those employees engaged in the use and transport of industrial chemicals. The rabbit test is most common *in vivo* method used to evaluate dermal irritation and/or corrosion. Several *in vitro* test methods have been developed, with Corrositex® being the first to gain approval by a regulatory agency (DOT). Several classes of industrial chemicals, 24 formulations, were tested using the Corrositex® method and the results were compared to standard animal data for each of the formulations. Based on the results, Corrositex® accurately predicted a corrosive endpoint in 8 of the 24 formulations, when compared to the animal data, and accurately predicted a non-corrosive endpoint for 1 of the 24 formulations. The Corrositex® assay overpredicted a corrosive endpoint for 9 of the 24 formulations, and underpredicted a corrosive endpoint for 6 of the 24 formulations. In addition, corrosive classifications (DOT Packing Groups) were also evaluated. The Corrositex® assay overpredicted the Packing Group classification for 12 of the 24 formulations tested and underpredicted 7 of the 24 formulations tested.

The Corrositex® assay did not adequately predict a corrosive endpoint or Packing Group for the 24 formulations used in this study. This study was a practical application of the Corrositex® method, and the method appears to have failed for predicting the corrosive hazards of the chemical classes included in this study.

360 FURTHER EVALUATION OF THE EPIDERM™ AND EPIOCULAR™ *IN VITRO* IRRITATION MODELS.

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Both EpiDerm™ and EpiOcular™ are commercially available *in vitro* models for assessing the skin and eye irritation potential, respectively, of chemicals. The EpiDerm™ and EpiOcular™ tissue models are organotypic three-dimensional human skin and corneal analogues derived from human epidermal keratinocytes. Both are colorimetric cytotoxicity models based on the ability of chemically exposed tissues to reduce MTT. An MTT effective time-50 (ET-50; time required to decrease cell viability by 50%) is established for each chemical. The objective of this study was to evaluate both EpiDerm™ and EpiOcular™ for their ability to assess the skin and eye irritation potential, respectively, of several water soluble and insoluble compounds previously evaluated *in vivo*. All animal data was obtained from previously published animal studies. No new *in vivo* testing was performed. The following compounds were examined with both EpiDerm™ and EpiOcular™ : benzyl alcohol; dibasic ester; heptyl acetate, propylene carbonate; N-methylpyrrolidone; sodium lignosulfate; sodium alkylnaphthalene sulfonate; polyethoxylated polyarylphenol; polysorbate 85; and sodium dodecylbenzene sulfonate. The following were examined only with EpiDerm™ : 2 and 100% 1-octyl-2-pyrrolidinone and an aromatic hydrocarbon. One or 0.3% Triton X-100 were used as positive controls for EpiDerm™ and EpiOcular™ , respectively. Of the 13 compounds evaluated, EpiDerm™ correctly identified 10 (77% concordance with *in vivo* data). EpiDerm™ overpredicted the remaining 3 compounds. EpiOcular™ correctly identified 7 of the 10 examined compounds (70% concordance with *in vivo* data). The eye irritancy of 2 compounds was underpredicted, while that of the remaining compound was overpredicted. Although these systems have proved useful for evaluating the irritancy potential of water soluble compounds, further evaluation of their ability to predict the skin and eye irritation potential of various classes of water insoluble compounds needs to be conducted.

361 A STRUCTURE-ACTIVITY RELATIONSHIP (SAR) MODEL FOR ESTERS THAT CAUSE HUMAN SKIN IRRITATION.

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A structure-activity relationship (SAR) model has been developed to discriminate active from inactive esters on the basis of their ability to cause skin irritation in humans. The model is based on patch test data gathered from a critical review of the literature. Esters were selected from a broader database of human irritants and represented a large subset of homologous chemicals. Nineteen physicochemical parameters that represented transport, steric and electronic properties, were calculated for each chemical. Best subset regression analysis identified models for further analysis. Regression analyses were performed to identify all significant models ($p < 0.05$) that had variables that were also significant ($p < 0.05$). These models were evaluated using linear discriminant analysis to determine if the irritant esters could be discriminated from non-irritant esters. Cross validation was employed to estimate the sensitivity and specificity of the model. The model with the greatest discriminating ability contained the parameters density, Hansen dispersion, Hansen hydrogen bonding, and hydrogen bond donor. The overall sensitivity of the model was 0.85, while the specificity was 0.76. Active irritant esters had lower densities, lower hydrogen bond donor and lower Hansen hydrogen bonding param ters, and higher Hansen dispersion parameter. These characteristics indicate that irritant esters would tend to be less water soluble and less likely to be involved in hydrogen bonding to protein components of the skin. Thus, they are more likely to penetrate the epidermis. Absent from the model are the electronic parameters to indicate a relationship between activity and reactivity. The stability of the model was tested using random subsets of the database. The above parameters were observed with consistency over the random subsets indicating stability with regard to parameters in subsets of the data. The results imply that the model should be predictive for the irritant activity of esters toward human skin. (Supported by NIOSH-CDC #0009653058.)

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