to visualize the localization of the fluorescently labeled ivermectin using a combination of confocal-differential interference contrast (DIC) microscopy and confocal fluorescent microscopy. The samples treated with Ivomec® and BODIPY-ivermectin exhibited fluorescence in the outermost layers of the stratum corneum. The samples that had verapamil added showed more fluorescence, and penetration through the stratum corneum and into the stratum granulosum. In the DMSO controls, fluorescence was present throughout the entire cross section of porcine skin with a higher concentration in the stratum corneum. The presence of ivermectin in the stratum corneum is consistent with what was expected because the highly lipophilic ivermectin would have an affinity for the lipid matrix of the stratum corneum. The co-administration of verapamil increased the absorption of ivermectin, presumably by inhibiting the action of P-glycoprotein. It is important to note that topical ivermectin is usually applied monthly, and an 8 hour experiment is a preliminary step in understanding its transport process.

2091 IN-VITRO HUMAN SKIN PENETRATION OF THE FRAGRANCE MATERIAL HMPCC.

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An in vitro human skin absorption study was conducted on the fragrance material HPMCC (4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxyaldehyde), under both unoccluded and occluded conditions. Skin permeation and distribution of HMPCC was determined using epidermal membranes from cosmetic surgery donors. Skin membranes were mounted into Franz-type diffusion cells with the stratum corneum facing the donor chamber. The average area available for diffusion was 1.2 cm^2. HMPCC was applied, at the maximum in-use concentration of 1.5% in 70/30 (v/v) ethanol/water to the skin surface at a target dose of 5 $\mu l/cm^2$. The donor chamber of the occluded cells was covered with a greased, glass coverslip immediately after dosing. Permeation was measured over 24 h at 12 time points, using PBS as receptor. At 24 h, 5.54 ± 0.6 $\mu g/cm^2$ (unoccluded) and 18.6 ± 1.9 $\mu g/cm^2$ (occluded) (mean ± standard error, SE) of HMPCC had permeated, corresponding to 7.37 ± 0.86% (unoccluded) and 24.8 ± 2.5% (occluded) of the applied dose of 75.2 $\mu g/cm^2$. The 24 hour surface wipes contained 43.4 ± 2.8% (unoccluded) and 31.2 ± 2.2% (occluded)HMPCC and donor chamber wash/wipes contained 20.7 ± 1.5 (unoccluded) and 16.8 ± 0.8% (occluded) of the applied dose. The stratum corneum contained 7.75 ± 0.62% (unoccluded) and 6.20 ± 0.61% (occluded) of the applied HMPCC. The epidermis plus any remaining stratum corneum after tape stripping contained 6.06 ± 0.60% (unoccluded) and 8.69 ± 0.57% (occluded). Levels of HMPCC in the epidermis (plus any remaining stratum corneum after tape stripping), filter paper membrane support and receptor fluid were combined (as per SCCNFP guidelines) to result in a total absorbed dose value of 14.3 ± 0.9% (unoccluded) and 36.4 ± 2.6% (occluded). Overall recovery of HPMCC at 24 h was 86.2 ± 2.0% (unoccluded) and 90.5 ± 0.7% (occluded). The evaporative loss of HMPCC was low when estimated by measuring the loss from PTFE (polytetrafluoroethylene) sheets.

2092 PREDICTING CUTANEOUS PERMEABILITY OF BIOCIDES USING LSER APPROACH.

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The permeation of a chemical through skin is influenced by its physico-chemical characteristics and the biological characteristics of the skin. In predicting dermal absorption, scientists have proposed different mathematical models to correlate physico-chemical (especially solvatochromatic parameters) and biological interactions occurring in the process of permeation. Previous studies have shown that hydrophobicity, polarity, molecular volume and hydrogen bonding capability of chemicals are among the most important characteristics to be used for predicting permeability. The aim of this study is to predict dermal absorption of different biocides (with wide range of Kow) using modified Linear Solvation Energy Relationship (LSER) approach, with a calibrated flow through diffusion system. Infinite doses of biocides belonging to five different classes; phenols, morpholines, oxazolidines, isothiazolines and triazines in aqueous solutions were applied to porcine skin flow through diffusion cells. These perfusates were analyzed by GC-MS and HPLC to determine skin permeability. The system coefficients (r, s, a, b, v) of a calibrated set of solutes of the system were determined from multiple linear regression analysis and plugged into the LSER equation to predict permeability values for the several biocides. Our preliminary data with 2 phenols; o-phenylphenol and p-chloro-o-cresol, have shown that the predicted permeability values were very close to observed values, demonstrating that our calibrated system can efficiently predict permeability of biocides. In further studies, the permeability of biocides will be determined in various solvents and commercially available metalworking fluids, so to assess the behavior of biocides in mixtures and to determine the solvatochromatic parameter that has the most prominent effect in predicting permeability.
NIH OH003669-06 supported this research.

2093 METABOLIC TRANSFORMATIONS OBSERVED DURING *IN VITRO* DERMAL PENETRATION STUDIES.

A. B. McEwen, G. R. Ford, S. G. Wood and K. H. Dummer. *BioDynamics Research Limited, Rushden, United Kingdom.* Sponsor: R. Harling.

Since the adoption of the European Commissions chemical strategy (REACH) and the Ground Water Directive (COM(2003)550) the environmental fate of a large number of chemicals, including pharmaceuticals, is becoming of increased public and regulatory concern. Under the proposed legislation risk assessments of a large number of chemicals, including dermal exposure, will be required.
The dermal penetration of [14C]-labelled parabens (octyl and propyl) was investigated in static Franz cells using isolated skin preparations obtained from both man and Sprague-Dawley rats. The rates of percutaneous absorption were compared to those obtained using standard reference compounds, [14C]-benzoic acid, [14C]-caffeine and [14C]-testosterone.
Since the skin possesses significant enzyme activities, some topically applied substances are metabolised as they pass through the skin. In the present study, the effect of metabolism on the percutaneous penetration of topically applied substances was investigated. Both octyl and propyl paraben were metabolised to p-hydroxy benzoic acid on passage through the skin, although the permeation rates were notably different. Testosterone was also metabolised, to andostenedione, on passage through the skin.

2094 HUMAN *IN VITRO* MODELS OF DERMAL METABOLISM.

A. Koganti, L. Brown, J. Smith, D. Mesa, J. Bonass, M. Fleischer and P. Silber. *Celsis In Vitro Technologies, Baltimore, MD.*

Dermal metabolism is recognized as an important consideration in evaluating the topical exposure of chemicals present in topically applied pharmaceutical and cosmetic products. Intact skin placed in flow-through diffusion cells, skin homogenates, and isolated keratinocytes are some of the models that have been used to study the metabolism of specific chemicals. The objective of this research was to establish human in vitro models for studying the dermal metabolism of chemicals. The metabolic capacity of freshly excised full thickness human skin and human keratinocytes was evaluated using probe substrates for known xenobiotic metabolizing cytochrome P450 (CYP) enzymes, transferases (N-acetyl, glucuronsyl, and sulfonyl) and esterases. Measurable CYP enzyme activities were observed for all transferases and esterases as well as for CYP1A2, CYP2B6, CYP2E1, and CYP3A4. Both freshly excised full thickness human skin and keratinocytes exhibited a similar pattern of enzymes with measurable activities, which correlated with enzyme activities previously reported in the literature. The effects of storage conditions, (1) storage medium, (ice vs Belzer UW solution) and (2) length of storage (up to 48 hours), on the metabolic capacity of freshly excised skin were also evaluated. The observed metabolic activities were well maintained by storage of the skin on ice for up to 48 hours. In conclusion, freshly excised human full thickness skin and human keratinocytes are suitable models for evaluating potential dermal metabolism of chemicals.

2095 *IN VIVO* AND *IN VITRO* DIBUTYL PHTHALATE SKIN ABSORPTION IN HAIRLESS GUINEA PIG SKIN.

J. J. Yourick, K. Doan and R. L. Bronaugh. *Office of Cosmetics and Colors, U.S. Food and Drug Administration, Laurel, MD.*

The in vitro assessment of skin absorption of lipophilic chemicals can be problematic when conducting in vitro diffusion cell skin absorption studies, because the chemicals may not freely partition from skin into an aqueous receptor fluid. In order to evaluate the in vitro-in vivo agreement in absorption of lipophilic chemicals, the cosmetic ingredient, dibutyl phthalate (DBP), was chosen as a model lipophilic compound due to reported toxicological concerns. Studies were done to measure DBP dermal absorption in vitro and in vivo using hairless guinea pig skin. Skin absorption was determined in these studies using an emulsion dosing vehicle containing 14C-DBP. In vitro absorption was measured for 24 or 72 hr by using flow-through diffusion cells (0.64 cm2) with a receptor fluid consisting of HHBSS (pH 7.4). In vivo absorption of DBP 24 hr after dermal application resulted in systemic absorption of 62.0 ± 2.0 (mean ± SEM) of the applied dose absorbed (%ADA) with 2.2 %ADA remaining in the skin. The majority of systemically ab-

The Toxicologist

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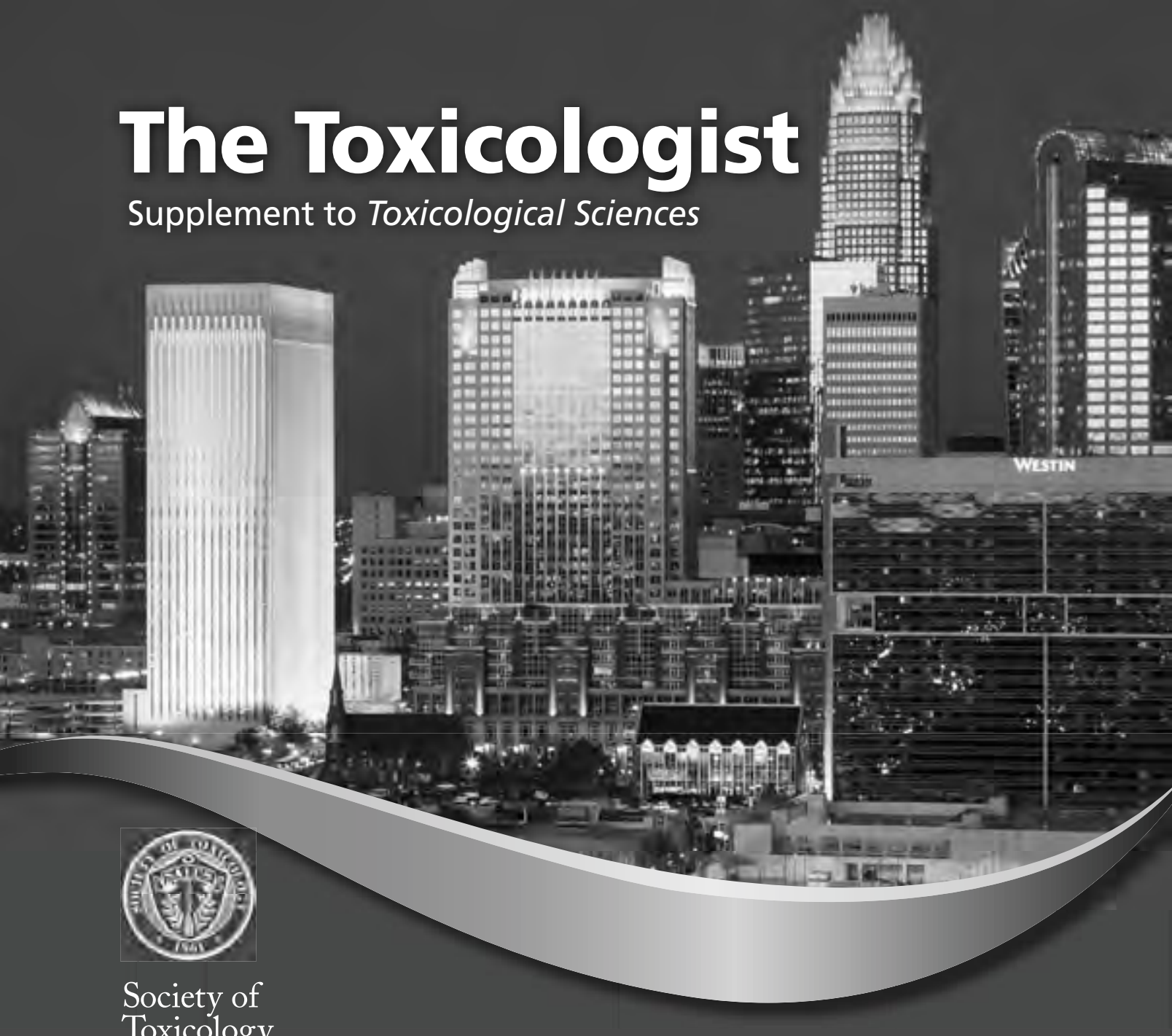

Society of Toxicology

46th Annual Meeting and ToxExpo™

Charlotte, North Carolina

An Official Journal of the Society of Toxicology

www.toxsci.oxfordjournals.org

OXFORD UNIVERSITY PRESS

ISSN 1096-6080
Volume 96, Number 1, March 2007

Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, and poster sessions of the 46th Annual Meeting of the Society of Toxicology, held at the Charlotte Convention Center, Charlotte, March 25–29, 2007.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 449.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 480.

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

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