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A solvatochromatic approach to quantifying formulation effects on dermal permeability†

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Dermal risk assessments are most often concerned with the occupational and environmental exposure to a single chemical and then determining solute permeability through *in vitro* or *in vivo* experimentation with various animal models and/or computational approaches. Oftentimes, the skin is exposed to more than one chemical that could potentially modulate dermal permeability of the chemical that could cause adverse health effects. The focus of this article is to demonstrate that these formulation effects on dermal permeability can occur with simple solvent formulations or complex industrial formulations and that these effects can be modeled within the context of a linear solvation energy relationship (LSER). This research demonstrated that formulation-specific strength coefficients ($r\ p\ a\ b\ v$) predicted ($r^2 = 0.75$–0.83) changes in the dermal permeability of phenolic compounds when formulated with commercial metal-working fluid (MWF) formulations or 50% ethanol. Further experimentation demonstrated that chemical-induced changes in skin permeability with 50% ethanol are strongly correlated ($r^2 = 0.91$) to similar changes in an inert membrane-coated fiber (MCF) array system consisting of three chemically diverse membranes. Changes in specific strength coefficients pertaining to changes in hydrogen donating ability (Δb) and hydrophobicity (Δv) across membrane systems were identified as important quantitative interactions associated with ethanol mixtures. This solvatochromatic approach along with the use of a MCF array system holds promise for predicting dermal permeability of complex chemical formulations in occupational exposures where performance additives can potentially modulate permeability of potential toxicants.

Keywords: mixtures; skin; membrane-coated fiber; solvation energy

1. Introduction

There are several exposure scenarios, for example, during a typical shower, where the dermal route can account for more than half as much uptake as from inhalation [1,2]. This significant increase in body burden associated with dermal exposure can result in toxicologically significant levels of a known toxicant in the general circulation, provided the exposure conditions promote skin permeability. The US EPA has adapted a quantitative structure-permeability relationship (QSPR) model approach as developed by Potts and Guy (1992) [3] to assess skin permeability (*Kp*) of single chemicals as outlined

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in their Dermal Risk Assessment Guidance document [4]. This QSPR model takes into account two descriptors, octanol–water partition coefficient (Ko/w) and molecular weight (MW) as described in the equation below:

$$\begin{aligned} &\log Kp = -6.36 + 0.72 \log Ko/w - 0.0059\, MW \\ &n = 93,\ r^2 = 0.67,\ s = 0.74,\ F = 92 \end{aligned} \tag{1}$$

It should be noted that this equation was derived from human skin permeability data cited in 15 sources and reported by Flynn [5] with significant inter-laboratory variability. The model is based on the permeability of 93 solutes with a wide range of molecular weights ($MW = 18$–765) and Ko/w values ($\log Ko/w = -2.3 - 5.5$).

However, this approach has severe limitations, in that permeability estimates are dependent on only two molecular descriptors, MW and $\log Ko/w$. Furthermore, it does not take into account important physicochemical interactions in the skin and topical dose that can be critical for extrapolations during the risk assessment process.

Numerous QSPR models have been since developed to model skin permeability with the intent to generate predictive models that can extrapolate diffusion for any given dermal exposure scenario [6–9]. While many of these models have been based on sound scientific physicochemical relationships, they have utilized experimental data derived from numerous sources where exposure and experimental conditions and absorption data analyses are inconsistent with coefficients of variation approximating 35% as recently described for inter-laboratory variability. Except for our first attempt in our laboratory to collapse mixture interactions into one 'mixture factor' albeit for a small chemical space [10], *there are no QSPR models available to address the issue of formulation or mixture effects which is the focus of this paper*. Taken together, these deficiencies alone can limit the utility of many of these QSPR models as a predictive tool in advancing the science of dermal risk assessment. Recent debates within the toxicology community have led to the conclusion that toxic effects following chemical mixture exposure are not simply additive, but can involve significant interactions which are sometimes not easily predictable [11–13]. It therefore follows that the final disposition of a toxicant following dermal exposure will be influenced by chemical–chemical and chemical–biological interactions on and in the skin environment.

In order to address some of these limitations in the current science of dermal risk assessments, this paper describes a solvatochromatic approach that utilizes changes in system/strength coefficients to predict formulation-induced changes in dermal permeability in simple and complex formulations. Within a similar solvatochromatic framework, this paper also describes the use of an inert membrane-coated fiber (MCF) array to predict formulation effects on dermal permeability using a simple ethanol formulation.

2. Materials and methods

2.1 *Solutes and formulations evaluated*

Table 1 provides a list of diverse series of 34 solutes and their corresponding molecular descriptors that were used in various *in vitro* membrane experiments and regression analyses described below. Of the 34 solutes selected for various components of this study, a subset of 20 solutes was used as a training set to determine skin permeability in the porcine skin system dosed in various formulations. In order to demonstrate formulation

Table 1. Molecular descriptors of training solutes and test* solutes from ADME Boxes software (Pharma Algorithms, Toronto, Canada).

Peak#	*Compounds*	*R*	π	α	β	*V*
1	Toluene	0.60	0.52	0.00	0.14	0.857
2	Chlorobenzene	0.72	0.65	0.00	0.07	0.839
3	Ethylbenzene	0.61	0.51	0.00	0.15	0.998
4	*p*-Xylene	0.61	0.52	0.00	0.16	0.998
5	Bromobenzene	0.88	0.73	0.00	0.09	0.891
6	Propylbenzene	0.60	0.50	0.00	0.15	1.139
7	4-Chlorotoluene	0.71	0.67	0.00	0.07	0.980
8	Phenol*	0.81	0.89	0.60	0.3	0.775
9	Benzonitrile	0.74	1.11	0.00	0.33	0.871
10	4-Florophenol*	0.67	0.97	0.63	0.23	0.793
11	Benzyl alcohol	0.80	0.87	0.39	0.56	0.916
12	Iodobenzene	1.19	0.82	0.00	0.12	0.975
13	Phenyl acetate	0.66	1.13	0.00	0.54	1.073
14	Acetophenone	0.82	1.01	0.00	0.48	1.014
15	*m*-Cresol	0.82	0.88	0.57	0.34	0.916
16	Nitrobenzene	0.87	1.11	0.00	0.28	0.891
17	Methyl benzoate	0.73	0.85	0.00	0.46	1.073
18	4-Chloroanisole	0.84	0.86	0.00	0.24	1.038
19	Phenylethyl alcohol	0.78	0.83	0.30	0.66	1.057
20	3-Methyl benzyl alcohol	0.82	0.90	0.33	0.59	1.057
21	4-Ethylphenol*	0.80	0.90	0.55	0.36	1.057
22	3,5-Dimethylphenol*	0.82	0.84	0.57	0.36	1.057
23	Ethylbenzoate	0.69	0.85	0.00	0.46	1.214
24	Methyl 2-methyl benzoate	0.77	0.87	0.00	0.43	1.214
25	Naphthalene	1.36	0.92	0.00	0.20	1.085
26	3-Chlorophenol*	0.91	1.06	0.69	0.15	0.897
27	4-Chloroaniline	1.06	1.13	0.30	0.31	0.939
28	4-Nitrotoluene	0.87	1.11	0.00	0.28	1.032
29	4-Chloroacetophenone	0.96	1.09	0.00	0.44	1.136
30	3-Bromophenol*	1.06	1.15	0.70	0.16	0.950
31	1-Methyl naphthalene	1.34	0.90	0.00	0.20	1.226
32	Biphenyl	1.36	0.99	0.00	0.22	1.324
33	4-*tert*-amylphenol*l	0.79	0.80	0.50	0.44	1.479
34	*o*-Phenylphenol*	1.55	1.40	0.56	0.49	1.383

effects in 'real-world' industrial formulations, porcine skin sections were exposed to industrial metal-working fluid (MWF) formulations (Astrocut-C® from Monroe Fluid Technology, NY or Tapfree-2® from Winfield Brooks Company, Inc., MA), and 17% methanol. Astrocut is a commercial soluble oil MWF (pH 9.2) and Tapfree is a commercial synthetic MWF (pH = 8.0). These formulations were also spiked with a test set of commercial phenolic biocides; namely, phenol, 4-florophenol, 4-ethylphenol, 3,5-dimethylphenol, 4-*tert*-amylphenol, *o*-phenylphenol, and 3-chlorophenol. The 50% ethanol formulation was only tested with the first four of these test solutes as well as 4-bromophenol. The first 32 solutes (Table 1) were used to as training and test sets for the MCF array system consisting of three different inert membranes exposed to either water or 50% ethanol. The MCF array system was not exposed to the MWF formulations. All training set and test set solutes were obtained from Sigma-Aldrich (St. Louis, MO).

2.2 *MCF experiments*

Membrane-coated fibers obtained from Supelco (Belfonte, PA) consisted of either 85-μm polyacrylate (PA), 100-μm polydimethylsiloxane (PDMS), and 50-μm carbowax (WAX) membranes coating a metal fiber as depicted in Figure 1. The MCFs were first conditioned as previously described [14] and then immersed into a solution containing the solutes of interest, and allowed for adequate equilibration time for the solute to partition into the fiber. As has been demonstrated with many chromatography columns, solutes will partition into and be retained in chemically similar membranes. For example, polar solutes will more likely partition into polar membranes such as WAX and nonpolar solutes will more likely partition into PDMS membranes. As these solutes are generally semi-volatile, the exposed MCFs were analyzed by GC–MS by direct insertion of the MCF into the injection port of the GC. For these analytical techniques which we have developed in our laboratory, the log partition coefficient describing solute distribution between the MCF and water or solvent mixture was calculated as follows:

$$\log K = \frac{C_{me}}{C_{de}} = \frac{n^o V_d}{V_m(V_d C_o - n^o)} \tag{2}$$

where C_{me} is the solute equilibrium concentration in the membrane, C_{de} is the equilibrium concentration in the donor solution, C_o is the initial concentration of the solute in the donor solution, V_d is the volume of the donor solution, and V_m is the volume of the membrane, and if the initial concentration of a given chemical is C_o, the equilibrium absorption amount measured with the MCF technique is n^o.

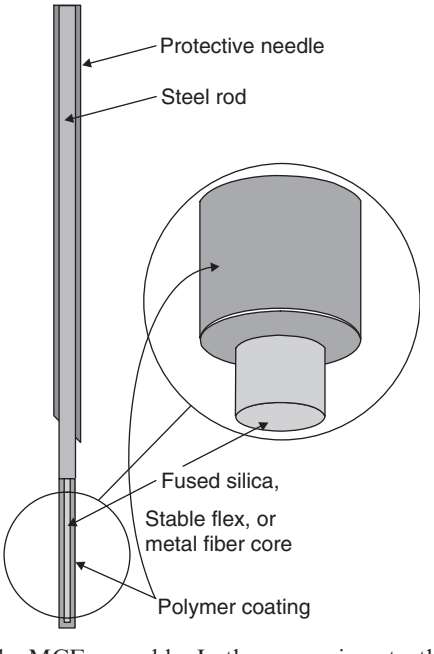

Figure 1. An illustration of the MCF assembly. In these experiments, the polymer coating consisted of either PDMS, PA, or WAX polymers.

2.3 *Skin permeability experiments*

These are *in vitro dermal* experiments which utilized porcine skin sections inserted in the Bronaugh flow-through diffusion cell (Figure 2). This flow-through diffusion cell system uses 14 flow-through diffusion cell blocks as previously described [15].

Skin from the abdomen of female weanling Yorkshire pigs was carefully excised and dermatomed to a thickness of 500 um using a Padgett dermatome. Circular skin sections were placed epidermal side up into each Teflon flow-through diffusion cell to provide a dosing area of 0.64 cm^2. The dermal side in each cell was bathed with receptor fluid (Krebs–Ringer bicarbonate buffer containing albumin and glucose with pH = 7.4) at a set flow rate (4 mL/h) by a multi-channel peristaltic cassette pump. The receptor fluid mimics *in vivo* plasma and facilitates absorption of lipid soluble solutes. Perfusate was collected at 0.25 h intervals for the first 2-h and 1-h intervals thereafter. An 8-h experimental period was selected for two primary reasons: (1) porcine skin sections were demonstrated to be uniformly viable by biochemical and morphological criteria during this time frame and (2) the average worker day is 8 h. Chemicals were assayed in perfusate over time using our developed MCF separation technique [16,17]. In brief, we selected a PDMS fiber which is immersed in micro-filtered perfusate samples, and then directly injected into the injection port of the GC–MS for analysis.

2.4 *GC–MS analytical methods*

Quantitative and qualitative analyses for these organic solutes were performed in a HP 5890 II gas chromatograph coupled with a HP 5970B mass selective detector. A HP 7675 automatic sampler is used to inject 4 μL of the calibration standard solution, while the MCFs are injected manually. The injector is maintained at 280°C for sample vaporization and thermal desorption. Three capillary columns were selected for separation of all the training compounds and test chemicals; HP-5MS for nonpolar and low polar, HP-50 for medium polar and HB-INNOWax for high polar compounds. The separation condition was optimized for resolution and sensitivity. An electronic pressure control was used to maintain a carrier gas flow of 1.00 mL min^{-1} helium. The chemicals that permeate into the MCF membrane were qualitatively analyzed in scan-mode. The identification of each compound in the complex mixture was accomplished by using a HP ChemStation software and matching its fingerprint spectra with a HP MS database. For quantitative analysis, the selected ion monitoring (SIM) mode, and characteristic ions (m/z) were selected for each compound referencing to its spectra acquired experimentally with

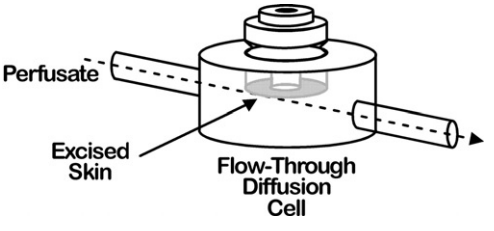

Figure 2. An illustration of an *in vitro* flow-through diffusion cell. Each of these diffusion cells are placed in a 14-cell heated block and maintained at 37°C. The dermal side of the excised skin was perfused with 4% BSA.

standard or from MS database. This approach has been used by our group to define the MCF technique [14].

2.5 *Data processing and statistical analysis*

A range of 4–5 replicates per mixture or treatment group were conducted for all flow-through diffusion cell studies. All real-time data was handled by our custom copyrighted computer database to facilitate data analysis. Solute *permeability* ($cm\,h^{-1}$) of in this diffusion cell system was determined from the following equation:

$$\text{Permeability } (cm\,h^{-1}) = \text{Flux}(\mu g\,cm^{-2}\,h^{-1})/\text{Dose } (\mu g\,cm^{-3}) \tag{3}$$

where steady state flux of the solute was determined from the steady state slope derived from a plot of cumulative solute flux *versus* time.

The primary objective of the MCF and skin studies is to obtain the regression or system coefficients (r, p, a, b, v) described in Abraham's five-descriptor model:

$$\log Kp = c + rR + p\pi + a\alpha + b\beta + vV \tag{4}$$

As we have demonstrated in several of our preliminary experiments with the MCF/Water system, when the vehicle changes in composition or proportion, the system coefficients will be altered. The changes in the system coefficients $[\Delta r\ \Delta p\ \Delta a\ \Delta b\ \Delta v]$ were obtained as follows:

$$[\Delta r\ \Delta p\ \Delta a\ \Delta b\ \Delta v] = [r\ p\ a\ b\ v]_x - [r\ p\ a\ b\ v]_o = [r_x - r_o\ p_x - p_o\ a_x - a_o\ b_x - b_o\ v_x - v_o] \tag{5}$$

where $[r\ p\ a\ b\ v]_o$ are the system coefficients of the original chemical mixture (e.g., water) from the skin or MCF experiments; $[r\ p\ a\ b\ v]_x$ are the system coefficients after the change of a major component in the formulation mixture. In these specific experiments that attempted to assess changes in system coefficients, skin or MCF systems were exposed to formulations containing 50% ethanol only. Stepwise regression analyses were used to assess the importance of each MCF or pairs of MCFs in predictability of skin permeability in the 50% ethanol formulation.

3. Results and discussion

3.1 *Changes in skin permeability*

Table 2 provides a summary of the dermal permeability ($\log Kp$) of the 25 solutes dosed in water and 50% ethanol. The permeability ($\log Kp$) for these diverse solutes ranged from $-1.91\,cm\,h^{-1}$ for phenylethyl alcohol to $-0.50\,cm\,h^{-1}$ for naphthalene in water and from $-3.13\,cm\,h^{-1}$ for 3-bromophenol to $-1.61\,cm\,h^{-1}$ for *p*-xylene in 50% ethanol. These data demonstrated that the presence of the ethanol in water significantly reduced the permeability of the 25 solutes by as much as 4.0-fold for several solutes (e.g., naphthalene and biphenyl). Almost similar formulation effects were observed in skin exposed to either 17% methanol, a soluble oil MWF formulation (Astrocut), or a synthetic MWF formulation (Tapfree) (Figure 3). When compared to an aqueous formulation such as 17% methanol, these commercial MWF formulations significantly reduced solute permeability. Furthermore, solute permeability was for the most part greater in the more aqueous MWF

Table 2. Skin permeability (log *Kp*) (cm h^{-1}) of 25 solutes (training set and test* set) in water or 50% ethanol.

Peak#	*Compound name*	*Water*	50% *ethanol*
2	Chlorobenzene	−1.08386	−1.73466
3	Ethylbenzene	−1.29801	−1.86984
4	*p*-Xylene	−1.05756	−1.61964
5	Bromobenzene	−0.83716	−1.87983
6	Propylbenzene	−0.97838	−2.17304
7	Chlorotoluene	−0.87964	−1.93709
8	Phenol*	−1.5458	−2.83987
9	Benzonitrile	−1.0574	−2.07615
10	4-Florophenol*	−1.72348	−2.72252
12	Iodobenzene	−0.55365	−2.00418
14	Acetophenone	−1.13019	−2.30276
15	*m*-Cresol	−1.62192	−2.726
16	Nitrobenzene	−0.83758	−1.92533
18	4-Chloroanisole	−0.65491	−2.13474
19	Phenylethyl alcohol	−1.91478	−2.68032
20	3-Methylbenzyl alcohol	−1.781	−2.71027
21	4-Ethylphenol*	−1.33931	−2.76956
22	3,5-Dimethylphenol*	−1.48282	−2.92321
25	Naphthalene	−0.50149	−2.1398
27	*p*-Chloroaniline	−0.96673	−2.49514
28	4-Nitrotoluene	−0.72813	−2.13308
29	Chloroacetophenone	−0.94065	−2.21808
30	3-Bromophenol*	−1.35022	−3.1361
31	1-Methyl naphthalene	−0.63201	−2.47989
32	Biphenyl	−0.57423	−2.61434

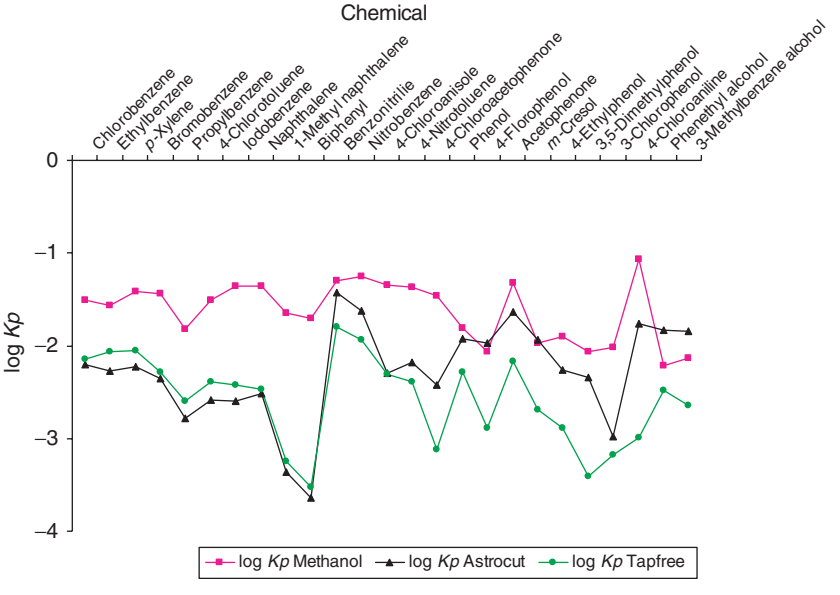

Figure 3. Porcine skin permeability (log *Kp*) (cm h^{-1}) of 25 diverse solutes dosed in either methanol, Astrocut MWF formulation, or Tapfree MWF formulation topically applied to *in vitro* porcine skin sections.

formulation (Tapfree) than in the soluble oil MWF formulation. These findings suggest that these specific formulations generally reduce solute permeation in skin; this runs contrary to our original hypothesis that formulation additives enhance solute permeation. Similar observations were reported in our laboratory and others for solute permeation in simpler formulations with defined solvent and surfactant compositions [18,19]. Data from these studies led to the hypothesis that lipophilic pesticides topically applied to the skin in formulations that enhance solubility in the formulation are least likely to partition from the formulation into the skin. This partitioning behavior was demonstrated with the dermal permeability of the biocide, triazine, in a chemically defined soluble oil MWF or synthetic MWF [20]. Compared to the phenolic biocides described in this article, triazine is more water soluble and therefore more permeable in a soluble oil formulation than an aqueous and less hydrophobic formulation. That is, since triazine is less soluble in soluble oil formulations, it would more likely partition from the soluble oil formulation into the skin membrane.

In the present study, phenolic biocide permeability in the more hydrophobic formulation (Astrocut) is less than in the more aqueous formulation (Tapfree). It should be noted that Astrocut contains heavy naphthenic oil and Tapfree contains polyalkylene glycol and fatty acids. While the 50% ethanol formulation shows a similar inhibitory effect on skin permeability as the MWF formulations, the magnitude of the differences between the ethanol formulation and the MWF formulations underscores the complexity of the interaction within the MWF formulation and skin which is difficult to predict. By grouping the above data into training solute sets and test solute sets, regression analysis described below attempts to generate predictive models for each of the formulations.

3.2 *Regression analysis of skin permeability data*

The following predictive models were obtained for skin permeability of a subset of 20 training solutes in 50% ethanol, Astrocut, and Tapfree formulations as depicted in Figure 4(a):

Skin/Astrocut system

$$\log K_{(\text{Skin/Astrocut})} = 0.96 - 0.47R + 0.34\pi - 0.35\alpha + 1.95\beta - 3.54V$$
$$r^2 = 0.94,\ s = 0.15,\ n = 20 \tag{6}$$

Skin/Tapfree system

$$\log K_{(\text{Skin/Tapfree})} = 1.27 - 0.19R - 0.67\pi - 1.5\alpha + 1.21\beta - 3.14V$$
$$r^2 = 0.84,\ s = 0.21,\ n = 20 \tag{7}$$

Skin/50% Ethanol system

$$\log K_{(\text{Skin/50\%Ethanol})} = 0.04 + 0.02R - 0.53\pi - 1.20\alpha - 0.35\beta - 1.59V$$
$$r^2 = 0.92,\ s = 0.12,\ n = 20 \tag{8}$$

The training set of 20 solutes have log octanol–water partition coefficients ($\log Ko/w$) ranging from 1.05 to 3.98. The test set consisted only of the following phenols which are most likely formulated with commercial MWFs and therefore of occupational

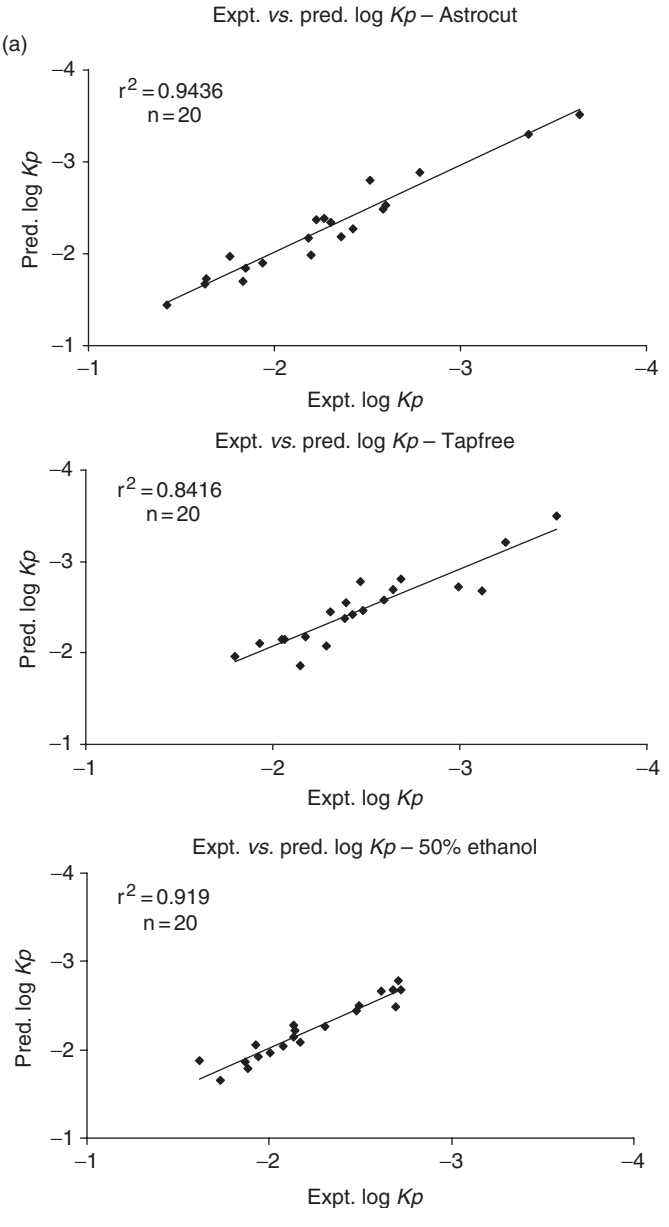

Figure 4. A plot of predicted *vs*. experimental log *Kp* values for (a) the 20 training set solutes and (b) the test solutes (phenols) dosed in Astrocut, Tapfree, or 50% ethanol. The predicted data is based on Equations (6)–(8).

concern: phenol, 4-florophenol, 4-ethylphenol, and 3,5-dimethylphenol evaluated in all three formulations with 3-chlorophenol, 4-*tert*-amylphenol, and *o*-phenylphenol also being evaluated in the two MWF formulations and 3-bromophenol evaluated in 50% ethanol formulation. Figure 4(b) depicts the correlation between predicted and experimental permeability of these phenols. The predictive model for the Astrocut formulation appears to be the most optimal ($r^2 = 0.83$) for predicting skin permeability of phenols compared to

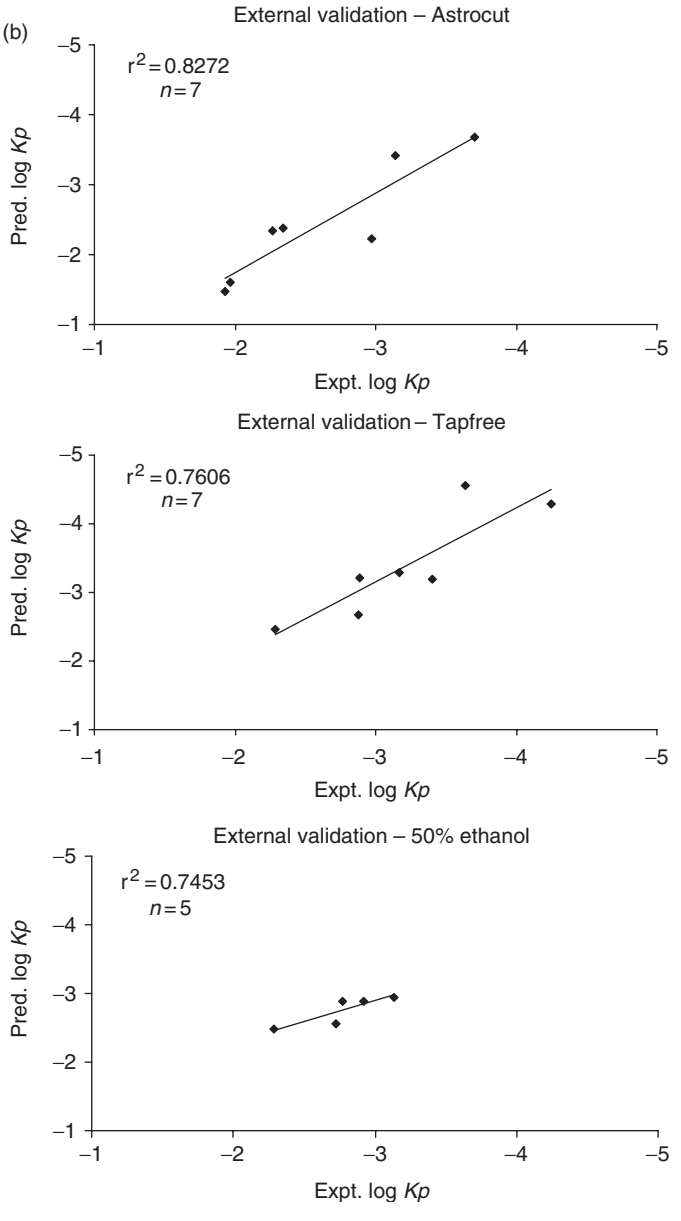

Figure 4. Continued.

the other predictive models ($r^2 = 0.74–0.76$) for their respective formulations. These phenols have log *Ko/w* values ranging from 1.50 to 3.83 which is inclusive of log *Ko/w* range for the 20-solute training set. It is possible that inclusion of a diverse series of phenols in the training set would improve the predictive model and the robustness of the three formulation models could have been better evaluated with a larger and more diverse series of phenolic compounds. However, these findings are suggestive that a model specific for a named formulation can be predictive of skin permeability of phenolic biocides used in MWF formulations that reflect dermal exposure to complex chemical formulations.

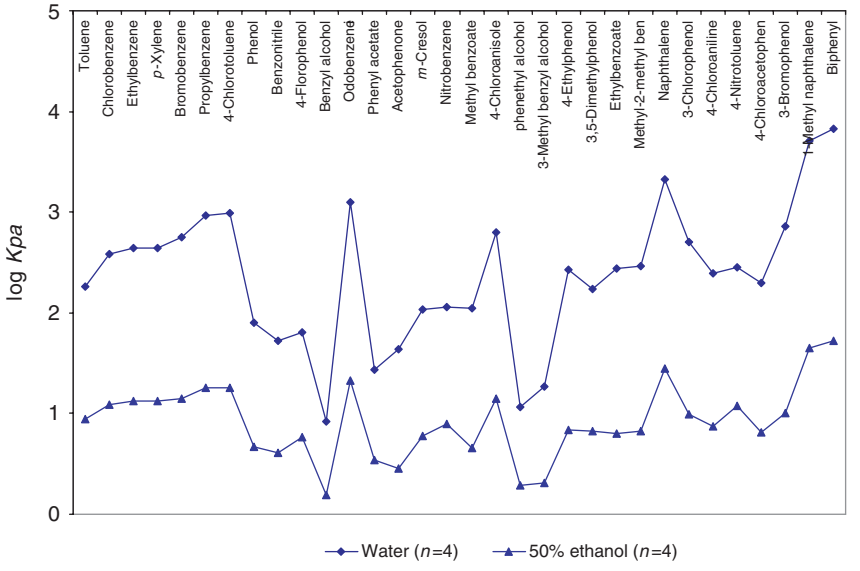

Figure 5. Distribution coefficients (log K_{pa}) for solutes #1 to #32 (Table 1) measured with PA MCF in water or 50% ethanol solutions.

3.3 *MCF partitioning*

Consistent with the trends in skin permeation data, MCFs exposed to 50% ethanol resulted in a significant decrease in partitioning of solutes into each of the three MCFs which have chemically diverse membrane properties. These membranes were selected because they display absorption kinetics [21] and not adsorption properties [22]. Figure 5 depicts the solvent effects for the PA fiber alone as ethanol concentration increased from 0 to 50%. This was demonstrated for the most part in the other two fibers (data not presented). The predictive models for PA/Water and PA/50% ethanol systems are:

$$\log K_{\mathrm{PA/Water}} = -0.268 + 0.59R + 0.071\pi - 0.013\alpha - 3.77\beta + 3.10V$$

$$n = 32,\ r^2 = 0.982 \tag{9}$$

$$\log K_{\mathrm{PA/50\%ethanol}} = -0.131 + 0.39R + 0.053\pi - 0.035\alpha - 2.025\beta + 1.29V$$

$$n = 32,\ r^2 = 0.97 \tag{10}$$

Figure 6 demonstrates that the greatest changes in system coefficients for both skin and all MCF membranes were for the '*b*' and '*v*' coefficients when ethanol was present.

The addition of ethanol to water appears to change hydrogen bond acidity (Δb) and hydrophobicity (Δv) more so than changes in other system coefficients. These changes in system coefficients are consistent with the hypothesis that the presence of ethanol in water increases the hydrophobicity of the solution and consequently reduces the hydrophobicity difference (Δv) between the MCF and water. Previous MCF studies [23] with only the PDMS fiber demonstrated the importance of hydrogen bonding contribution and the hydrophobicity difference between the MCF and formulation as the ethanol concentration increased from 0 to 25 to 35% ethanol. Based on preliminary studies in our laboratory, one can assume that this concentration effect on specific molecular descriptors is

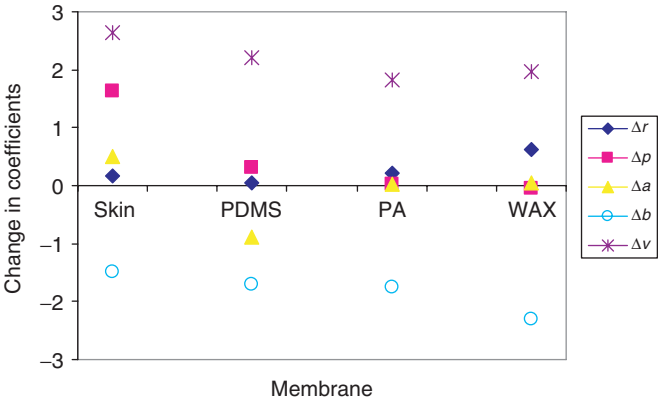

Figure 6. Changes in system coefficients [Δr Δp Δa Δb Δv] in skin and PDMS, PA, and WAX fibers when comparing exposure to 50% ethanol and water.

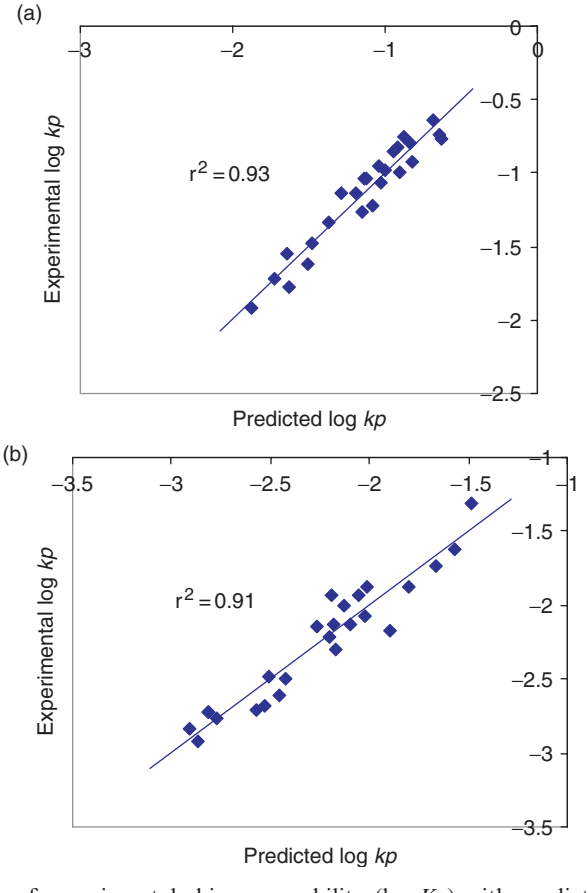

Figure 7. Correlation of experimental skin permeability (log *Kp*) with predicted skin permeability (*Kp*) from the three-MCF array in (a) water and (b) 50% ethanol.

comparable across all three MCFs. However, further work needs to be completed to confirm these specific interactions in MCF and skin. Having established these tentative relationships, our final objective was to demonstrate whether the ethanol induced changes in skin permeability can be predicted from a single or any combination of MCFs.

3.4 *Predictive MCF model of skin permeability in ethanol*

Regression analysis demonstrated that the full three-MCF array adequately predicted skin permeability ($r^2 > 0.91$) of the 25 solutes in water (Figure 7a) and in 50% ethanol (Figure 7b). The predictive model previously described [24] for the three-MCF array for skin permeability of the 25 solutes in water is as follows:

$$\log K_{\text{Skin/Water}} = -2.34 - 0.124 \log K_{\text{PDMS/Water}} + 1.91 \log K_{\text{PA/Water}} - 1.17 \log K_{\text{Wax/water}}$$
$$n = 25,\ r^2 = 0.93,\ F = 93,\ s = 0.101 \tag{11}$$

The absence of one or two of the fibers in this array resulted in less than optimal fits with r^2 values ranging from 0.39 to 0.61 for correlations between skin permeability and partitioning into any single MCF. Combinations of pairs of MCFs improved the correlations ($r^2 = 0.63$–0.90) between MCF and skin permeability with the PA and WAX pair being the most optimal pair of MCFs.

The three-MCF array adequately predicted changes in skin permeability in mixtures containing 50% ethanol as previously described [25] in the following predictive model:

$$\log K_{\text{Skin/50\%ethanol}} = -1.18 + 0.36 \log K_{\text{PDMS/50\%ethanol}} + 0.80 \log K_{\text{PA/50\%ethanol}} - 1.32 \log K_{\text{Wax/50\%ethanol}}$$
$$n = 25,\ r^2 = 0.91,\ F = 75,\ s = 0.133 \tag{12}$$

The presence of 50% ethanol changed the coefficients for each corresponding MCF with the greatest effect seen with the PA fiber albeit it remained a positive contribution to the model. The PDMS fiber appeared to provide a negative contribution in water but positive contribution to the predictive model with ethanol while the WAX fiber provided a slightly more negative contribution in ethanol.

The PDMS fiber is more physicochemically similar to skin epidermis than the other fibers and it should not be surprising that the MCF predictive model for skin permeability demonstrated a positive contribution for this MCF. The PDMS or silicone membrane has been used in several studies as an inert membrane to model dermal permeability [26]; however, despite this polymer possessing lipophilic properties similar to the skin, its homogenous composition is very dissimilar to the heterogenous lipid–protein matrix in skin. These biochemical differences explain in part why the PDMS fiber alone did not adequately predict dermal permeability but required contributions from the other two MCFs that are more polar than PDMS. Polyacrylate is characterized by heavy π^*-electrons for polarizible interactions [21] and WAX is a polyethylene glycol (PEG) polymer membrane having characteristic hydrogen bonding donor and acceptor interactions. It is plausible to assume that these interactions in the MCF array is comparable to those interactions in skin exposed to water but can be modulated when a solvent such as ethanol is present in the topical formulation. Recent correlation analysis

of these changes in system coefficients across skin and the MCF array supports the importance of each MCF and especially the contribution of the PDMS fiber [27]. Our laboratory is currently utilizing the MCF array to assess interactions recently observed with MWF formulation effects on biocide permeability [28]. While it is very likely that modeling of these interactions may require more than three MCFs as MWF formulations become more complex, this MCF array approach holds promise as a high throughput and reproducible screen for assessing formulation effects on skin permeability.

4. Conclusions

This article demonstrated formulation effects with simple mixtures (50% ethanol) as well as complex commercial formulations used in the metal machining industry. The effects of MWF formulations on the dermal permeability of phenolic biocides were characterized within a linear solvation energy relationship (LSER). MWF formulations consist of hundreds of performance additives which can potentially influence solute permeability via various mechanisms described above, therefore several if not all of these effects on skin permeability can be predicted within the context of a LSER model. The limitations of the proposed models include formulation specificity and biocide selection. This study also demonstrated the use of an LSER approach and MCF array to predict permeability changes for solutes exposed to 50% ethanol solution. The model was optimal for MCF array and not for individual MCFs or pairs of MCFs for predicting changes in skin permeability when ethanol is added to an aqueous solution. Future work is focused on determining whether the MCF approach, which is a highly reproducible and high throughput system, can be predictable of skin permeability in more complex formulations such as MWF formulations.

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