Assessing Mixture and Formulation Influence on Skin Absorption

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Conflict of Interest Statement

- THERE IS NO CONFLICT OF INTEREST
Outline/Objectives

- How do formulations additives alter skin permeability?
- Formulation effects on pesticide absorption
- Formulation effects on MWF absorption
  - (e.g., biocides, amines)
- Can QSPRs be predictive of mixture/formulation effects
- Summary
Effect of Formulation Additives on Skin

- Hydration
- Delipidization
- Protein Denaturation
Experimental Approaches for Comparing Formulations: Diffusion Cell Systems (Ideally Human or Pig Skin)

Diffusion cells used to quickly assess permeability of drugs prior to live animal exposures.
Talk Outline

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- Formulation effects on pesticide absorption
- Formulation effects on MWF absorption
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- Summary
Does the Label Suggests the Pesticide will be Absorbed Across the Skin?

- Pesticide Formulation
  - Active ingredients (a. i.); generally, OPs > Pyrethrins
    - Pesticides with $\text{Log P} \ 1-3$ will more likely have higher absorption
  - Inert or other ingredients; proprietary and not useful ??

- One product with malathion insect spray concentrate
  - 50% malathion, 50% inert ingredients
  - Will diluting this concentrate lead to less skin absorption??

- No two product labels are always the same !!!!
Effect of Solvents (Acetone, DMSO, and Ethanol) on DEET Absorption in Three Species

Mice

Rats

Pigs
Effects of Solvent Concentration and Surfactants on Carbaryl Absorption

Add more solvent
Acetone or DMSO

Add surfactant, SLS

CA+40%Solvent

CA+80%Solvent

CA+40%Solvent+5%SLS

CA+80%Solvent+5%SLS
Influence of DEET On Carbaryl Absorption
Formulation Effects on SC Penetration of Abamectin

Porcine Skin Stratum Corneum
8 Hour Flow Through

% Dose

Ivomec 1.89
Eprinex 1.39
100% Isopropanol 5.12

Formulation
Beware of Extrapolations Across Species and Formulation: *In Vitro* Dermal Studies for Abamectin

<table>
<thead>
<tr>
<th>Formulations</th>
<th>% Dose Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivomec</td>
<td>0.10 (ab)</td>
</tr>
<tr>
<td>Eprinex</td>
<td>0.10 (a)</td>
</tr>
<tr>
<td>100% Isopropanol</td>
<td>0.09 (b)</td>
</tr>
</tbody>
</table>

### Absorption

![Absorption Graph](image_url)

Legend:
- □ Porcine
- □ Caprine
- □ Bovine
- □ Ovine
Does Repeat Exposure Increase Skin Absorption?

<table>
<thead>
<tr>
<th>Chemical</th>
<th>1-day</th>
<th>4-day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naphthalene</td>
<td>1.73</td>
<td>1.65</td>
</tr>
<tr>
<td>Ethyl benzene</td>
<td>1.98</td>
<td>4.07</td>
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<tr>
<td>Trimethyl benzene</td>
<td>1.93</td>
<td>4.56</td>
</tr>
<tr>
<td>Cyclohexyl benzene</td>
<td>3.02</td>
<td>1.81</td>
</tr>
<tr>
<td>o-Xylene</td>
<td>1.88</td>
<td>4.21</td>
</tr>
<tr>
<td>Nonane</td>
<td>3.03</td>
<td>2.23</td>
</tr>
<tr>
<td>Dodecane</td>
<td>1.65</td>
<td>3.50</td>
</tr>
<tr>
<td>Tridecane</td>
<td>0.74</td>
<td>4.90</td>
</tr>
</tbody>
</table>
Talk Outline

- How do formulations additives alter skin permeability?
- Formulation effects on pesticide absorption
- Formulation effects on Metal Working Fluid absorption (e.g., biocides, amines).
- Can QSPRs be predictive of mixture/formulation effects?
- Summary
Skin Absorption of Metal Working Fluids (MWFs) and Complexities Inherent in Additional Components
Additives in MWF Formulations

- **Soluble oil and synthetic fluids:**
  - Mineral oil, PEG

- **Surfactants:**
  - Linear alkylbenzene sulfonate (LAS)

- **Lubricants:**
  - Ricinoleic acid

- **Biocides:**
  - Triazine, Phenols

- **Corrosive inhibitors:**
  - Triethanolamine; dicyclohexylamine (DCHA)
Can These Additives Influence the Dermal Absorption of Other Additives?

- **YES**
  - Biocides
  - Corrosive Inhibitors

Minimal Effect
- Lubricants
- Surfactants
Influence of MWF Contaminants on Triazine: Effects of TCE, NDLEA, Ni
O-Phenylphenol

Experimental vs. pooled predicted log Kp of 4 phenolic biocides in 4 mixtures
Influence of MWFs on Two Classes of Amines

**Hydrophilic Ethanolamines**
(LogP: -1.08 to -1.05)

MEA, DEA and TEA: SO>SS = SYN.

**Lipophilic Amines had reverse pattern**
(Log P: (2.86 to 3.69)

DCHA: SYN>SS = SO
DPA: SYN>SS ≥ SO
DBEA: SS ≥ SYN ≥ SO

Thermodynamic activity of these amines in the various formulations could explain the permeability differences between MWF formulations.
Summary MWF Mixture Effects

- Biocides and DCHA more readily absorbed (1 - 4% dose) than LAS (<0.3% dose) or RA (< 0.3% dose) during an 8-hr exposure.

- Permeability differences were observed between soluble oil and synthetic fluid formulations.

- Formulation and contaminant-induced changes in additive absorption associated with the presence of single or combinations of additives.

- These observations may be associated with changes in partitioning and diffusion from the MWF formulation into skin.
Talk Outline

- How do formulations additives alter skin permeability?
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- Formulation effects on MWF absorption
  - (e.g., biocides, amines).
- Can QSARs be predictive of mixture/formulation effects?
- Summary
Can LSER Such as QSPRs Predict Skin Absorption of Complex Mixtures and Formulations?

- MWF formulations consist of hundreds of performance additives which can potentially influence solute permeability via various mechanisms

- Therefore several, if not all, of these effects on skin permeability can be predicted within the context of a LSER model
Linear Solvation Energy Relationships (LSERs) (Abraham Solvatochromatic QSPR)

- Log permeability (Log Kp) = c + r R + sπ + aα + bβ + vVx

- The Five Molecular Descriptors are Fixed Solute Properties
  - R = excess molar refractivity (represents molecular force of lone pair electrons),
  - π = solute dipolarity/polarizability,
  - α = solute overall or effective hydrogen bond acidity,
  - β is solute overall or effective hydrogen bond basicity,
  - Vx is McGowan characteristic volume.
    - R and Vx are calculated values
    - π, α, and β are determined experimentally from water/solvent partition systems.

- The Strength Coefficients: ‘r’ = the tendency of solvent or phase to interact with π- and n-electron pairs of the solutes, ‘s’ = the tendency of phase to interact with dipolar/polarizable solutes, ‘a’ = phase hydrogen bond basicity, ‘b’ = phase hydrogen bond acidity and ‘v’ = phase hydrophobicity or cavity formation term
Influence of MWFs on Two Classes of Amines: QSPR

Amine permeability in water and MWFs using:

(a) A simple Abraham multiple linear regression model
(b) Adding a vehicle indicator to this model
Porcine Skin Permeability (Log Kp) of 25 Diverse Solutes Dosed in Methanol, Astrocut (e.g., SO MWF) or Tapfree (e.g., SYN MWF)
Predicted vs. Experimental Log Kp Values for (A) the 20 Training Set Solutes and (B) the Test Solutes (Phenols) Dosed in Astrocut or Tapfree MWFs

- \( \log K_{\text{(Skin/Astrocut)}} = 0.96 - 0.47 R + 0.34 \pi - 0.35 \alpha + 1.95 \beta - 3.54 V \)
- \( \log K_{\text{(Skin/Tapfree)}} = 1.27 - 0.19 R - 0.67 \pi - 1.5 \alpha + 1.21 \beta - 3.14 V \)
Summary of Biocide Skin Permeation in MWF Formulations

- Large and hydrophobic biocides tend to be retained in commercial MWFs.
- More basic biocides will tend to permeate skin.
- Some ingredients in MWFs can limit biocide skin permeation.
Recap

- Formulations additives can alter skin permeability
- Formulations can increase or decrease pesticide absorption
- Formulations can increase or decrease MWF absorption
  - (e.g., biocides, amines).
- QSPRs can be predictive of mixture/formulation effects
Other Related Work

- Instead of fitting one simple model for each experimental condition, we developed an expanded version of the Abraham LSER model to adjust for the heterogeneity introduced by various MWF formulations.

- IVIVC for ortho-phenylphenol in progress
References

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