Role of Bioavailability in Risk Assessment of Cosmetic Ingredients: Kinetics, Permeation and Metabolism

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Outline

• Background
• Oral-to-dermal extrapolation
• Bioavailability classification
  – Prediction of permeability from oral and dermal routes
  – Prediction of liver and skin metabolism: metabolic profilers
• Including kinetics
• Future directions
Background

- Inclusion of bioavailability aspects to TTC decision workflow
  - Developed the decision tree in consideration of bioavailability and exposure cases
- Skin permeability database
  - More than 50% are cosmetics-related chemicals (total of ~450).
- Metabolism knowledge development for skin
Bioavailability

Oral formulation
Dissolution
Intestinal excretion
Intestinal efflux
Liver metabolism
GI metabolism
Passive and active GI absorption
Hepatic clearance
Skins metabolism
Skin binding
Concentration in relevant compartments
PBPK models

Pharmacokinetic processes

Protein binding
Extrahepatic metabolism
Passive and active distribution into tissues
Tissue binding
General circulation
Excretion
Excretion

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Why oral-to-dermal extrapolation?

Main sources of repeated dose toxicity data

Oral formulation

Dissolution

Passive and active GI absorption

Liver metabolism

General circulation

GI metabolism

Intestinal efflux

Skin metabolism

Main route

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What oral-to-dermal extrapolation?

- Oral formulation
  - Dissolution
  - Passive and active GI absorption
    - Liver metabolism
      - GI metabolism
        - Intestinal efflux
  - General circulation
    - Evaluate differences between the rate and the extent of absorption via dermal and oral routes
    - Evaluate metabolism differences between skin and liver
      - Skin metabolism
What oral-to-dermal extrapolation?

Evaluate metabolism differences between skin and liver

Evaluate differences between the rate and the extent of absorption via dermal and oral routes

Prediction of oral absorption
(PAMPA database / new models)

High
Low

Prediction of dermal absorption
(Skin absorption database
Potts and Guy / Kasting)

High
Low

Skin / liver metabolism profiler
<table>
<thead>
<tr>
<th>DERMAL high</th>
<th>ORAL high</th>
<th>ORAL low</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCENARIO 1:</strong> oral~dermal or oral&gt;dermal</td>
<td></td>
<td><strong>SCENARIO 2:</strong> oral&lt;dermal</td>
</tr>
<tr>
<td>Consider first pass metabolism</td>
<td></td>
<td>Most problematic case, although rare!</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DERMAL low</th>
<th>ORAL high</th>
<th>ORAL low</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCENARIO 3:</strong> oral&gt;&gt;dermal</td>
<td></td>
<td><strong>SCENARIO 4:</strong> oral and dermal low</td>
</tr>
<tr>
<td>Oral NOAEL over-protective</td>
<td></td>
<td>This is in general not a problem since oral and dermal NOAEL will both be high.</td>
</tr>
</tbody>
</table>
Metabolic potential decision tree

oral~dermal or oral>dermal

true

Liver metabolic rules

Oral NOAEL is acceptable.

hits

Toxicification

oral~dermal or oral>dermal
Absorption

Oral NOAEL may be conservative. May need to consider adjustment or find dermal NOAEL.

Oral NOAEL is acceptable.

Detoxification

Sulfation, Glucuronication, etc.

Oral NOAEL is acceptable.
Dermal absorption: database

Dermal absorption data sources
- EDETOX database: University of Newcastle (Prof. Faith Williams)
- EDETOX update and new studies: Kent University donation
- COSMOS partners’ harvesting of cosmetics ingredients
  - ~163 (of total 464 chemicals) are found in the Cosmetics Inventory

- 1210 in vitro studies
  - 172 chemicals
- 817 in vivo studies
  - 152 chemicals

- 241 in vitro studies
  - 76 chemicals
- 142 in vivo studies
  - 43 chemicals

- All in vitro (human) studies
- 65 studies updated EDETox
  - 32 chemicals
- 520 new studies
  - 121 mostly drugs
- 422 studies from EDETox

Results total 2484 in vitro studies

Studies - vehicle and species

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Dermal absorption: Kasting

Skin absorption/permeability profile: multiphase microscopic diffusion model (MIRA)
Two-dimensional (biphasic) microtransport model by incorporating 15 layers of partially and fully hydrated corneocytes and 6 bilayers of anisotropic lipid matrix.
Solute motion through the SC is expressed by (mass-balance) transport equation

Kp, Jmax calculated for the entire skin permeability database (482 chemicals).
Compared for in vitro 151 data points (removed the points where the measured Jmax is extreme: log Jmax > |4.5|)

Topological arrangement of individual lipid bilayers:
- diffusion processes within each bilayer
- anisotropy of lipid phase transport

Bilayers continue indefinitely from unit cell to unit cell without interruption

Each corneocyte is completely surrounded by intact lipid bilayers - the progress from one layer of corneocytes to the next requires a transbilayer transport step
To be able to classify compounds for oral and dermal absorption, a systematic literature search has been conducted for oral and intestinal absorption. A dataset of human oral absorption has been compiled from these literature data, whilst more thorough harvesting of in vitro PAMPA assay are in progress.
Liver metabolic rules

- aromatic_hydroxylation
- aromatic_oxidation
- carbonyl_reduction
- carboxylation
- decarboxylation
- dehalogenation
- dehydrogenation
- glucuronidation
- glycination
- hydrolysis
- methylation
- N-acetylation
- N-deacetylation
- N-dealkylation
- N-oxidation
- O-deacetylation
- O-demethylation
- oxidation
- sulfation
Modelling hepatic clearance

- Hepatic clearance $CL_H = CL_T - CL_R$
- Difficulties:
  - complexity of the phenomena
  - scarcity of data (small datasets with heterogeneous data)

Plot of experimental vs. predicted values for one particular random split into modeling and test sets (left) and plot of experimental vs. 10-fold cross-validated predictions for the entire set obtained for the best in silico 70+R1NN model.
PBPK models from *in vitro* to *in vivo*

Liver concentration as a function of time for a single dose ingestion of 500 mg/kg acetaminophen for a PBPK model derived from in vitro data and QSAR model (green), rat data (red) or human data (blue)


Future directions

• Improve the quality of the models for skin and oral absorption

• Develop COSMOS tools
  – KNIME workflows for the bioavailability classification
  – Selected metabolic rules and toxic alerts in ChemoTyper and KNIMIE nodes
  – PBPK tool
The research leading to these results has received funding from the European Community’s Seventh Framework Program (FP7/2007-2013) COSMOS Project under grant agreement n° 266835 and from Cosmetics Europe.