Guidance on Derivation of Dermal Absorption for PPP - ECPA's Perspective based on an Industry database

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Overview

- **Introduction: ECPA Project**
- **Issue EFSA guidance on dermal absorption (DA)**
  - Conservative conclusions for DA
    - Increased testing, wasted resources, animal use
- **Comparison of EFSA and ECPA data**
- **ECPA Proposal: conservative but reasoned, harmonised, and health-protective alternative**
**Introduction - ECPA project I**

- Industry-wide concern with impact of EFSA Guidance Document
- EFSA Guidance document considered a Tier 1 assessment
- Higher-tier assessment required for more reliable conclusions

**Project summary**

- Tiered approach for data compilation and analysis
- 2 datasets (1\textsuperscript{st} dataset published, 2\textsuperscript{nd} dataset evaluation ongoing)
- Compiled data from 190 1\textsuperscript{st} (~170 2\textsuperscript{nd}) \textit{in vitro} human skin studies (all compliant with OECD TG 428)
  - Provided ~300 (~450) DA values
  - 97 (~110) active substances, 10 (~19) formulation types
  - Wide range of molecular weights (169-1053 (1632) g/mol), logPow (-3.2 – 7 (9)), concentrates (0.06-745 g/L) and sprays (0.004 (0.00075) – 110 (187) g/L)
Introduction - ECPA project II

Publication 1\textsuperscript{st} dataset (190 studies) Aggarwal \textit{et al.}, 2014

\begin{itemize}
\item 2\textsuperscript{nd} dataset (~172 studies)
\item Data evaluation (merged 1\textsuperscript{st} and 2\textsuperscript{nd} dataset) under preparation
\item Check reliability of conclusions from 1\textsuperscript{st} dataset with extended database
\item Increase the number of formulation types \rightarrow improve read across approach
\end{itemize}
Analysis used worst-case definition of DA:

- receptor fluid + receptor chamber wash + skin minus upper layer (tape strip 1 and 2) of stratum corneum (SC)

Notes on this definition:

1. Assumes all material in skin is absorbed (except upper layer of SC)

   ➔ It is always **incorrect** – always overestimates absorption

   ➔ good correlation of absorption from **in vitro** to **in vivo** human when comparing absorption in receptor fluid without skin residues; Lehman et al 2011; Skin Pharmacol Physiol. 2011;24(4):224-30.
   

2. Bioavailability from skin into bloodstream always <<100%

Definition is **highly** conservative
Issue I: New conservatism in DA

1. Default values

2. Read-across
   - Inability to rely on existing data
   - *The ±25% rule – EFSA can address directly*

3. Extrapolation to more dilute sprays
## Comparison of EFSA and ECPA dataset

<table>
<thead>
<tr>
<th></th>
<th>EFSA data-set&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ECPA data-set 1</th>
<th>ECPA data-set 2</th>
<th>ECPA data-set combined</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study type</strong></td>
<td>Variable - in vitro rat and human, in vivo rat and monkey, triple-pack, default, expert judgment</td>
<td>Homogeneous - in vitro human only, as preferred by EU Regulation for PPP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP / OECD TG compliance</td>
<td>Not reported</td>
<td>All studies are GLP-compliant and follow OECD TG 428</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure and study duration</td>
<td>Not reported</td>
<td>6-10 hour exposure, total study duration 24 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermal absorption calculation</td>
<td>Inconsistent – with regards to the skin residue and correction factor that was used for triple-pack studies</td>
<td>Consistent – all dermal absorption calculations are based on EFSA guidance worst-case option with skin residue (except first 2 tape strips)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of active substances</td>
<td>63</td>
<td>97</td>
<td>Approx. 110</td>
<td>Approx. 150</td>
</tr>
<tr>
<td>Number of studies</td>
<td>Not reported</td>
<td>120</td>
<td>Approx. 170</td>
<td>Approx. 290</td>
</tr>
<tr>
<td>Number of dermal absorption values</td>
<td>Approximately 63 for concentrate and 63 for dilution</td>
<td>123 for concentrate 167 for dilution</td>
<td>Approx. 185 for concentrate 270 for dilution</td>
<td>Approx. 305 for concentrate 435 for dilution</td>
</tr>
</tbody>
</table>

<sup>1</sup> Of the endpoints used for analysis, ~3% are default values, ~14% are for human skin *in vitro*, ~9% are for human and rat skin *in vitro*, ~26%/~5% are *in vivo* rat/monkey, and ~30% are “triple pack”
1. Default values – Concentrate I

**EFSA GD:**
25%

1\textsuperscript{st} dataset

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Dermal absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=121)</td>
</tr>
<tr>
<td>Median</td>
<td>0.5</td>
</tr>
<tr>
<td>75\textsuperscript{th}</td>
<td>1.3</td>
</tr>
<tr>
<td>95\textsuperscript{th}</td>
<td>4.8</td>
</tr>
</tbody>
</table>

2\textsuperscript{nd} dataset (preliminary information)

2\textsuperscript{nd} dataset is consistent with 1\textsuperscript{st} dataset
1. Default values – Concentrate II
Concentration dependency

**EFSA GD:**

<table>
<thead>
<tr>
<th>Concentration</th>
<th>1st dataset</th>
<th>2nd dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5% a.s.</td>
<td>&lt;5% a.s.</td>
<td>&gt;5% a.s.</td>
</tr>
<tr>
<td>&gt;5% a.s.</td>
<td>&gt;5% a.s.</td>
<td>&gt;5% a.s.</td>
</tr>
</tbody>
</table>

1st dataset

<table>
<thead>
<tr>
<th>Dermal absorption</th>
<th>Percentile</th>
<th>1st dataset</th>
<th>2nd dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5% a.s.</td>
<td>Median</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>75th</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>95th</td>
<td>4.2</td>
<td>5.1</td>
</tr>
</tbody>
</table>

2nd dataset (preliminary information)

2nd dataset is consistent with 1st dataset
1. Default values – In use dilutions

**EFSA GD:**
75%

### 1st dataset

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Dermal absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=121)</td>
</tr>
<tr>
<td>Median</td>
<td>6.9</td>
</tr>
<tr>
<td>75th</td>
<td>14.1</td>
</tr>
<tr>
<td>95th</td>
<td>28.0</td>
</tr>
</tbody>
</table>

### 2nd dataset (preliminary information)

2nd dataset is consistent with 1st dataset
1. Default values – ECPA conclusions

**EFSA GD**
- **Concentrate**
  - 25% for >5% a.s.
  - 75% for ≤5% a.s.
- **Dilution**
  - 75%

**ECPA proposal**
- **Concentrate**
  - 6% for liquid; 2% for solid
  - No impact of a.s. level
- **Dilution**
  - 30%
2. Read-across

**EFSA GD**
- No relationship to formulation type
- Read-across rare – test every formulation

**ECPA proposal**
- Relationship to formulation type
  - Solvent-based > water-based > solid (EC, EW, SE > SL, SC, OD > WG, WP, SG, FS)
  - EC is worst-case
- Confirmed by 2\textsuperscript{nd} dataset
  - Solvent-based data valid for read-across to water-based or solid formulations

![Graph showing data distribution for different formulations](image)
3. Extrapolation to more dilute sprays

**EFSA GD**
- Absorption increases linearly with increasing dilution
  - e.g., Increase dilution 10-fold = increase absorption 10-fold
- Assume linear increase up to 75% default

**ECPA proposal**
- Absorption is not proportional to concentration
  - 96% of times, increase in absorption was NOT linear
  - 23% of times it did NOT increase at all
  - Line of best fit increase 4x max. (up to 36x dilution)
- Assume linear or 5x up to 30% default
ECPA proposal:

- Align with EFSA – use their worst-case DA definition and data percentile (95th) to ensure reasonable DA default values:
  - Concentrate: Liquids 6%; Solids 2%
  - Dilutions: 30%
  - Solvent-based read-across for water-based or solid formulations

- Dilution adjustment factor limit of 5x up to default of 30%
- Adjust 25% rule (EFSA agrees)
- 1st dataset evaluation published
  - 2nd dataset (merged evaluation with 1st dataset) publication imminent

CRD, EFSA and SANCO valued ECPA’s proposals, EFSA obtained mandate from SANCO for detailed review → ECPA shares detailed raw data with EFSA
Thank you very much for your kind attention!
Backup
Introduction – DA for PPP

- Mandatory input to all risk assessments
- Operators, bystanders and workers
- Exposed to
  - Concentrate
  - Spray dilution
  - Residue
- Used to estimate systemic exposure
- Compared to AOEL
  - 100-fold safety factor
  - \( \leq 100\% \) of AOEL = acceptable risk
Skin structure & Dermal absorption

Penetration to dermis via:
- Passive diffusion
- Hair follicles
- Between cells
- DA < oral absorption

Skin – multilayered

Stratum corneum (SC)
- No blood supply
- Residue in SC cannot be absorbed
- Must reach dermis
- Major function – barrier

Slide 18
Issue II: Compounded, unrealistic conservatism

Conservatism at every step of risk assessment:

- NOAELs based on barely adverse effects
- AOEL SF at least 100 vs. MS policies for 25-30
- DA study surrogates - in vitro vs. in vivo
- DA definition
- Maximum values vs. percentiles
- Tier 1 risk models

Conservatisms multiply to give irrelevant outcomes
2. Read across: the ±25% rule

Does the new formulation need to be tested for DA?

<table>
<thead>
<tr>
<th>Formulation components</th>
<th>Existing (%)</th>
<th>New (%)</th>
<th>Differences (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>20</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>33</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Emulsifier</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Solvent</td>
<td>30</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Anti-freeze</td>
<td>5</td>
<td>7.5</td>
<td>+ 50%</td>
</tr>
<tr>
<td>Water</td>
<td>9</td>
<td>6.5</td>
<td>- 28%</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>-</td>
</tr>
</tbody>
</table>

Yes, according to EFSA GD Section 6.2, page 18
This is not sensible, and needs to be corrected – EFSA agrees