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

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Overview

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- **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

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- **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 (1st dataset published, 2nd dataset evaluation ongoing)
  - Compiled data from **190 1st** (**~170 2nd**) *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

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Publication 1st dataset (190 studies) Aggarwal *et al.*, 2014

http://www.sciencedirect.com/science/article/pii/S0273230014000130

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Assessment of *in vitro* human dermal absorption studies on pesticides to determine default values, opportunities for read-across and influence of dilution on absorption

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2nd dataset (~172 studies)

Data evaluation (merged 1st and 2nd dataset) under preparation

- **Check reliability of conclusions from 1st dataset with extended database**
- **Increase the number of formulation types ➔ improve read across approach**

Introduction - ECPA project IV

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- **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. http://www.karger.com/Article/FullText/324884)

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

Definition is highly conservative

Issue I:
New conservatism in DA

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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

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

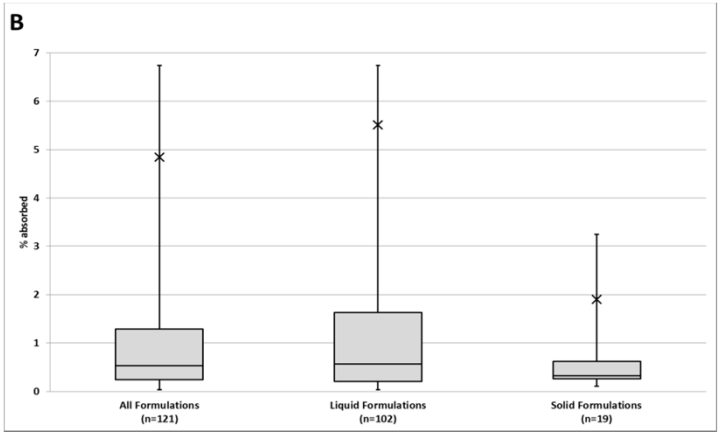
[1] Of the endpoints used for analysis, ~3% are default values, ~14% are for human skin *in vitro*, ~9% are for human and rat skin *in vitro*, ~26%/~5% are *in vivo* rat/monkey, and ~30% are "triple pack"

1. Default values – Concentrate I

EFSA GD:

25%

1st dataset



Percentile	Dermal absorption		
	All (n=121)	Liquids (n=102)	Solids (n=19)
Median	0.5	0.6	0.3
75th	1.3	1.6	0.6
95th	4.8	5.5	1.9

2nd dataset (preliminary information)

2nd dataset is consistent with 1st dataset

1. Default values – Concentrate II

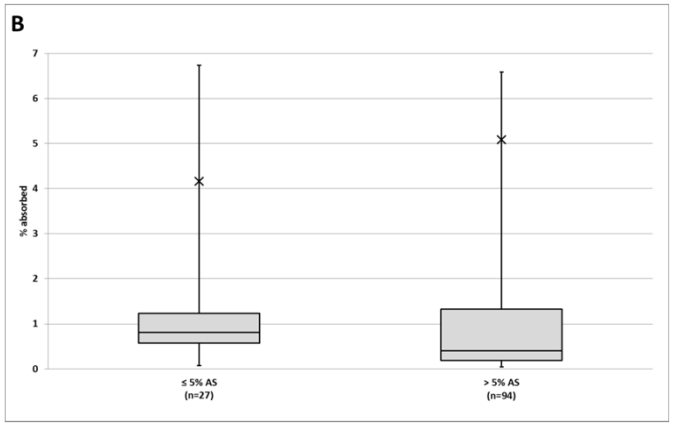
Concentration dependency

EFSA GD:

75% ——— **≤5% a.s.**

25% ——— **>5% a.s.**

1st dataset



Percentile	Dermal absorption	
	≤5% a.s. (n=27)	>5% a.s. (n=94)
Median	0.8	0.4
75th	1.2	1.3
95th	4.2	5.1

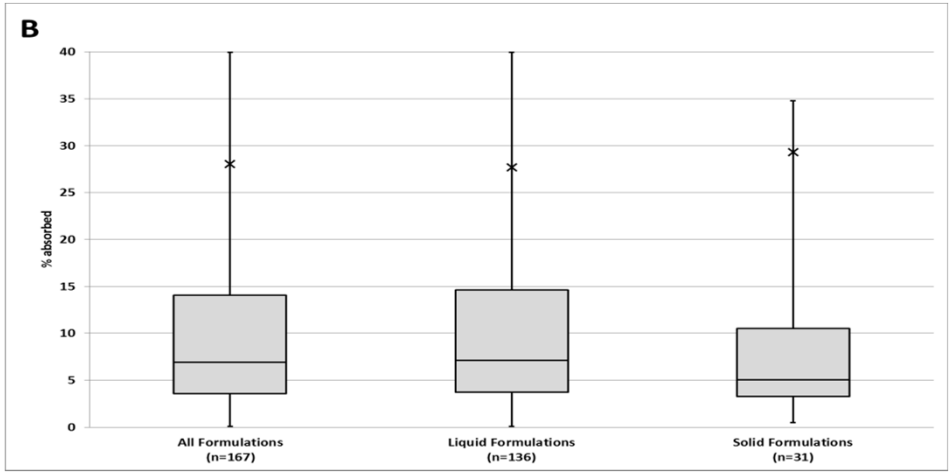
2nd dataset (preliminary information)

2nd dataset is consistent with 1st dataset

1. Default values – In use dilutions

EFSA GD:
75%

1st dataset



Percentile	Dermal absorption		
	All (n=121)	Liquids (n=102)	Solids (n=19)
Median	6.9	7.1	5.0
75th	14.1	14.6	10.5
95th	28.0	27.7	29.3

2nd dataset (preliminary information)

2nd dataset is consistent with 1st dataset

1. Default values – ECPA conclusions

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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

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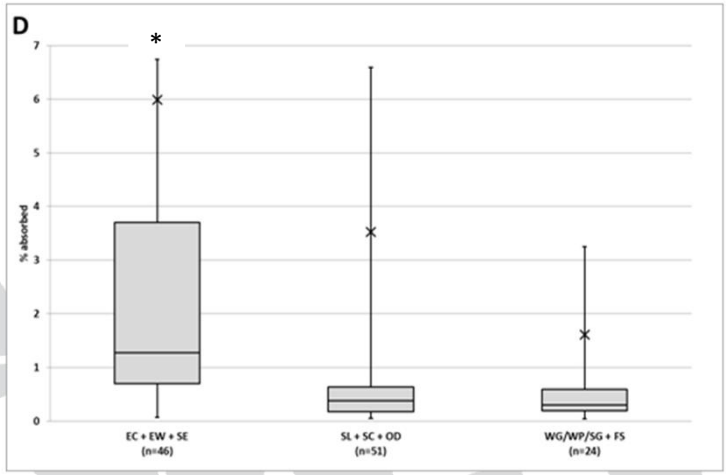
EFSA GD

- 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 2nd dataset
- Solvent-based data valid for read-across to water-based or solid formulations

3. Extrapolation to more dilute sprays

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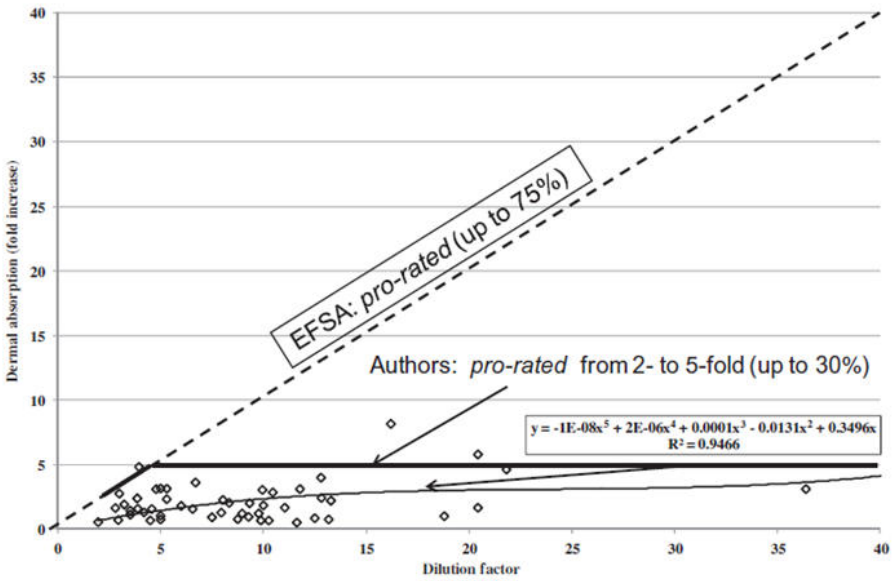
EFSA GD

- **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:

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- **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

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Thank you very much for your kind attention!

Backup

Introduction – DA for PPP

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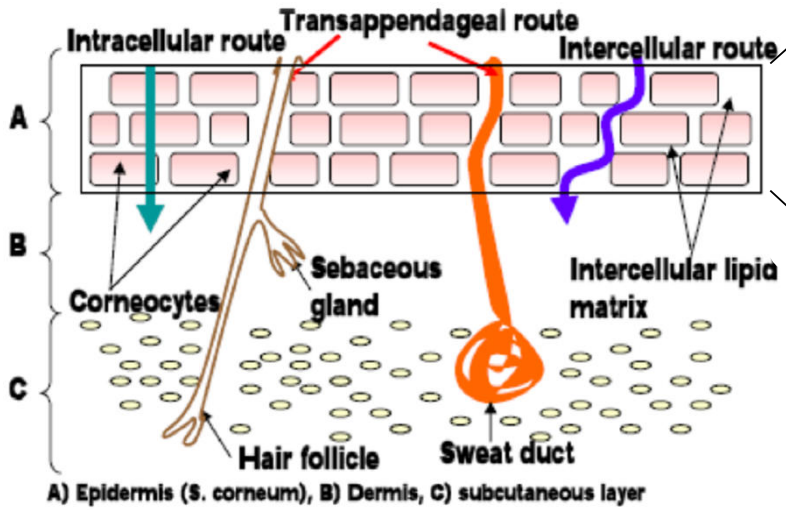
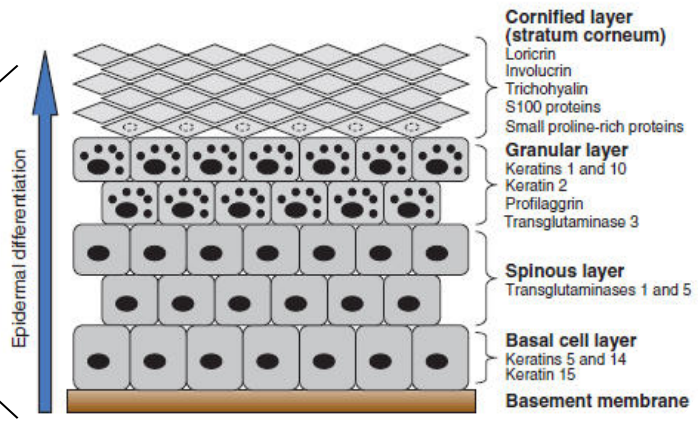
- **Mandatory input to all risk assessments**
- **Operators, bystanders and workers**
- **Exposed to**
  - Concentrate
  - Spray dilution
  - Residue
- **Used to estimate systemic exposure**
- **Compared to AOEL**
  - 100-fold safety factor
  - ≤ 100% of AOEL = acceptable risk

Skin structure & Dermal absorption



A) Epidermis (S. corneum), B) Dermis, C) subcutaneous layer



- 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

Issue II:
Compounded, unrealistic conservatism

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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

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Does the new formulation need to be tested for DA?

Formulation components	Existing (%)	New (%)	Differences (%)
Active	20	20	0
Adjuvant	33	33	0
Emulsifier	3	3	0
Solvent	30	30	0
Anti-freeze	5	7.5	+ 50%
Water	9	6.5	- 28%
Total	100	100	-

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