EFSA DA GD 2017: Industry Thoughts

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on behalf of ECPA

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EFSA stakeholder workshop on DA

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EFSA GD 2017

- **New data from ECPA and BfR were reviewed and the defaults were revised, however**
  - Homogeneity of the BfR data?
  - Statistical methodology applied?
- **Better read-across opportunities**
  - Multi-to-one approach
- **Refined criteria for accounting variability**
  - Application of k factor rather than arbitrary >25% SD rule
- **Excel sheet based calculator would be handy, once the bugs are being fixed**
- **Calculation of t0.5 seems more scientific**
- **Rounding of numbers is sensible**
- **……..**

Default values (%)

	ECPA	*SCCS*	MSSSI*	EFSA	Prof. Hothorn
Concentrate (Solid and water-base)	2[$]	*10*	10	10	13
Concentrate (Solvent-based)	6[$]		25	25	16
Spray (Solid and water-base)	30	*50*	50	50	29
Spray (Solvent-based)				70	42

[$]2% for solids and 6% for liquids

✓ These defaults were derived from different datasets and/or using different methodologies

*__Spanish ministry:__ Ministerio de Sanidad, Servicios Sociales e Igualdad (MSSSI)/Ministry of Health, Social Services and Equality

EFSA default values (%)

	95th percentile	95th percentile - including all variabilities	Upper 95th percentile - including all variabilities	Defaults
Concentrate (Solid and water-base)	3	6	8	10
Concentrate (Solvent-bas	5	11	13	25
Spray (Solid water-base)	23	40	46	50
Spray (Solvent-based)	36	56	62	70

3-5x

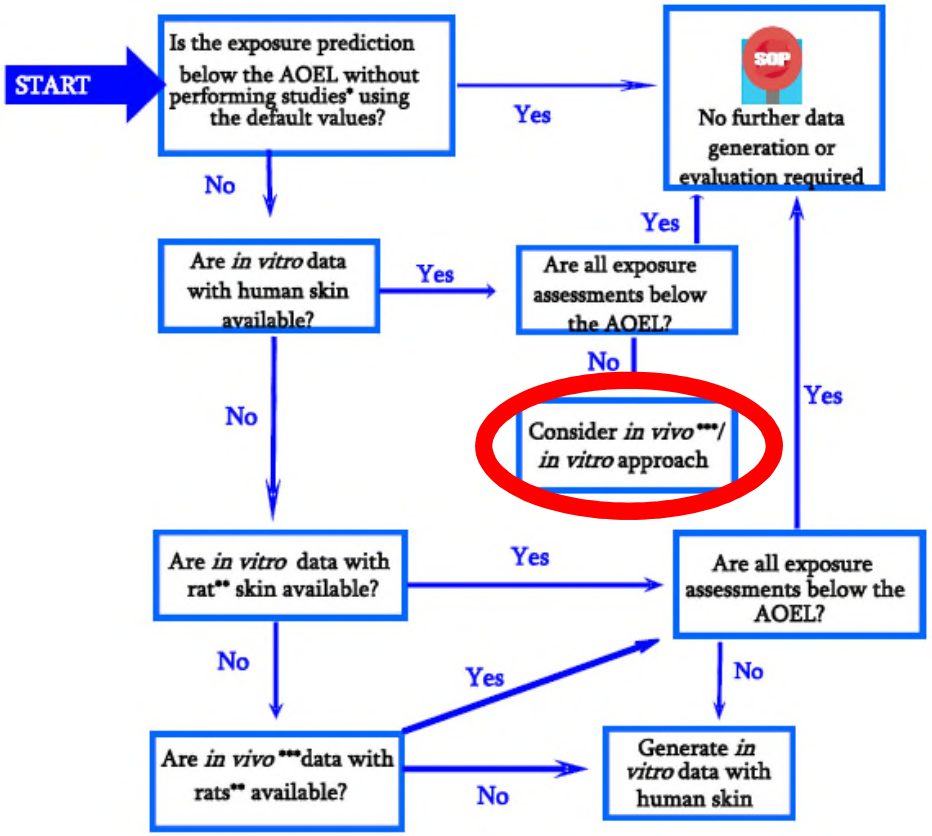
2x

Statistics should marry with biology!

- Calculated DA include all skin residue (except first 2 layers) - conservative estimates.
- Percentiles are calculated using individual replicates (not on mean basis), therefore, percentiles already cover any study variabilities. Nevertheless, Inter- and intra-study variabilities account up to 9% only.
- EFSA model 95th percentiles and ECPA empirical 95th percentiles are similar!

See Tables B.10 and B.5 in EFSA GD, 2017.

In vivo and triple pack studies?



* Studies should be on a representative formulation.

*** Existing *in vivo* studies.

See Flow chart 2 in EFSA GD, 2017.

- Overly conservative rules apply to calculate DA from *in vitro* studies
- Same rules apply to *in vivo* studies, even though they are multi-day duration study
- No new *in vivo* and/or triple pack recommended in the GD
- *Need room for manoeuvre to allow for refinement of DA!*
- **What data can be generated to reduce the uncertainty about the fate of the skin residue?**

An example – Skin residue?

	Mean (%)	SD
Receptor fluid + compartment wash		
OECD TG DA	0.82	0.40
Skin residues	24.5	3.8
Absorption + skin residue	25.3	6.5
Total recovery	90.2	
EFSA DA	25.3 + 6.5 + 3.5 = 35.2	

43x

- ✓ Mean max. flux is 0.001 µg/cm^2/h which equates to max. DA of **1.15%** in 24 h, highlight **inclusion of all skin residue hugely overestimate absorption**.

- ✓ ECPA is interested to learn what additional data might help to remove or significantly reduce the proportion of skin residue added to absorption?
  - ✓ Separation of skin compartments – dermis, epidermis, SC?
  - ✓ Modelling of flux values?
  - ✓ Anything else?

% max. DA = [(mean max. flux x 24) / applied dose x 100]

Low absorption and recovery?

	Concen-tration	*Mean recovery*	Receptor compartment	Skin residues	EFSA 2012	EFSA 2017 **corrected to 100%**
A	*SC formulation*					
Concentrate	500	99.07	0.01	0.03	0.04	0.04
Spray 1	1.67	100.95	0.02	0.21	0.4	0.4
Spray 2	0.33	**95.01**	0.18	0.87	1	1
B	*SC formulation*					
Concentrate	125	96.3	0.01	0.07	0.1	0.1
Spray 1	0.417	92.9	**0.05**	0.74	2	**9.5**

- ✓ What is needed to allow normalisation (rather addition) of 'missing' recovery for 'low absorption' compound as well?
- ✓ Would a WoE case be acceptable?

DA for untested spray

Example	%DA
Concentrate	3
Spray I: 1 + 100	12
Spray II: 1 + 400	19
Spray III: 1 + 600	?

- **EFSA GD:** 19 x 600/400 = 28.5%. This rule should apply when DA from only one spray is available.
- **ECPA:** Use DA from Sprays I and II, to calculate potential increase in DA for Spray III, i.e.
  - 4-fold increase in dilution increased DA by 7%, further 1.5-fold would increase DA by 2.6% (= 7/4 x1.5)
  - Therefore, DA for Spray III = 19 + 2.6 = 21.6%
- If no increase in DA from Spray I to Spray II, no adjustment in DA for Spray III should be needed.

A clarification on the above would be helpful.

Compounded conservatism

Risk = *f* Hazard x Exposure

- **AOEL**
  - ✓ LOAEL based on barely adverse effects
  - ✓ LOAEL to NOAEL dose spacing 2x -10x
  - ✓ Minimum 100x SF [10x inter-species & 10x intra-species]
  - ✓ Correction method for oral absorption

- **Tier 1 exposure estimation models**

- **DA**
  - ✓ Study - *in vitro vs. in vivo*
  - ✓ DA calculation (*e.g., vs.* reality)
    - ✓ Skin residue is absorbable
    - ✓ Adjustment for recovery and SD
  - ✓ DA from multiple days (*in vivo* studies) *vs.* AOEL per day

AOEL = Acceptable Operator Exposure Level
LOAEL = Lowest Observed Adverse Effect Level
NOAEL = No Observed Adverse Effect Level
SF = Safety Factor

Compounded conservatism multiplies to give irrelevant outcomes!

Thank you so much for your kind attention!

Amount in the skin?

- **Assumes all material in skin is absorbed**
  (except upper 2 layers of SC in some cases)
  - It is always **incorrect** – always a big overestimate of absorption
  - ✓ Bioavailability from dermis into bloodstream always <100%
  - ✓ **Good correlation** between ***in vitro*** **receptor fluid** to ***in vivo*** **human**

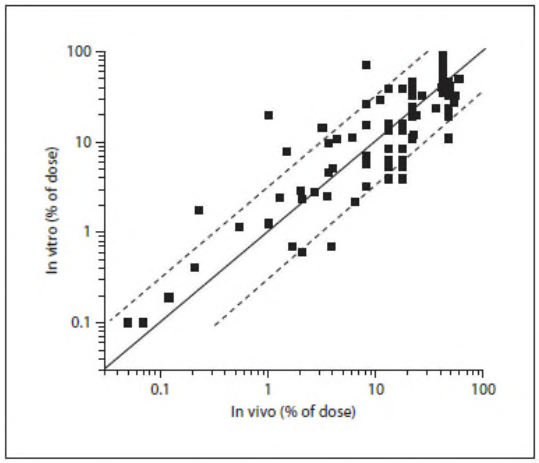


Fig. 1. IVIV ratios of total absorption for all 92 data sets plotted on log-log scale. The IVIV ratios ranged from 0.18 to 19.7, with an overall mean of 1.6. Solid line: ideal 1:1 correlation. Dashed lines: ±3-fold difference from ideal.

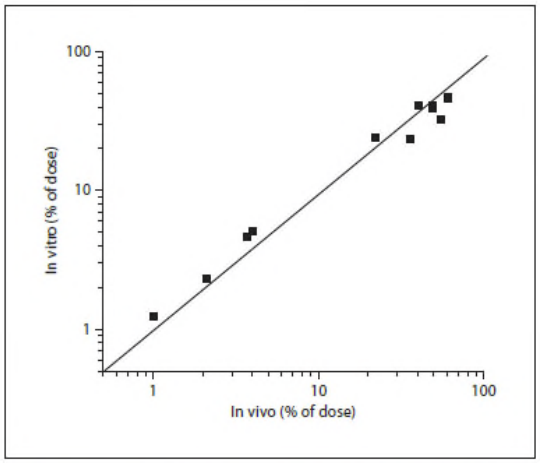


Fig. 2. IVIV ratios of total absorption for 11 fully harmonized data sets plotted on log-log scale. The IVIV ratios ranged from 0.58 to 1.28, with an overall mean of 0.96. Line: ideal 1:1 correlation.

Lehman *et al.*, 2011

*The in vitro-in vivo (IVIV) correlation was examined using only the data on total absorption (percent of applied dose) into the receptor solution (in vitro), **ignoring residual compound contained within the skin** at the time of study conclusion.*

- **Epidermis can be separated from dermis and shouldn't be included in the absorbed dose.**