Update of EFSA Guidance on dermal absorption

A few case studies by a Member State

Tamara Coja

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AGES, Institute for Plant Protection Products

Most of us are probably in the same position…

- Not actively involved in the development of the (Update) GD…
- End-users but not developers and not active scientists…
- We have to get used to new developments…

You might have expected…

- Lower default values…
- Lower (default) values for worker (dried residues)…
- Re-consideration of *pro rata* approach
- More revisions than just *in vitro* part (but “out of scope”)…

New elements

Which elements are so new/different?...

- "Minimum requirement" for *in vitro* studies: at least 4 replicates
- Calculation of t0.5 (permeation occurring within half of the sampling period)

$$t0.5 = 100\% \times \sum_{i=1}^{n} \frac{RF12_i}{RF24_i} \times \frac{1}{n} \qquad n = \text{number of valid replicates}$$

- Mean value is calculated from normalised replicates
- If recovery<95%: missing value added (especially if dermal absorption <5% and recovery <95%) or replicates normalised
- Variability within the results: SD multiplied with a factor (dependant on number of replicates) and result added to the mean value

Which elements are so new/different?...

- Rounding to two significant figures (leading zeros are not significant)

- For *in vitro* studies: calculation of the absorption pro replicate and than derivation of the mean value and SD

- New default values:
  - No more 10% for molecular weight >500 and log Pow <-1 or >4
  - Organic solvents (and “others”): 25% concentrate, 70% dilution
  - Water based and solids: 10% concentrate and 50% dilution

Which elements are so new/different?...

- Use of data on similar formulations: the acceptable changes (%) graduated according to original concentration
- Table for changes in active substance content included
- A step forward for inclusion of a new co-formulant (≤0.5%...)
- Application of QSARs rather a future
- ...

BfR Template

	Replicate	1	2	3	4	5	6	7	8
[%]	Donor ID								
Receptor fluid	Receptor fluid	0,048	0,021	0,019	0,021		0,021	0,012	0,022
Receptor chamber wash	Receptor compartment wash	0,48	0,183	0,288	0,263		0,253	0,239	0,387
Donor chamber wash	Donor compartment wash	1,681	0,054	0,13	2,1		0,203	0,058	1,472
	Tape strips								
Tape strips 1+2	1	0,425	0,048	0,013	0,724		0,064	0,022	0,137
Tape strips 1+2	2	0,362	0,026	0,011	0,271		0,096	0,013	0,073
Tape strips 3-x	3	0,29	0,025	0,019	0,351		0,042	0,013	0,282
Tape strips 3-x	4								
Tape strips 3-x	5								
Tape strips 3-x	6								
Tape strips 3-x	7								
Tape strips 3-x	8								
Tape strips 3-x	9								
Tape strips 3-x	10								
Tape strips 3-x	11								
Tape strips 3-x	12								
Tape strips 3-x	13								
Tape strips 3-x	14								
Tape strips 3-x	15								
Skin wash	Skin wash	96,039	96,892	94,516	89,126		98,098	97,378	91,401
Skin preparation	Stripped skin	2,844	0,211	0,242	7,693		0,779	0,159	4,416
T0.5 Receptor fluid	Receptor fluid after 12 hours	0,0581	0,0315	0,0233	0,043		0,0377	0,0139	0,0266
T1 Receptor fluid	Receptor fluid after 24 hours	0,276	0,1359	0,1167	0,1228		0,1253	0,0741	0,129

BfR Template

Results and discussion				
	Concentrate		Dilution 1 (1:200)	
Target concentration [mg/mL]	0		0	
Target dose [µg/cm^2]	0		0	
Mean actual applied dose [µg/cm^2]				
Recovery [%]	Mean	SD	Mean	SD
Dislodgeable dose				
Skin wash after x hours	94,78	3,35	95,35	3,62
Donor chamber wash	0,81	0,90	0,28	0,13
Skin associated dose				
Tape strips 1-2	0,33	0,40	0,35	0,17
Tape strips 3-x	0,15	0,15	0,27	0,14
Skin preparation	2,33	2,87	1,99	0,77
Absorbed dose				
Receptor fluid	0,02	0,01	0,07	0,03
Receptor chamber wash	0,30	0,10	4,24	1,55
Total recovery	98,72	2,26	102,55	4,14
Absorbed at t_0.5	18,00	5,61	10,01	7,37
Absorption complete?	No		No	
Measured absorption, if t_0.5<=75%	2,80	3,05	6,58	2,23
Measured absorption, if t_0.5>75%	N/A	N/A	N/A	N/A
Measured absorption corrected	2,80	3,05	6,58	2,23
Relevant absorption estimate	5,607		8,293	
Final estimate (rounded)	5,6		8,3	
Remarks				
Add your remarks here.				

- User friendly
- "Example" file with all explanations
- Copes with differences in study reports…
- It can be easily updated based on users feedback

- It does not cover – currently – the different options for cases where recovery <95% and DA <5%
- Difficulties to calculate kinetic (in the template) if very low absorption
- >12 replicates not possible to include

Case studies

Case study 1

…Case study (1)

EC formulation	Concentrate (60 g/L)	Dilution (1:200)
Recovery	>95 %	>95%
Nr. replicates	7	9
Absorption essentially complete at the end of the study (>75% absorption within half the study duration)	No	No
Dermal absorption acc. to the current EFSA Guidance	5.8% (2.8% + 3% SD)	8.8% (6.6% + 2.2% SD)
Dermal absorption acc. to the updated EFSA Guidance	5.6% (2.8% +*0.92**3%) ↓↑	8.3% (6.6% + *0.77**2.2%) ↓↑

Case study 2

…Case study (2)

EC formulation	Concentrate (66 g/L)	Dilution (1:100)
Recovery	>95 %	>95%
Nr. replicates	7	6
Absorption essentially complete at the end of the study (>75% absorption within half the study duration)	No	Yes
Dermal absorption acc. to the current EFSA Guidance	3.3% (1% + 2.3% SD)	5.1% (5.1%, *SD <25%*)
Dermal absorption acc. to the updated EFSA Guidance	3.1% (1% +*0.92**2.3%) ↓↑	5.6% (5.1% + *1**0.55%) ↓↑

Case study 3

…Case study (3)

SC formulation	Concentrate (500 g/L)	Dilution 1 (1.3 g/L)	Dilution 2 (0.2 g/L)
Recovery	>95 %	>95%	<95% (94.4 %)
Nr. replicates	7	7	8
Absorption essentially complete at the end of the study (>75% absorption within half the study duration)	No	No	Yes
Dermal absorption acc. to the current EFSA Guidance	0.75% (0.42 + 0.33% SD)	9.2% (3.9% + 5.3% SD)	10.2% (5.7% (normalised) + 4.5% SD)
Dermal absorption acc. to the updated EFSA Guidance	0.72% (0.42 + *0.92**0.33%) ↓↑	8.7% (3.9 + *0.92**5.3%) ↓↑	9.3% OR 8.2% OR 12.6% OR **15%** ↓↑

…Case study (3)

8.2%

Missing amount added (to 100%) for recovery <95%

Only mean and no addition of ks

9.3%

Replicates normalised for recovery <95%

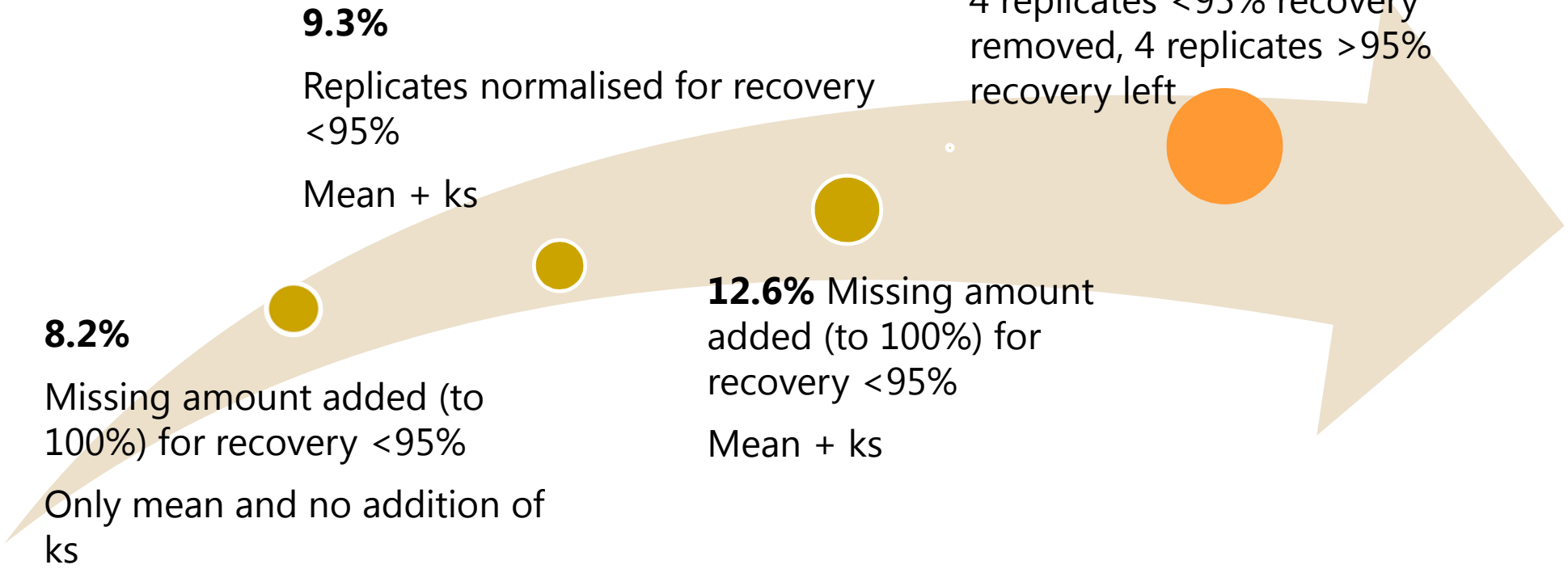
Mean + ks

12.6% Missing amount added (to 100%) for recovery <95%

Mean + ks

15%

4 replicates <95% recovery removed, 4 replicates >95% recovery left



Case study 4

…Case study (4)

SC formulation	Concentrate (125 g/L)	Dilution (0.4 g/L)
Recovery	>95 %	<95% (94%)
Nr. replicates	8	8
Absorption essentially complete at the end of the study (>75% absorption within half the study duration)	No	No
Dermal absorption acc. to the current EFSA Guidance	0.14% (0.07% + 0.07% SD)	1.6% (sum normalised for recovery <95% and SD added (>25%))
Dermal absorption acc. to the updated EFSA Guidance	0.13% (0.07% + *0.84**0.07%) ↑↓	**1.3% OR 5.8% OR 9.5%** ↑

…Case study (4)

9.5% *(6x higher than acc. to current GD)*

Missing amount added (to 100%) for recovery <95%

Mean + **ks (overestimated?)**

5.8%

Missing amount added (to 100%) for recovery <95%

Only mean and no addition of ks (there should be no uncertainty about the mean due to sampling variability)

1.3%

Replicates normalised for recovery <95%

Mean + ks

Conclusions

…Conclusion…encouraging aspects prevail

- Content of relevant components in the formulation is within permitted variation and similar chemical types of co-formulants might be grouped
- Use of data on similar formulations: the acceptable changes (%) graduated according to original concentration (in alignment with CLP)
- Table for changes in active substance content included
- Multi-to-one approach might be acceptable if variety of products always end up in the same range of dermal absorption
- Inclusion of a new co-formulant possible (≤0.5%...) and expert judgement included

…Conclusion…encouraging aspects prevail

- Factor k (instead of adding SD) reduces the absorption (compared to the current version) unless SD is <25% of the mean
- Default values lowered based on new data
- BfR template – really helpful and very much acknowledged tool

…Conclusion…be aware of

- Expert judgement if recovery <95% and dermal absorption <5% :

a) addition of "missing" material, plus addition of ks to the mean *versus*
b) taking only the "overestimated" mean (after addition of "missing" material) as a worst case to cover variability

- Testing of adjuvants in the dilution *("the test item should contain these adjuvants as well due to an expected impact on dermal absorption")*

- Only in *exceptional cases* oral absorption can be used instead of default values

Dr. Tamara Coja, MSc Toxicology
Senior Expert Toxicology, ERT

AGES – Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH

Spargelfeldstrasse 191
A-1220 Wien
T +43 (0) 50 555-33436

tamara.coja@ages.at
www.ages.at