Member state view: Ctgb, NL

Jessica Broeders, PhD, ERT

Scientific Risk Assessor Mammalian Toxicology

Board for the Authorisation of Plant Protection Products and Biocides

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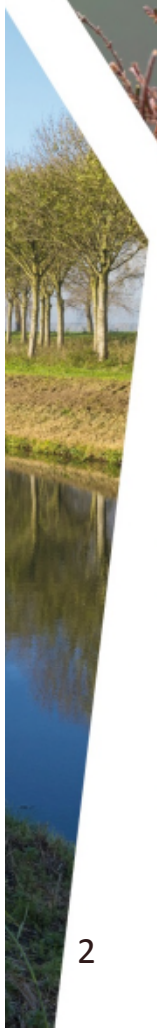

Introduction

- Focus on sections 5 and 6
- Each subsection discussed; differences compared to 2012GD; small examples
- Case study
  - Applying new version guidance
  - Comparison to previous version
- Pros and cons
- Considerations for the future

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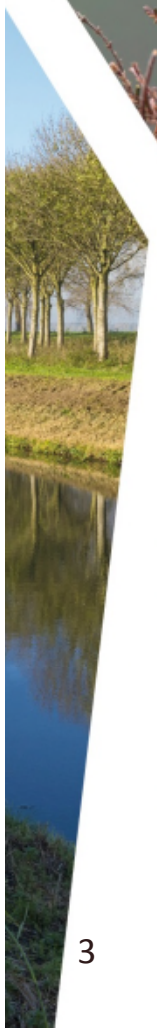

Differences I

5.1 Tape stripping

- Calculation to determine >75% within half sampling period

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

  Based on individual wells/animals

- t0.5 close to 75% -> determine confidence interval

Example → next slide

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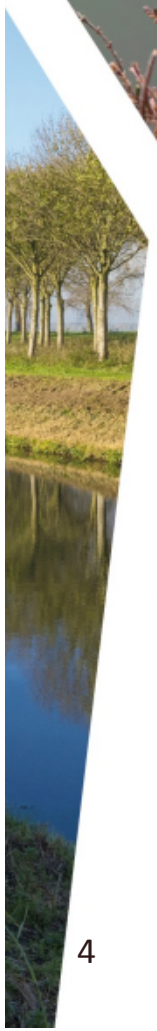

Example: t0.5 calculation

Difference

1) calculation based on mean
2) calculation each well and then take mean

	Well 1	Well 2	Well 3	Well 4	Well 5	Well 6	Well 7	Well 8		Mean
12h	5.19	9.14	10.25	23.71	14.87	13.05	7.22	5.49		11.12
24h	6.13	10.71	11.52	25.12	27.92	28.88	8.05	6.12		15.56
									t0.5	71.45%
										Mean
t0.5	84.67%	85.34%	88.98%	94.39%	53.26%	45.19%	89.69%	89.71%		78.90%

1) <75% tape strips included
2) >75% tape strips not included

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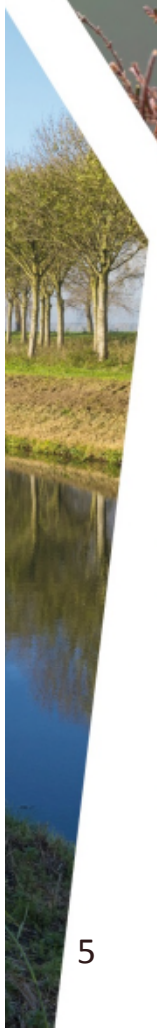

Differences II

5.2 Recovery

- To be calculated for each individual well/animal (also SD calculation possible)
- Options:
  - Overall recovery consistently low → worst case: missing material considered absorbed
    - This should certainly apply when DA <5% and recovery <95%
  - Normalisation = preferred option
    - Except for DA <5% and recovery <95 → addition rule
- Critical evaluation of data to determine if significant amounts of missing material could have been absorbed.

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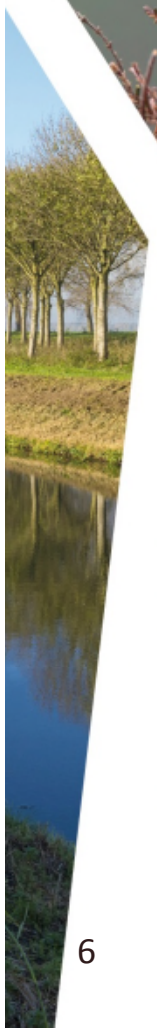

Differences II

5.2 Recovery

Correction by normalisation included in calculation sheet

Replicate	1	2	3	4
T0.5 <= 75 %				
Absorbed dose	0,061	0,035	0,107	0,62
Tape strips 3-x	0,86	0,88	0,62	0,94
Skin preparation	0,4	0,27	0,2	0,26
Sum	1,321	1,185	0,927	1,82
Relevant data normalised	**1,47513707**	**1,35420833**	**1,03752784**	1,82
T0.5 > 75 %				
Absorbed dose	0,061	0,035	0,107	0,62
Skin preparation	0,4	0,27	0,2	0,26
Sum	0,461	0,305	0,307	0,88
Relevant data normalised	**0,51479045**	**0,34855151**	**0,34360415**	0,88
Non-absorbed dose	88,23	86,32	88,42	93,85
Total Recovery	**89,551**	**87,505**	**89,347**	**95,67**

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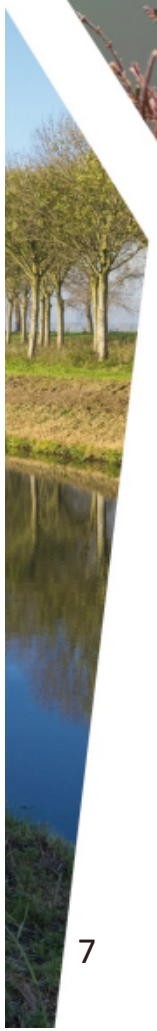

Differences III

5.3 Variability and outliers

- Add a multiple of the SD to the mean.
- Take number of replicates into account:

Table 1: Approach for the treatment of variability within the results

Number of replicates (n)	Multiplication factor (k)
4	1.6
5	1.2
6	1.0
7	0.92
8	0.84
9	0.77
10	0.72
11	0.67
12	0.64
13	0.60
14	0.58
15	0.55
16	0.53

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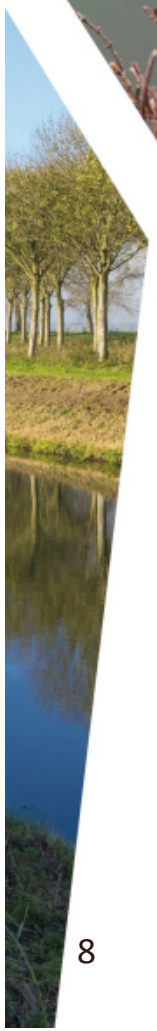

Differences III

5.3 Variability and outliers – Example

Mean: 15.15 and SD: 4.55

Mean + SD = 19.7 = 20%

Number of replicates	Mean + k*SD	Final DA based on 2017 GD
4	22.43	22%
5	20.61	21%
6	19.70	20%
7	19.34	19%
8	18.97	19%
9	18.65	19%
10	18.43	18%
11	1820	18%
12	18.06	18%
13	17.88	18%
14	17.79	18%
15	17.65	18%
16	17.56	18%

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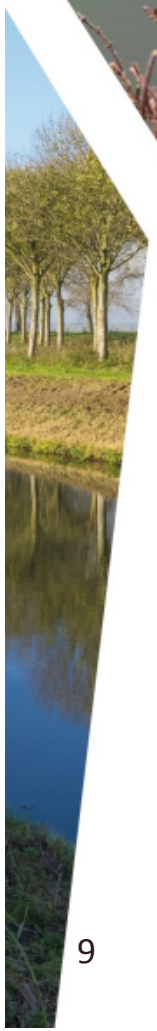

Differences IV

5.4 Rounding of values

- Max. 2 significant figures

5.5 Dilution rates

- Still pro rata correction

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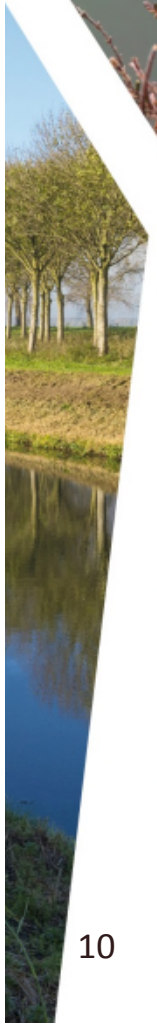

Differences V

6.1 Default values

- New default values
- Based on formulation category

Table 2: Default values to be used in the absence of experimental data

Formulation category	Concentration status	Default value
Organic solvent-based[(a)] or other[(b)]	Concentrate	25%
	Dilution	70%
Water-based/dispersed[(c)] or solid[(d)]	Concentrate	10%
	Dilution	50%

(a): Formulation types: emulsifiable concentrate (EC), emulsion, oil in water (EW), suspo-emulsion (SE), dispersible concentrate (DC), oil miscible liquids (OL/OF), oil-based suspension concentrates (OD), emulsion for seed treatment (ES), microemulsion (ME).

(b): Formulation types: bait concentrate (CB), capsule suspension (CS), gel for direct application (GEL/GD), bait, ready for use (RB), mixture of capsule suspension and suspension concentrate (ZC), seed coated with a pesticide (PS), experimental solution of active substances in solvent (AI).

(c): Formulation types: soluble concentrate (SL), suspension concentrate (SC), flowable concentrate for seed treatment (FS), flowable (FL) (–SC).

(d): Formulation types: wettable powder (WP), water-dispersible granules (WG/WDG), water-soluble granules (SG), water-soluble powder (SP), powder for dry seed treatment (DS).

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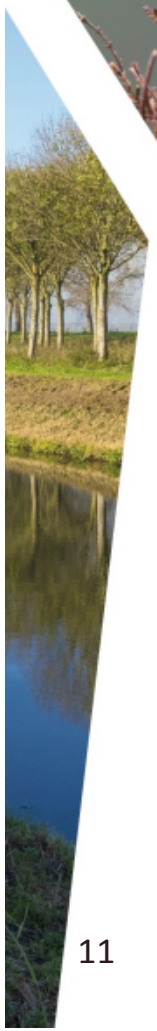


Differences VI

6.2 Use of data on similar formulations

Table 3: Permitted variation for similar formulation

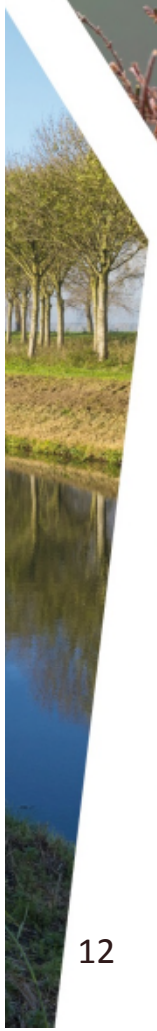
Initial concentration range of the constituent (% w/w)	Permitted (relative) variation (%)
≤ 0.5	±100
≤ 1.0	±50
≤ 2.5	±30
2.5 < c ≤ 10	±20
10 < c ≤ 25	±10
25 < c ≤ 100	±5

c: concentration.

Table 4: Permitted variation for active substance in similar formulations (from 'Manual on development and use of FAO and WHO specifications for pesticides', 2016)

Initial concentration range of the constituent (% w/w)	Permitted (relative) variation (%)
≤ 2.5	±15 for homogeneous formulations (EC, SC, SL), or ±25 for heterogeneous formulations (GR, WG)
2.5 < c ≤ 10	±10
10 < c ≤ 25	±6
25 < c ≤ 50	±5
≥ 50	±2.5

c: concentration; EC: emulsifiable concentrate; SC: suspension concentrate; SL: soluble concentrate; GR: granules; WG: water-dispersible granules.



Case study

- In vitro human skin
- Concentrate and 2 dilutions
  - Filling in sheet
  - Implications
  - questions

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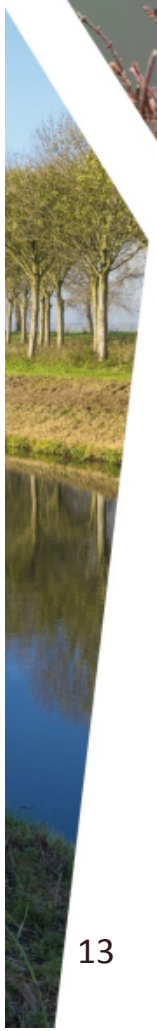

Concentrate

Calculation sheet filled in for each replicate

Enter values in %. [%]	Replicate / Donor ID	1	2	3	4	5	6	7	8
Receptor fluid	Receptor fluid	0,02	0,04	0,04	0,03		0,05	0,04	0,05
Receptor chamber wash	Receptor compartment wash	0	0	0	0		0	0	0,01
Donor chamber wash	Donor compartment wash	0,12	0,01	0,11	0,01		0,02	0,09	0,04
	Tape strips								
Tape strips 1+2	1+2	0,01	0,03	0,09	0,01		0,03	0,01	0
Tape strips 3-x	3 to 5	0,01	0,01	0,04	0,02		0,01	0,01	0
Tape strips 3-x	6 to 10	0,01	0	0,03	0,01		0,01	0,01	0
Tape strips 3-x	11 to 15	0,01	0	0,02	0		0	0,01	0
Tape strips 3-x	16 to 20	0	0	0	0		0	0	0
Skin wash	Skin wash	99,79	102,14	100,84	99,05		101,62	98,72	99,99
Skin preparation	Stripped skin	0,01	0,02	0,14	0,05		0,01	0,04	0,02
T0.5 Receptor fluid	Receptor fluid after 12 hours	0,01	0,03	0,02	0,02		0,03	0,02	0,03
T1 Receptor fluid	Receptor fluid after 24 hours	0,02	0,04	0,04	0,03		0,05	0,04	0,05

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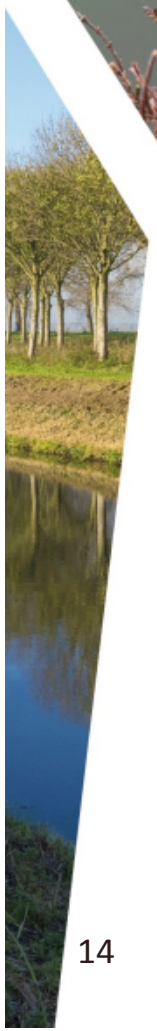

Concentrate

Drop-down menus

Enter values in %. [%]	Replicate / Donor ID	1	2	3	4	5	6	7	8
Receptor fluid	Receptor fluid	0,02	0,04	0,04	0,03		0,05	0,04	0,05
Receptor chamber wash	Receptor compartment wash	0	0	0	0		0	0	0,01
Donor chamber wash	Donor compartment wash	0,12	0,01	0,11	0,01		0,02	0,09	0,04
	Tape strips								
Tape strips 1+2	1+2	0,01	0,03	0,09	0,01		0,03	0,01	0
Tape strips 3-x	3 to 5	0,01	0,01	0,04	0,02		0,01	0,01	0
Tape strips 3-x	6 to 10	0,01	0	0,03	0,01		0,01	0,01	0
Tape strips 3-x	11 to 15	0,01	0	0,02	0		0	0,01	0
Tape strips 3-x	16 to 20	0	0	0	0		0	0	0
Skin wash	Skin wash	99,79	102,14	100,84	99,05		101,62	98,72	99,99
Skin preparation	Stripped skin	0,01	0,02	0,14	0,05		0,01	0,04	0,02
T0.5 Receptor fluid	Receptor fluid after 12 hours	0,01	0,03	0,02	0,02		0,03	0,02	0,03
T1 Receptor fluid	Receptor fluid after 24 hours	0,02	0,04	0,04	0,03		0,05	0,04	0,05

Tape strips were pooled; cannot delete lines in calculation sheet.

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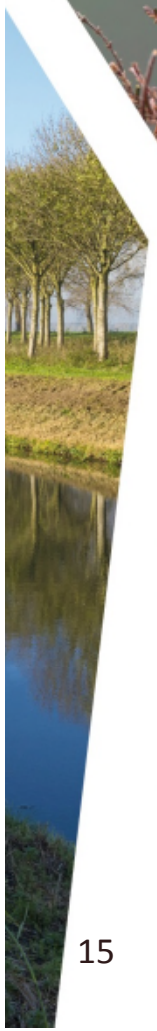

Concentrate

Drop-down menus

Enter values in %. [%]	Replicate / Donor ID	1	2	3	4	5	6	7	8
Receptor fluid	Receptor fluid	0,02	0,04	0,04	0,03		0,05	0,04	0,05
Receptor chamber wash	Receptor compartment wash	0	0	0	0		0	0	0,01
Donor chamber wash	Donor compartment wash	0,12	0,01	0,11	0,01		0,02	0,09	0,04
	Tape strips								
Tape strips 1+2	1+2	0,01	0,03	0,09	0,01		0,03	0,01	0
Tape strips 3-x	3 to 5	0,01	0,01	0,04	0,02		0,01	0,01	0
Tape strips 3-x	6 to 10	0,01	0	0,03	0,01		0,01	0,01	0
Tape strips 3-x	11 to 15	0,01	0	0,02	0		0	0,01	0
Tape strips 3-x	16 to 20	0	0	0	0		0	0	0
Skin wash	Skin wash	99,79	102,14	100,84	99,05		101,62	98,72	99,99
Skin preparation	Stripped skin	0,01	0,02	0,14	0,05		0,01	0,04	0,02
T0.5 Receptor fluid	Receptor fluid after 12 hours	0,01	0,03	0,02	0,02		0,03	0,02	0,03
T1 Receptor fluid	Receptor fluid after 24 hours	0,02	0,04	0,04	0,03		0,05	0,04	0,05

Non-absorbed: option donor chamber wash. However, this includes multiple measures: skin wash, tissue swab, pipette tip, possibly at multiple time points (e.g. 6h and 24h)

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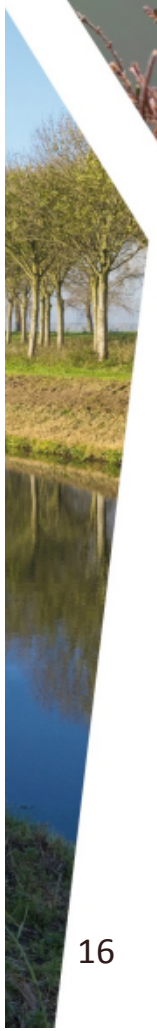

Concentrate

	2012 Guidance		2017 Guidance	
	Mean	**SD**	**Mean**	**SD**
Dislodgeable dose				
Skin wash	100.31	1.28	100.31	1.28
Donor chamber	0.06	0.05	0.06	0.05
Skin associated dose				
Tape strips 1-2	0.03	0.03	0.03	0.03
Tape strips 3-20	0.04	0.03	0.04	0.03
Skin	0.04	0.05	0.04	0.05
Absorbed dose				
Receptor fluid	0.04	0.01	0.04	0.01
Receptor chamber wash	0.01	-	0.01	-
Total recovery	100.50	1.29	100.50	1.29
% Absorbed at t0.5	**58.81**		**49.15**	**8.88**
Absorption complete?	No		No	
Absorption	0.11	0.07	0.11	0.07
Correction SD needed?	Yes		Yes	
Absorption	**0.2**		**0.18**	

Difference in t0.5 calculation, however, tape strips should be included anyway

Difference in rounding of the final value

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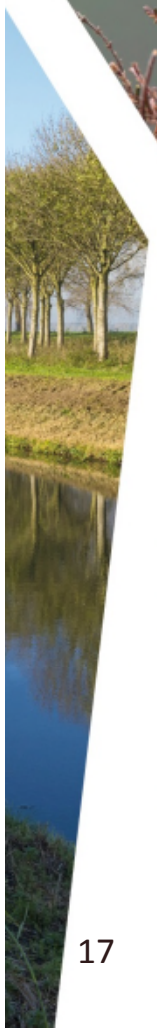

t0.5 calculation

- Guidance 2017: if t0.5 close to 75% → estimate confidence interval
  - Mean – k*s, where s is standard deviation and k is the k-value for correction based on nr of replicates in study.
- This is included in the calculation sheet, but:
  - What is defined as ‘close to 75%’?
  - Calculation sheets seems to take CI anyway, independent of initial t0.5-value
  - Bugs in calculation sheet….

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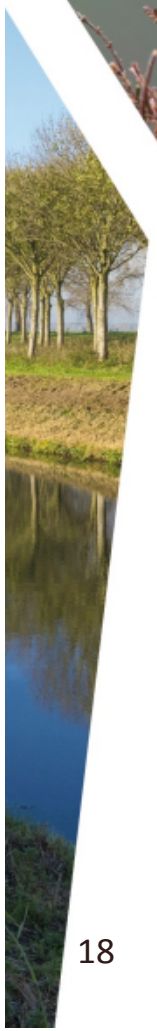

Concentrate sheet

7	58,81	9,66	75
Mean lower limit of confidence	49,15		
k*SD	8,88426467		

7 replicates, mean t0.5 = 58,81 with SD 9,66
Mean lower CI: 58,81-8,884 = 49,93
(and not 49,15, which is 58,81-9,66)

Summary sheet

	Concentrate	
Target concentration [mg/mL]	125	
Target dose [µg/cm²]	1298,82	
Mean actual applied dose [µg/cm²]		
Recovery [%]	Mean	SD
Dislodgeable dose		
Skin wash after x hours	100,31	1,28
Donor chamber wash	0,06	0,05
Skin associated dose		
Tape strips 1-2	0,03	0,03
Tape strips 3-x	0,04	0,03
Skin preparation	0,04	0,05
Absorbed dose		
Receptor fluid	0,04	0,01
Receptor chamber wash	0,01	N/A
Total recovery	100,50	1,29
Absorbed at t_0.5	49,15	8,88
Absorption complete?	No	
Measured absorption, if t_0.5<=75%	0,11	0,07
Measured absorption, if t_0.5>75%	N/A	N/A
Measured absorption corrected	0,11	0,07
Relevant absorption estimate	0,178	
Final estimate (rounded)	0,18	

T0.5 given is already lower limit of CI (calculated with SD instead of k*SD)
SD given is actually k*SD

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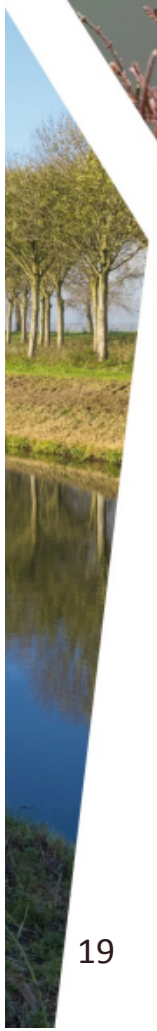

Dilution 1

	2012 Guidance		2017 Guidance	
	Mean	**SD**	**Mean**	**SD**
Dislodgeable dose				
Skin wash	87.01	5.37	87.01	5.37
Donor chamber	0.35	0.19	0.35	0.19
Skin associated dose				
Tape strips 1-2	0.34	0.25	0.34	0.25
Tape strips 3-20	1.43	1.23	1.43	1.23
Skin	5.10	3.12	5.10	3.12
Absorbed dose				
Receptor fluid	10.76	3.31	10.76	3.31
Receptor chamber wash	0.35	0.14	0.35	0.14
Total recovery	105.33	0.58	105.33	0.58
% Absorbed at t0.5	**75.05**		**68.73**	**5.81**
Absorption complete?	**Yes**		**No**	
Absorption	16.09	4.69	17.64	5.44
Correction SD needed?	Yes		Yes	
Absorption	**21%**		**23%**	

- Initially calculated t0.5 only 75.05% → to be considered as ‘close to 75%’, CI to be determined.
- Difference in t0.5 calculation, resulting in difference tape strips to be included or not.

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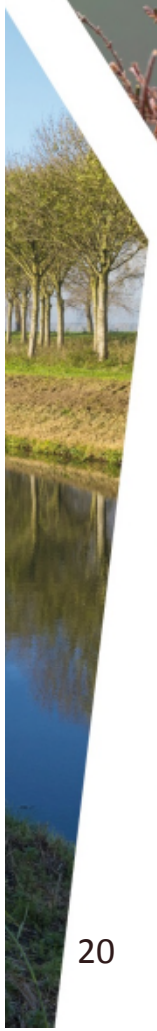

Dilution 2

	2012 Guidance		2017 Guidance	
	Mean	**SD**	**Mean**	**SD**
Dislodgeable dose				
Skin wash	77.12	11.01	77.12	11.01
Donor chamber	0.31	0.37	0.31	0.37
Skin associated dose				
Tape strips 1-2	0.46	0.30	0.46	0.30
Tape strips 3-20	1.72	0.86	1.72	0.86
Skin	3.63	2.80	3.63	2.80
Absorbed dose				
Receptor fluid	15.56	9.97	15.56	9.97
Receptor chamber wash	0.54	0.37	0.54	0.37
Total recovery	99.34	2.37	99.34	2.37
% Absorbed at t0.5	**78.90**		**60.22**	**15.69**
Absorption complete?	**Yes**		**No**	
Absorption	19.73	11.89	21.45	12.29
Correction SD needed?	Yes		Yes	
Absorption	**32%**		**32%**	

- Initially calculated t0.5 is 78,9% → to be considered as ‘close to 75%’ or not?
- Difference in t0.5 calculation, resulting in difference tape strips to be included or not.
- Mostly found in receptor fluid, not in tape strips → decision tape strips to be included or not does not influence final outcome.

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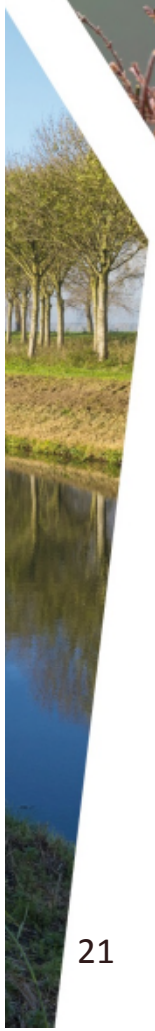

Pros and cons of the updated version

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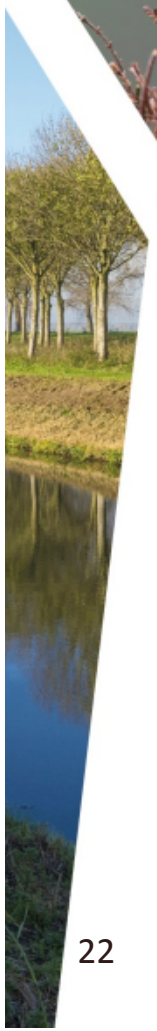

Pros

- Update based on actual data
- Reflects actual situation better
- More specific guidance given (e.g. t0.5 calculation)
- Standard calculation sheet
- More possibilities for ‘similar formulations’

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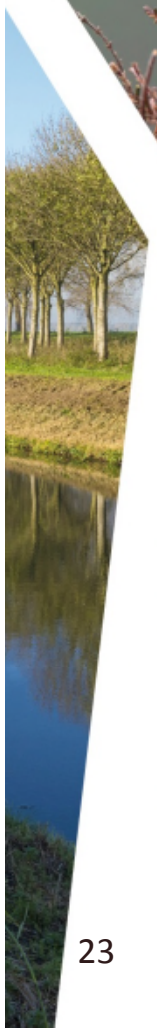

Cons

- Time to get used to calculation sheet
- Bugs in calculation sheet
- …….

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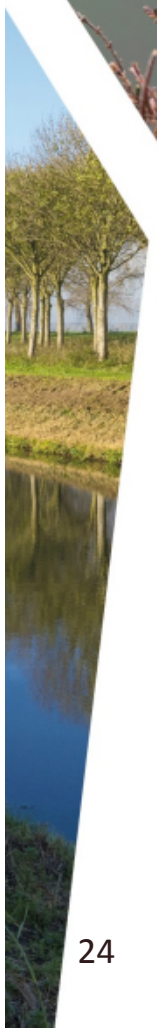
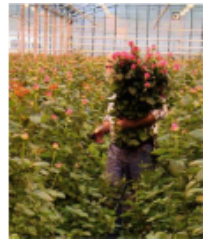


Considerations for the future

- More guidance needed
  - What is ‘close to 75%’ for the t0.5?
  - Pro rata correction, no guidance on when not needed (*there is no change of DA within the relevant dilution/concentration ranges*)
  - Worker dermal absorption



- Applicant fills in calculation sheets, (z)RMS to peer review?
- When guidance into force?

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