Changes to the guidance on dermal absorption

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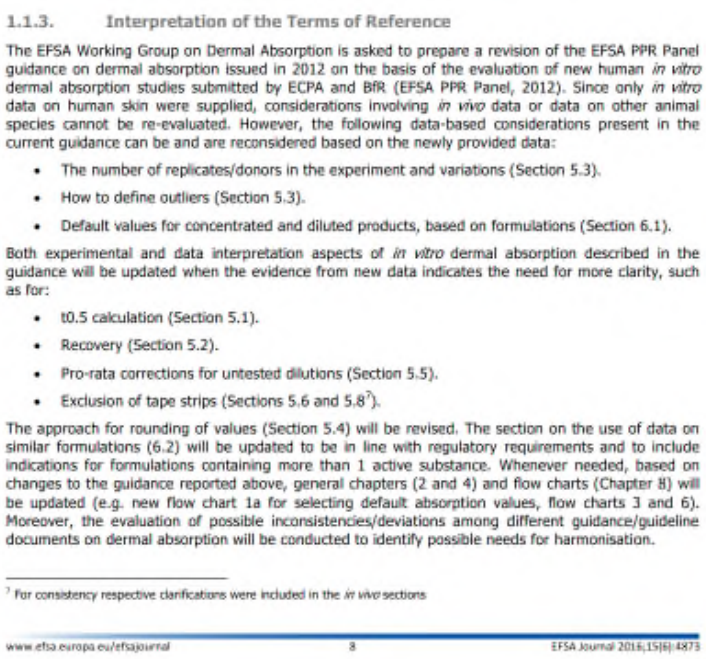
CHANGES TO THE GUIDANCE: OVERVIEW

EFSA guidance (2012) updated base on data analysis, experimental/interpretation aspects, harmonisation with regulatory requirement and whenever needed.

Final revision after public consultation to provide more clarifications, examples and transparency in data analysis.



1.1.3. Interpretation of the Terms of Reference

The EFSA Working Group on Dermal Absorption is asked to prepare a revision of the EFSA PPR Panel guidance on dermal absorption issued in 2012 on the basis of the evaluation of new human *in vitro* dermal absorption studies submitted by ECPA and BfR (EFSA PPR Panel, 2012). Since only *in vitro* data on human skin were supplied, considerations involving *in vivo* data or data on other animal species cannot be re-evaluated. However, the following data-based considerations present in the current guidance can be and are reconsidered based on the newly provided data:

- The number of replicates/donors in the experiment and variations (Section 5.3).
- How to define outliers (Section 5.3).
- Default values for concentrated and diluted products, based on formulations (Section 6.1).

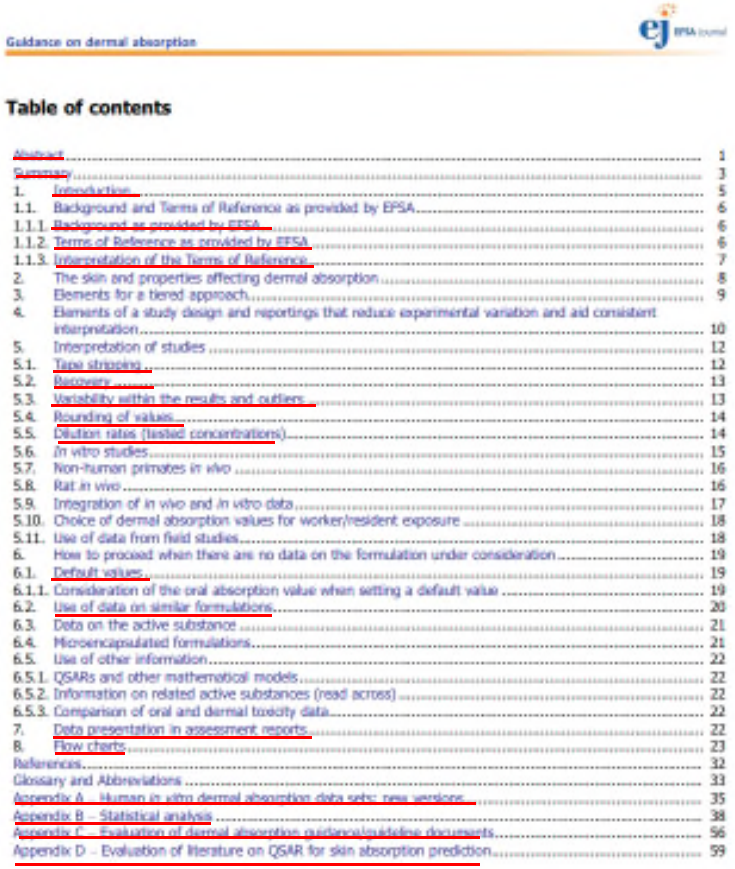
Both experimental and data interpretation aspects of *in vitro* dermal absorption described in the guidance will be updated when the evidence from new data indicates the need for more clarity, such as for:

- t0.5 calculation (Section 5.1).
- Recovery (Section 5.2).
- Pro-rata corrections for untested dilutions (Section 5.5).
- Exclusion of tape strips (Sections 5.6 and 5.8[7]).

The approach for rounding of values (Section 5.4) will be revised. The section on the use of data on similar formulations (6.2) will be updated to be in line with regulatory requirements and to include indications for formulations containing more than 1 active substance. Whenever needed, based on changes to the guidance reported above, general chapters (2 and 4) and flow charts (Chapter 8) will be updated (e.g. new flow chart 1a for selecting default absorption values, flow charts 3 and 6). Moreover, the evaluation of possible inconsistencies/deviations among different guidance/guideline documents on dermal absorption will be conducted to identify possible needs for harmonisation.

[7] For consistency respective clarifications were included in the *in vivo* sections

www.efsa.europa.eu/efsajournal 8 EFSA Journal 2016;15(6):4873



Guidance on dermal absorption

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CHANGES TO THE GUIDANCE: VARIABILITY AND OUTLIERS

Chapter 5: Variability within results and outliers

EFSA guidance 2012: *'If there is significant variation between replicates (i.e. the standard deviation is ≥ 25% of the mean of the absorption..)..the preferred approach would be the addition of a standard deviation to the mean value.'*

Issues identified:

- No scientific basis for 25% of the mean as cut-off
- Addition of 1 SD to the mean for high variability (for cosmetics: 1 SD by default and 2 SD for high variability/protocol deviations)
- Identification of outliers

EFSA guidance 2017:

- Add multiple of SD to the mean
- Multiplication factor (k) based on the number of replicates (Appendix B for justifications)
- Clarification for outliers identification, exclusion (from all other parameters calculations) and reporting (plausible cause)

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

Values of k were calculated assuming an underlying normal distribution as an approximation for variability and random sampling.

CHANGES TO THE GUIDANCE: TAPE STRIPPING

Chapter 5: Tape stripping

EFSA guidance 2012*: 'Only if absorption is essentially complete at the end of the study (> 75% of total absorption occurring within half of the study duration) can all tape stripped material be excluded.'*

Issue identified:

- t0.5 calculation:
  a) ∑(RF12h/RF24h*100)/n,
  b) (∑ RF12h/n) / (∑ RF24h/n) *100,
  c) ∑(RF12h)/n
     - where n is number of replicates.

EFSA guidance 2017: '.. *the mean relative permeation into the receptor fluid occurring within half of the sampling period (t0.5) should be calculated from the individual replicate data on amounts recovered in receptor fluid (RF) at 12h (RF12) and 24h (RF24) as follows:*

$$t0.5 = 100\% \times \sum_{i=1}^{n} \frac{RF12_i}{RF24_i} \times \frac{1}{n}$$

n = number of valid replicates

- t0.5 calculation clarified
- BfR template for calculations
- Case when t0.5 is close to 75% (CI to be calculated)

CHANGES TO THE GUIDANCE: RECOVERY

- **Chapter 5: Recovery**

EFSA guidance 2012*: 'When recovery is below the set limit (mean < 95%) there is a need to consider whether the missing material should be considered as absorbed. If all wells have a low recovery, as a worst case assumption the missing material could either be considered as absorbed, or alternatively, a "normalisation" approach could be applied'*

Issues identified:

- Recovery calculation
- When normalise or add the missing material to absorbed amount (worst case assumption)?
- Possible cases

EFSA guidance 2017:

- Mean to be calculated based on recoveries determined for each individual animal/replicate
- 2 approaches: normalisation and add missing material (worst case assumption)
  - Add missing material when calculated dermal absorption value < 5%: a high level of recovery required
- Provide additional evidence to identify the element of assay associated with missing material (e.g. non-absorbed material)
- No clear conclusion case: possible to use only values from high recovery samples to derive DA

CHANGES TO THE GUIDANCE: ROUNDING OF VALUES

Chapter 5: Rounding of values

EFSA guidance 2012*: 'Dermal absorption studies tend to have a relatively high level of variability associated with the results. So as not to imply spurious accuracy, dermal absorption values:*

- *of or above 10% should be rounded to two significant figures*
- *between 1% and 9% should be rounded to one significant figure*
- *below 1% should be rounded to one significant figure (if the data are reasonably consistent, report as a value below 1%, i.e. do not round up to 1%).*

For example:
0.15% = 0.2%
1.43% = 1%
2.65% = 3%
10.4%= 10%
15.6%= 16%..'

Issues identified:

- Complicated and not considering percentage of change
- From public consultation: request to simplify the procedure and to clarify when should be applied (e.g. before or after pro-rata)

EFSA guidance 2017:

- *'Dermal absorption studies tend to have a relatively high level of variability associated with the results. So as not to imply spurious precision, final dermal absorption (i.e. after pro-rata or triple pack corrections) values should be rounded to a maximum two significant figures.'*

CHANGES TO THE GUIDANCE: PRO-RATA APPROACH

Chapter 5: Dilution rates (tested concentrations)

EFSA guidance 2012: *'The concentration(s) tested should cover the extremes of those recommended on the product label. If the lowest concentration tested is greater than the lowest concentration recommended on the label, consideration should be given to increasing the dermal absorption pro rata to account for any limitation of absorption due to the amount of material applied to the test site.'*

Issues identified:

- More clarity needed on the considered formulation and concentrations ranges
- From public consultation: examples to be revised

EFSA guidance 2017: *'If the lowest concentration tested is greater than the lowest concentration of the same formulation recommended on the label, consideration should be given to increasing the dermal absorption pro rata to account for any limitation of absorption due to the amount of material applied to the test site.'*

- Specified that the formulation should be the same tested
- Specified ranges of dilutions tested
- Possibility for refinement of the default approach but justification to be provided (data and statistical uncertainty)

CHANGES TO THE GUIDANCE: DEFAULT VALUES (1)

Chapter 6: Default values

EFSA guidance 2012: *'A default dermal absorption value of 25% may be applied for products containing > 5% (50 g/kg for solids or 50 g/L for liquids) active substance. A default value of 75% should be used for products or in use dilutions containing ≤ 5% active substance. If log Pow < -1 or > 4 and MW > 500 a default dermal absorption value of 10% may be applied (de Heer et al., 1999).*

Issues identified:

- Update needed based on data analysis

EFSA guidance 2017:

- New DVs organised for concentration status and formulation category (based on the chemical composition of tested product: Table B.2 and FAO/WHO Manual can be used for the selection)
- Pragmatic proposals, taking into account 95% UCL of 95th percentile of empirical and predicted (random effects logit regression) relative absorption data, as well as uncertainties relating to the representativeness of the dataset.
- 10% DV dismissed based on data analysis

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: EC, EW,SE, DC, OL/OF, OD, ES, ME
(b): Formulation types: CB, CS, GEL/GD, RB, ZC, PS, AI
(c): Formulation types: SL, SC, FS, FL =SC
(d): Formulation types: WP, WG/WDG, SG, DS

CHANGES TO THE GUIDANCE: DEFAULT VALUES (2)

- **Chapter 6/Appendix B: Default values**
  - **70% DV for** organic-solvent and 'other' dilutions: overall value covering the upper confidence/credibility limits of both analyses and considering the scarcity of data available for the 'other' heterogeneous group.
  - **25% DV** for organic-solvent concentrates: proposed to be maintained DV of current guidance (2012), since the analysis of the new data does not suggest a substantially different value as well as the scarce and heterogeneous 'other' group.

Formulation category (number of studies)		Organic solvent + Other (158 + 22)	Organic solvent + Other (158 + 22)
Concentration status		dilution	concentrate
Analysis approach	Empirical	55	20
	Model	62	13
Current DV (2012)		75	25*
New DVs (2017)		**70**	**25**

*75 if a.s. content <5%

CHANGES TO THE GUIDANCE: DEFAULT VALUES (3)

- **Chapter 6/Appendix B: Default values**
  - **50%** and **10% DVs** for solids and water-based formulations, diluted and concentrated, respectively: from the outcomes of both empirical and model-based analyses

Formulation category (number of studies)		Water-based + Solid (161 + 77)	Water-based + Solid (161 + 77)
Concentration status		dilution	concentrate
Analysis approach	Empirical	48	9
	Model	46	8
Current DV (2012)		75	25*
New DV (2017)		**50**	**10**

*75 if a.s. content <5%

DEFAULT VALUES FOR DERMAL ABSORPTION

- **EFSA Guidance 2012**
  - **25%** for concentrate products containing > 5% a.s.
  - **75%** for concentrate products or dilutions containing ≤ 5% a.s.
  - Data: 63 a.s. tested *in vivo* (rat), *in vitro* (rat, human), using different protocols
  - Statistical analysis: not conducted, upper and lower absorption value considered (CRD, 2010).
- **ECPA (*Aggarwal et al*, 2015):**
  - **6%** (liquid) and **2%** (solid) for concentrated products
  - **30%** for spray dilutions
  - Data: 152 a.s. and 19 formulation types
  - Statistical analysis: sequential with no consideration for potential confounding effects, could lead to inappropriate conclusions.
- **EFSA Guidance 2017:**
  - Water-based/dispersed or solid formulations: **10%** for concentrate products and **50%** for dilutions
  - Organic solvent-based or other formulations: **25%** for concentrate products and **70%** for dilutions
  - Data: 199 a.s. and 31 formulation types
  - Statistical analysis: empirical and 2 model-based approaches, all variables analysed jointly. Different percentiles (95, 97.5 and 99th) and their uncertainty (95% UCL) presented for both approaches. Proposed values (based on 95% UCL of 95th percentile) are pragmatic and reasonable worst case.

CHANGES TO THE GUIDANCE: BRIDGING OF DATA (1)

Chapter 6: Use of data on similar formulations

EFSA guidance 2012*: 'Synergist and safener content is within +/-25% w/v of that in the reference formulation'* (same for co-formulant).

Issues identified:

- Need to harmonise with Regulation (EC) No 1272/2008 and SANCO guidance on significant and non-significant changes
- No guidance concerning permitted variation for active substance
- No guidance for addition of substances not contained in the reference formulation

EFSA guidance 2017:

- Permitted variation ranges for relevant components in the formulation to be assessed
- Rule for addition of substances not contained in the reference formulation
- More clarity for grouping of co-formulants
- Permitted variation for active substance in similar formulations (FAO/WHO Manual on specifications for pesticides, 2016)
- Multi-to-one approach acceptable in exceptional cases

CHANGES TO THE GUIDANCE: DATA IN REPORTS

- **Chapter 7: Data presentation in assessment reports**

EFSA guidance 2012

Issues identified:

- Not clear for: individual data, t0.5, outliers (with justification)

EFSA guidance 2017

- Updated table
- BfR template for calculations

In vitro and in vivo studies
Material/product tested (name/code number)
Type of formulation
Concentration of active substance in the formulation
Vehicle used (if any)
Dilution rates
Surface area dose in micrograms of active substance per cm^2
Exposure time
Sampling duration (time of last sample)
Animal species/strain and skin sample source/application site
Group size/number of replicates/donor's ID for replicate
Total recovery (individual values for replicates, mean values ± SD)
Amount absorbed (individual values for replicates, mean values ± SD)
Samples contributing to the amount absorbed and samples removed as outliers (with justification)
Type of tape strip used
In vivo studies
Amount in excreta (individual values, mean values ± SD)
Amount in carcass (individual values, mean values ± SD)
Amount in exhaled volatiles/CO_2 (individual values, mean values ± SD)
75% excreted in first half of study?
Amount in stripped application site (individual values, mean values ± SD)
Amount in tape strips 3 to ∞ (individual values, mean values ± SD)
Amount in tape strips 1 + 2 (individual values, mean values ± SD)
Amount in application site washes (individual values, mean values ± SD)
Swabbing
In vitro studies
Type of diffusion cell **Receptor fluid composition**
Specification of solubility in receptor fluid as recommended
$t_{0.5}$ value
Amount in receptor fluid and chamber wash (individual values for replicates, mean values ± SD)
Amount in stripped skin sample (individual values for replicates, mean values ± SD)
Amount in tape strips 3 to ∞ (individual values for replicates, mean values ± SD)
Amount in tape strips 1 + 2 (individual values for replicates, mean values ± SD)
Amount in skin sample washes (individual values for replicates, mean values ± SD)
Swabbing

CHANGES TO THE GUIDANCE: ANALYSIS OF DATA & INFO

APPENDICES

- **A**: Human in vitro dermal absorption data sets: new versions ✓
- **B**: Statistical analysis ✓
- **C**: Evaluation of dermal absorption guidance/guideline documents
- **D**: Evaluation of literature on QSAR for skin absorption prediction

CHANGES TO THE GUIDANCE: APPENDIX C

C: Evaluation of dermal absorption guidance/guideline documents

- Collection of discrepancies among dermal absorption documents
- Aim: to identify potential inconsistencies/discrepancies on the same factor/criterion for experimental and data analysis aspects

Factor/ criterion	**OECD 428** 'Guideline for the testing of chemicals' (2004)	**OECD 28** 'Guidance document for the conduct of skin absorption studies' (2004c)	**OECD 156** 'Guidance notes on dermal absorption' (2011)	**EFSA** 'Scientific Opinion on the science behind the revision of the guidance document of dermal absorption' (2011)	**EFSA** 'Guidance on dermal absorption' (2012)	**ECPA** (from Study Reports)	**SCCS** 'Basic criteria for the in vitro assessment of dermal absorption of cosmetic ingredients' (2010)	**SCCS/1564/15** 'The SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation' (2015)	**WHO** 'Environmental Health Criteria for dermal absorption' (2006)	**EMA** 'Guidance on quality of transdermal patches' (2013)	**ECETOC** Monograph No. 20 'Percutaneous absorption' (1993)	**EPA** 'Dermal absorption exposure assessment' (1992)
Experimental												
Data analysis												

CHANGES TO THE GUIDANCE: APPENDIX C (2)

C: Evaluation of dermal absorption guidance/guideline documents

- Results
  - Experimental variability: sample number, outlier identification, how to address high variability within replicates
  - Data analysis: recovery criteria, default values, t0.5 calculation, pro-rata/bridging
- Conclusions
  - Identified diverging recommendations to reduce experimental variability, recovery acceptability criteria and default values
  - Need for improved harmonisation among guidance/guideline documents on dermal absorption
- Recommended to revise OECD documents for a more harmonised approach for assessing dermal absorption of chemicals

SPSF submitted by EFSA/BfR to OCED for revision of GD 28 and GN 156 (possibly TG 428): project included in OECD work plan for Test Guidelines Programme

CHANGES TO THE GUIDANCE: APPENDIX D

D: Evaluation of literature on QSAR for skin absorption prediction

QSAR is still not recommended in the guidance

- Literature revision on QSARs and mathematical models
- Recommendation to perform an extensive review of all available models (including mixture models) for testing their reliability of predictions in silico project

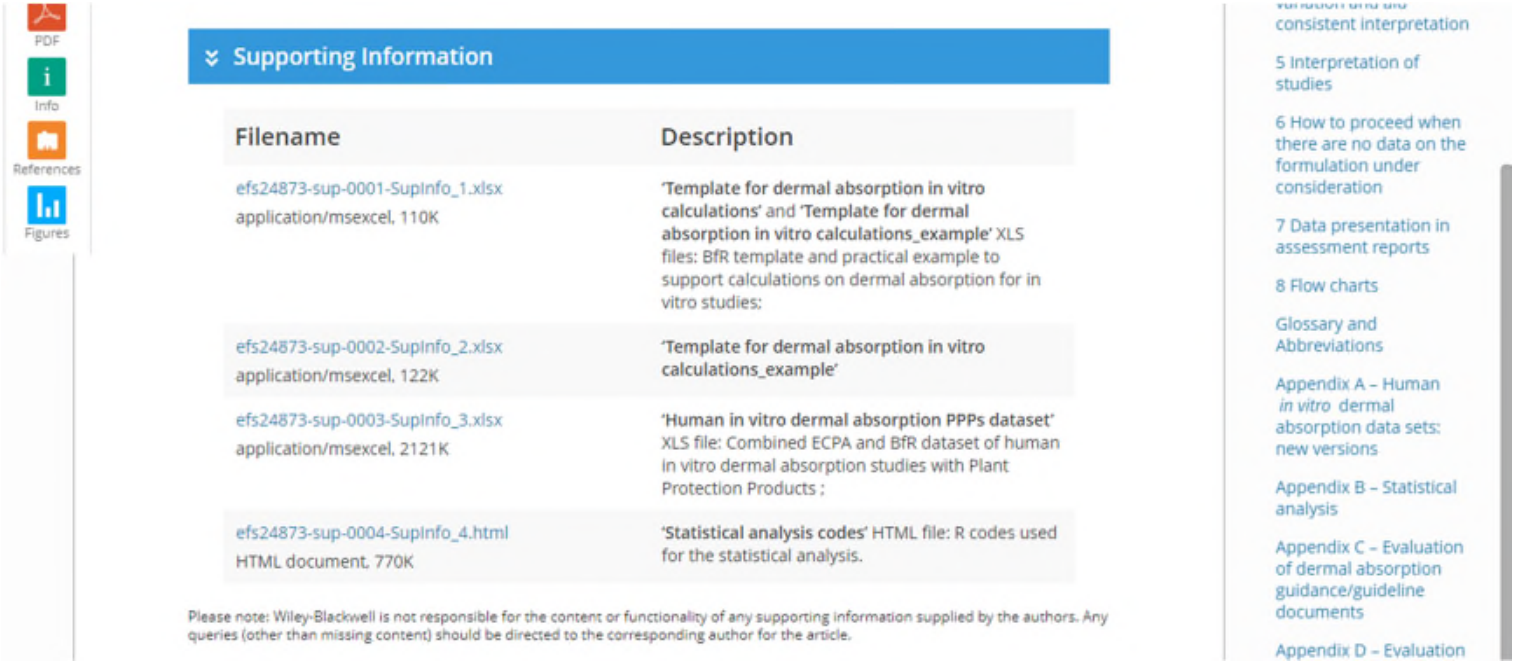
➡ Procurement OC/EFSA/PRAS/2016/02 'Applicability of in silico tools for the prediction of dermal absorption for pesticides'

- Main objective: to evaluate the applicability of existing in silico models for prediction of dermal absorption of pesticides, using the dataset of human in vitro dermal absorption studies with PPPs

CHANGES TO THE GUIDANCE: SUPPORTING INFORMATION

- BfR template for DA *in vitro* calculation and practical example
- Dataset (ECPA + BfR) used for the analysis
- R codes used for statistical analysis

published with the EFSA Guidance 2017 at:
http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.4873/full



PDF
Info
References
Figures

Supporting Information

Filename	Description
efs24873-sup-0001-SupInfo_1.xlsx application/msexcel, 110K	**'Template for dermal absorption in vitro calculations'** and **'Template for dermal absorption in vitro calculations_example'** XLS files: BfR template and practical example to support calculations on dermal absorption for in vitro studies;
efs24873-sup-0002-SupInfo_2.xlsx application/msexcel, 122K	**'Template for dermal absorption in vitro calculations_example'**
efs24873-sup-0003-SupInfo_3.xlsx application/msexcel, 2121K	**'Human in vitro dermal absorption PPPs dataset'** XLS file: Combined ECPA and BfR dataset of human in vitro dermal absorption studies with Plant Protection Products ;
efs24873-sup-0004-SupInfo_4.html HTML document, 770K	**'Statistical analysis codes'** HTML file: R codes used for the statistical analysis.

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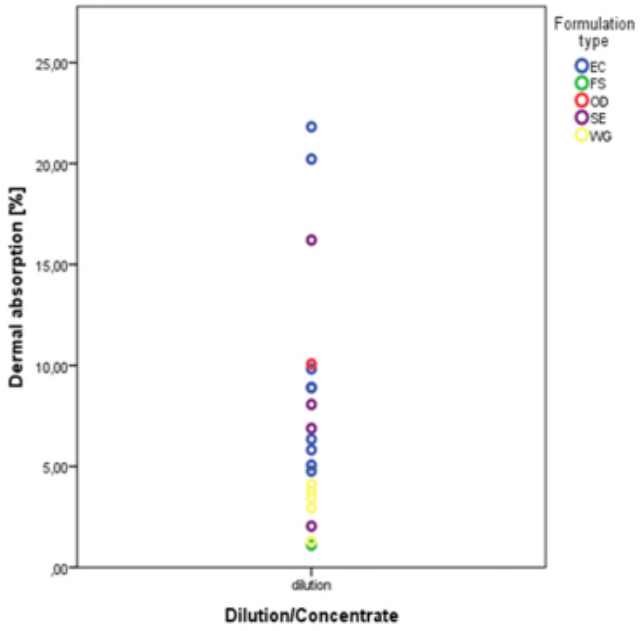
consistent interpretation
5 Interpretation of studies
6 How to proceed when there are no data on the formulation under consideration
7 Data presentation in assessment reports
8 Flow charts
Glossary and Abbreviations
Appendix A – Human *in vitro* dermal absorption data sets: new versions
Appendix B – Statistical analysis
Appendix C – Evaluation of dermal absorption guidance/guideline documents
Appendix D – Evaluation

CHANGES TO THE GUIDANCE: TECHNICAL REPORT

Technical Report on the public consultation of draft guidance

- Answers to (>)259 submitted comments including further specific clarifications, examples
  - e.g. dermal absorption of pyraclostrobin in different dilutions of several formulation types



- 'Hand-book' that can be used in addition to the guidance document

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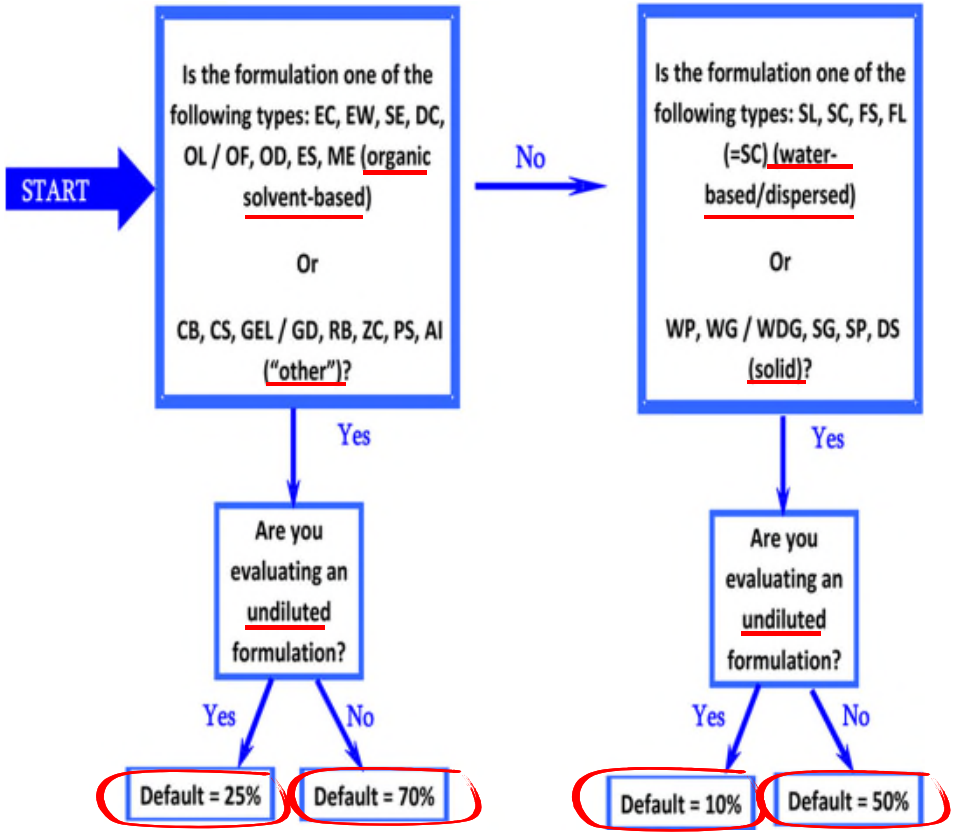
BACK-UP SLIDES

CHANGES TO THE PPR GUIDANCE: DEFAULT VALUES



FLOW CHART 1a: Procedure to select default absorption values

CHANGES TO THE PPR GUIDANCE: grouping formulation types

	Code	Description	Number of studies	Details and justification for grouping[a]
1	EC	Emulsifiable concentrate	90	The active substance is dissolved in suitable organic solvents, together with any other necessary formulants. It should be in the form of a stable homogeneous liquid, free from visible suspended matter and sediment, to be applied as an emulsion after dilution in water.
	DC	Dispersible concentrate	1	The active substance is dissolved in suitable organic solvents, together with any other necessary formulants. It should be in the form of a stable homogeneous liquid, free from visible suspended matter and sediment, to be applied as a dispersion after dilution in water.
	EW	Emulsion, oil in water	15	A stable emulsion of active substance(s) in an aqueous phase, intended for dilution with water before use. The active substance is normally a liquid and forms the dispersed oil phase, but it is also possible to emulsify a solid or liquid active ingredient dissolved in a water-immiscible solvent. EW are emulsions with organic solvents as the inner phase in which the active substance is dissolved.
	SE	Suspo-emulsion	29	Multiphase formulation whereby an emulsified active substance is combined with active suspended in water. SEs are emulsions/suspensions with an organic solvents(s) as a phase in which the active substance is dissolved.
	OL/OF	Oil-miscible liquids	1	A solution of the active substance, together with any other necessary formulants, in organic solvent; no water is contained. It should be free of visible suspended matter and sediment, intended for dilution with organic liquid before use.
	OD	Oil-based suspension concentrate	18	An oil dispersion is a stable suspension of active substance(s) in an organic fluid, which may contain other dissolved active substance(s); no water is contained. It is intended for dilution with water before use.
	ES	Emulsion for seed treatment	1	A water-based emulsion containing the active substance, together with large amounts of organic solvents and any necessary formulants including colouring matter. It should be easy to homogenise, and suitable for dilution with water if necessary, application to the seed either directly or after dilution. ES are emulsions with organic solvents as inner phase in which the active substance is dissolved.
	ME	Micro-emulsion	3	A mixture of water, water-insoluble and water-soluble components forming a visually homogeneous, transparent liquid. One or more active substances may be present in either the aqueous phase, the non-aqueous phase, or in both phases. A variety of micro-emulsion formulations may be prepared in which the aqueous phase can be considered the dispersed phase, the continuous phase or, alternatively, where the two phases are considered bicontinuous. In all cases, micro-emulsions will disperse into water to form either conventional emulsions or dilute micro-emulsions.
2	SL	Soluble concentrate	21	Water-based formulation in which a salt of pesticide acid is dissolved in water, together with any other necessary formulants. It should be in the form of a clear or opalescent liquid, free from visible suspended matter and sediment, to be applied as a true solution of the active substance in water.
	SC	Suspension concentrate	121	A stable suspension of active substance(s) in an aqueous continuous phase, intended for dilution with water before use.
	FS	Flowable concentrate for seed treatment	18	A suspension of fine particles of the active substance in an aqueous phase together with suitable formulants, including colouring matter. After gentle stirring or shaking, the material shall be homogeneous and suitable for further dilution with water if necessary.
	FL	Flowable	1	As described for the product, it is a SC formulation.
3	WP	Wettable powder	12	A homogeneous mixture of the active substance(s) together with filler(s) and any other necessary formulants. It should be in the form of a fine powder free from visible extraneous matter and hard lumps.
	WG/WDG	Water-dispersible granules	57	Intended for application after disintegration and dispersion in water by conventional spraying equipment.
	SG	Water-soluble granules	5	Granules containing the active substance, and, if required, suitable carriers and/or necessary formulants. It shall be homogeneous, free from visible extraneous matter and/or hard lumps, free flowing, and nearly dust-free or essentially non-dusty. The active substance should be soluble in water.
	SP	Water-soluble powder	2	A homogeneous mixture of the active substance, together with any necessary formulants. It should be in the form of a powder to be applied as a true solution of the active substance after solution in water, but which may contain insoluble inert ingredients.
	DS	Powder for dry seed treatment	1	A powder for application in the dry state directly to the seed; a homogeneous mixture of the active substance together with suitable fillers and any other necessary formulants including colouring matter. It should be in the form of a fine free-flowing powder, free from visible extraneous matter and hard lumps
4	CB	Bait concentrate	1	A solid or liquid intended for dilution before use as a bait. Sugar or other food ingredients or components like talcum are often the main compounds.
	CS	Capsule suspension	6	A stable suspension of micro-encapsulated active substance in an aqueous continuous phase, intended for dilution with water before use.
	GEL/GD	Gel for direct application	1	A gel-like preparation, intended to be applied undiluted. A gel for direct application consists of one or more active substances, a structuring agent and other formulants if appropriate. The active substance is homogenised in suitable solvents, together with any other necessary formulants. It should be in the form of a clear or opalescent gel, free from visible suspended matter and sediment. These formulations are different from organic or water based formulations.
	RB/Pellets/Wax block/Pasta bait	Bait (ready for use; paste, wax bloc, pasta bait included)	6	A formulation designated to attract and be eaten by the target pests. Wax blocs or paste baits are included. For example, in the case of a rodenticide, it is a solid bait and is based on grains, cereals and/or large amounts of wax. RB differs from other solid formulations.
	ZC	CS and SC mixture	3	A mixed formulation of CS and SC and is a stable suspension of microcapsules and solid fine particles, each of which contains one or more active substances. The formulation is intended for dilution into water prior to spray application.
	PS	Seed coated with a pesticide	1	Seed coated with a pesticide. PS formulations probably contain only the active substance, colour and carrier formulants.
	AI	Experimental solution of active substance in solvent	4	The vehicle can be organic or water-based. Because of the absence of other co-formulants, these solutions are not comparable with organic- or water-based formulations.
				Excluded from statistical analysis:
	XX/NA		6	No information on formulation type available

LEGEND
1) Primarily organic solvent-based, 2) Primarily water-based/dispersed, 3) Solid, 4) Other

(a): Based on the FAO/WHO, 2016.

CHANGES TO THE GUIDANCE: BRIDGING OF DATA (2)

- **Chapter 6: Use of data on similar formulations**
  - Permitted variation ranges for relevant components in the formulation to be assessed (CLP regulation and SANCO guidance):

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

  - Permitted variation for active substance in similar formulations (FAO/WHO Manual on 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