CropLife Europe- DAPT position on the applicability of the EFSA guidance on dermal absorption in the context of the draft Brazilian regulation and guidance on Exposure assessment of operators, workers, residents and bystanders for the risk assessment to pesticides

1 INDUSTRY POSITION ON APPLICABILITY OF THE EFSA GUIDANCE ON DERMAL ABSORPTION FOR PESTICIDE REGULATION IN BRAZIL

Although the EFSA guidance is in place for pesticide regulation in Europe, several aspects of the guidance as such and the overall implication in the context of non-dietary risk assessment are criticized as being scientifically and regulatory-wise imbalanced. The one-to-one transfer into the Brazilian regulation will significantly impact the newly introduced non-dietary risk assessment for the following reasons.

- There is compounded conservatism in non-dietary risk assessment. The use of *in vitro* dermal absorption estimation contributes significantly to this and the European assessment approach of dermal absorption studies leads additionally to a tremendous overestimation of risk and unnecessary risk assessment failure. This can only be overcome by either time and cost-intensive higher tier field data or use group removal or even complete product removal from the market.
- The anticipated regular failure of the tier 1 non-dietary risk assessment based on the high dermal absorption default values proposed will trigger massive product testing for the Brazilian market for which no GLP-compliant laboratory experience and capacity is implemented in Brazil and which is further affected by the Brazilian legal prevention of conducting studies through human skin. This will most severely affect small-scale local pesticidal product manufacturers.

- Based on the very stringent bridging criteria applied in the EFSA guidance, product-to-product bridging will hardly be possible, since for example even the addition of an additional mixing partner (active ingredient) will not allow any bridging. The same applies for the exchange of low content formulants within the product properties of which are not expected to impact the dermal absorption properties of the active ingredient, e.g. biocidal components or antifoaming agents.
- The compounded conservatism included in the study acceptance and secondary study interpretation criteria implemented in the EFSA dermal absorption guidance, which is unique for a single study type interpretation and thus not in line with other kinetic or toxicology study evaluation criteria will further contribute to the higher likelihood of risk assessment failure. All EFSA study interpretation criteria aim to increase the dermal absorption estimate and do not intend a better prediction of actual absorption.

The current EU non-dietary risk assessment approach is very conservative due to multiple worst-case default assumptions. Using high percentiles on risk assessment parameters is very protective but obviously biased towards failing due to compounded conservatism. Detailed assessments on unaccounted uncertainty factors included in the risk assessment equations for non-dietary risk assessment of pesticides have recently been published (Cochran and Ross, 2017; Kluxen et al., 2021). This generic overprediction will not allow appropriate and efficient risk management or provide realistic risk communication which should be considered when transferring one-to-one into the Brazilian guidance development on non-dietary risk assessment.

In the following, the relevant criticized aspects of the EFSA dermal absorption guidance are detailed regarding potential impact when applied in the Brazilian non-dietary risk assessment equation.

2 DERMAL ABSORPTION IN THE CONTEXT ON NON-DIETARY RISK ASSESSMENT

2.1 Criticism on the EFSA guidance included conservatism in the context of non-dietary risk assessment

Dermal absorption is an integral parameter in the non-dietary risk assessment to translate body external dermal exposure estimates or measures into systemic exposure to allow comparison with systemic reference values characterizing the hazard within the risk assessment equation. To cover uncertainty within the risk assessment, uncertainty factors are applied. Some UFs used in human risk assessment are based on toxicokinetic considerations (Dankovic et al., 2015). However, the common UF of 100, which is used within the EU Regulation (EC) 1107/2009, was generically set (possibly based on Lehman and Fitzhugh (1954)) and only subsequently reinterpreted to relate to toxicokinetic/toxicodynamic inter- and intra-species differences (Dourson and Stara, 1983; WHO and IPCS, 2005; WHO et al., 1994). UFs are intended to cover both the uncertainty associated with deriving the hazard characteristic estimate and biological variation between species used for hazard assessment and also variability in the human target population (Dankovic et al., 2015;

Hayes and Kruger, 2014; Ragas, 2011; Vermeire et al., 1999). Depending on the severity of effects or the steepness of the dose-response observed in the toxicological studies, or other uncertainties defined in the hazard data package, additional (e.g. 3X) arbitrary safety factors may be used in deriving reference values.

Further uncertainty factors are also included when characterizing the exposure with modelling approaches. In Europe, uncertainty associated with non-dietary exposure estimates is additionally accounted for by using high empirical percentiles or other statistical approaches (EFSA, 2014; EFSA et al., 2017). Since uncertainty is taken into account both in hazard and exposure assessment, it is reasonable to assume that the "intended" margin of exposure of at least 100 is substantially exceeded by compounding in the European non-dietary risk assessment approach.

2.2 Statistical background on compounded conservatism

When deriving default values, there are regulatory concerns associated with the approach taken and the intended meaning of a default value.

The non-dietary exposure calculations used in Europe are simple multiplications of application rates, and percentile default values based on an experimental database. The issue with this approach is that the individual default values are independently derived, and no overall correlation to exposure is considered. This will, by default, result in a serious over-estimation of exposure (and correspondingly risk), as demonstrated in the following taken from the publication of Kluxen et al (Kluxen et al., 2021).

Figure 1 shows the theoretical exposure calculation based on multiplication of three similar randomly-generated log-normally-distributed default values (Figure 1A), which seems to be a common distribution for exposure values (Crowley and Holden, 2019; Korpalski et al., 2005). Multiplying just three individual default mean values substantially overpredicts the mean of a hypothetical exposure distribution and here already relates to the distribution's 80th percentile (Figure 1B). Multiplying higher percentiles, i.e. the 95th, results in the 99.8th percentile of the resampled distribution. Multiplying more default values would additionally increase the overprediction. This demonstrates the in-built conservatism when multiplying deterministic point estimates, which has been investigated in more detail before (Cullen, 1994). It also shows that the mean, or "typical value" of a normally distributed measure, is conservative when several means are multiplied. An average value also captures variation of the exposure, with higher and lower exposures regressing to an average exposure dose.

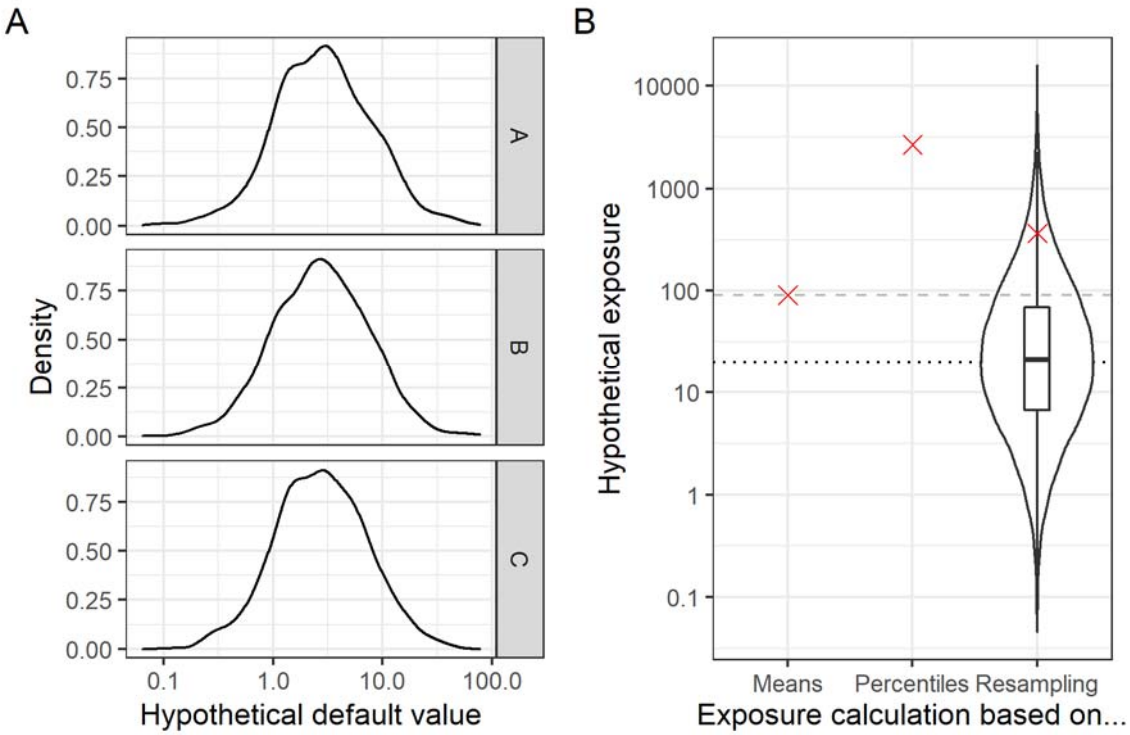


Figure 1: Hypothetical exposure assessment using three default values from a log-normally distributed population with a mean of 1 (which corresponds to Euler's number e) and a standard deviation of 1 on log-scale (n = 1000). (A) shows the individual distributions for the hypothetical default values. (B) shows the results from a hypothetical exposure calculation (Exposure = A × B × C)

2.3 Industry position on included conservatism in EFSA guidance derived dermal absorption estimates in the context of non-dietary risk assessment

The EFSA guidance on dermal absorption (EFSA et al., 2017) already covers several such high percentile estimates which contribute to the compounded overprediction.

2.3.1 Included conservatism in EFSA guidance derived default values

The database that was used by EFSA to derive the default values is publicly available under Human in vitro dermal absorption PPPs dataset | Zenodo includes studies with different exposure durations. While the CLE provided database subset only covered studies that apply to the EFSA guidance recommendation that the exposure period should cover a work-day (i.e. 6-10 hours), the subset provided by the German authority BfR also included a substantial set of 61 studies with an exposure duration of 24 hours. As the cumulative absorption increases with exposure duration this subset drives the database to higher absorption values leading to higher percentile estimates.

Further, the statistics applied for derivation of the EFSA default is based on the upper 95th confidence limit of the random effects logit regression model applying a 95th percentile of variability (see Appendix B, in particular Table B.10 of the EFSA guidance).

2.3.2 Included conservatism in EFSA dermal absorption guidance applied study interpretation

With regard to study interpretation, several factors contribute to overall high percentile of dermal absorption estimates based on (EFSA et al., 2017) criteria although they cannot always be numerically captured.

In general, it should be acknowledged that dermal absorption estimates derived from the *in vitro* penetration studies through human skin disregard any ADME effects that can lower the internal systemic concentration cumulating over 24 hours. Standard assays conducted according to OECD TG 428 consider a 14-18-hour follow-up observation period after a 6-10-hour exposure period. Hence, the dermal absorption estimate from such studies assumes cumulative 24-hour exposure uptake. Just using absorption kinetics thus overestimates internal exposure by default, since the exposure model assumes that total daily external exposure starts at t=0 of the exposure scenario. The cumulative dermal absorption value assumes that everything that actually penetrates only after 24 hours would penetrate at t=0, i.e. at initial exposure. Hence, the typical lag-phase and chronologically increasing absorption are ignored. Also, metabolic detoxification and clearance by excretion are not taken into account. All these factors decrease the overall area under the internal exposure over time curve see extracted Figure 2A of Kluxen et al 2021 (Kluxen et al., 2021). Thus, in reality only a fraction of the internal exposure dose is available at any given time point, as internal exposure is dynamic.

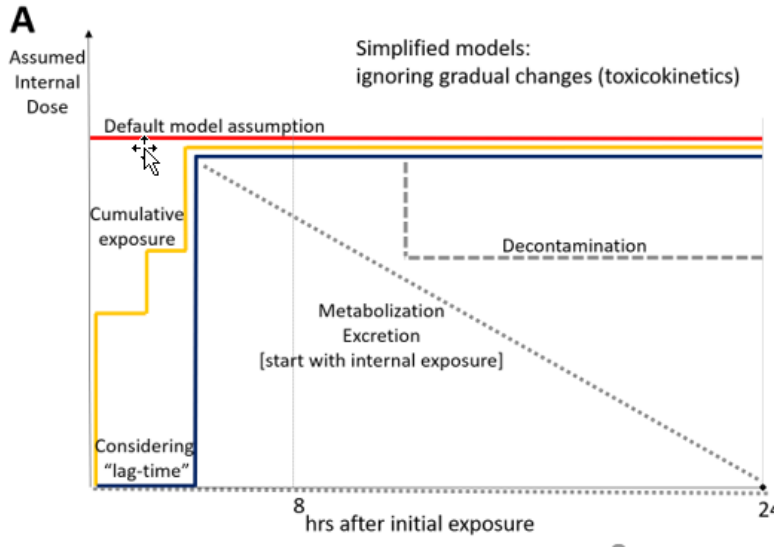


Figure 2 A) Conceptual European exposure model assumptions on dermal exposure in the context of risk assessment. The default model maximizes internal exposure. Plotted is the internal dose after initial exposure against the time after multiple exposure events within 8 hours over 24 hours in total. The default model assumes full work-day exposure at the time of first exposure. Cumulative exposure will, however, only happen over time, either by multiple exposure events or due to a lag-time of diffusion/absorption through the skin (here symbolized by a 4-hour lag and a single exposure event at 4 hours). Internal dose is further affected by ADME/toxicokinetics and decontamination procedures, which is indicated by the dotted and dashed grey lines in the plot, but actually results in gradual/dynamic changes of the internal dose, which is ignored here. It is obvious that the models result in vastly different internal exposures. Usually only the default model is used in pesticide risk assessment in Europe. Dermal absorption studies often report a certain lag-time until exposure of the systemic compartment surrogate, such a lag-time also leads to reduced internal exposure estimates.

One further aspect included is the addition of skin residues determined after the 24-hour study duration to the absorbed dose. The reasoning is that it could potentially penetrate later but it ignores the fact that risk assessment is conducted in comparison to 24-hour based reference values. One of the major changes in the original EFSA dermal absorption guidance (EFSA, 2012) and its revision (EFSA et al., 2017) was to consider also residues in the *stratum cornea* to contribute to systemic exposures, based on kinetic parameters, even if the residue did not penetrate into the systemic compartment surrogate "receptor fluid" within 24 hours. The argument is curious because it is used in conjunction with cumulative absorption, where such temporal/kinetic considerations are ignored.

Therefore, compounds that do not penetrate efficiently but remain in the skin are disproportionally penalized with overpredicted 24-hour relative dermal absorption values. For low absorption compounds these added skin residues can easily end up in a more than 2 to 10 fold or even more than 10-fold increase of the estimated absorption presented in Figure 3 below as so-called additional skin depot safety factor.

While human data shows that systemic exposure correlates best with the *in vitro* receptor fluid values (Lehman et al., 2011), this did not affect the approach for deriving potentially more relevant dermal

absorption values. Hence, it would make sense to discuss within the regulatory community how this assumption can be countered by data, even if the *a priori* assumption is implausible with respect to the risk assessment framework.

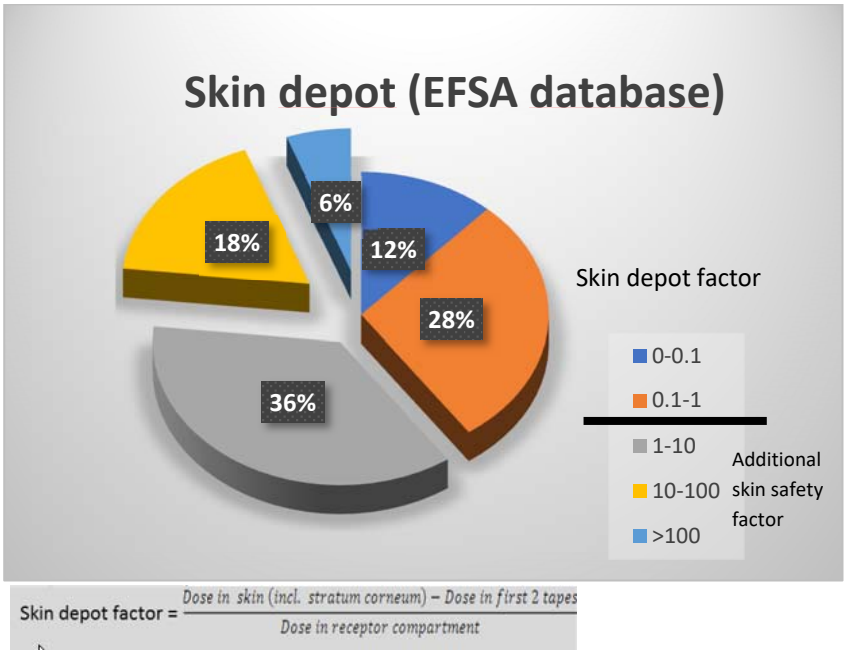


Figure 3: Added safety factor by considering skin residues as absorbed.

From the statistical perspective there is another level of conservatism included in the EFSA guidance study interpretation accounting for study variability. In contrast to the evaluation of ADME studies, EFSA (2012) introduced secondary evaluation criteria to assess specifically dermal absorption studies. If the variability in the results, measured by standard deviation, for relative absorption, which is compounded by adding various fractions of residues recovered in the assays (*stratum corneum*, remaining skin, receptor fluid), exceeds a predefined threshold of 25% of the mean absorption, the standard deviation is added to the mean to derive the dermal absorption estimate. However, this procedure disconnects the estimate from the applied dose and other parameters measured in the study, e.g. washed-off fraction. As both mean and standard deviation are biased by extreme values in either direction, but this bias is only accounted for in one direction in this process, one may end up with grossly overpredicted absorption estimates. Especially for low absorption compounds, single high values may increase the standard deviation to be higher than the mean value (for examples detailing this consideration please refer to Kluxen et al. (2021)). While the reasoning in the dermal absorption guidance revision of 2017 (EFSA et al., 2017) is given as a refined estimation based on the amount of data (addition of standard deviation multiplied by a number of replicate dependent multiplication factor), the 2012 guidance argues that studies with increased variation may be unreliable; “If there is significant

variation between replicates consideration should be given to using a value other than the mean or rejecting the study entirely", which conflicts with OECD TG 428 (OECD, 2004).

It needs to be noted that the approach does not "take account of variation" but specifically increases dermal absorption estimates due to variation. In reality, variation, especially when skin donor-driven, means that the dermal absorption value may be underpredicted for some but overpredicted for other individuals, but only if other factors driving dermal absorption are ignored. Overall, it may be discussed whether mean and standard deviation represent the dermal absorption data well at all. According to EFSA et al. (2017) they do not (see Appendix B in the guidance document) -- but are still recommended to be used. Especially for compounds with predominantly low absorption other measures, such as the geometric mean, may be more appropriate. For further illustration please refer to Kluxen et al. (2021). It should further be noted that his approach is unique in assessment of study values, and thus different to use of other ADME parameters like e.g. oral bioavailability

There are additional factors that may contribute to the compounded overprediction in dermal absorption study interpretation according to EFSA guidance which are detailed in Kluxen et al. (2021) as well.

3 DEFAULT VALUES

3.1 Background on default values proposed by EFSA

In 2012, EFSA (EFSA, 2012) gave guidance on how to conduct studies and how to assess dermal absorption in relation to plant protection product risk assessment. In this context, data-based default values were introduced, which can be used if no specific dermal absorption data are available. The basis for the derived default values was limited but diverse (EFSA, 2011) and reviewed in Aggarwal 2014 (Aggarwal et al., 2014) comprising about sixty data points from *in vivo* rat, *in vitro* rat, *in vitro* human or triple pack approach values as well as expert judgement values. Therefore, the CropLife Europe (CLE) the former European Crop Protection Association (ECPA) collected and analyzed an extensive data set (*CLE data*), to systematically investigate whether lower dermal absorption default values are warranted when studies of homogenous and OECD and GLP-compliant quality are assessed. CLE published the analysis including a proposal for new default values based on empirical percentiles (Table 1) in two documents (Aggarwal et al., 2014; Aggarwal et al., 2015). This subsequently triggered the EU commission to request EFSA to review the existing dermal absorption guidance based on the extended database or to develop a new guidance when required. EFSA analyzed CLE's data and merged it with a previously unpublished dermal absorption data set collected by the German Federal Institute for Risk Assessment, BfR (*BfR data*), resulting in a *joint data* set.

Table 1: Default values as proposed by CLE based on non-parametric percentiles

	Based on 95th percentile of the CLE database	
Concentration category	Physical state of formulation	Value (%absorption)
Concentrate	Solid	2
	Liquid	6
Spray dilute	All	30

EFSA in their updated guidance of 2017 (EFSA et al., 2017) (guidance and commenting published on EFSA webpage on June 30th, 2017; https://www.efsa.europa.eu/de/efsajournal/pub/4873) combined database publicly available under Human in vitro dermal absorption PPPs dataset | Zenodo also revised the default values (Table 2) based on a statistical modelling procedure. By doing so EFSA introduced new conservatisms in assessing dermal absorption studies, on which CLE commented extensively. Here, several issues are apparent when the applied statistical methods are reviewed, which have been communicated in detail to EFSA, but have not been resolved in the final version.

3.2 Criticism on the EFSA guidance approach to derive default values

CLE is of the opinion that if a modelling approach should be followed to derive values a statistical consensus has to be established in first place. The current methodology applied by EFSA is questioned by an independent academic assessment of the published database.

The statistical approach chosen by EFSA is presented in Table 2 in comparison to an alternate statistical approach.

Table 2: Default values based on different modelling approaches on combined BfR and CLE data

		EFSA guidance 2017	Independent statistician
		Modelling by random effect logit transformation of data	Modelling by most likely transformation (mlt) of data
Formulation type		Value (% absorption)	
Organic solvent based or other	Concentrate	25	16
	Spray dilute	70	42

Water based or solid	Concentrate	10	13
	Spray dilute	50	29

There are several issues:

a) The overall database (CLE and BfR datasets combined) is heterogenous with regard to study design in relation the use condition of plant protection products. CLE data alone comprises only OECD 428 compliant studies with plant protection products and appropriate exposure duration up to 12 hours.

b) The database evaluated shows a very left skewed distribution. Furthermore, the data have a very complex hierarchical data structure. Consequently, modelling of a default value out of such a database requires a dedicated statistical methodology which is currently not available.

c) The EFSA chosen modelling approach (Table 2) is one out of several options to handle this complex data but does not fit as confirmed by EFSA itself in their guidance.

d) Other possible approaches which may be more suitable for the database where not considered. Each approach based on the underlying statistical assumptions will result in different proposed default values (as illustrated in Table 2) when comparing the EFSA approach to an alternative approach proposed by an independent statistician. Therefore, a consensus on the most appropriate modelling procedures has to be found by experts. This is a common procedure in other regulatory areas e.g. when evaluating clinical studies for medical product approval.

e) The option proposed by CLE to apply percentiles is an established non-parametric method that is as well used for regulatory purposes e.g. in non-dietary risk assessment. It is a reproducible and understandable approach that can be easily applied and checked by independent authorities. The empirical percentiles derived by EFSA in their analysis based on the combined dataset in the Appendix B (page 51) of the 2017's guidance match closely to the empirical percentiles presented by CLE.

f) As detailed above the combination of the CLE and the BfR database and by this the inclusion of studies with extended exposure duration of 24 hours drove the distribution towards the higher range distribution which of course also affect the statistical outcome applied.

3.3 Industry position on default values proposed by EFSA

The EFSA guidance proposal as published in June 2017 is hampered by the appropriateness of the chosen statistical approach that led to the default value derivation. It is the CLE position that a statistical modelling approach should not be used to derive default values unless a consensus has been obtained by a statisticians' expert panel. Instead the non-parametrical percentiles proposed by CLE provide a suitable approach to derive default values for dermal absorption in the non-dietary risk assessment.

4 BRIDGING APPROACH

4.1 Background of the EFSA guidance bridging approach

The bridging approach as applied in the EFSA guidance with its strict composition criteria is based on the EU guidance document for significant and insignificant changes of composition in plant protection products (EC SANCO, 2012) which details which information is needed for significant changes in composition to allow an appropriate hazard assessment of the product. This criteria were one-to-one transferred into the EFSA guidance on dermal absorption (EFSA et al., 2017). Within the guidance some further explanations and possible deviations are mentioned which in theory would allow a bridging from one to the other product. Within the EFSA guidance on dermal absorption, these criteria as applicable for co-formulants where further amended by criteria for changes in active ingredient content as taken from the FAO and WHO specifications for pesticides (WHO, 2016). These criteria are applicable for both the change in content for the active ingredient of interest as well as changing of content of mixing partner active ingredients including addition of new mixing partner or complete removal of mixing partners.

A further bridging approach that might, according to EFSA guidance 2017, be applicable in exceptional cases is the so-called multi-to-one approach. This considers the bridging opportunity to have a range of studies conducted with the same active ingredient but applied in a variety of pesticidal product and to use this study range in combination with the knowledge on product type and composition to derive a reasonable worst-case estimate for the not tested product.

4.2 Criticism on the EFSA guidance bridging approach

Up to the implementation of these criteria by the EFSA guidance the bridging approaches were done based on expert judgement applying a weight-of-evidence approach. For instance, data obtained for an organic solvent-based product were used to cover water-based products for which a lower relative absorption is expected due to the missing organic solvent that increased solubility of the active ingredient of concern. As dermal penetration is a passive diffusion process the level of solubilized active ingredient is key for the penetration. Further, it should be considered that, from a formulation development perspective, organic solvents and thus development of organic solvent-based formulation types is only considered when water solubility in the spray solution is limiting the technical applicability or biological effectivity.

For the active ingredient under consideration a change in content outside of the triggers set in the guidance can be covered by the results for the tested product e.g. by considering the tested product as worst-case when the content in the tested product is lower than in the product to be assessed or by applying pro-rata approaches when content in the tested product is higher than in the product to be assessed. This option was however, not considered when developing the EFSA guidance.

Moreover, the impact of mixing partner active ingredients may be of limited importance for the skin barrier penetration of the active ingredient of concern. If an interaction of active ingredients would be anticipated and determined in the biological activity testing which also requires passage of biological barriers this would

possibly prevent any further development of the product. Both from the knowledge on product composition and the overall dataset available for physico-chemical properties, biological activities and product related hazard-data it would be possible to develop a weight-of-evidence bridging approach by expert judgement.

Instead, when considering the above detailed stringent criteria, it becomes obvious that for any new formulation the hurdle is easily hit not allowing bridging one-to-one.

The remaining multiple-to-one approach which may be acceptable in exceptional cases will give advantage to big globally playing companies that already have sufficiently large databases in hand as opposed to the smaller or locally based entities which generally will have smaller portfolios and will likely never get a sufficiently large database to apply this approach.

4.3 Industry position on the applicability of the EFSA guidance bridging approaches

Based on the arguments provided above an applicability of bridging for pesticidal product registration in Brazil is rarely met, which in turn will require each and every product that fails in the tier 1 risk assessment to be tested for dermal absorption. Again, the lack of opportunities to conduct such tests in Brazil will provide a significant hurdle for smaller local-based companies.

5 STUDY QUALITY CRITERIA NOT IN LINE WITH OECD TEST GUIDELINE – ACCEPTABLE RECOVERY RANGE AND CORRECTION MEASURES FOR NOT ACHIEVING THE RECOMMENDED LOWER RECOVERY BOUNDARY OF THE EFSA GUIDANCE

The EFSA approach on considering dermal absorption studies with low mass balance and specifically studies that show low dermal absorption estimates was extensively reviewed by Kluxen et al. (2019).

5.1 Background of the EFSA guidance recovery range

EFSA guidance 2017 suggests changing OECD TG 428 (OECD, 2004) recovery ranges from 90-110% to 95-105%, due to scientific progress in analytics and as laboratories could often achieve revised ranges.

5.2 Criticism on the EFSA guidance recovery range

The EFSA guidance-introduced recovery range was not data-driven or indeed, driven by better analytical methods as claimed by EFSA guidance. Details are given in Kluxen et al. 2019.

EFSA argued that the revised recovery ranges would be regularly achieved due to “modern analytical and pipetting technique”. This was most likely driven by a single European commercial laboratory, that claimed to often achieve the revised mass balance criteria but only by driving the measured range to a higher exceedance of the upper boundary of 105% (Heylings, 2020; Kluxen et al., 2020) . This disregards that other laboratories might not achieve the mass balance criteria, and that there are substances where the criteria cannot be achieved, see e.g. (Grégoire et al., 2019). Both are worrying. The EFSA approach also ignored whether there is actually a need to refine the ranges, i.e. whether the dermal absorption estimates from cells that do not achieve the recovery ranges are underpredicted.

An analysis of the EFSA dataset shows that recovery ranges of 90-110% are supported based on the available data; the range corresponds to the 5% and 95% percentile of the EFSA dataset. A decrease of the range to 95-105% could result in a rejection of a third of tested dermal absorption cells and the range corresponds to approximately the 25-75% percentile of studies in the EFSA database.

Heylings (2020) recently argued in a non-peer reviewed letter to the editor that laboratories would be able to often achieve the revised recovery ranges and showed a dataset to support the claim. However, while the data showed that the lower limit is indeed more often achieved than in the EFSA database, the publication missed that the presented data exceeded the required EFSA guidance range more often. This may be related to systematic overdosing. Hence, in total the data presented in Heylings (2020) supports also OECD TG 428 (OECD, 2004) recovery ranges, as the data in Heylings (2020) is as often outside the recovery range as data in the EFSA database. This was discussed in Kluxen et al. (2020).

5.3 Criticism on the EFSA guidance corrections measures

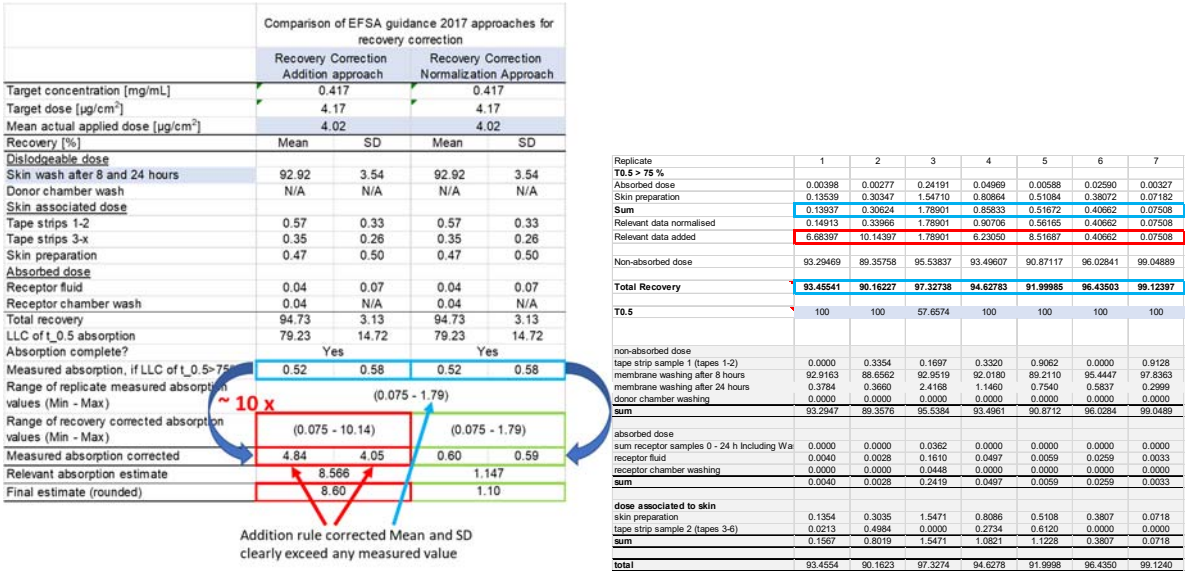
The key issue with the revised recovery range and the addition of material for cells with low dermal absorption values <5%, when the recovery is <95%, is that specifically increases the dermal absorption of low exposure and thus low risk products and, worse, thus biases the assessment to specifically failing low risk products.

In studies where the EFSA guidance recovery range criteria are not met the guidance gives two options to account for.

The guidance gives either the option to remove the low recovery estimates from the number of valid replicates. This may subsequently lead to an increase in the multiple application factor being reversely dependent on the number of replicates or even lead to a study repeat due to insufficient number of valid replicates.

Alternatively, secondary correction measures for the not recovered material (normalization or addition approach) are introduced in the guidance to correct the replicates not fulfilling the recommended recovery criteria.

Here, criticism particularly refers to the EFSA recommended assessment of low-absorption compounds (<5% absorbed dose before correction), where the EFSA guidance recommends that not recovered material shall be added to the absorbed dose. By this approach not only individual replicate absorption estimates are easily ending up in more than 10-fold higher absorption. In addition, due to the artificial increase of absorption estimate variation of replicates between those that require addition and those that do not require addition this approach not only increases the dose group mean but also the standard-deviation – which based on the EFSA criteria is added to the mean. Both values are significantly driven to the higher end and often even above the range of measured values. An example that illustrates this artificial manipulation of measured data is given in below.



	Comparison of EFSA guidance 2017 approaches for recovery correction			
	Recovery Correction Addition approach		Recovery Correction Normalization Approach	
Target concentration [mg/mL]	0.417		0.417	
Target dose [µg/cm²]	4.17		4.17	
Mean actual applied dose [µg/cm²]	4.02		4.02	
Recovery [%]	Mean	SD	Mean	SD
Dislodgeable dose				
Skin wash after 8 and 24 hours	92.92	3.54	92.92	3.54
Donor chamber wash	N/A	N/A	N/A	N/A
Skin associated dose				
Tape strips 1-2	0.57	0.33	0.57	0.33
Tape strips 3-x	0.35	0.26	0.35	0.26
Skin preparation	0.47	0.50	0.47	0.50
Absorbed dose				
Receptor fluid	0.04	0.07	0.04	0.07
Receptor chamber wash	0.04	N/A	0.04	N/A
Total recovery	94.73	3.13	94.73	3.13
LLC of t_0.5 absorption	79.23	14.72	79.23	14.72
Absorption complete?	Yes		Yes	
Measured absorption, if LLC of t_0.5>75	0.52	0.58	0.52	0.58
Range of replicate measured absorption values (Min - Max)	(0.075 - 1.79)			
Range of recovery corrected absorption values (Min - Max)	(0.075 - 10.14)		(0.075 - 1.79)	
Measured absorption corrected	4.84	4.05	0.60	0.59
Relevant absorption estimate	8.566		1.147	
Final estimate (rounded)	8.60		1.10	

~ 10 x

Addition rule corrected Mean and SD clearly exceed any measured value

Replicate	1	2	3	4	5	6	7
T0.5 > 75 %							
Absorbed dose	0.00398	0.00277	0.24191	0.04969	0.00588	0.02590	0.00327
Skin preparation	0.13539	0.30347	1.54710	0.80864	0.51084	0.38072	0.07182
Sum	0.13937	0.30624	1.78901	0.85833	0.51672	0.40662	0.07508
Relevant data normalised	0.14913	0.33966	1.78901	0.90706	0.56165	0.40662	0.07508
Relevant data added	6.68397	10.14397	1.78901	6.23050	8.51687	0.40662	0.07508
Non-absorbed dose	93.29469	89.35758	95.53837	93.49607	90.87117	96.02841	99.04889
Total Recovery	**93.45541**	**90.16227**	**97.32738**	**94.62783**	**91.99985**	**96.43503**	**99.12397**
T0.5	100	100	57.6574	100	100	100	100
non-absorbed dose							
tape strip sample 1 (tapes 1-2)	0.0000	0.3354	0.1697	0.3320	0.9062	0.0000	0.9128
membrane washing after 8 hours	92.9163	88.6562	92.9519	92.0180	89.2110	95.4447	97.8363
membrane washing after 24 hours	0.3784	0.3660	2.4168	1.1460	0.7540	0.5837	0.2999
donor chamber washing	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
sum	93.2947	89.3576	95.5384	93.4961	90.8712	96.0284	99.0489
absorbed dose							
sum receptor samples 0 - 24 h including Wa	0.0000	0.0000	0.0362	0.0000	0.0000	0.0000	0.0000
receptor fluid	0.0040	0.0028	0.1610	0.0497	0.0059	0.0259	0.0033
receptor chamber washing	0.0000	0.0000	0.0448	0.0000	0.0000	0.0000	0.0000
sum	0.0040	0.0028	0.2419	0.0497	0.0059	0.0259	0.0033
dose associated to skin							
skin preparation	0.1354	0.3035	1.5471	0.8086	0.5108	0.3807	0.0718
tape strip sample 2 (tapes 3-6)	0.0213	0.4984	0.0000	0.2734	0.6120	0.0000	0.0000
sum	0.1567	0.8019	1.5471	1.0821	1.1228	0.3807	0.0718
total	93.4554	90.1623	97.3274	94.6278	91.9998	96.4350	99.1240

Figure 4: Application of the EFSA addition rule for low recovery compound with low absorption, impact on study result interpretation

Kluxen et al. (2019) shows that dermal absorption is not dependent on mass balance, as low recovery cells have similar, or even higher absorption than higher recovery cells. Hence there is no scientific reason to exclude dermal absorption values from low recovery cells or to artificially increase their dermal absorption estimates.

In conclusion the approaches for mass balance correction of EFSA guidance (EFSA et al., 2017) have no scientific basis.

5.4 Industry position on recovery range and corrections measures

OECD test guideline 428 recovery range criteria are supported by the available data and should thus be applicable. While OECD TG recovery ranges assure certain quality criteria, there is no scientific need to increase dermal absorption estimates based on recovery, as this only artificially increases internal dose, with no true associated increased risk and no scientific background.

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