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Assessment of new scientific studies on human *in vitro* dermal absorption

EFSA Working Group on Dermal Absorption

Abstract

This EFSA scientific report describes the results from the evaluation of new human *in vitro* studies on dermal absorption made available by European Crop Protection Association (ECPA) and the German public organisation Bundesinstitut für Risikobewertung (BfR) and their possible impact on the guidance on dermal absorption (EFSA, 2012). A quality check was performed in order to verify if new studies were conducted according to the current regulatory standards and to identify potential deviations from EFSA guidance on dermal absorption. In addition, a plausibility check to validate the correctness of data entry in the datasets from sources (study reports) was undertaken applying a two tiers (I and II) validation protocol. Although a number of deviations from the EFSA guidance on dermal absorption have been identified, the outcome of the evaluation indicates that the new studies comply with the current regulatory standards. EFSA recommendations to address the variability within studies and to improve the consistency of interpretation have not been applied routinely. In addition the datasets as provided to EFSA are not completed, lacking individual data or other information addressing variability. However, the overall conclusion regarding the scientific quality of the provided datasets is that they are consistent and solid and include a relevant number of *in vitro* dermal adsorption studies with human skin. The new data provide sufficient information for the revision of the current guidance or the development a new guidance on dermal absorption. For the exploitation of the new datasets, in the revision of the current guidance or the development of a new guidance on dermal absorption, it is recommended to add the missing information, to compile a comprehensive dataset and to analyse dermal absorption data applying a model-based statistical protocol.

Keywords: dermal absorption, human *in vitro,* pesticides

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Table of contents

Abstract 1
1. Introduction 4
1.1. Background and Terms of Reference as provided by the requestor 4
1.2. Interpretation of the Terms of Reference 4
1.3. Additional information 5
1.3.1. Dermal Absorption and regulatory standards 5
2. Data and Methodologies 5
2.1. Data 5
2.1.1. ECPA dataset/manuscripts 5
2.1.2. BfR dataset 6
2.2. Methodologies 6
2.2.1. ECPA dataset 6
2.2.2. BfR dataset 6
3. Assessment 6
3.1. ECPA dataset 6
3.2. BfR dataset 8
3.3. Statistical considerations 9
3.3.1. ECPA manuscripts 9
3.3.2. ECPA dataset 9
4. Conclusions 10
5. Recommendations 11
References 12
Abbreviations 13

1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

A "Scientific Opinion on Guidance on Dermal Absorption" was issued by the EFSA Panel on Plant Protection Products and their Residues in April 2012 (EFSA, 2012). During the development of the guidance, the PPR) Panel had a consultation with the Standing Committee on the Food Chain and Animal Health (SCoFCAH) on risk management issues of the guidance. Amongst the issues considered was the default values to be used when data is lacking, the value of +/- 25 w/w content of types of co-formulants for read across between formulations. The proposed values were confirmed. Subsequently the SCoFCAH took note of the guidance and it entered into force in the EU by December 2012.

In April 2013, the European Crop Protection Association (ECPA) indicated to the Commission and to EFSA that the Guidance was in their opinion excessively conservative and that it did not take into account new relevant scientific studies. In particular, ECPA referred to a manuscript submitted to a scientific journal for publication where several amendments to the EFSA Guidance on dermal absorption were proposed (Aggarwal et al., 2014).

EFSA accepted to consider the new data, provided that access to the original study reports referred to in the scientific publication was ensured. Agreement was reached with ECPA that confidentiality about the original study reports would be respected within the limits of Reg. 1049/2001[1] on EU rules for access to documents. The study reports were submitted to EFSA for assessment in June 2014.

In September 2014, ECPA indicated that an additional 170 *in vitro* dermal absorption studies with human skin conducted during the period 2012-2014 had been added to the existing database of approximately 190 studies conducted during the period up until 2012. The additional studies were submitted to EFSA in October 2014, together with a manuscript (Aggarwal et al., 2015) submitted to a scientific journal for publication where those studies are analysed.

The Commission asks EFSA to assess in the first instance the scientific quality of all the new studies available and to compile a comprehensive database of the dermal absorption studies. This should include all studies in line with the regulatory standards for this type of experiments and made available by the industry as well as by public institutions.

Subsequently, based on the evaluation of the studies, the Commission asks EFSA to consider whether the current guidance on dermal absorption shall be revised or, if more appropriate, a new guidance developed.

1.2. Interpretation of the Terms of Reference

After consultation of Members States by the Commission, Germany informed EFSA that a structured database containing a large dataset on human *in vitro* dermal absorption has been compiled developed by Bundesinstitut für Risikobewertung (BfR). Data have been extracted from original study reports of Plant Protection Products (PPP's) submissions and the database includes also rat *in vivo*/*in vitro* dermal absorption data.

The objective of this scientific report is to assess the scientific quality and relevance of the dermal absorption studies made available by the industry and by public institutions. On the basis of recommendations formulated in the current report, it will be considered whether the current guidance on dermal absorption should be revised or, if more appropriate, a new guidance would be required. A public consultation will be conducted before formal approval by EFSA and publication on the EFSA website.

A comprehensive dataset will be developed containing the information provided by ECPA and BfR.

[1] Regulation (EC) No 1049/2001 on Access to European Parliament, Council and Commission documents

1.3. Additional information

1.3.1. Dermal Absorption and regulatory standards

The estimation of dermal absorption is a critical element in the risk assessment of plant protection products (PPPs) for operators, workers, bystanders and residents. Authorisation of substances or products produced or placed on the market according to Regulation (EC) 1107/2009[2] is possible if they do not have any harmful effect on human health.

Dermal absorption guidance was developed to assist risk assessors, notifiers, users of test facilities and Member State authorities on critical aspects related to the setting of dermal absorption values to be used in risk assessments of PPPs. The criteria proposed in the guidance document are based on the EFSA opinion on dermal absorption (EFSA, 2011), that provides relevant data, evaluations and references.

The details of *in vivo/in vitro* dermal absorption experimental design and data interpretation are described in the internationally agreed test guidelines and guidance documents (OECD 2004a; OECD 2004b; OECD 2004c; OECD 2011). These guidance documents are designed to cover a range of chemicals and do not focus specifically on the assessment of PPPs. However, the EFSA guidance provides recommendations specific to performing and interpreting dermal absorption studies with PPPs. EFSA is aware that its guidance has been adopted also for assessment of other groups of chemicals, namely biocides, supplementing the OECD documents (ECHA, 2013). The guidance also covers scenarios where there are no data on dermal absorption for the PPP under evaluation, including the use of default values, and data from a similar formulation.

Default values recommended in the guidance are based on the analysis of available data on dermal absorption for PPPs supported by data on products with other uses (CRD, 2010; EFSA, 2011). Values were agreed upon from a range of pesticides formulations and their dilutions (63 active substances) tested *in vivo* (rat) or *in vitro* (rat, human). The default values were based on upper extremes of the dataset. However, the evaluated studies had not been performed according to standard protocols nor have they been evaluated against standard criteria.

Analysis of the results indicated that *in vitro* studies with human skin can be used as stand-alone tests to derive dermal absorption values in humans. However, the available data were considered to be very limited to draw any conclusions on the potential to extrapolate between formulation types, mainly because few active substances were tested in different formulations. Nevertheless, it was still recommended for example, based on the CLP regulation (EC No 1272/2008) that if the content of co-formulant (e.g. solvent, stabiliser, surfactant, detergent, emulsifier, adhesive, antifreezing substance) is within +/- 25% w/w of that in the reference formulation, the data from the reference formulation could be used for the estimation of dermal absorption for both the formulation and spray dilutions. Other considerations were also proposed to be taken into account when 'bridging' to a reference formulation.

2. Data and Methodologies

2.1. Data

2.1.1. ECPA dataset/manuscripts

ECPA pooled data from 295 Good Laboratory Practice (GLP) and OECD 428-compliant *in vitro* human dermal absorption studies (Aggarwal et al., 2014 and 2015). A dataset was created covering physico-chemical properties for 152 agrochemical active substances (a.s.), 19 formulation types, tested at

[2] EU, 2009. Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EC and 91/414/EEC. Official Journal L 309, 1-50. 24 November 2009

different concentrations to provide 762 records[3] in total. Exposure and sampling time were 6-10 h and 24 h, respectively.

2.1.2. BfR dataset

BfR collected data from 316 original study reports on *in vitro* and *in vivo* dermal absorption studies using rat or human skin in a database. Curated data was obtained for 122 different a.s., 23 formulation types, tested at different concentrations. At the time of evaluation, the database contained 679 records from rat *in vivo*, 384 records from rat *in vitro* and 490 records from *in vitro* human skin studies effectively compliant with OECD TG 427and 428. Studies were either performed under GLP or in compliance with GLP criteria. To create the BfR dataset with human *in vitro* data, 480 records from *in vitro* studies on human skin were extracted from the database, exposure time was 6-24 h, and the duration of sampling period was 24 h. A manuscript describing the dataset is in preparation.

2.2. Methodologies

2.2.1. ECPA dataset

A quality check was performed on dermal absorption studies in order to verify if studies were conducted according to GLP, in compliance with OECD test guideline 428 and to identify deviations from EFSA guidance. A plausibility check to validate the correctness of data entry in the dataset from sources (study reports) was undertaken applying a validation protocol at two tiers (I and tier II). In tier I full source data verification (all parameters) was undertaken for a limited number (17[4]) of studies, randomly selected. Under tier II selected key parameters were checked for 28[5] study reports. Dermal absorption parameters included in the quality check were: mean and standard deviation (SD) of amount in receptor fluid, mean and SD of amount in skin, mean and SD of amount in tape strips, mean and SD of overall recovery.

In both tier I and II plausibility and completeness of dataset entries[6] for the parameters of selected studies were checked versus data in the respective study reports (sources).

2.2.2. BfR dataset

A quality check in order to verify if studies were conducted according to GLP, in compliance with OECD test guideline 428 and to collect deviations from EFSA guidance was performed during data entry by BfR. In addition, a validation protocol at two tiers (I and II) was applied post-hoc on the data entered into the database. In tier I a full source data verification of all parameters was undertaken for a limited number of randomly selected study reports (5)[7]. In tier II selected key parameters were checked for 25 study reports corresponding to the same number of records exported into the dataset for use by EFSA. The following absorption parameters were included: mean and SD of amount in receptor fluid, mean and SD of amount in skin, mean and SD of amount in tape strips, mean and SD of overall recovery. In both tier I and II plausibility and completeness of database entries for the parameters of selected studies were checked versus data in the related study reports (sources) in order to verify missing data (e.g. empty fields) and errors.

3. Assessment

3.1. ECPA dataset

The quality check and assessment demonstrated that:

[3] Rows in the dataset with structured dermal absorption data from a.s. concentration tested in the experiment.
[4] Corresponding to 39 records.
[5] Corresponding to 71 records.
[6] Field entries in the dataset are cells with information/numerical values.
[7] Corresponding to 20 records exported from the BfR database into the dataset used by the EFSA WG.

1. Individual values from each replicate of the dermal absorption human *in vitro* studies are not reported in the dataset. For the (762) records mean values and standard deviations of dermal absorption parameters are provided at different levels of completeness, some fields of the records being empty. Data on variability among replicates (i.e. SDs) for total absorption (i.e. directly absorbed dose + whole skin residue excluding amount in tape strips 1/2) is not included in the dataset.

2. EFSA guidance recommendations for sample numbers (at least 4 donors and 8 replicates) in the *in vitro* experiment are not followed; on the other hand, minimum required replicates (4, irrespective of donors) as from OECD test guideline 428 were included in the studies. From the analysis of study reports replicates distribution over the donors is variable and in some cases this information is not reported.

3. Dermal absorption parameters calculation can differ among study reports (e.g. whole skin residue[8], directly absorbed dose[9], non-absorbed dose[10]) and in some cases single replicates are excluded without any justified reason in the study report (although required by the EFSA guidance). Also, in many cases the absorption values at half study duration (t0.5) that were not included in the dataset are not tabulated in the study reports being graphically reported only.

4. Dermal absorption was calculated as described in the EFSA guidance. Residues in tape strips 1 and 2 were excluded from the calculation of absorbed dose, information on the absorption at t0.5 not considered. It is noted that the OECD guidance document (OECD, 2004c) indicates that residue in tape stripped skin need to be included in the absorbed fraction unless there is a strong justification to support the use of the receptor fluid value alone. Often the time course of absorption yields valuable information for the interpretation of the study results, e.g. with respect to the importance of a possible skin reservoir. Therefore, ideally time course information should be included in the data set.

5. Adjustments for low recoveries (when mean <95%) and for high variability between replicates (when SDs ≥25% of the mean) as required by the EFSA guidance, were not applied. However, in 635 of 762 records (83.3%) recoveries were within EFSA criteria (≥95%) and in 733 of 762 records (96.2%) recoveries are within OECD 428 criteria (90-110% range).

6. Missing data[11] (empty fields) in the dataset are 456 of 762 records (60%), and in particular variability (SD) is not reported for 424 of 762 records (56%).

7. The tier I of the quality check showed that 1212 of 1287[12] (94%) of field entries were identical between the dataset and the original source. Mostly, deviations were given by missing values in the dataset (approximately 5%). True entry mistakes were rare with 11 cases (0.9%), 4 of them were small (<15%). Tier II examining key dermal absorption parameters for a larger number of studies showed that 924 of 1065[13] (87%) of field entries were numerically identical to the original source. Most deviations were given by missing values in the dataset (7%). True entry mistakes were found in 67 cases (6%) and 36 of them were small (<15%).

[8] Whole skin residue is given in the experiment by stratum corneum residue (amount in tape strips)+ skin membrane residue (after tape stripping). In some studies it was calculated as epidermis + dermis, in others as tape epidermis + remaining skin + stratum corneum.

[9] Directly absorbed dose is given in the experiment by receptor fluid + receptor chamber wash. In some studies it was calculated as receptor fluid + receptor chamber wash + wash out, in others by perfusates.

[10] Non-absorbed dose is given in the experiment by donor chamber wash + skin wash at the end of the exposure. In some studies it was defined as 'skin excess', in other calculated as skin wash 6h+ tissue swab 6h + pipette tips 6h + skin wash 24h+ tissue swab 24h+ pipette tips 24h + donor cell wash. Other cases have been captured.

[11] For one or more dermal absorption information requested in Table 1 of the EFSA guidance on dermal absorption (to be submitted in the Draft Assessment Reports and Registration Reports).

[12] 33 parameters checked for 39 records (17 studies).

[13] 15 parameters checked for 71 records (28 studies).

3.2. BfR dataset

The quality check and assessment demonstrated that:

1. Individual values (replicates) from dermal absorption human *in vitro* studies are not reported in the dataset exported from the BfR database. For all (480) records mean values, standard deviations and group sizes of dermal absorption parameters are provided. Data on variability among replicates (i.e. SDs) for total absorption (i.e. directly absorbed dose + whole skin residue excluding amount in tape strips 1/2) is included for 424 of 480 records (88%) in the dataset.

2. EFSA guidance recommendations for sample numbers (at least 4 donors and 8 replicates) in the *in vitro* experiment are not followed; on the other hand, minimum required replicates (4, irrespective of donors) as from OECD test guideline 428 were included in the studies. Replicates distribution over the donors was not analysed.

3. Absorption values at half study duration (t0.5) were not included in the dataset. Often the time course of absorption yields valuable information for the interpretation of the study results, e.g. with respect to the importance of a possible skin reservoir. Therefore, ideally time course information should be included in the dataset.

4. Residues in tape strips 1 and 2 were reported in the dataset when available in the study reports and can thus be excluded from the calculation of absorbed dose.

5. Adjustments for low recoveries (when mean <95%) and for high variability between replicates (when SDs ≥25% of the mean) required by the EFSA guidance were not applied. However, information on SD is available in the dataset[14] and can be taken into consideration for further analysis.

6. The high level of mean recovery as recommended by EFSA (2012) of 95% was not achieved in a large number of studies. Of all valid i*n vitro* studies on human skin, 327 of 480 records (68%) showed a recovery of ≥95%, and for 398 of 480 records (83%) recoveries are within OECD 428 criteria (90-110% range).

7. Intra-assay variability is considered high by EFSA (2012) when the relative standard deviation (RSD) of the absorbed fraction (i.e. amount in receptor fluid + receptor wash + whole skin residue excluding tape strips 1/2) reaches 25%. This was observed for 334 of 424 records (79%) of human *in vitro* studies for which SD was reported in the dataset. On average, the RSD was 47% for evaluated human *in vitro* studies.

8. Tier I of the quality check showed that 1117 of 1164[15] (96%) of field entries were identical between the database and the original source. Mostly, relative deviations of numerical values between the database and study report were small (<15%) and resulted, for example, from recalculation of group means and SD from individual data during data entry rather than use of tabulated means or inclusion of extreme values that were considered as outliers without adequate justification in the study report. True entry mistakes (e.g. typing errors) were rare with 9 cases (0.8%). Tier II examining key parameters for a larger number of studies showed that 194 of 275[16] (97.8%) of dataset entries were numerically identical to the original source. In 67% of the inaccurate entries, deviations were small (<15%), likely resulting from rounding/re-calculation of group means/SDs.

[14] For SD, the information is currently limited to 88% of records.
[15] 29 record-specific and 49 shared parameters (relating to more than one record) checked for 20 records (5 studies). Checked database field entries (1164) correspond to 1560 entries in the dataset generated by export from the database.
[16] 8 absorption parameters and 3 further physicochemical parameters for 25 records (25 studies).

3.3. Statistical considerations

3.3.1. ECPA manuscripts

The statistical analysis carried out by ECPA (Aggarwal et al., 2014, 2015) proceeded sequentially. The first step of this analysis attempted to relate dermal absorption to the physical form (solid/liquid). This step consisted of creating a boxplot representation of dermal absorption values for solids and liquids separately. The second step consisted in attempting to relate dermal absorption values to the concentration of active substance. This was done by providing boxplot representations of dermal absorption values for two classes of concentrations (<5% and ≥5%) of active substance. In a third step, the analysis attempted to relate dermal absorption to the formulation type. Boxplots of dermal absorption values were given for up to nine formulation types and then for formulation types aggregated into three types only. The fourth step consisted of fitting a non-linear regression model (fifth order polynomial) relating dermal absorption to dilution factor. In a last step, the analysis attempted to relate dermal absorption to physico-chemical properties, i.e. MW and logPow. This was done by a providing a scatter-plot representations of dermal absorption against MW and then of dermal absorption against logPow.

The ECPA analysis constitutes a useful descriptive step. However, it overlooks a number of statistical pitfalls which could lead to inappropriate conclusions:

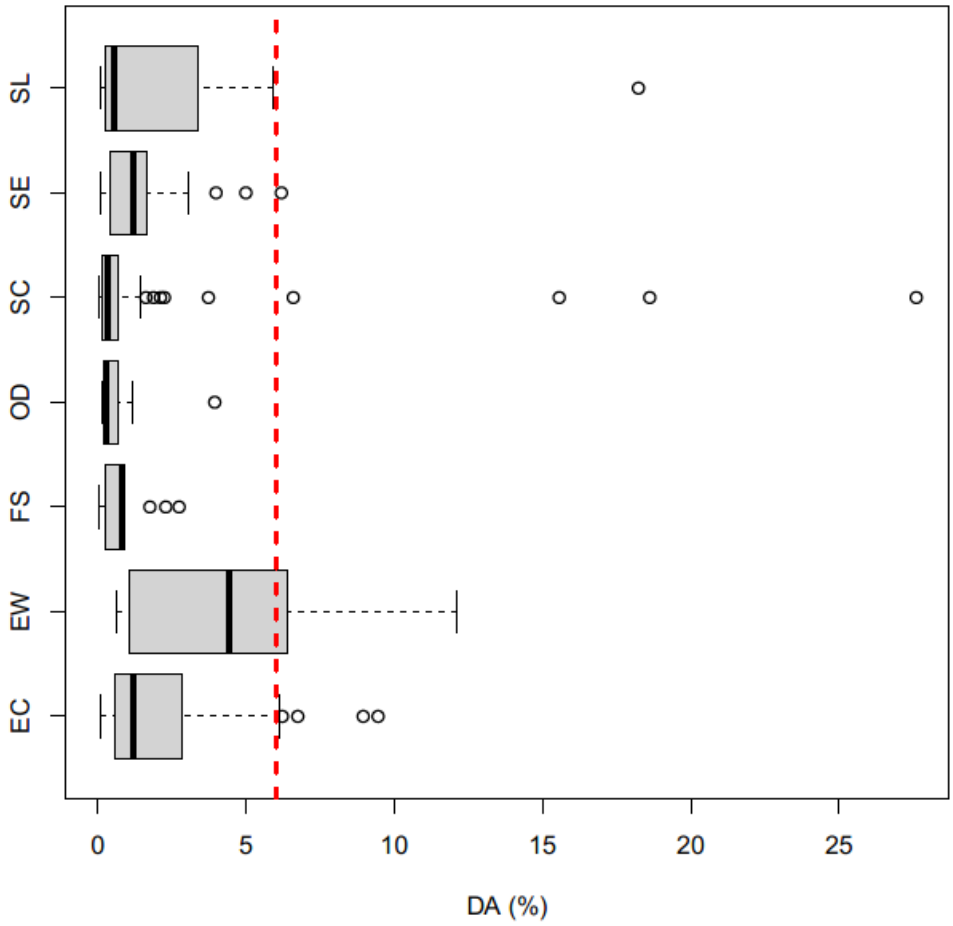
- While this approach acknowledges that each factor considered may have an effect on dermal absorption, these potential effects are assessed one by one. This approach implicitly assumes that the effect of a factor is independent of the variation of other factors. This is a strong assumption that has not been justified. For example, one can imagine that the physical form and the concentration both have an effect on dermal absorption but that the effect of physical form on dermal absorption is obscured by the effect of concentration in the analysis of dermal absorption versus physical form alone. In other words, this approach does not account for potential confounding effects.
- The conclusions of the ECPA analysis rely to a large extent on a graphical exploratory analysis. This makes it difficult to assess quantitatively the magnitude of the various investigated effects, it also lacks a rigorous assessment of the statistical significance of the various conclusions.

3.3.2. ECPA dataset

A more in depth examination of the ECPA dataset taking into account some of the potential confounding effects within a model-based approach, suggests that the conclusions of Aggarwal et al., 2015 are not fully supported.

For example it is observed that dermal absorption (i.e. directly absorbed dose+whole skin residue excluding amount in tape strips 1/2) among liquid concentrates depends on formulation type. More specifically, the 95% quantile of dermal absorption for liquid concentrates of formulation type 'Emulsion, oil in water' is 10.35%, hence 75% higher than the default 6% value proposed by Aggarwal et al., 2015. This claim is supported by graphical evidence (Figure 1) but it is also supported by a model-based approach. Indeed an analysis of variance (ANOVA) restricted to liquid concentrates with formulation type as explanatory variable and dermal absorption as response yields a *p*-value of 0.006 for the hypothesis of absence of effect of formulation type. This conclusion contrasts with the findings of Aggarwal et al., 2015.

A classical ANOVA as outlined and implemented above focuses on variation of the mean of DA values. It is observed that a model attempting to relate variation of the 95% quantile of dermal absorption values (quantile regression) yields a qualitatively similar conclusion, with several differences in quantiles among formulation types having a high significance (p-values under 5% and even 1%).



DA: dermal absorption; EC: emulsifiable concentrate; EW: emulsion, oil in water; FS: flowable concentrate for seed treatment; OD: Oil-based suspension concentrate; SC: suspension concentrate; SE: suspo-emulsion; SL: soluble concentrate.
Each boxplot displays the median (central line), the 25% and 75% quantiles (sides of rectangles) and the 5% and 95% quantiles (thin vertical segments).

Figure 1: Dermal absorption (%) for liquid concentrates by formulation type

A more systematic analysis should be model-based and assess the potential effect of the various factors jointly. The so-called Linear Model is the standard technique to analyse the effect of the variation of a set of variables on a response variable. This should be used here using all potential explanatory variables (a.s. properties including MW and logPow, concentration, formulation type) jointly (in contrast with one at a time as by Aggarwal et al. 2014, 2015) in combination with variable selection techniques to identify the main causes of variation in dermal absorption values.

However, the standard linear model would address only partially the problem as it focuses on variation of mean values while EFSA guidance recommends focusing on 95% quantiles. It would be appropriate therefore to implement also a quantile regression model together with variable selection techniques to identify the main cause of variation in quantiles.

4. Conclusions

The data on human skin *in vitro* dermal absorption submitted by ECPA and BfR are considered by the EFSA working group relevant for the revision of the EFSA guidance on dermal absorption. As mentioned in the guidance and in the opinion, data from human *in vitro* studies performed in line with regulatory standards (i.e. in compliance with OECD 428) can be used as stand-alone data to predict dermal absorption of a.s. from pesticide products in humans. The procedures (default assumptions

and decision criteria) described in the guidance to be followed in the absence of data on dermal absorption for a PPP are based on the analysis of data from a limited number of heterogeneous studies. Differently, the new datasets as submitted by ECPA and BfR, are aimed to provide a consistent dataset from a large number of studies.

The **quality check** of the datasets made available to EFSA demonstrates that the studies have been conducted in compliance with OECD 428 testing guideline, confirming that new data fulfil the regulatory standards. However, some deviations from the EFSA guidance have been identified. In particular:

- Recommendations for performing and interpreting dermal absorption studies with PPPs to address the variability within studies and to improve interpretation have been scarcely applied;
- Individual data or other information addressing variability within the dataset have not been provided;
- The mean values for some parameters (e.g. t0.5 and other information on the time-course) are missing.

Moreover, in order to assess the impact of different formulations on dermal absorption and the possibility for read across among formulations, information on the composition of tested formulations should be provided, especially the identity, concentration and function of the co-formulants. This information should allow a refinement of the dermal absorption estimations. Currently, the provided datasets contain information only concerning the formulation type and dilution tested.

The EFSA working group noted that additional recommendations for data analysis and further examples would improve quality and harmonisation of assessment. In some cases, clarifications may be needed for existing recommendations in the current EFSA guidance.

The EFSA working group concluded that a model-based statistical analysis should be applied to the final comprehensive dataset for the revision of the EFSA guidance on dermal absorption, taking into account all the variables jointly.

Overall, it was concluded that there is sufficient information to support the revision of the current EFSA guidance/develop a new guidance on dermal absorption.

5. Recommendations

It was recognised that ECPA and BfR provided to EFSA consistent and solid datasets with a relevant number of new human *in vitro* dermal adsorption studies performed in compliance with GLP and OECD test guideline (428). On the basis of this, the recommendations are:

- To complete the ECPA and BfR datasets including missing entries. Then, the final comprehensive dataset should be developed and duplicates between the two datasets (same studies) should be removed.
- To analyse dermal absorption data as compiled in the final comprehensive dataset applying a model-based statistical protocol in order to revise the current guidance/develop a new EFSA guidance on dermal absorption.

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Abbreviations

a.s.	Active Substance
BfR	Bundesinstitut für Risikobewertung
DA	Dermal Absorption
ECHA	European Chemicals Agency
ECPA	European Crop Protection Association
GLP	Good Laboratory Practice
h	hours
logPow	Partition coefficient octanol/water
MW	Molecular Weight
OECD	Organisation for Economic Co-operation and Development
PPP	Plant Protection Product
SCoFCAH	Standing Committee on the Food Chain and Animal Health
SD	Standard Deviation
t0.5	Absorption at half study duration