



# EFSA guidance on dermal absorption: overview

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## EC MANDATE: BACKGROUND

- PPR Scientific Opinion on Guidance on Dermal Absorption issued in 2012<sup>1</sup>
- European Crop Protection Association (ECPA) indicated that the PPR Guidance on Dermal Absorption was in their opinion excessively conservative and that it did not take into account new relevant scientific studies on human *in vitro* DA<sup>2,3</sup>
  - ECPA data set of human *in vitro* DA studies
- MSs consultation by EC (Dec 2014) on data availability
  - German BfR compiled a database of *in vivo* and *in vitro* DA studies

<sup>1</sup>EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on Dermal Absorption. EFSA Journal 2012;10(4):2665. [30 pp.] doi:10.2903/j.efsa.2012.2665. Available online: [www.efsa.europa.eu/efsajournal.htm](http://www.efsa.europa.eu/efsajournal.htm)

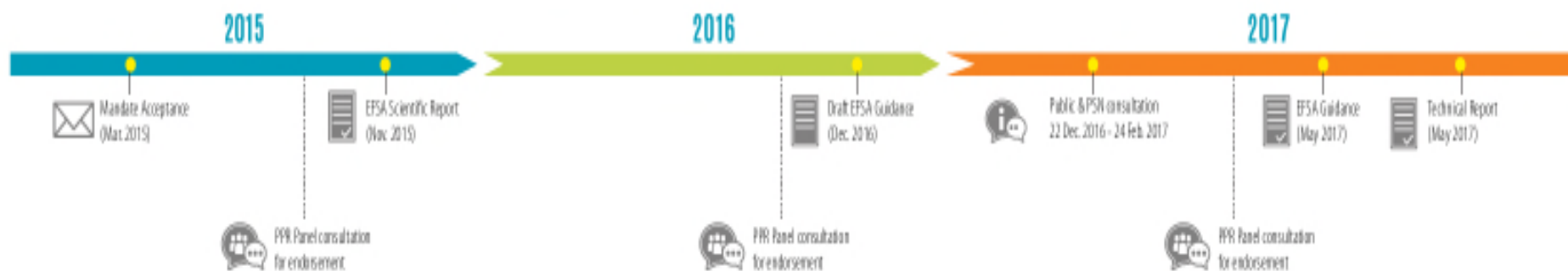
<sup>2</sup>Aggarwal et al. (2014). Assessment of *in vitro* human dermal absorption studies on pesticides to determine default values, opportunities for read-across and influence of dilution on absorption. *Regul Toxicol Pharmacol.* 68(3):412-423.

<sup>3</sup>Aggarwal et al. (2015). Assessment of an extended dataset on *in vitro* human dermal absorption studies on pesticides to determine default values, opportunities for read-across and influence of dilution on absorption. *Regul Toxicol Pharmacol.* 72 (1):58-70.

## EC MANDATE: TOR AND DELIVERABLES

- 1) To assess scientific quality of new dermal absorption studies from industry and public institutions and compile a comprehensive data set of dermal absorption studies with PPPs
  - 1st deliverable: EFSA Scientific Report by Feb 2016
- 2) To consider whether, based on the studies evaluation, the current guidance should be revised or, whether more appropriate, a new guidance would be required
  - 2nd deliverable: EFSA Guidance by May 2017

# PROJECT MILESTONES



## SCIENTIFIC REPORT OF EFSA



ADOPTED: 30 October 2015  
doi:10.2903/j.efsa.2015.4304

### Assessment of new scientific stu dermal absorp

EFSA Working Group on De

#### Abstract

This EFSA scientific report describes the results from the ev dermal absorption made available by European Crop Prote public organisation Bundesinstitut für Risikobewertung ( guidance on dermal absorption (EFSA, 2012). A quality che studies were conducted according to the current regula deviations from EFSA guidance on dermal absorption. In a correctness of data entry in the datasets from sources (stud

PUBLISHED: 11 November 2015

## TECHNICAL REPORT

APPROVED: 24 May 2017  
doi:10.2903/jp.efsa.2017.EN-1250

### Outcome of the public consu Guidance on dern

European Food Safety Authority (EFSA), Harrie Hougaard Bennekou, Carsten Kneuer, Kyriaki Machera, Gilles Guillot and

#### Abstract

EFSA was asked by the Commission to revise the guid the basis of the evaluation of new data on human dermal absorption and BFR. After endorsement by the PPR Panel, a pub 2016 until February 24<sup>th</sup> 2017. The Authority receiv guidance and appendices. All the comments were d



## GUIDANCE

ADOPTED: 24 May 2017  
doi: 10.2903/j.efsa.2017.4873

### Guidance on dermal absorption

European Food Safety Authority (EFSA), Harrie Buist, Peter Craig, Ian Dewhurst, Susanne Hougaard Bennekou, Carsten Kneuer, Kyriaki Machera, Christina Pieper, Daniele Court Marques, Gilles Guillot, Federica Ruffo and Arianna Chiusolo

#### Abstract

This guidance on the assessment of dermal absorption has been developed to assist 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 active substances in Plant Protection Products (PPPs). It is based on the 'scientific opinion on the science behind the revision of the guidance document on dermal absorption' issued in 2011 by the EFSA Panel on Plant Protection Products and their Residues (PPR). The guidance refers to the EFSA PPR opinion in many instances. In addition, the



# CONTRIBUTORS

## ■ **WG members**

Carsten Kneuer and Christina Pieper (BfR); Harrie Buist (TNO); Ian Dewurst (CRD); Kyriaki Machera (BPI); Peter Craig (Durham University); Susanne Hougaard Bennekou (Danish EPA)

## ■ **EFSA PRAS staff**

Arianna Chiusolo; Daniele Court Marques; Gilles Guillot

## ■ **PPR Panel for endorsement**

## ■ **Hearing expert**

Manoj Aggarwal on behalf of ECPA

## ■ ***Stakeholders***



## 1<sup>st</sup> DELIVERABLE: EFSA SCIENTIFIC REPORT

Main outcome: scientific quality of new human in vitro dermal absorption studies complies with regulatory standards (OECD) and data provide sufficient information for revision of the current PPR guidance (2012)

- Remarks:
  - Missing data in data sets
  - Deviations from EFSA recommendations
  - Pitfalls in ECPA manuscripts statistical analysis (*Aggarwal et al, 2014 and 2015*)
    - assess potential effects of each factor on dermal absorption one-by-one, implicitly assuming that the effect of a factor is independent of the variation of other factors: strong assumption not justified.
- Recommendations:
  1. to include missing entries and finalise the combined ECPA and BfR data set
  2. to analyse data by applying a model-based statistical protocol

# DERMAL ABSORPTION DATA SETS

- New data sets submitted in 2016 by ECPA and BfR with individual values

	ECPA	BfR <sup>^</sup>
<b>Studies (GLP and OECD 428-compliant)</b>	295	125
<b>Active substances</b>	152	94
<b>Formulation types</b>	19	23
<b>Exposure time</b>	6-10 h	6-24 h
<b>Observation time</b>	24 h	24 h
<b>Records*</b>	5,180	2,273

*\* Record: rows (individual values) with structured dermal absorption data from a.s. concentration tested in the experiment*

<sup>^</sup> Procurement NP/EFSA/PRAS/2016/01 'Refinement of the BfR human in vitro dermal absorption dataset'



## 2<sup>nd</sup> DELIVERABLE: EFSA GUIDANCE (DRAFT) (1)

Update based on data analysis, experimental/interpretation aspects, harmonisation with regulatory requirement and whenever needed.

### ■ **Chapter 5-Interpretation of studies:**

- Tape stripping (t<sub>0.5</sub> calculation)
- Recovery (missing material absorbed or normalisation approach)
- Dilution rates (pro-rata approach)
- Variability within results and outliers (multiplication factor of standard deviation, outliers identification)
- Rounding of values (10% variation threshold, for harmonisation with EFSA SC 'Guidance on selected default values', 2012)

### ■ **Chapter 6-How to proceed when there are no data on the formulation under consideration:**

- Default values (DVs)
- Similar formulations (harmonise with Regulation 1272/2008 and SANCO guidance on significant and non-significant changes)



## 2<sup>nd</sup> DELIVERABLE: EFSA GUIDANCE (DRAFT) (2)

- **Table 7** (Table 1 in current guidance) and **Flow Chart 1** (DVs)
- **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

## DRAFT GUIDANCE: STAKEHOLDERS CONSULTATIONS

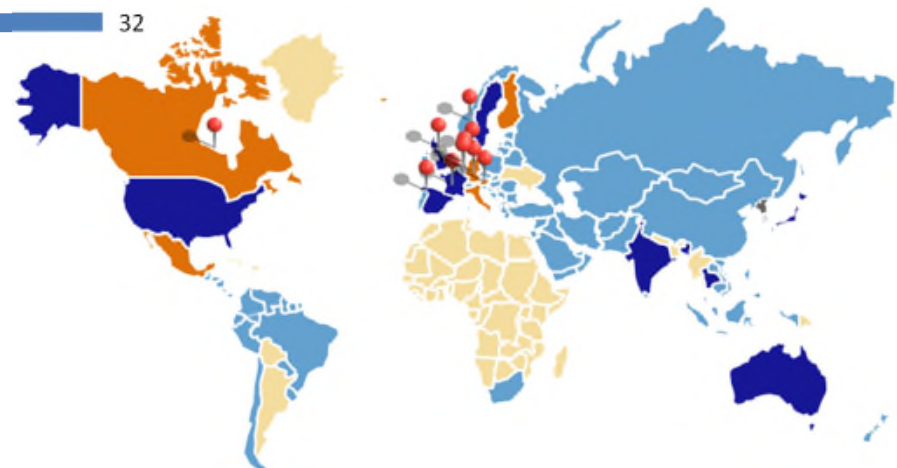
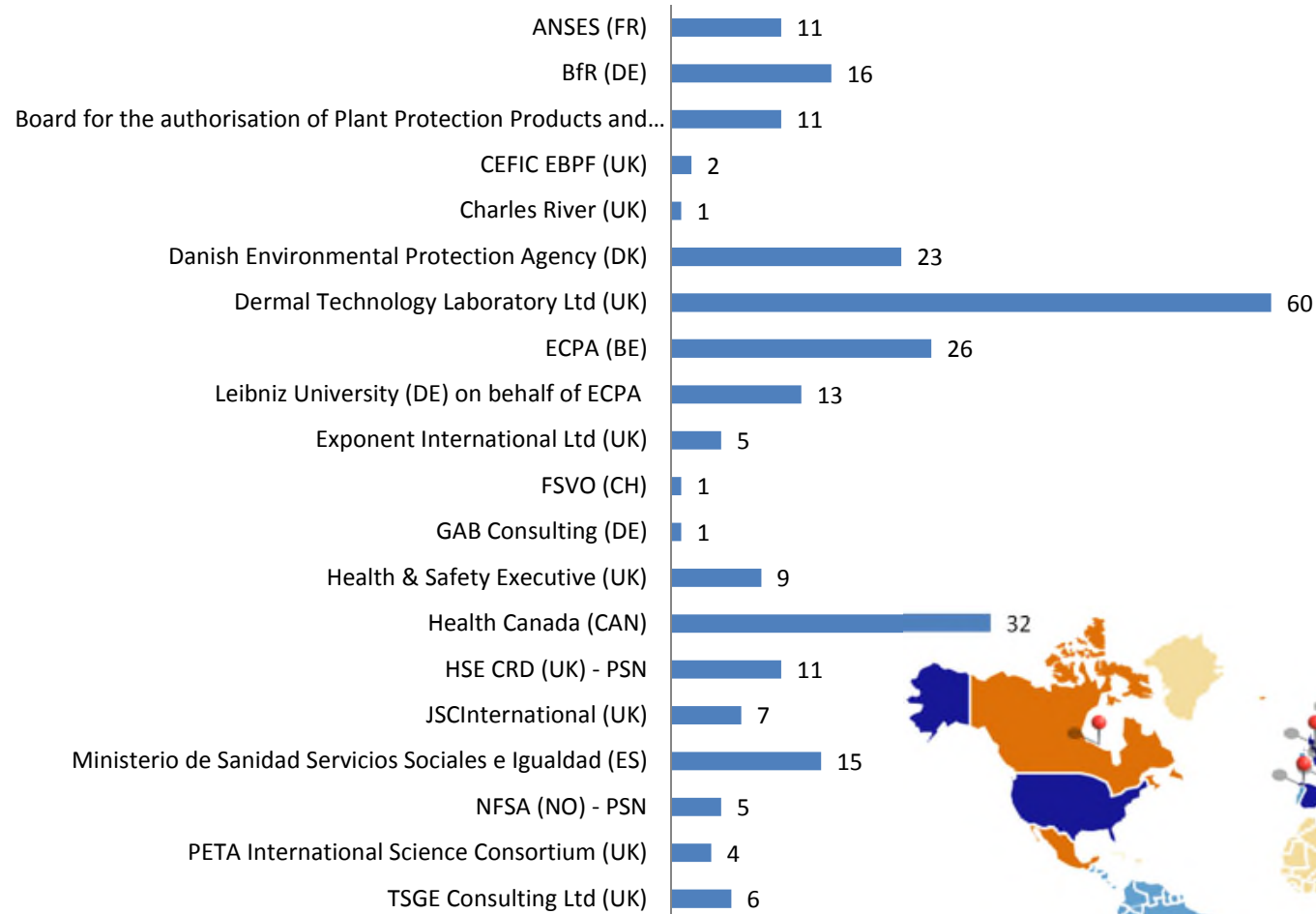
### Public consultation

- conducted from 22 Dec 2016 to 28 Feb 2017
- notification of stakeholders via different EFSA networks
- a total of 243 comments from 18 interested parties received

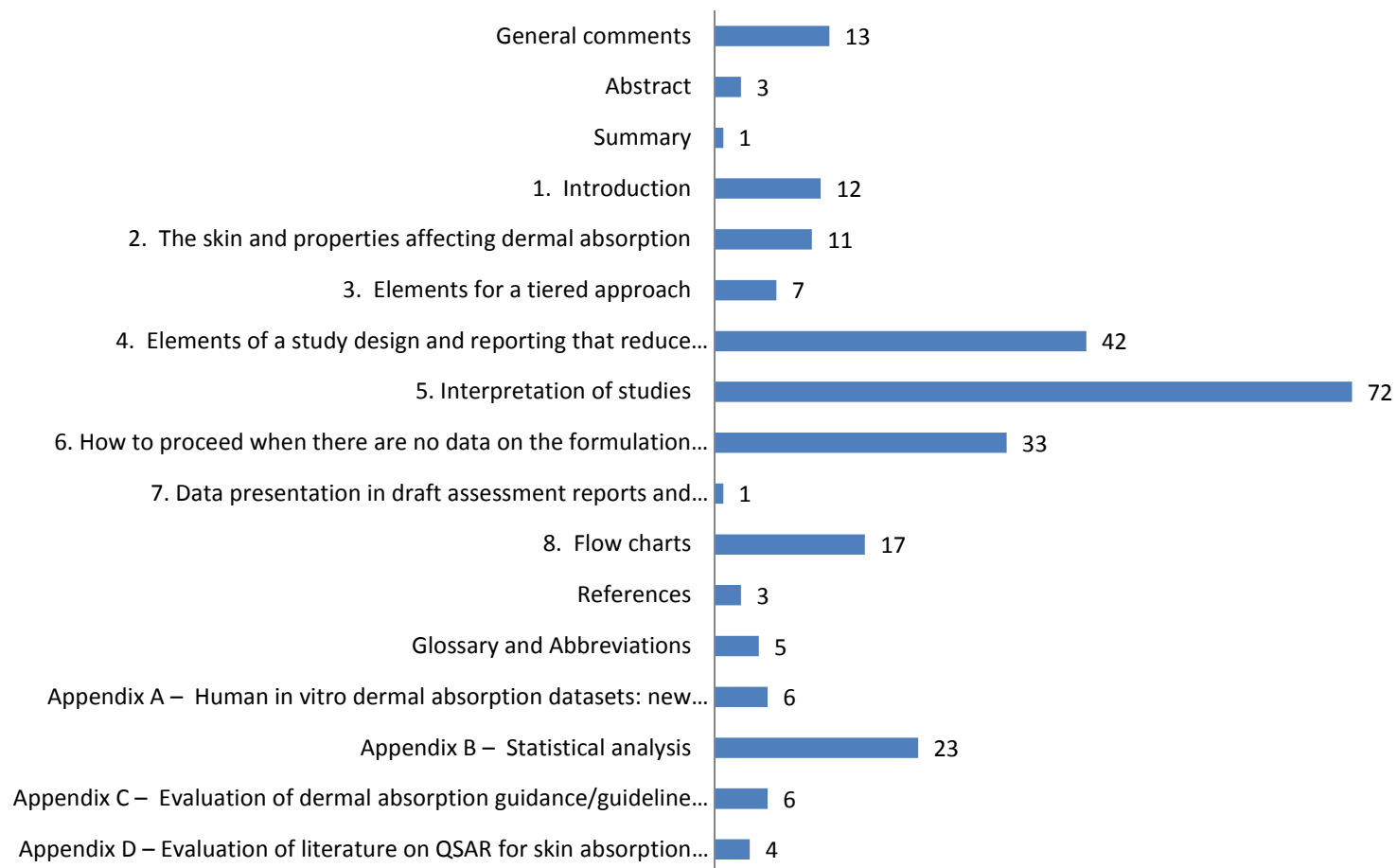
### PSN consultation

- conducted from 22 Dec 2016 to 28 Feb 2017
- a total of 16 comments from 2 Member States (UK and NO) received
- no interest in proposed dedicated web conference
- no collegial position of PSN and comments addressed as submitted from individual Organisations

# PUBLIC CONSULTATION: COMMENTS BY ORGANISATION



# PUBLIC CONSULTATION: COMMENTS BY SECTIONS



## DRAFT GUIDANCE: STAKEHOLDERS CONSULTATIONS (2)

- 259 comments (multiple comments in 1 entry)
- All comments scrutinised, tabulated and discussed during the WG 1.5 day meeting and addressed in the Technical Report on the public consultation on the draft EFSA guidance on dermal absorption
- Many comments to sections not revised by the WG: *'out of the scope of the mandate. Except for factual mistakes and inconsistencies, notes have been taken for these comments, to be considered under the mechanism in EFSA for the regular revision of guidance documents'*

## 2<sup>nd</sup> DELIVERABLE: EFSA GUIDANCE (FINAL)

Guidance amended in order to provide more clarifications, examples and transparency in data analysis

### ■ **Chapter 5:**

- Tape stripping: clarifications on  $t_{0.5}$  calculation
- Variability within results and outliers: dismissed 25% cut-off
- Rounding of values: clarifications and proposed rounding to 2 significant figures (dismissed 10% variation threshold)
- Dilution rates: further clarifications

### ■ **Chapter 6:**

- Use of data on similar formulations: clarifications and inclusion of case of formulations containing more than 1 a.s. (previous 6.5)

- **Appendix B:** clarifications and more details on the statistical modelling (B-regression), on the dismissed 10% DV, on empirical percentiles and further explanation on set DVs based from statistical proposals

# EFSA GUIDANCE: SUPPORTING INFORMATION

Supporting information published with the EFSA Guidance <http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.4873/full>:

- BfR template for *in vitro* calculations and a practical example
- Human *in vitro* dermal absorption PPPs data set (combined ECPA and BfR) used for the analysis
- R codes applied for statistical analysis

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



# THANK YOU FOR YOUR ATTENTION



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# BACK-UP SLIDES

## MILESTONES AND LINKS

- Mar 2015 – Acceptance of EC mandate
- Nov 2015 – Publication of the PPR Panel endorsed EFSA Scientific Report 'Assessment of new scientific studies on human in vitro dermal absorption' (EFSA-Q-2015-00169): [EFSA Journal 2015; 13\(11\): 4304](#)
- Dec 2016 - PPR Panel endorsement of the draft EFSA Guidance on dermal absorption
- Dec 2016 to Feb 2017 – Public consultation and PSN consultation
- May 2017 – PPR Panel endorsement and EFSA approval of the EFSA Guidance on dermal absorption
- Jun 2017 – Publication of the EFSA Guidance on dermal absorption (EFSA-Q-2015-00633): [EFSA Journal 2017;15\(6\):4873](#)
- Jun 2017 – Publication of the Technical Report 'Outcome of the public consultation on the draft EFSA Guidance on dermal absorption' (EFSA-Q-2015-00634): [EFSA website](#)
- Sep 2017 – Info session with Stakeholders  
<http://www.efsa.europa.eu/en/events/event/170927>