Scientific Panel on Plant Protection Products and their Residues

Minutes of the 6th meeting of the EFSA Working Group on Dermal Absorption Guidance

Held on 21-22 (morning) March 2017, Parma (Italy)
(Agreed on 7 April 2017)

Participants

- **Working Group Members:**

  Carsten Kneuer (via tele-conference), Christina Pieper, Harrie Buist, Ian Dewhurst, Kyriaki Machera, Peter Craig and Susanne Hougaard Bennekou

- **Hearing Experts[1]:**

  Not applicable

- **European Commission and/or Member States representatives:**

  Not Applicable

- **EFSA:**

  Pesticides Unit: Arianna Chiusolo (chair), Marcella De Maglie

  AMU Unit: Gilles Guillot

- **Others:**

  Not Applicable

[1] As defined in Article 17 of the Decision of the Executive Director on the selection of external experts: http://www.efsa.europa.eu/en/keydocs/docs/expertselection.pdf.

1. Welcome and apologies for absence

The Chair welcomed the participants. Apologises for absence were received by Daniele Court Marques.

2. Adoption of agenda

The agenda was adopted.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes[2] and the Decision of the Executive Director on Declarations of Interest[3], EFSA screened the Annual Declaration of Interest and the Specific Declaration of Interest filled in by the working group members invited for the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process or at the Oral Declaration of Interest at the beginning of this meeting.

4. Agreement of the minutes of the 5th Working Group meeting held on 12-13 October 2016, Athens

The minutes of the 5th Working Group meeting held on 12-13 October 2016 in Athens were agreed on 9 December 2016 and published on the EFSA website.

5. Scientific topic(s) for discussion

5.1. EC request to assess new scientific studies on dermal absorption submitted to EFSA and, if appropriate, to revise the guidance document on dermal absorption (EFSA-Q-2015-00633)

Comments received from public consultation and Pesticides Steering Network (PSN) consultation (tabulated into the technical report 'Outcome of the public consultation on the draft Dermal Absorption guidance') were revised by the WG and the needed changes to the guidance were agreed. Actions for the finalisation of the guidance and the technical report on the

[2] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[3] http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014.pdf

public consultation were agreed. The guidance will be submitted to the PPR Panel for endorsement during the Plenary in May (17-18) and subsequently it will be published in the EFSA website with the technical report on the public consultation.

The WG agreed that comments submitted by the PSN were minor or editorial or out of the scope of the mandate. Thus, the WG view is that a collegial position of the PSN to the guidance cannot be achieved and comments should be addressed as submitted from individual Organisations.

The WG agreed that the organisation of a technical hearing with ECPA experts, proposed by ECPA, is not necessary for the finalisation of the output, as from EFSA policy (http://www.efsa.europa.eu/sites/default/files/efsa_rep/blobserver_assets/paneloperation.pdf).

The WG was informed that the EFSA/BfR proposal for the revision of OECD TG/GD/GN documents on dermal absorption (OECD SPSF on dermal absorption) has been positively assessed for addition to the work plan of the Test Guidelines Programme during the 29th Meeting of the Working Group of the National Coordinators of the Test Guidelines Programme (WNT) in April 2017.

The WG was informed that an info session with stakeholders, to elucidate changes in the guidance, is planned on 27-28 September 2017.

6. Any Other Business

Not applicable

7. Next meeting(s)

Not applicable

Scientific Panel on Plant Protection Products and their Residues

Minutes of the 5th meeting of the EFSA Working Group on Dermal Absorption Guidance

Held on 12 - 13 (morning) October 2016, Athens
(Agreed on 09 December 2016)

Participants

- **Working Group Members:**

  Carsten Kneuer, Christina Pieper, Harrie Buist, Kyriaki Machera, Peter Craig and Susanne Hougaard Bennekou (via tele-conference).

- **Hearing Experts[1]:**

  Not applicable

- **European Commission and/or Member States representatives:**

  Not Applicable

- **EFSA:**

  Pesticides Unit: Arianna Chiusolo (chair)

  AMU Unit: Gilles Guillot

- **Others:**

  Not Applicable

1. Welcome and apologies for absence

The Chair welcomed the participants. Apologises for absence were received by Ian Dewhurst and Daniele Court Marques.

[1] As defined in Article 17 of the Decision of the Executive Director on the selection of external experts: http://www.efsa.europa.eu/en/keydocs/docs/expertselection.pdf.

2. Adoption of agenda

The agenda was adopted.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes[2] and the Decision of the Executive Director on Declarations of Interest[3], EFSA screened the Annual Declaration of Interest and the Specific Declaration of Interest filled in by the working group members invited for the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process or at the Oral Declaration of Interest at the beginning of this meeting.

4. Agreement of the minutes of the 3rd Working Group meeting held on 5-6 July 2016, Parma

The minutes of the 4th Working Group meeting held on 7-8 September 2016 were agreed on 21 October 2016 and published on the EFSA website.

5. Scientific topic(s) for discussion

5.1. EC request to assess new scientific studies on dermal absorption submitted to EFSA and, if appropriate, to revise the guidance document on dermal absorption (EFSA-Q-2015-00633)

The updated guidance document was reviewed and discussed by experts. Actions were agreed for the finalisation of specific sections in the draft version.

The planning for updated guidance finalisation was presented, including the public consultations on the draft revised guidance that will be launched by end of December 2016, pending the PPR Panel endorsement.

6. Any Other Business

Not applicable

[2] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[3] http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014.pdf

7. Next meeting(s)

21st -22nd (morning) March 2017

Scientific Panel on Plant Protection Products and their Residues

Minutes of the 4th meeting of the EFSA Working Group on Dermal Absorption Guidance

Held on 7 (afternoon) -8 (morning) September 2016, Parma (Italy)
(Agreed on 12 October 2016)

Participants

- **Working Group Members:**

  Harrie Buist, Peter Craig, Ian Dewhurst, Susanne Hougaard Bennekou, Carsten Kneuer, Kyriaki Machera, Christina Pieper

- **Hearing Experts[1]:**

  Not applicable

- **European Commission and/or Member States representatives:**

  Not Applicable

- **EFSA:**

  Pesticides Unit: Arianna Chiusolo (Chair), Daniele Court Marques

  AMU Unit: Gilles Guillot (day 1)

- **Others:**

  Not Applicable

[1] As defined in Article 17 of the Decision of the Executive Director on the selection of external experts: http://www.efsa.europa.eu/en/keydocs/docs/expertselection.pdf.

1. Welcome and apologies for absence

The Chair welcomed the participants.

Apologies were received from Gilles Guillot (day 2).

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes[2] and the Decision of the Executive Director on Declarations of Interest[3], EFSA screened the Annual Declaration of Interest and the Specific Declaration of Interest filled in by the working group members invited for the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process or at the Oral Declaration of Interest at the beginning of this meeting.

4. Agreement of the minutes of the 3rd Working Group meeting held on 5-6 July 2016, Parma.

The minutes of the 3rd Working Group meeting held on 5-6 July 2016 were agreed on 7 September 2016 and published on the EFSA website.

5. Scientific topic(s) for discussion

5.1. EC request to assess new scientific studies on dermal absorption submitted to EFSA and, if appropriate, to revise the guidance document on dermal absorption (EFSA-Q-2015-00633) [4]

The outcomes from statistical analysis (using empirical and model-based approaches) of data in the new ECPA and BfR DSs were presented.

A template for data extraction from ECPA validation studies using 3 reference compounds (caffeine, testosterone and benzoic acid) was

[2] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[3] http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014.pdf
[4] http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2015-00633

presented, including data/information from two study reports. Considering the low number of studies performed using standard protocol, experts agreed that the statistical analysis of this data is not possible.

Specific sections of the draft updated guidance were revised and further needed changes were agreed.

The WG was updated on the outcomes from the TC with OECD and BfR held on September with the aim to prepare a project proposal to ask for the update of OECD DA TG/GD documents.

6. Any Other Business

Not applicable

7. Next meeting(s)

12-13 (morning) October 2016 in Athens

Scientific Panel on Plant Protection Products and their Residues

Minutes of the 3rd meeting of the EFSA Working Group on Dermal Absorption Guidance

Held on 5 (afternoon) -6 (morning) July 2016, Parma (Italy)
(Agreed on 29 July 2016)

Participants

- **Working Group Members:**

  Harrie Buist, Peter Craig (day 1), Ian Dewhurst (by teleconference), Susanne Hougaard Bennekou, Carsten Kneuer, Kyriaki Machera, Christina Pieper (day 2)

- **Hearing Experts[1]:**

  Not applicable

- **European Commission and/or Member States representatives:**

  Not Applicable

- **EFSA:**

  Pesticides Unit: Arianna Chiusolo (Chair), Daniele Court Marques

  AMU Unit: Gilles Guillot (day 1)

- **Others:**

  Not Applicable

[1] As defined in Article 17 of the Decision of the Executive Director on the selection of external experts: http://www.efsa.europa.eu/en/keydocs/docs/expertselection.pdf.

1. Welcome and apologies for absence

The Chair welcomed the participants.

Apologises were received from Peter Craig (day 2), Gilles Guillot (day 2) and Christina Pieper (day 1)

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes[2] and the Decision of the Executive Director on Declarations of Interest[3], EFSA screened the Annual Declaration of Interest and the Specific Declaration of Interest filled in by the working group members invited for the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process or at the Oral Declaration of Interest at the beginning of this meeting.

4. Agreement of the minutes of the 2nd Working Group meeting held on 3 May 2016, Copenhagen (Danish EPA)

The minutes of the 2nd Working Group meeting held on 3 May 2016 were agreed on 5 July 2016 and published on the EFSA website.

5. Scientific topic(s) for discussion

5.1. EC request to assess new scientific studies on dermal absorption submitted to EFSA and, if appropriate, to revise the guidance document on dermal absorption (EFSA-Q-2015-00633) [4]

Last changes to the new ECPA and BfR datasets (DSs) have been presented. Errors found were corrected with ECPA support for a.s. name and negative values. Missing values for TS1&2 were calculated. The OECD cut off for mass balance recovery was applied.

[2] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[3] http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014.pdf
[4] http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2015-00633

The update from the statistical analysis of data in the new ECPA and BfR DSs (version including last changes mentioned above) was presented. The effect of 13 factors on DA was evaluated using different statistical models. The WG agreed to evaluate the effect of a.s. using a random-effect model.

Documents received from ECPA on validations generated by test facilities using 3 reference compounds (caffeine, testosterone and benzoic acid) were reviewed. It was evidenced that only few of them are relevant for the evaluation of experimental variability. Some experiments are not run under standard conditions (e.g. higher applied volume than recommended by OECD TG 428) and deviances from the standard protocol makes difficult to evaluate data reproducibility. The WG agreed to identify studies performed applying the standard protocol to evaluate if data extraction for statistical analysis would be feasible.

Recent literature and data on QSAR models for dermal absorption prediction of chemicals was presented and the WG agreed on the need for a revision of last enhancements of the in silico prediction tools and the evaluation of their performances using homogeneous data on PPPs.

Outcomes from collection of discrepancies for the same DA factor/criteria among several DA guidance documents (OECD, EFSA, SCCS, WHO, EMA, ECETOC and EPA) was presented. The WG agreed that a better harmonisation is needed. A project proposal to ask for OECD DA TG/GD update will be prepared.

The WG was informed on the outcomes from the ECHA workshop "Dermal absorption from antifouling products and other matrices that form a dry film during testing" (19 May 2016 at BfR).

6. Any Other Business

Not applicable

7. Next meeting(s)

7th (afternoon)-8th (morning) September 2016 in Parma

Scientific Panel on Plant Protection Products and their Residues

Minutes of the 2nd meeting of the EFSA Working Group on Dermal Absorption Guidance

Held on 3 May 2016, Copenhagen (Danish EPA)
(Agreed on 5 July 2016)

Participants

- **Working Group Members:**

  Harrie Buist, Peter Craig, Ian Dewhurst, Susanne Hougaard Bennekou, Carsten Kneuer, Christina Pieper. Kyriaki Machera has participated via teleconference (afternoon).

- **Hearing Experts[1]:**

  Manoj Aggarwal, European Crop Protection Association (ECPA)

- **European Commission and/or Member States representatives:**

  Not Applicable

- **EFSA:**

  Pesticides Unit: Arianna Chiusolo (chair), Daniele Court Marques (by teleconference), Federica Ruffo

  AMU Unit: Gilles Guillot

- **Others:**

  Not Applicable

[1] As defined in Article 17 of the Decision of the Executive Director on the selection of external experts: http://www.efsa.europa.eu/en/keydocs/docs/expertselection.pdf.

1. Welcome and apologies for absence

The Chair welcomed the participants.

Apologies were received from Kyriaki Machera (morning).

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes[2] and the Decision of the Executive Director on Declarations of Interest[3], EFSA screened the Annual Declaration of Interest and the Specific Declaration of Interest filled in by the working group members invited for the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process or at the Oral Declaration of Interest at the beginning of this meeting.

4. Agreement of the minutes of the 1st Working Group meeting held on 24-25 February 2016, Parma

The minutes of the 1st Working Group meeting held on 24-25 February 2016 were agreed on 18 March 2016 and published on the EFSA website.[4]

5. Scientific topic(s) for discussion

5.1. EC request to assess new scientific studies on dermal absorption submitted to EFSA and, if appropriate, to revise the guidance document on dermal absorption (EFSA-Q-2015-00633).[5]

5.2. The refined BfR dataset (DS) including individual replicate values was presented. Results from the performed plausibility check (individual replicate values in the new refined DS vs mean values in the combined BfR/ECPA DS) evidenced a low number of relevant findings mainly due to errors in the combined ECPA/BfR DS (including mean values) and in T0.5 ('absorption occurring within

[2] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[3] http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014.pdf
[4] https://www.efsa.europa.eu/sites/default/files/Dermalwg2016.pdf
[5] http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2015-00633

half duration of the study') calculation. Similar relevant findings were evidenced from the same plausibility check performed to the refined ECPA DS including individual replicate values. It was confirmed the necessity to revise in the current EFSA guidance the section on T0.5 calculation.

5.3. Considerations on the preliminary analysis of the impact of agreed factors on dermal absorption (DA) and appropriate statistical model to be used were made. It was agreed to reduce the number of factors on the basis of outcomes from the preliminary analysis and identify top-models for the final analysis.

5.4. A proposal for the revision of the 'Dilution rates (tested concentrations)' and for the 'Use of data on similar formulations' sections of the current guidance was presented and agreed.

5.5. 4.2. Technical Hearing

5.6. The hearing expert from ECPA replied to the questions from the WG, as follows:

Elucidate the content of the new dataset (including intra-laboratory validation data using reference compounds): the new DS including individual replicate values was presented in details. It was clarified that all studies reported in the DS concerns approved a.s. and that some information e.g., physico-chemical properties of the a.s. have been extrapolated from EFSA conclusions. It was confirmed that in some studies the skin region of the donor is not clear but this is due to not detailed information in the study report. Moreover, it was evidenced that in some cases a replicate was excluded for a parameter e.g., total recovery but included in the DS for other parameters e.g., dermal absorption calculations (not possible to be identified as not highlighted in the remarks column).

5.7. The ECPA activity on DA data collection from validation studies with reference compounds (caffeine, testosterone and benzoic acid) among different laboratories to address intra-study and inter-laboratory variability is still ongoing. ECPA contacted multiple laboratories for availability of the data on reference compounds but data are limited or generated under different experimental conductions, thus a meaningful comparison is not feasible. The hearing expert will ask validation studies to laboratories that performed DA studies to be submitted to the WG by mid-June. Data from a validation study (performed by Jai Research Foundation) for human and rat skin using the reference compounds were presented.

5.8. ECPA team is working with different laboratories/CROs for possibilities to generate new data with a potential harmonised protocol.

i) Methodology for study selection: the hearing expert clarified that all human in vitro skin studies (OECD TG 428- and GLP-compliant) available between 1998 until February 2014 from each company of the ECPA Consortium were identified and data extracted to develop the DS. Further details are provided in the 2 publications.

ii) Statistical analysis described in the 2 manuscripts: the hearing expert confirmed that no specific statistical analysis of data was performed, except for data used to determine read-across for concentrate among different formulation types, where ANOVA was applied.

5.9. The WG thanks the hearing expert for his participation to the meeting.

6. Any Other Business

6.1. A new developed methodology to apply and test dry residue for in vitro DA with human skin was presented by the hearing expert for information only, as out of the scope of the mandate received from the EC. The objective of the WG is to revise the guidance on the basis of the analysis of new available data on human in vitro studies conducted following regulatory standards. The new proposed methodology is not following regulatory standard (OECD TG 428) for the residue transfer process and a specific assessment of the validation status for the proposed approach should be conducted before its application in the regulatory field of pesticides risk assessment.

7. Next meeting(s)

5 (afternoon)-6 (morning) July 2016 in Parma

Scientific Panel on Plant Protection Products and their Residues

Minutes of the 1st meeting of the EFSA Working Group on Dermal Absorption Guidance

Held on 24 (afternoon) - 25 (morning) February 2016, Parma (Italy)
(Agreed on 18 March 2016)

Participants

- **Working Group Members:**

  Carsten Kneuer, Christina Pieper, Harrie Buist, Kyriaki Machera. Susanne Hougaard Bennekou, Ian Dewhurst and Peter Craig (24th afternoon only) have participated via teleconference.

- **Hearing Experts[1]:**

  Not Applicable

- **European Commission and/or Member States representatives:**

  Not Applicable

- **EFSA:**

  Pesticides Unit: Arianna Chiusolo (chair), Andrea Terron, Federica Ruffo.

- **Others:**

  Not Applicable

1. Welcome and apologies for absence

[1] As defined in Article 17 of the Decision of the Executive Director on the selection of external experts: http://www.efsa.europa.eu/en/keydocs/docs/expertselection.pdf.

The Chair welcomed the participants.

Apologies were received from Harrie Buist, Daniele Court Marques (EFSA Pesticides Unit), Peter Craig (25th morning), and Gilles Guillot (EFSA AMU Unit).

2. Adoption of agenda

The agenda was adopted with some changes:

- The statistical evaluation of the DA comprehensive dataset was not presented (due to absence)
- 2 additional presentations and 1 update:
  - Rationale for default values for dermal absorption
  - How to calculate t0.5
  - Update on the draft minutes from the ECPA Workshop.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes[2] and the Decision of the Executive Director on Declarations of Interest[3], EFSA screened the Annual Declaration of Interest and the Specific Declaration of Interest filled in by the working group members invited for the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process or at the Oral Declaration of Interest at the beginning of this meeting.

4. Scientific topic(s) for discussion

4.1. EC request to assess new scientific studies on dermal absorption submitted to EFSA and, if appropriate, to revise the guidance document on dermal absorption (EFSA-Q-2015-00633) [4]

Final comprehensive dataset on DA human *in vitro* studies from ECPA and BfR datasets was presented. ECPA and BfR are developing a new version of their datasets in order to include single replicate values from DA human *in vitro* experiments. A new version of the comprehensive DA dataset will be created and the statistical analysis of data will be performed after the application of the plausibility check to the new comprehensive DA dataset.

[2] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[3] http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014.pdf
[4] http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2015-00633

Bridging concepts for similar formulations were discussed and discrepancies in the evaluation of data from different formulation types following different guidance documents were evidenced. It was decided to harmonise the approach and update the EFSA guidance accordingly.

The WG discussed on the aspects influencing DA and a list of factors to be evaluated in the new comprehensive dataset was agreed. Considerations and issues behind the rationale to be used in setting up new default values for dermal absorption based on submitted data were discussed. Factors possibly impacting on data variability were listed.

A proposal for EFSA guidance revision concerning t0.5 ('absorption occurring within half duration of the study') calculation was presented. A text with more clarity in terminology and the calculation for t0.5 was agreed.

The WG was informed on the outcomes from the ECPA workshop 'Understanding Formulation Design and Dermal Absorption: Technical, Scientific and Regulatory Perspectives' (16-17 November 2015).

The WG agreed to invite to the next meeting a hearing expert from ECPA in order to receive information on the new DA dataset, the methodology for study selection and statistical analysis described in the 2 manuscripts.

5. Any Other Business

Not Applicable

6. Next meeting(s)

3 May 2016 in Copenhagen (Danish EPA)