



Scientific Panel on Plant Protection Products and their Residues/Pesticide Peer Review Unit

MINUTES OF THE 13th MEETING OF THE EFSA WORKING GROUP ON COMPARATIVE *IN VITRO* METABOLISM STUDIES

Held on 21 October 2021 (teleconference)

(Agreed on 03 November 2021)

Participants

■ Working Group Members:

Ursula Gundert-Remy
Jochem Louisse
Emanuela Testai
Olavi Pelkonen (Chair)
Serge Rudaz
Gerrit Wolterink

■ European Commission and/or Member States representatives:

Sandra Coecke (Joint Research Center) (absent)

■ Hearing experts¹

Carsten Kneuer (BfR) (morning 10.00-11.00)
Matthew Himmelstein (CropLife EU) (afternoon 14.00-14.30)

■ EFSA:

Pesticides Peer Review (PREV) Unit: Juan Parra Morte, Martina Panzarea
Scientific Committee and Emerging Risk (SCER) Unit: Jean Lou Dorne (absent)

¹ As defined in Article 15 of the Decision of the Executive Director concerning the selection of members of the Scientific Committee, the Scientific Panels, and the selection of external experts to assist EFSA with its scientific work:
http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/expertselection.pdf

1. Welcome and apologies for absence

The Chair welcomed the WG members and the hearing expert, Carsten Kneuer (in the morning) and Matthew Himmelstein (in the afternoon). Apologies were received from Ms Sandra Coecke (Joint Research Center) and Mr Jean Lou Dorne (SCER Unit).

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 Independence² and the Decision of the Executive Director on Competing Interest Management³, EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Hearing Expert (s)

Carsten Kneuer and Matthew Himmelstein were invited as hearing experts to present the point of view of a Member State and Industry on the draft Scientific Opinion, respectively.

5. Scientific topic(s) for discussion

Critical comments on the draft Scientific Opinion.

Hearing experts were asked to give a short presentation on those areas of the draft Scientific Opinion heavily commented during the public consultation phase (i.e. study design, trigger of 5% for the identification of metabolites, uncertainty factor approach for a disproportionate human metabolite, timing on conducting comparative *in vitro* metabolism study).

The WG members thanked the hearing experts and asked some clarification on some of the points presented.

Finalisation of the Scientific Opinion

Comments provided by the Working Group experts were addressed along the Technical Report. The draft Scientific Opinion was amended accordingly (where needed).

6. Any Other Business

The draft Scientific Opinion will be sent out to the PPR Panel for revision on the **26th of October** and final comments are expected by the 5th of November.

7. Next meeting(s)

None.

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

³ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf



Scientific Panel on Plant Protection Products and their Residues/Pesticide Peer Review Unit

MINUTES OF THE 12TH MEETING OF THE EFSA WORKING GROUP ON COMPARATIVE *IN VITRO* METABOLISM STUDIES

Held on 21 September 2021 (teleconference)

(Agreed on 29 September 2021)

Participants

■ **Working Group Members:**

Ursula Gundert-Remy
Jochem Louisse
Emanuela Testai
Olavi Pelkonen (Chair)
Serge Rudaz
Gerrit Wolterink (absent)

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

Sandra Coecke (Joint Research Center)

■ **EFSA:**

Pesticides Peer Review (PREV) Unit: Juan Parra Morte, Martina Panzarea
Scientific Committee and Emerging Risk (SCER) Unit: Jean Lou Dorne (absent)

1. Welcome and apologies for absence

The Chair welcomed the WG members. Apologies were received by Gerrit Wolterink and Jean Lou Dorne.

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 Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Scientific topic(s) for discussion

The working group (WG) reviewed the main comments received during the Public Consultation (PC). The experts mainly discussed on the definition of disproportionate/unique human metabolites, the 5 % threshold to trigger identification of the major metabolites, timing with regards to the conduction of the *in vitro* metabolism studies, uncertainty factor (UF) approach and non-testing approach methodology. Internal TTC and 20 % threshold to consider the 24 hours incubation were also tackled.

5. Any Other Business

The allocation of tasks and the invitation of hearing experts to the next meeting were discussed and agreed upon.

The Draft Scientific Opinion will be sent out to the PPR Panel for revision on the 26th of October and final comments are expected by the 5th of November.

6. Next meeting(s)

Next WG meeting is planned on the 21st of October 2021 by teleconference.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf



Scientific Panel on Plant Protection Products and their Residues/Pesticide Peer Review Unit

MINUTES OF THE 11TH MEETING OF THE EFSA WORKING GROUP ON COMPARATIVE *IN VITRO* METABOLISM STUDIES

Held on 17 June 2021 (teleconference)

(Agreed on 7 July 2021)

Participants

■ **Working Group Members:**

Ursula Gundert-Remy, Jochem Louisse, Emanuela Testai, Olavi Pelkonen (Chair), Serge Rudaz, Gerrit Wolterink.

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

Sandra Coecke (Joint Research Center).

■ **EFSA:**

Pesticides Peer Review (PREV) Unit: Juan Parra Morte, Martina Panzarea.

1. Welcome and apologies for absence

The Chair welcomed the WG members. Apologies were received by Jean Lou Dorne.

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 Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Scientific topic(s) for discussion

The comments received from the PPR Panel's reviewers were addressed throughout the document.

The discussion was mainly focused on the approach to assess the toxicological profile of metabolites, application of uncertainty factors for the derivation of health-based guidance values (HBGVs), definition of distal metabolites and interindividual differences in the formation of DHM and UHM.

The structure of the recommendation chapter and the scientific terminology used (e.g. *mass balance*) were also tackled.

5. Any Other Business

The WG discussed about the next steps: presentation of the scientific opinion to the 111th PPR Panel (23rd of June) for possible endorsement for public consultation.

6. Next meeting(s)

Next meetings should be set after the public consultation (if endorsed by the PPR Panel). Dates to be determined.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf



Scientific Panel on Plant Protection Products and their Residues/Pesticide Peer Review Unit

MINUTES OF THE 10TH MEETING OF THE EFSA WORKING GROUP ON COMPARATIVE *IN VITRO* METABOLISM STUDIES

Held on 28 May 2021 (teleconference)

(Agreed on 17 June 2021)

Participants

■ Working Group Members:

Ursula Gundert-Remy, Jochem Louisse, Emanuela Testai, Olavi Pelkonen (Chair), Serge Rudaz, Gerrit Wolterink (absent in the morning).

■ European Commission and/or Member States representatives:

Sandra Coecke (Joint Research Center) (absent).

■ Hearing Expert¹ :

None

■ EFSA:

Pesticides Peer Review (PREV) Unit: Juan Parra Morte (absent), Martina Panzarea (absent in the morning).

Scientific Committee and Emerging Risk (SCER) Unit: Jean Lou Dorne (absent)

¹ As defined in Article 15 of the Decision of the Executive Director concerning the selection of members of the Scientific Committee, the Scientific Panels, and the selection of external experts to assist EFSA with its scientific work:
http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/expertselection.pdf

1. Welcome and apologies for absence

The Chair welcomed the WG members. Apologies from the absents were received.

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 Independence² and the Decision of the Executive Director on Competing Interest Management³, EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Scientific topic(s) for discussion

The main changes from the last meeting were presented to the experts.

5. Any Other Business

The WG was informed about the next steps in the process and the deadline to be fulfilled: on June 1st, a consolidated draft scientific opinion should be sent to the PPR Panel for the final review, their comments are expected by the **15th of June**. This plan would allow the WG to present the draft scientific opinion for public consultation endorsement to the 111th PPR Panel (**23rd of June**).

New tasks were allocated to the experts.

6. Next meeting(s)

The next WG meeting will be held on the **17th of June 2021 (10- 17)** by teleconference.

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

³ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Scientific Panel on Plant Protection Products and their Residues/Pesticide Peer Review Unit

MINUTES OF THE 9TH MEETING OF THE EFSA WORKING GROUP ON COMPARATIVE *IN VITRO* METABOLISM STUDIES

Held on 10 and 11 May 2021 (teleconference)

(Agreed on 21 May 2021)

Participants

■ **Working Group Members:**

Ursula Gundert-Remy, Jochem Louisse, Emanuela Testai, Olavi Pelkonen (Chair), Serge Rudaz, Gerrit Wolterink.

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

Sandra Coecke (Joint Research Center).

■ **Hearing Expert¹ :**

Tamara Coja

■ **EFSA:**

Pesticides Peer Review (PREV) Unit: Juan Parra Morte, Martina Panzarea
Scientific Committee and Emerging Risk (SCER) Unit: Jean Lou Dorne

¹ As defined in Article 15 of the Decision of the Executive Director concerning the selection of members of the Scientific Committee, the Scientific Panels, and the selection of external experts to assist EFSA with its scientific work:
http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/expertselection.pdf

1. Welcome and apologies for absence

The Chair welcomed the WG members.

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 Independence² and the Decision of the Executive Director on Competing Interest Management³, EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Hearing Expert (s)

Ms Tamara Coja was invited being one of the PPR Panel reviewers commenting the scientific opinion. She was asked to give clarification, where needed, on the comments provided along the draft scientific opinion.

5. Scientific topic(s) for discussion

PPR Panel comments and amendments done

The main changes from the last meeting were presented to the experts. The WG members thanked the hearing expert and discussed in detailed the different chapters of the opinion in order to address the comments received.

During the meeting, the general overview of the study design and the experimental strategy were addressed in priority. Olavi Pelkonen prepared a revised version of the relevant chapters and presented a new schematic figure to summarize the layout of the scientific opinion.

Additionally, both the recommendation and the analytical chapters were reviewed in detailed by the experts. The other sections of the opinion were also tackled and amended.

Feedback from subgroup meeting

The outcome of the subgroup meeting held on April on disproportionate metabolite and its toxicological coverage was presented to the WG for their feedback.

Appendices overview

The discussion on the appendices was focused on non-hepatic metabolism, non-specific binding, reactive metabolites, and test report recommendations.

6. Any Other Business

The WG was informed about the next steps in the process and the deadline to be fulfilled: 31st of May a consolidated draft scientific opinion should be sent to the PPR Panel for the final review, their

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

³ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

comments are expected by the 15th of June. This plan would allow the WG to present the draft scientific opinion for public consultation endorsement to the 111th PPR Panel (23rd of June).

New tasks were allocated to the experts.

7. Next meeting(s)

The next WG meeting will be held on the 17th of June 2021 by teleconference; additional WG (28th May 2021) could be further organized (to be confirmed).



Scientific Panel on Plant Protection Products and their Residues/Pesticide Peer Review Unit

MINUTES OF THE SUBGROUP MEETING ON DHM AND ITS TOXICOLOGICAL COVERAGE OF THE EFSA WORKING GROUP ON COMPARATIVE *IN VITRO* METABOLISM STUDIES

Held on 12 April 2021 (teleconference)

(Agreed on 20 April 2021)

Participants

■ **Working Group Members:**

Olavi Pelkonen (Chair) and Gundert-Remy Ursula.

■ **EFSA:**

Pesticides Peer Review (PREV) Unit: Juan Parra Morte and Martina Panzarea.

1. Welcome and apologies for absence

The Chair welcomed the WG members.

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 Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Scientific topic(s) for discussion

Toxicological coverage of a DHM

The chapter on Toxicological coverage of a disproportionate human metabolite (DHM) of the draft Scientific Opinion was discussed.

The terminology was also discussed, 'added' instead of 'modified' and 'uncertainty' instead of 'safety' should be used while referring to the additional uncertainty factor.

A flow chart to be included in a new annex was presented. A proposal to include the flow chart as a figure in the main text was discussed.

5. Any Other Business

It was agreed to discuss the structure of the opinion at the PPR Panel, where a decision whether to reduce the chemical analysis chapter should be taken.

6. Next meeting(s)

Next WG meeting is planned on the 10th and 11th of May 2021 by teleconference.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf



Scientific Panel on Plant Protection Products and their Residues/Pesticide Peer Review Unit

Minutes of the 8th meeting of the EFSA Working Group on Comparative *In Vitro* Metabolism studies

Held on 17 and 18 March 2021 (teleconference)

(Agreed on 30 March 2021)

Participants

■ **Working Group Members:**

Ursula Gundert-Remy, Jochem Louisse, Emanuela Testai, Olavi Pelkonen (Chair), Serge Rudaz, Gerrit Wolterink.

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

Sandra Coecke (Joint Research Center)

■ **EFSA:**

Pesticides Peer Review (PREV) Unit: Juan Parra Morte, Martina Panzarea

Scientific Committee and Emerging Risk (SCER) Unit: Jean Lou Dorne

1. Welcome and apologies for absence

The Chair welcomed the WG members.

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 Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Scientific topic(s) for discussion

Feedback from the 108th PPR Panel: main comments and amendments done

The content of the comments received from the PPR Panel 108th were presented to the WG members. First, the main comments relevant for the whole opinion were discussed (e.g. selection of test system, reactive metabolites, structure of the document). Secondly, specific comments by section were tackled.

Overview of the work done and revision of the draft opinion.

The main changes from the last meeting were presented and discussed. Comments provided by the Working Group members were addressed along the draft Scientific Opinion. The main points of discussion were reported below.

Toxicological assessment of human metabolites chapter

The most critical points of the chapter (e.g. toxicological assessment, in vivo follow up and TTC approach) were discussed by the WG's experts. In silico and in vitro methods will be defined in the Scientific opinion under the broader term New Approach Methodologies (NAMs).

New Annex: Determination disproportionate human metabolite (DHM) in vitro

This annex focusses on the reasoning behind the choice of three concentrations and three time point for testing the DHM in vitro.

Revision of the opinion: other chapters.

Comments provided by the experts were addressed along the Draft Scientific Opinion on: definition of the terms "secondary metabolite", interindividual differences, structure of the chemical analysis chapter, stereoisomers, relevant species for setting HBGVs and biomonitoring in humans.

The "recommendation chapter" and "annexes" were also reviewed.

5. Any Other Business

The Pesticides Steering Network (PSN) will be informed on the status of the project in the next PSN meeting (29th of March 2021).

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

A consolidated version of the Scientific Opinion will be presented to the PPR panel (21st of April 2021). A plan to consider the information under Annexes in the perspective article for publication was presented.

The WG was informed about the software MetaPath and the forthcoming EFSA's webinars on data entry tools MSS and DER composer.

6. Next meeting(s)

Next meeting is planned for May 2021 by teleconference.



Scientific Panel on Plant Protection Products and their Residues/Pesticide Peer Review Unit

Minutes of the 7th meeting of the EFSA Working Group on Comparative *In Vitro* Metabolism studies

Held on 10 and 11 February 2021 (teleconference)

(Agreed on 22 February 2021)

Participants

■ **Working Group Members:**

Ursula Gundert-Remy, Jochem Louisse, Emanuela Testai, Olavi Pelkonen (Chair), Serge Rudaz, Gerrit Wolterink.

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

Sandra Coecke (Joint Research Center).

■ **EFSA:**

Pesticides Peer Review (PREV) Unit: Juan Parra Morte, Mathilde Colas, Martina Panzarea.
Scientific Committee and Emerging Risk (SCER) Unit: Jean Lou Dorne

1. Welcome and apologies for absence

The Chair welcomed the WG members.

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 Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Scientific topic(s) for discussion

Chapter 8: Relevance assessment of Human Metabolites

The content and the work done by members of the working group to finalise the sections of chapter 8 were presented by Olavi. The most critical points of the chapter (e.g. *in silico*, *in vitro* and *in vivo* testing methods) were discussed by working group' members.

Appendixes

The main changes from the last meeting were presented to the experts. The definition of the term and the approaches to study and characterize the reactive metabolites were discussed. Comments provided by the Working Group members were addressed along the draft Scientific Opinion.

Update from the sub-group meeting 6.1 on Chemical Analysis

The outcome of the sub-group meeting 6.1. was presented by Serge and Olavi and discussed by the experts of the working group.

Discussion on the remaining comments of the Draft Scientific Opinion

Comments provided by the experts were addressed along the Draft Scientific Opinion: on disproportionate metabolites, human unique metabolites, human biomonitoring and experimental design and strategy.

The updated "recommendation chapter" was presented by Jean-Lou.

5. Any Other Business

It was proposed to invite a hearing expert to review recommended default incubation conditions (i.e. number of time points, concentrations, and replicates).

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

EFSA is currently working on additional appendix in the Scientific Opinion to specify how comparative in vitro metabolism data to be reported in IUCLID. The working group members will review this appendix.

The WG was informed that three members of the PPR panel will review the draft opinion by the next PPR Panel Meeting (24th February 2021).

The Pesticides Steering Network (PSN) will be informed on the status of the project in the next PSN meeting (March, 2021).

The new action points were also allocated to the working group members.

6. Next meeting(s)

Next meeting is planned for March 2021 by teleconference.



PESTICIDE PEER REVIEW UNIT

MINUTES OF THE SUBGROUP MEETING ON ANALYTICAL METHODS OF THE EFSA WORKING GROUP ON COMPARATIVE *IN VITRO* METABOLISM STUDIES

Held on 16 December 2020 (teleconference)

(Agreed on 4 January 2021)

Participants

■ **Working Group Members:**

Olavi Pelkonen and Serge Rudaz

■ **Hearing Experts:**

Not applicable

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

Not applicable

■ **EFSA:**

Pesticide Peer Review (PREV) Unit: Juan Parra Morte (Chair) and Mathilde Colas.

1. Welcome and apologies for absence

The Chair welcomed the WG members.

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 Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Scientific topic(s) for discussion

The chapter on chemical analysis of the draft Scientific Opinion was discussed.

Analytical workflow for unique human metabolite

The experts discussed the confidence in defining a unique human metabolite. The different steps of the workflow were agreed to enable the detection of unique human metabolites (e.g. incubation of the radiolabelled compound, the comparison of the relative peak area to the sum of radioactivity recovered, etc.).

Analytical workflow for disproportionate metabolites

The experts also drafted the analytical workflow to cover disproportionate metabolites. Specific topics were highlighted, such as the use of biological replicates with the related statistical method and the recommended criteria for considering the ratio of 4 in the chemical analysis chapter.

Other points of discussion

The use of radiolabelled and non-radiolabelled material to perform comparative in vitro metabolism studies was questioned. In addition, the concept of stereoisomers was introduced as well as the detection of potential reactive intermediate.

5. Any Other Business

Not applicable.

6. Next meeting(s)

Next WG meeting is planned on the 10th and 11th of February 2020 by teleconference.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf



PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 6TH MEETING OF THE EFSA WORKING GROUP ON COMPARATIVE *IN VITRO* METABOLISM STUDIES

Held on 23 and 24 November 2020 (via teleconference)

(Agreed on 4 December 2020)

Participants

■ **Working Group Members:**

Ursula Gundert-Remy, Jochem Louisse, Emanuela Testai, Olavi Pelkonen and Serge Rudaz

■ **Hearing Experts:**

Gerrit Wolterink

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

Sandra Coecke (Joint Research Center)

■ **EFSA:**

Pesticides Peer Review (PREV) Unit: Juan Parra Morte (Chair) and Mathilde Colas
Scientific Committee and Emerging Risk (SCER) Unit: Jean Lou Dorne

1. Welcome and apologies for absence

The Chair welcomed the WG members and the hearing expert, Gerrit who was invited to give his advice on how metabolites and degradation products of pesticides should be assessed regarding human health.

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 Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Scientific topic(s) for discussion

Status of the comparative *in vitro* metabolism project: adoption of a new charter and terms of reference

The status of the project was presented by Juan. The amended charter considering extension of the deadline, the second problem formulation of the charter (i.e. toxicological relevance of human metabolites) as well as the stronger involvement of the PPR Panel in the project was presented. The next steps of the project were presented to the experts, including working group meetings and the public consultation.

Definition of the terms "unique human metabolite" and "disproportionate metabolite"

The terms "unique human metabolite" and "disproportionate metabolite" were defined and agreed by the Working Group members.

Discussion on the second problem formulation

The second problem formulation regarding the toxicological relevance of disproportionate and unique human metabolites was approached. In line with the toxicological data package available or recommended in other guidelines (e.g. EFSA guidance on the Residue definition), the relevance assessment of human metabolites was examined under different scenarios. The hazard and risk assessment of disproportionate and unique human metabolite were considered. Theoretical case studies and examples of calculations were presented by the experts.

Presentation of the main changes and remaining comments

The main changes from the last meeting were presented to the experts. Comments provided by the Working Group members were addressed along the draft Scientific Opinion.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

5. Any Other Business

A sub-group (Olavi, Serge and EFSA) dedicated on the analytical part will be organised in December. Hearing experts from the industry and academia will be invited to address specific questions during the next working group meeting on the second problem formulation.

6. Next meeting(s)

Next meeting is planned for December 2020 by teleconference.



PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 5TH MEETING OF THE EFSA WORKING GROUP ON THE GUIDANCE ON THE *IN VITRO* COMPARATIVE METABOLISM STUDIES

Held on 8 and 9 July 2020 (Teleconference)

(Agreed on 22 July 2020)

Participants

■ **Working Group Members:**

Ursula Gundert-Remy, Jochem Louisse, Emanuela Testai, Olavi Pelkonen and Serge Rudaz.

■ **Hearing Experts:**

Not applicable.

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

Sandra Coecke (Joint Research Center).

■ **EFSA:**

Pesticide Peer Review (PREV) Unit: Alfonso Lostia (Chair), Juan Parra Morte (Co-Chair) and Mathilde Colas.

Scientific Committee and Emerging Risk (SCER) Unit: Jean Lou Dorne

1. Welcome and apologies for absence

The Chair welcomed the participants.

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 Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Scientific topic(s) for discussion

Discussion on experimental layout

The interpretation part on disproportionate metabolites was discussed with the support of an example of calculation. Case studies were presented by one expert to contribute to the definition of criteria to be recommended for the study design (i.e. concentrations, time points).

Discussion on the remaining comments of the draft guidance

Comments provided by the experts were addressed along the draft guidance on the study design and experimental strategy, *in vitro* system, test item and reference compounds, *in vitro* method, chemical analysis, and interpretation of the results.

Hearing experts

The experts agreed to invite hearing experts for the next meeting to discuss the study design for long-term incubation using plated hepatocytes (e.g. pooling, positive controls, sampling points, etc).

5. Any Other Business

Use of teams

The experts were trained on the use of Teams. From now on the experts will work on Teams.

6. Next meeting(s)

Next meeting is planned on the 12th and 13th of October 2020 by teleconference.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf



PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 4TH MEETING OF THE EFSA WORKING GROUP ON THE GUIDANCE ON THE *IN VITRO* COMPARATIVE METABOLISM STUDIES

Held on 12 June 2020 (Teleconference)

(Agreed on 2 July 2020)

Participants

■ **Working Group Members:**

Ursula Gundert-Remy, Jochem Louisse, Emanuela Testai, Olavi Pelkonen and Serge Rudaz.

■ **Hearing Experts:**

Not applicable

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

Sandra Coecke (Joint Research Center).

■ **EFSA:**

Pesticides Peer Review (PREV) Unit: Alfonso Lostia (Co-Chair), Juan Parra Morte (Chair) and Mathilde Colas.

Scientific Committee and Emerging Risk (SCER) Unit: Jean Lou Dorne

1. Welcome and apologies for absence

The Chair welcomed the participants.

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 Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Scientific topic(s) for discussion

Discussion on remaining comments of the draft guidance

Some of the remaining comments on the draft guidance were addressed directly by all the WG members. The general editorials changes were accepted and the relevant references were included in the draft guidance. The discussion focused in particular on the interpretation part, the study design and the strategy recommended. Therefore, a more advanced version of the guidance has been designed.

5. Any Other Business

Not applicable

6. Next meeting(s)

Next meeting is planned on July 2020 (8-9th) by teleconference.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf



PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 3RD MEETING OF THE EFSA WORKING GROUP ON THE GUIDANCE ON THE *IN VITRO* COMPARATIVE METABOLISM STUDIES

Held on 04-05 May 2020 (Teleconference)

(Agreed on 20 May 2020)

Participants

■ **Working Group Members:**

Ursula Gundert-Remy, Jochem Louisse, Emanuela Testai, Olavi Pelkonen and Serge Rudaz.

■ **Hearing Experts:**

Ugo Zanelli (Monday 04th, 14.00-16.00) and Paul Whalley (Tuesday 05th, 9.00-11.00).

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

Sandra Coecke (Joint Research Center).

■ **EFSA:**

Pesticide Peer Review (PREV) Unit: Alfonso Lostia (Co-Chair), Juan Parra Morte (Chair) and Mathilde Colas.

Scientific Committee and Emerging Risk (SCER) Unit: Jean Lou Dorne

1. Welcome and apologies for absence

This meeting, originally scheduled as a physical meeting, was converted into a teleconference to avoid traveling to EFSA in line with the measures established to reduce the risk of coronavirus infection.

The Chair welcomed the participants.

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 Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Scientific topic(s) for discussion

Discussions with hearing experts.

The hearing experts Ugo Zanelli and Paul Whalley were asked to present their views on several issues related to *in vitro* metabolism assessment. Ugo Zanelli presented his view on the study design (positive control, concentration, time points, species), long-term incubation, preliminary clearance experiment, the use of radiolabel and non-radiolabel material and structural determination. Paul Whalley presented his views on rationale for testing one concentration and one time point, the definition of unique and disproportionate metabolite and their follow-up.

The WG members thanked the hearing experts and discussed some points on study design, methodologies for specific cases (slow metabolism, disproportionate metabolites), clearance measurements and analytical methods.

Discussions on experimental strategy, the interpretation part and review of main comments on the draft guidance

During the meeting, the interpretation part was addressed in priority. Jochem Louisse prepared and presented his synthesis on the specific case of disproportionate metabolites and discussions were undertaken with the WG members.

Additionally, discussions were focused on the study design such as the number of time-points and concentrations required, and recommendations for species in short-term incubation. The section on analytical methods described by Serge Rudaz was also reviewed by all experts.

Main comments on the draft guidance were reviewed and agreed by all the WG members. Tasks were allocated for the next WG meeting to the experts.

5. Any Other Business

The potential extension of the WG's project was introduced to the experts and will be further defined by EFSA during the next following meeting.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

6. Next meeting(s)

Next meetings are planned on July 2020 (8-10th) by teleconference. An additional meeting in mid-June may take place.



PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 2ND MEETING OF THE EFSA WORKING GROUP ON THE GUIDANCE ON THE *IN VITRO* COMPARATIVE METABOLISM STUDIES

Held on 18-20 February 2020, Parma (Italy)

(Agreed on 11 March 2020)

Participants

■ **Working Group Members:**

Ursula Gundert-Remy, Jochem Louisse, Olavi Pelkonen, Serge Rudaz.

■ **Hearing Experts:**

Not applicable.

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

Sandra Coecke (Joint Research Center).

■ **EFSA:**

Pesticides Peer Review (PREV) Unit: Alfonso Lostia (Co-Chair), Juan Parra Morte (Chair) and Mathilde Colas.

Scientific Committee and Emerging Risk (SCER) Unit: Jean Lou Dorne (attending 20th February).

1. Welcome and apologies for absence

The Chair welcomed the participants. Apologies were received from Ms Emanuela Testai.

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 Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Scientific topic(s) for discussion

Interpretation chapter with support of theoretical case-studies

During the 2nd meeting of the EFSA WG, discussions were mainly focused on the interpretation chapter. Case-studies were presented by the WG members to support the discussion. The main topics addressed were the strategy for long-term exposure, the definition of slow-metabolised chemicals and unique human metabolite and metabolic competence. Additionally, recommendations about the criteria for selecting the most appropriate test system (s), test item and reference compounds were set by the EFSA WG. The case of disproportionate metabolites was also addressed. Based on the discussion, a new structure of the guidance was proposed.

Analytical methods chapter

Most relevant methods of analysis to be recommended for *in vitro* comparative metabolism studies were commented by the WG members. The main points of discussion were about identification methods, the case of isomers, tentative analysis to qualify *in vitro* rat compared to *in vivo* rat and radioactive techniques.

5. Any Other Business

Hearing experts

The experts agreed to invite hearing experts for the next WG meeting to support the discussion on the experimental layout and concentrations. Specific questions were prepared by the WG.

6. Next meeting(s)

Next meeting is planned on May 2020.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf



PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 1ST MEETING OF THE EFSA WORKING GROUP ON THE GUIDANCE ON THE *IN VITRO* COMPARATIVE METABOLISM STUDIES

Held on 20-22 November 2019, Parma (Italy)

(Agreed on 11 December 2019)

Participants

■ **Working Group Members:**

Ursula Gundert-Remy, Jochem Louisse, Olavi Pelkonen, Serge Rudaz and Emanuela Testai.

■ **Hearing Experts:**

Not applicable.

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

Not Applicable.

■ **EFSA:**

Pesticide Peer Review (PREV) Unit: Alfonso Lostia (Chair) and Mathilde Colas.

Scientific Committee and Emerging Risk (SCER) Unit: Jean Lou Dorne.

1. Welcome and apologies for absence

The Chair welcomed the participants. Apologies were received from Ms Sandra Coecke (European Commission, DG Joint Research Center) and Mr Juan Manuel Parra Morte (EFSA, PREV Unit).

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 Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Scientific topic(s) for discussion

Introduction and presentation of the project

EFSA introduced the Peer review process and presented the three Work Packages (WP) of the *in vitro* comparative metabolism project: Workshop (WP1), Guidance (WP2) and Public Consultation (WP3). The chair presented the outcome of the Workshop on *in vitro* metabolism held in November 2018 in Parma (EFSA, 2018). The planning for Guidance finalisation and Public Consultation was shared with the experts (i.e. First Quarter 2020).

Case-studies

The WG members presented and discussed examples from the peer review process as case-studies. Recommendations about the biological test systems, test item, reference control and the study design were set by the WG.

Structure and chapters of the EFSA draft guidance

The structure of the guidance (table of contents) was determined by the WG and each chapter was allocated to WG members for the draft.

5. Any Other Business

Promotion of the project

The project will be presented in the future externally during conferences or through publications in a scientific journal.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Endorsement of the EFSA Guidance by the PPR Panel

The WG agreed with the endorsement by the PPR Panel. Olavi kindly agreed to regularly inform the PPR Panel on the guidance development.

6. Next meeting(s)

Next meeting is planned on February 2020.

Next discussions will focus on the “interpretation” chapter.