PESTICIDE PEER REVIEW UNIT

SCIENTIFIC PANEL ON Plant Protection Products and their Residues /PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 26TH MEETING OF THE WORKING GROUP ON "Developing Integrated Approaches on Testing and Assessment (IATA) case studies on Developmental Neurotoxicity"

Held on 8 of December 2020, teleconference

(Agreed on 21 of December 2020)

Participants

- Working Group Members:

  Kevin Crofton

  Antonio F. Hernández-Jerez

  Martin Paparella

  Martin Wilks

  Susanne Hougaard Bennekou

  Ioanna Tzoulaki

- Hearing Experts[1]:

  Ellen Fritsche

- European Commission and/or Member States representatives:

  Anna Price. JRC-EC

  Verena HAUDEK-PRINZ. AGES-Austria

- EFSA:

  PREV Unit: Andrea Terron (Chair of the teleconference), Iris Mangas, Martina Panzarea

- Observers:

  Not Applicable

[1] As defined in Article 17 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/en/keydocs/docs/expertselection.pdf.

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 Independence[2] and the Decision of the Executive Director on Competing Interest Management[3], 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)

Ellen Fritsche answered a question as regards of the integration of the In vitro battery methods and results in the Draft Scientific Opinion.

5. Scientific topic(s) for discussion

5.1. Status, objectives of the meeting and next steps

The chair presented an overview of the status of the Draft of the Scientific Opinion and its related Appendices. In order to transparently report the scientific assessment conducted, the Scientific Opinion will include the 5 appendices as follows containing all the data and assessments of the WG for the IATA case studies:

Appendix A	Protocol of the Scientific Opinion
Appendix B1	Statistical analysis report
Appendix B2.1	List of included studies and excluded, and their due justification, for deltamethrin
Appendix B2.2	List of included studies and excluded, and their due justification, for flufenacet
Appendix B3.1	Outcome of the ROB for deltamethrin
Appendix B3.2	Outcome of the ROB for flufenacet
Appendix B3.3	Outcome of the ROB for the IVB (In vitro battery)
Appendix B4.1	Graph report In vivo and in vitro deltamethrin

[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

Appendix B4.2 Human evidence table

Appendix B4.3 Graph report In vivo and in vitro for flufenacet

Appendix B5.1 Uncertainty analysis tables for deltamethrin

Appendix B5.2 Uncertainty analysis tables for flufenacet

Appendix C AOP development and assessment (OECD template)

Appendix D IATA for deltamethrin (OECD template)

Appendix E IATA for flufenacet (OECD template)

5.2. IATA, final draft text for discussion and appointment of internal reviewer

The comments received on the Draft text were discussed and solved. The draft IATA for deltamethrin case study was agreed by the WG and an internal reviewer was appointed in the WG for a further revision of the text to be addressed by EFSA and the Chair of the WG.

5.3. AOP final draft text for discussion and appointment of internal reviewer

The comments received on the Draft text were discussed and solved. The draft AOP for deltamethrin case study was agreed by the WG and an internal reviewer was appointed in the WG for a further revision of the text to be addressed by EFSA and the Chair of the WG. It was agreed that before sending this document to the OECD for publication of the AOP further revision would be needed.

5.4. Appendix A and B, final draft text

Draft Appendix B was presented, it is considered finalized.

5.5. Drafting of the SO

A Draft of the Scientific Opinion was presented and discussed. Recommendations were further discussed by the WG and drafted during the meeting. Further revision of the text would be needed in the next days before sending it to the reviewers of the PPR Panel on the 20th December.

5.6. Human observational studies (HOS), final draft text

Final text was agreed by the WG after being presented by the epidemiology experts.

5.7. Flufenacet case study

A Draft of the text was presented by EFSA and it will be finalized during the following week.

6. Next meeting(s)

Meeting to address the Panel reviewers' comments in 1Q 2021.

PESTICIDE PEER REVIEW UNIT

SCIENTIFIC PANEL ON Plant Protection Products and their Residues /PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 25TH MEETING OF THE WORKING GROUP ON "Developing Integrated Approaches on Testing and Assessment (IATA) case studies on Developmental Neurotoxicity"

Held on 3 December 2020, teleconference

(Agreed on 17 December 2020)

Participants

- Working Group Members:
  Susanne Hougaard Bennekou

- Hearing Experts:
  Ellen Fritsche

- European Commission and/or Member States representatives:
  Verena HAUDEK-PRINZ. AGES-Austria

- EFSA:
  PREV Unit: Andrea Terron (Chair of the teleconference), Iris Mangas, Martina Panzarea

- Observers:
  Not Applicable

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 Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] 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)

Ellen Fritsche answered a question as regards of the test systems and test methods of the assays included in the IATA for deltamethrin.

5. Scientific topic(s) for discussion

5.1. Status, objectives of the meeting and next steps

The chair presented an overview of the status of the Draft of the IATA for deltamethrin and the plan for the IATA for flufenacet following OECD template.

5.2. Addressing the comments of the document and finalization of the IATA for deltamethrin.

The conclusion of the IATA was discussed, and the specific comments provided in the document were addressed. The contextualization of the human data will be drafted by the epidemiology experts and the Draft document will be sent to the WG members for commenting during next WG meeting.

6. Next meeting(s)

TC between 14-18h on the 8th of December.

[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 24th MEETING OF THE WORKING GROUP ON "Developing Integrated Approaches on Testing and Assessment (IATA) case studies on Developmental Neurotoxicity"

Held on 24th November 2020 (teleconference)

(Agreed on 14 December)

Participants

- Working Group Members:
  Susanne Hougaard.

- Hearing Experts:
  Ellen Fritsche

- European Commission and/or Member States representatives:
  Verena Haudek-Prinz (AGES)

- EFSA:
  PREV Unit: Andrea Terron (chair of the TC), Iris Mangas
  AMU Unit: Elisa Aiassa, Laura Martino, Federica Barrucci

- Others:
  Not applicable

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 Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] 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

4.1. Evidence synthesis, integration of the evidence in the AOP informed IATA and uncertainties analysis

The following points were presented and discussed by the WG:

The plan for the development of the IATA was discussed and agreed by the working group.

4.2. IATA case study.

This meeting was conducted with a limited number of working group members and a hearing expert. The intent was to finalise the text of the IATA case study. The hearing expert was consulted for the appropriateness of the text describing the test methods used in the DNT IVB and for the interpretation of the outcome of the DNT IVB.

The experts during the meeting also discussed how to include the outcome of the Bayesian network analysis in the discussion and conclusion of the IATA case study.

4.3. Actions for the next meetings:

Finalization of the IATA case study.

5. Any Other Business

Not applicable.

6. Next meeting(s)

8th of December 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 23rd MEETING OF THE WORKING GROUP ON "Developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity".

Held on 23 November 2020 (teleconference)

(Agreed on 14 December 2020)

Participants

- Working Group Members:
  Martin Paparella, Kevin Crofton.

- Hearing Experts:
  Not applicable.

- European Commission and/or Member States representatives:
  Verena Haudek-Prinz (AGES)

- EFSA:
  PREV Unit: Andrea Terron (chair of the TC), Iris Mangas
  AMU Unit: Elisa Aiassa, Laura Martino, Federica Barrucci

- Others:
  Tim Shafer from the US EPA was invited as observed

1. Welcome and apologies for absence

The Chair welcomed the participants. The chair welcomed Tim Shafer from the US EPA. Tim Shafer was invited because his recognized expertise in mechanistic studies conducted in the microelectrode array with many chemicals including pyrethroids.

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[1] and the Decision of the Executive Director on Competing Interest Management[2,] 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

4.1. Postulated AOP network and Bayesian network analysis

This meeting was held with selected WG members with the intention to discuss practical details for the finalization of the Appendix C on the postulated AOP network. The experts agreed on the final version of the overall quantitative weight of evidence of the postulated AOP network.

The experts also agreed to include a "consistency table" summarising the available evidence, including the adverse outcome, from additional pyrethroids. The evidence summarised in the table will be retrieved from the DNT IVB and from the scientific studies appraised for the prototypical substance used for the development of the postulated AOP network. The AO would however be retrieved from available regulatory studies for which a systematic review would not be conducted.

4.2. Actions for the next meetings:

Finalization of the Appendix C of the Scientific Opinion "Postulated AOP network".

5. Any Other Business

None

6. Next meeting(s)

8th of December 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

PPR/PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 22nd MEETING OF THE WORKING GROUP ON "Developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity"

Held on 10, 16 and 17 November 2020 (teleconference)

(Agreed on 7 December 2020)

Participants

- Working Group Members:

  Antonio Hernandez (chair), Martin Wilks, Martin Paparella, Kevin Crofton, Susanne Hougaard, Ioanna Tzoulaki.

- Hearing Experts:

  Ellen Fritsche

- European Commission and/or Member States representatives:

  Anna Price (JRC), Verena HAUDEK-PRINZ (AGES)

- EFSA:

  PREV Unit: Andrea Terron (chair of the TC), Iris Mangas

  AMU Unit: Elisa Aiassa, Laura Martino, Federica Barrucci

- Others:

  Not applicable.

1. Welcome and apologies for absence

The Chair welcomed the participants. Apologies were received from Ioanna Tzoulaki on the 16th November and from Verena Haudek-Prinz on the 17th.

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[1] and the Decision of the Executive Director on Competing Interest Management[2,] 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

4.1. Evidence synthesis, integration of the evidence in the AOP informed IATA and uncertainties analysis

The following points were presented and discussed by the WG:

The plan for the development of the IATA was discussed and agreed by the working group.

4.2. EFSA Proposal on the evidence synthesis and integration to establish a putative AOP.

The working group discussed the overall assessment of the AOP and the contribution of the Bayesian network analysis. The following items were discussed: 1) overall assessment of the conditional probabilities analysis 2) impact of the joint probabilities analysis on the postulated AOP network and on individual AOP strings; impact of the KEs and testing thereof on the mechanistic understanding of the AOP, 3) impact of the marginal probability analysis on the quantification of the overall WoE.

4.3. Human observational studies:

A draft text was discussed by the working group. A new draft is expected to be presented at the next meeting for inclusion in the SO and IATA case study.

4.4. Actions for the next meetings:

One meeting will be dedicated to the finalization of the AOP. Two meetings will be dedicated to the finalization of the IATA. A final working group meeting will be dedicated to the first draft of the SO.

[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

The working group discussed the possibility to submit the postulated AOP network to the OECD for inclusion in the AOP wiki.

6. Next meeting(s)

8th of December by teleconference.

PPR /PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 21ST MEETING OF THE WORKING GROUP ON "Developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity"

Held on 13, 14, 15 and 16 October 2020 (teleconference)

(Agreed on 29 October 2020)

Participants

- Working Group Members:

  Kevin Crofton

  Antonio F. Hernández-Jerez (Chair of the working group)

  Martin Paparella

  Martin Wilks (participated on the 13th from 17 to 18h)

  Susanne Hougaard Bennekou

  Ioanna Tzoulaki (participated on 13th, 14th (until 16h)

- Hearing Experts:

  Ellen Fritsche

- European Commission and/or Member States representatives:

  Verena Haudek-Prinz (AGES-Austria)
  Anna Price (European Commission JRC,Institute for Health and Consumer Protection)

- EFSA:

  Pesticide Peer Review (PREV) Unit: Andrea Terron (Chair), Iris Mangas, Martina Panzarea

  Assessment and Methodology (AMU) Unit: Laura Martino, Federica Barrucci

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 Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], 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)

Ellen Fritsche

5. Scientific topic(s) for discussion

5.1. Status, objectives of the meeting and next steps

The chair presented an overview of the status of the Scientific Opinion and the objectives of the meeting.

5.2. Introduction to the Bayesian network and application for the probability estimation for KER and overall AOP

AMU Unit presented EFSA proposal to use a Bayesian Network (BN) approach to assess the AOP (probability of the KER and the overall AOP Network). The goal is to shift from the deterministic approach to a probabilistic approach for the AOP assessment. The reasons to use a BN approach were discussed: BN: (1) describe the global dependency structure among MIEs, KEs and AOs described in the AOP network; (2) It allows to measure the impact of introducing new information and updating the probabilities; (3) It allows to factorise the multivariate probability distribution of the set of variables included in the AOP network using lower-dimensional 'local distributions' taking the form of conditional probability tables for each node that depend only on its parents.

[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

BN has been applied in the area of skin sensitization (McDowell and Jaworska 2002; Jaworska and Hoffmann, 2010; Jaworska et al., 2010, 2011, 2013) and for quantification of Adverse Outcome Pathway networks (Carrigera et al., 2016; Jannicke Moe., 2020).

In short, a BN is a probabilistic graphical model that represents a set of variables and their conditional dependencies via a Directed Acyclic Graph. They are defined as:

- a *Network structure* that expresses the conditional dependence/independence relationships among the variables of the set X=(MIE1, …., AO1) in the model
- a *Directed Acyclic Graph* (DAG) composed of a set of nodes X = {MIE1, …., AO1} and a set of arcs V which are identified by pairs for nodes in X, e.g. vij = (xi , xj)
- a *Global probability distribution of X*

The BN allows to update the initial belief about the probability occurrence of each KE or AO (elicited in the previous steps of the process) based on the knowledge of occurrence of MIE or other KEs (i.e. to derive conditional probabilities) and to combine the conditional probabilities and derive the global probability of the AOP network based on lower-dimension local probability distributions. It is important to highlight that BN cannot be used to compare AOP networks with different number of nodes (the greater the number the lower is the expected overall probability) and to describe loops or cycles in the AOP network.

The experts were asked to conduct the exercise independently in the next morning, for that AMU prepared a Bayesian Network dossier for elicitation of the AOP criteria.

5.3. Finalize comments on the proposed AOP

This point was briefly discussed since most of the critical points (major changes on the Network) were previously solved and the minor changes were decided to be solved after the WG meeting.

As a result of the Deltamethrin IATA case study, the WG developed an Evidence-based AOP Network. This AOP Network will be used in the IATA case study to answer the regulatory problem formulation on DNT hazard characterization of DNT for deltamethrin. It is noteworthy that this AOP network is stressor driven, using deltamethrin as a prototype chemical. For that, all the experimental evidence from the systematic literature review was used and the outsourced in vitro testing battery was included in a second step.

All the KEs included are the product of this evidence-based approach and the KERs will be developed for each adjacent upstream-downstream pair of KEs. KERs will be evaluated using a quantitative probabilistic approach for its biological plausibility, empirical support, and quantitative understanding (see Item 5.5). A draft graphical format of the AOP network was discussed at the WG meeting and will be used to develop the AOP network.

5.4. Contextualization of human data

The WG discussed a proposal for the integration of the human evidence in the DNT hazard characterization of deltamethrin. Three aspects were considered relevant:

1. To include in the text considerations on the biological plausible mechanistic link to support evidence, if any, between deltamethrin and AO in human, based on the available evidence.

2. To provide a summary table on the human evidence for deltamethrin as retrieved from the literature.

3. To provide a summary of the uncertainty analysis on the human evidence including the weaknesses and strengths of the human observational studies, risk of bias, potential confounders and coexposure to other factors.

The work will be part of the scientific opinion and a new draft text will be presented at the next WG meeting.

5.5. Probability estimation of the KERs

Nine experts conducted the elicitation exercise in the Bayesian Network dossier independently.

The experts were asked to assess the three criteria Biological plausibility, Essentiality and dose and temporal concordance for each KERs having in mind that exposure to the stressor deltamethrin occurs (E0) as follows:

Criteria to assess the relationship	Assessment
What is the level of Biological plausibility that KEn is occurring when also KEn-1 occurs	Low/Moderate/High
What is the level of Essentiality of the occurrence of KEn-1 for the- KEn to occur	Low/Moderate/High
Is there a Dose response and temporal concordance in the relationship between KEn and KEn-1	Low/Moderate/High

Special attention in the discussion was given to the case of KE that were conditioned by to upstream KE ("triplets"; e.g. KE2 conditioned by KE1 and KE7 in the draft Figure presented).In this case the experts were asked to consider that the downstream KE is occurring under the condition that the two upstream KEs are 1-1, 1-0, 0-1 and 0-0 , meaning 1 that is happening and 0 that is not happening.

The assessment and rational were discussed along days 2, 3 and 4 of the WG meetings. A consensus judgement was agreed for each of the criteria and KERs. This consensus judgement was translated to a consensus conditional probability that quantifies the certainty of each KER of the Network. The consensus probability was preestablished considering the different possible combinations of the answers for the criteria for AOP assessment (see table above). The more evidence is available for these conditioned combinations, the more the probability value may deviate from 0.5.

A BN dossier with the consensus judgement, the consensus probability and the rational was created by EFSA to summarize the exercise and it will be part of the Scientific Opinion.

5.7. Ability of the network to predict behaviour of others pyrethroids (assessment of data consistency)

A consistency table was created by EFSA including evidence from other pyrethroids for each of the KE. It was noted that this evidence was not systematically retrieved and appraised.

There was no time to further discuss how to integrate this evidence in the AOP and this discussion was postponed to the next meeting.

6. Next meeting(s)

TC between 14-18h on the 10th, 16th and 17th of November.

PPR /PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 20th MEETING OF THE WORKING GROUP ON "Developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity"

Held on 16, 23, 29 and 30 July 2020 (teleconference)

(Agreed on 16 August 2020)[1]

Participants

- Working Group Members:

  Kevin Crofton

  Antonio F. Hernández-Jerez

  Martin Paparella

  Susanne Hougaard Bennekou

  Martin Wilks

  All have participated via teleconference, in all points of the agenda.

- Hearing Experts:

  Kristina Bartmann (University Dusseldorf, Germany)

  Jonathan Blum (University of Konstanz, Germany)

  Stefan Masjosthusmann (University Dusseldorf, Germany)

  Ellen Fritsche (University Dusseldorf, Germany)

  Marcel Leist (participated only the 16, 23 and 30th; University of Konstanz, Germany).

- European Commission and/or Member States representatives:

  Verena Haudek-Prinz (AGES-Austria)
  Anna Price (European Commission JRC)

[1] Minutes should be published within 15 working days of the final day of the relevant meeting.

- EFSA:

  Pesticide Peer Review Unit: Andrea Terron (Chair); Iris Mangas; Martina Panzarea

  Assessment and Methodology Unit: Laura Martino; Federica Barrucci

- Observers:

  Ingo Bichlmaier European Chemicals Agency (ECHA)

  Ulla Simanainen European Chemicals Agency (ECHA)

  Kathrin Bothe (Bayer Crop Science)

  Anja Hueser (Bayer Crop Science)

  Dennis Mueller (Bayer Crop Science)

  Gaby Schmuck (Bayer Crop Science)

  Majorie Van Duursen (NGO observer, Vrije Universiteit Amsterdam)

1. Welcome and apologies for absence

The Chair welcomed the participants.

2. Adoption of agenda

The agenda was adopted, for practical reason in order to be able to finalize all the points of the agenda an additional TC-meeting day was needed, and it was ad-hoc planned on the 30th of July.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence[2] and the Decision of the Executive Director on Competing Interest Management[3], 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)

The WG invited the hearing expert for answering the following question:

How can we map the uncertainties and inconsistencies of the test methods and test systems used in the in vitro test battery?

A presentation was provided from the hearing experts and they answered specific questions from the WG experts during the uncertainties analysis exercise (see scientific topic 5.2).

5. Scientific topic(s) for discussion

5.1. Update on the DNT IATA project, presentations for the observers.

EFSA PREV unit provided a summary of the project including the scope, the Terms of Reference, problem formulation and methodology applied, results from the systematic literature review, results from the critical appraisal of the evidence exercise, current status of the evidence synthesis and uncertainty analysis and plan for public consultation of the EFSA Scientific Opinion. EFSA AMU unit provided a summary of the uncertainty analysis methodology including a presentation on Expert Knowledge Elicitation (EKE) including a practical example of the Roulette method.

[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

5.2. EFSA report; brief introduction to the test methods and test systems.

The hearing experts provided a detailed presentation on the test methods and test systems used including the rationale for their selection for the outsourced in vitro testing battery under EFSA grant OC/EFSA/PRAS/2017/01 (see Figure 1).

The University of Konstanz used as biological system hiPSCs-derived neural crest cells (NCC). The detailed methods of the cMINC (migration of NCC) and the neurite outgrowth assays were presented, this will be part of the Scientific Report from the contractors.

The Leibniz Research Institute for Environmental Medicine used as biological system primary human NPC cells commercially available in Lonza Bioscience laboratories and differentiated into neurons, radial glia or oligodendrocytes in a mixed culture in IUF laboratory. The detailed methods of the migration, differentiation and human neuronal network formation (hNNF) assay were presented, this will be part of the Scientific Report from the contractors.

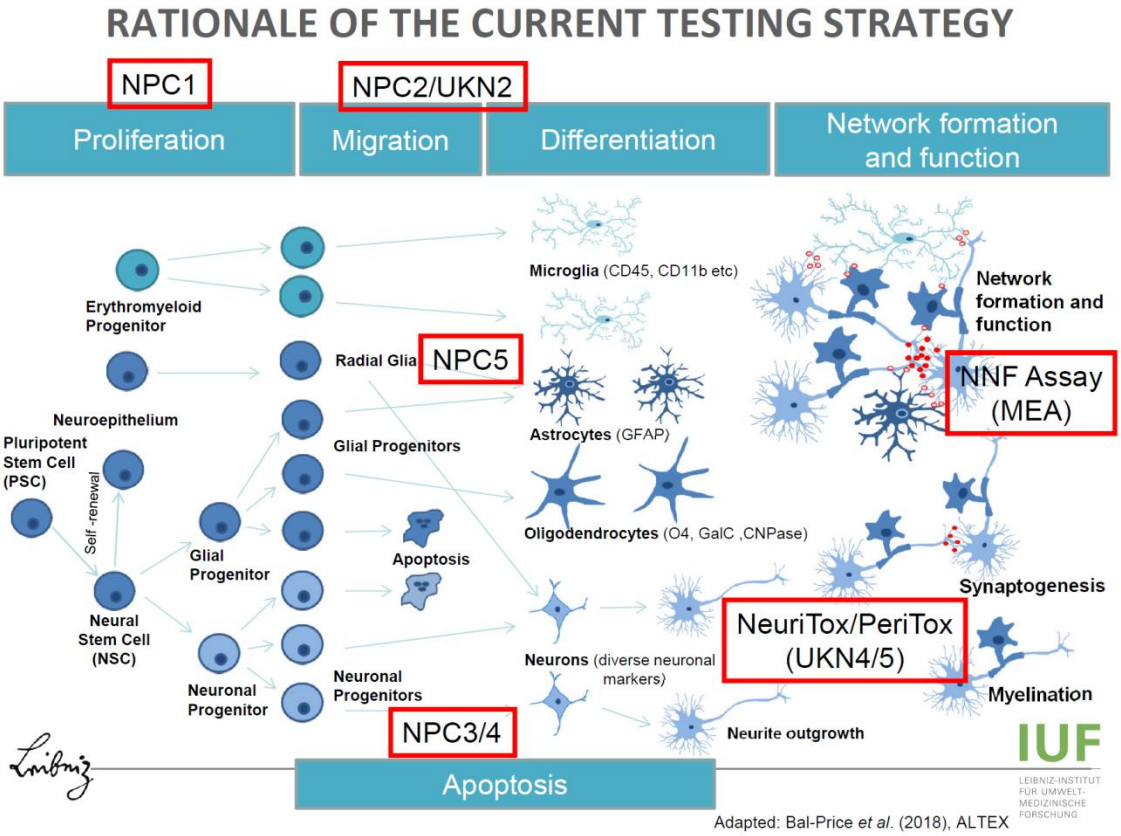


Figure 1

5.3. Questions from the observers.

Questions were received mainly as regards of (1) the definition of Hit (specific/unspecific/borderline/no-Hit) in both laboratories; (2) the categorization of compounds based on prediction models and differences with public literature evidence approaches and (3) the maximum concentrations assayed in the in vitro test.

Hearing experts provided a detailed answer for 1 and 2 that will be part of the Scientific Report from the contractors**.** One expert of the WG commented that the term of 'prediction' models used in the battery report could need a revision and would be more appropriate to use the term/s: results classification or (data) analysis models; since this models are algorithms used to fit the data to curves but do not 'predict' anything beyond the testing itself.
For question 3 hearing experts explained that 20 uM was used in all assays as a practical approach and this explanation will be also included in the report.

End of day 1

DAY 2

5.4. In-vitro endpoints discussion for deltamethrin

Experts conducted an uncertainty analysis for the in vitro evidence guided by AMU unit, where several questions provided by EFSA Staff assessed the different sources of uncertainty and inconsistency within specific endpoints and within key events. All the data was extracted using Distiller software and graphs were prepared using R Software in order to independently and transparently assess data based first on statistically significance and second on biologically relevance, during the discussion. The evidence was integrated using the AOP framework to map and classify the endpoints and the following key events (KE) were analysed: Neuronal morphology, migration, proliferation, oligodendrocyte differentiation, synaptogenesis and apoptosis.

First, the questions were independently answered by the in vivo experts, supported by EFSA staff. Second, the uncertainties were discussed and agreed by the full WG, and a final conclusion on the uncertainties and inconsistencies was drawn by specific endpoint and by KE using a probabilistic approach to answer these final questions:

1. Q1:Is it probable that exposure to DM triggers the KE (assuming a monotonic concentration-response relationship) in human and/or rat and/or mouse neuro cells in development? Biological response is based on expert judgements using EC50/IC50/BMR50 taking into consideration also the uncertainties in the experiments. NO: Prob<=0.66; YES: Prob>0.66
2. Q2: What is the lowest concentration at which the exposure to DM triggers the KE (assuming a monotonic concentration-response relationship) in human and/or rat and/or mouse neuro cells in development? Biological response is based on expert judgements using EC50/IC50/BMR50 taking into consideration also the uncertainties in the experiments.

End of day 2

DAY 3

5.5. In-vitro endpoints (NNF and patch clamp) discussion for deltamethrin

Experts conducted the uncertainty analysis, guided by AMU unit, on the multielectrode array (MEA) studies for the neural network formation evidence. Several questions were provided by EFSA Staff in order to assess the different sources of uncertainty and inconsistency within specific endpoints, endpoints categories, and within the KE.

For that purpose, all the data was extracted using Distiller software and graphs were prepared using R Software in order to independently and transparently assess data based first on statistically significance and second on biologically relevance, during the discussion. The evidence was integrated in three endpoints categories: general activity, bursting activity and network connectivity.

End of day 3

DAY 4

5.5. In-vitro endpoints (NNF) discussion for deltamethrin

The different NNF endpoints were integrated into a potential KE and the EKE methodology was used in order to draw conclusions. The AMU unit guided the experts and the following questions were used; experts answered them independently in as unbiased a manner as possible:

Q1: Is it probable that exposure to deltamethrin triggers the KE as measured in acute and developmental protocol (wash-out yes/no) (assuming a monotonic concentration-response relationship) in human and/or rat and/or mouse neuronal cells in development? Exposure might have a duration ranging from less than one hour up to 28 days. There are no commonly accepted thresholds for biologically significant effects. Biological response was based on expert judgements using EC50/IC50/BMR50 taking into consideration also the uncertainties in the experiments. NO: Prob<=0.66; YES: Prob>0.66

Q2: What is the lowest concentration at which the exposure to DM triggers the KE as measured in acute and developmental protocol (wash-out yes/no) (assuming a monotonic concentration-response relationship) in human and/or rat and/or mouse neuronal cells in development? Exposure might have a duration ranging from less than one hour up to 28 days. There are no commonly accepted thresholds for biologically significant effects. Biological response was based on expert judgements using EC50/IC50/BMR50 taking into consideration also the uncertainties in the experiments.

A total of 12 experts including EFSA PREV staff participated in the elicitation and a probability distribution for the lowest concentration based on the answers of all them was calculated.

Patch clamp evidence was not discussed and will be done by written procedure in September before the next WG meeting together with the Molecular Initiating Events (MiE) evidence.

5.6. Questions from the observers.

No more questions were received from the observers.

6. Any Other Business

Not Applicable

7. Next meeting(s)

TC between 14 to 16th of October

PPR / PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 19th MEETING OF THE WORKING GROUP ON "Developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity"

Held on 13 of July 2020 (teleconference)

(Agreed on 03 August 2020)

Participants

- Working Group Members:
  Kevin Crofton
  Antonio F. Hernández-Jerez
  Martin Paparella
  All have participated via teleconference, in all points of the agenda.

- Hearing Experts:
  Not Applicable

- European Commission and/or Member States representatives:
  Not Applicable

- EFSA:
  Pesticide Peer Review Unit (Chair): Iris Mangas, Andrea Terron, Martina Panzarea
  Assessment and Methodology Unit: Laura Martino, Federica Barrucci

- Observers:
  Not Applicable

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 Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] 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)

Not Applicable

5. Scientific topic(s) for discussion

5.1. Zebrafish evidence synthesis, integration and analysis: uncertainties analysis of the specific AO endpoints and EKE

Experts finalized the Uncertainty analysis for the zebrafish evidence for that purpose several questions were provided by EFSA Staff in order to assess the different sources of uncertainty and inconsistency within specific endpoints. For that purpose, all the data was extracted using Distiller software and graphs were prepared using R Software in order to independently and transparently assess all the data based first on statistically significance and second on biologically relevance, during the discussion.

The questions were independently answered by the in zebrafish experts. Second the uncertainties were discussed and agreed by the full WG and a final conclusion on the uncertainties and inconsistencies by specific endpoint and by the adverse outcome (zebrafish behaviour) was drawn using a probabilistic approach and answering the final questions:

1. Is it probable (Prob >0.66) that deltamethrin exposure cause this endpoint category?
2. What is the lowest concentration at which exposure to DM is expected to cause end point category? triggering an effect.

[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. Any Other Business

Not Applicable

7. Next meeting(s)

Teleconference between 14-18h on the 16th, 23rd ,29th and 30th of July.

PPR/ PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 18th MEETING OF THE WORKING GROUP ON "Developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity"

Held on 18 and 19 of June 2020 (teleconference)

(Agreed on 30 June 2020)

Participants

- Working Group Members:

  Susanne Hougaard-Bennekou

  Kevin Crofton

  Antonio F. Hernández-Jerez

  Martin Wilks (19 June only)

  Martin Paparella

  All have participated via teleconference, in all points of the agenda.

- Hearing Experts:

  Ellen Fritsche, University Dusseldorf, Germany

  Marcel Leist, University of Konstanz, Germany

- European Commission and/or Member States representatives:

  Verena HAUDEK-PRINZ. AGES-Austria (participated only in the second day of the TC)

- EFSA:

  Pesticide Peer Review Unit (Chair): Andrea Terron, Iris Mangas, Martina Panzarea, Mathilde Colas

  Assessment and Methodology Unit: Elisa Aiassa, Federica Barrucci, Laura Martino

- Observers:

  Kristina BARTMANN University Dusseldorf, Germany

  Jonathan BLUM University of Konstanz, Germany

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 Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], 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)

Ellen Fritsche (University Dusseldorf, Germany) and Marcel Leist (University of Konstanz, Germany) participated as hearing experts in this WG meeting with the aim of providing them background information on the Uncertainty Analysis and Expert Knowledge Elicitation methodologies for their future participation in the in answering the questions for the in vitro analysis.

5. Scientific topic(s) for discussion

5.1. In vivo evidence synthesis, integration and analysis: uncertainty analysis of the specific adverse outcome endpoints and EKE

Experts finalized the Uncertainty analysis for the in vivo evidence, for that purpose several questions were provided by EFSA Staff in order to assess the different sources of uncertainty and inconsistency within specific endpoints. All the data was extracted using Distiller software and graphs were prepared using R Software. This allowed the experts to independently and transparently assess all the data based first on statistically significance and second on biological relevance, during the discussion.

The questions were independently answered by the in vivo experts. Second the uncertainties were discussed and agreed by the full WG and a final conclusion on the uncertainties and inconsistencies by specific endpoint and by endpoint categories (learning, memory, startle, motor activity, swimming behaviour and anxiety) was drawn using a probabilistic approach and answering the final questions:

[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

1. Is it probable (Prob >0.66) that deltamethrin exposure affects this endpoint category?
2. What is the lowest dose at which exposure to DM is expected to affect the endpoint category, triggering an effect?

End of day 1

5.2. In vivo evidence synthesis, integration and analysis: adverse outcome EKE

The different specific endpoints were integrated into a potential adverse outcome (behavioral) and using the EKE

In order to draw conclusions, the Expert Knowledge Elicitation methodology was used.

AMU unit guided the experts and the following questions were used, experts answered them independently in as unbiased a manner as possible,

Q1 Is it probable that deltamethrin exposure causes this apical AO?

Q2 What is the lowest dose at which exposure to DM is expected to cause the AO triggering an effect?

The EKE was conducted by 7 experts or EFSA PREV Staff and a probability distribution for the lowest dose based on the answers of all them was calculated.

5.3. Zebrafish evidence synthesis, integration and analysis: uncertainties analysis of the specific AO endpoints and EKE

EFSA presented an overview of the zebrafish evidence analysis conducted by the experts supported by PREV Staff in an excel table containing the uncertainty and inconsistencies analysis for specific endpoints and endpoint category.

There was no time to finalize all the specific endpoints and it was decided to plan an additional ad-hoc meeting on July for finalization.

6. Any Other Business

Not Applicable

7. Next meeting(s)

TC between 14-18h on the 13rd of July.

PPR/Pesticide Peer Review Unit

MINUTES OF THE 17th MEETING OF THE WORKING GROUP ON "Developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity"

Held on 03, 04 and 05 June 2020 (teleconference)

(Agreed on 26 June 2020)

Participants

- Working Group Members:

  Susanne Hougaard-Bennekou

  Kevin Crofton

  Ioanna Tzoulaki (participated only the first day of the meeting)

  Antonio F. Hernández-Jerez

  Martin Wilks

  Martin Paparella

  All have participated via teleconference, in all points of the agenda.

- Hearing Experts:

  Ellen Fritsche, University Dusseldorf, Germany

  Marcel Leist, University of Konstanz, Germany

- European Commission and/or Member States representatives:

  Anna Price, EU-JRC, Institute for Health and Consumer Protection

  Verena HAUDEK-PRINZ. AGES-Austria

- EFSA:

  Pesticide Peer Review Unit: Andrea Terron (Chair), Iris Mangas, Martina Panzarea

  Assessment and Methodology Unit: Elisa Aiassa, Federica Barrucci, Laura Martino

- Observers:

  Kristina BARTMANN University Dusseldorf, Germany

  Jonathan BLUM University of Konstanz, Germany

1. Welcome and apologies for absence

The Chair welcomed the participants.

2. Adoption of agenda

The agenda was adopted, for practical reasons it was decided to move the point 3 of the 3rd day to the first day (Human evidence synthesis, integration and analysis: uncertainty analysis of the specific endpoints for human adverse neurodevelopmental outcomes).

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] 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)

Ellen Fritsche (University Dusseldorf, Germany) and Marcel Leist (University of Konstanz, Germany) participated as hearing experts in this WG meeting with the aim of provide to them background information on the Uncertainty Analysis and Expert Knowledge Elicitation methodologies for their future participation in the in answering the questions for the in vitro analysis.

5. Scientific topic(s) for discussion

5.1. Human evidence synthesis, integration and analysis: uncertainties analysis of the specific human adverse outcome endpoints

Experts finalized the Uncertainty analysis for the human evidence. For that purpose, several questions were provided by EFSA Staff in order to assess the different sources of uncertainty. The questions were independently answered by the human experts. Second the uncertainties were discussed and agreed by the full WG and a final conclusion on the uncertainties and inconsistencies was drawn for the 5 endpoint categories (behavioural, cognitive impairment, ADHD, communication, impaired psychomotor development) using an approximate probabilistic approach and answering the final question: Q1: What is the probability that an association between individual

[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

deltamethrin exposure in uterus and the group of endpoints occurs (NB mothers might have been exposed via dietary and non-dietary sources).

AMU Unit guided the experts and reported all the answers in the excel sheet that will be publicly available with the scientific opinion.

End of day 1

5.2. In vivo evidence synthesis, integration and analysis: uncertainty analysis of the specific adverse outcome endpoints and EKE

During the second- and third-day in vivo evidence was discussed.

EFSA presented an overview of the in vivo evidence analysis conducted by the experts supported by PREV Staff in an excel table containing the uncertainty and inconsistencies analysis for specific endpoints. AMU unit presented the list of questions for the uncertainty analysis of specific endpoint, endpoint category and adverse outcome. The following sources of uncertainty, among others, were discussed: lack of clear dose/response relationship, maternal toxicity, study precision/confidence intervals, species, sex, strain differences, risk of bias, positive controls and historical control data, and biological plausibility of the effect.

The in vivo evidence and conflicts were thoroughly discussed and agreed by the experts. All the discussion points were included in the uncertainty analysis table that will be published with the Scientific Opinion.

There was no time to finalize all the endpoints and it was decided to plan an additional ad-hoc meeting on the 18th and 19th of June for finalization.

6. Any Other Business

Not Applicable

7. Next meeting(s)

TC between 14-18h on the 18th and 19th June.

PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 16th MEETING OF THE WORKING GROUP ON "Developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity"

Held on 14 May 2020, via teleconference

(Agreed on 10 June 2020)

Participants

- Working Group Members:

  Susanne Hougaard-Bennekou

  Kevin Crofton

  Ioanna Tzoulaki

  Antonio F. Hernández-Jerez

  Martin Wilks

  Martin Paparella

  All have participated via teleconference, in all points of the agenda.

- Hearing Experts:

  Not Applicable.

- European Commission and/or Member States representatives:

  Verena Haudek-Prinz (Austria)

- EFSA:

  Pesticide Peer Review Unit: Andrea Terron (chair), Iris Mangas, Luca Martinenghi

  Assessment and Methodology Unit: Elisa Aiassa, Federica Barrucci, Laura Martino

- Others:

  Not Applicable.

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 Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] 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)

Not Applicable.

5. Scientific topic(s) for discussion

5.1. Human evidence synthesis, integration and analysis: conflicts resolution and discussion of the evidence

EFSA presented an overview of the human evidence analysis conducted by the experts. AMU unit presented the list of questions for the uncertainty analysis of the human evidence and conflicts were thoroughly discussed and agreed by the experts. All the discussion points were included in the uncertainties analysis table that will be published with the Scientific Opinion.

There was no time to finalize all the endpoints and it was decided to continue in the next Working Group meeting.

6. Any Other Business

Not Applicable

7. Next meeting(s)

Teleconference between 14-18h on the 2-3-4th of June.

[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 15th MEETING OF THE WORKING GROUP ON "Developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity"

Held on 15 April 2020, via teleconference

(Agreed on 28 April 2020)

Participants

- Working Group Members:

  Kevin Crofton

  Ioanna Tzoulaki

  Antonio F. Hernández-Jerez

  Martin Wilks

  Martin Paparella

  All have participated via teleconference, in all points of the agenda.
- Hearing Experts:

  Marcel Leist

  Ellen Fritsche

  Jonathan Blum

- European Commission and/or Member States representatives:

  Anna Price (EC)

  Bettina Hrdinazodl (Austria)

  Verena Haudek-prinz (Austria)
- EFSA:

  Pesticide Peer Review Unit: Andrea Terron (chair), Iris Mangas, Luca Martinenghi

  Assessment and Methodology Unit: Elisa Aiassa, Fulvio Barizzone, Federica Barrucci, Laura Martino
- Others:

  Not Applicable

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 Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] 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)

Hearing experts participated at the WG meeting to present the work of the EFSA Contract/grant number: OC/EFSA/PRAS/2017/01.

5. Scientific topic(s) for discussion

5.1. In vitro testing battery, presentation of the draft report

Hearing experts were asked to present the current status of the work conducted under the contract/grant OC/EFSA/PRAS/2017/01 on Implementation and interpretation of an in-vitro testing battery for the assessment of developmental neurotoxicity. The presentation focused on the methodology with description of the material and methods of the assays conducted and an overview of the status of the studies and of the plan for data presentation. The final draft report is expected to be delivered to EFSA for approval by the end of May, pending no additional complication consequent to the Covid19 pandemic will occur.

Any Other Business

Not Applicable

6. Next meeting(s)

TC between 14-18h on the 14th of May.
TC between 14-18h on the 03rd,04th and 05th of June.

[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 14th MEETING OF THE WORKING GROUP ON "Developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity"

Held on 14 April 2020, via teleconference

(Agreed on 28 April 2020)

Participants

- Working Group Members:

  Susanne Hougaard-Bennekou

  Kevin Crofton

  Ioanna Tzoulaki

  Antonio F. Hernández-Jerez

  Martin Wilks

  Martin Paparella

  All have participated via teleconference, in all points of the agenda.

- Hearing Experts:

  Not Applicable

- European Commission and/or Member States representatives:

  Not Applicable

- EFSA:

  Pesticide Peer Review Unit: Andrea Terron(Chair), Iris Mangas, Luca Martinenghi

  Assessment and Methodology Unit: Elisa Aiassa, Fulvio Barizzone, Federica Barrucci, Laura Martino

- Others:

  Not Applicable

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 Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], 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)

Not Applicable.

5. Scientific topic(s) for discussion

5.1. Human evidence synthesis, integration and analysis

EFSA staff presented an overview of the plan for the human evidence synthesis, integration and analysis. AMU unit presented the summary of evidence from the literature review in an evidence table containing the studies characteristics and the results. The list of questions for the uncertainty analysis of the human evidence was presented and thoroughly discussed and agreed by the experts.

5.2 Training, practical exercise uncertainties analysis for human evidence

A training exercise was presented analysing the endpoint behaviour and going through the questions for the uncertainties analysis.

6. Any Other Business

Not Applicable

7. Next meeting(s)

TC between 14-18h on the 14th of May.

[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

PPR / Pesticide Peer Review Unit

MINUTES OF THE 13th MEETING OF THE WORKING GROUP ON "Developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity"

Held on 12 March 2020, via teleconference

(Agreed on 18 March 2020)

Participants

- Working Group Members:

  Antonio F. Hernández-Jerez

  Martin Wilks

  Martin Paparella

  Kevin Crofton

  Susanne Hougaard-Bennekou

  Ioanna Tzoulaki

- Hearing Experts:

  Ellen Fritsche

- European Commission and/or Member States representatives:

  Anna Price (JRC)

- EFSA:

  Pesticides Peer Review Unit (PREV Unit): Andrea Terron (Chair), Iris Mangas, Luca Martinenghi

  Assessment and Methodology Support Unit (AMU Unit): Elisa Aiassa, Laura Martino, Federica Barrucci

- Others:

  Not Applicable

1. Welcome and apologies for absence

The Chair welcomed the participants.

Apologies were received from Ioanna Tzoulaki.

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[1] and the Decision of the Executive Director on Competing Interest Management[2], 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

4.1. Evidence synthesis, integration of the evidence in the AOP informed IATA and uncertainties analysis

The following points were presented and discussed by the WG:

Summary of the project and of the methodology applied including problem formulation, literature review, evidence appraisal and data extraction (Critical Appraisal Tool for the risk of bias analysis), assessment at the level of individual study and at the level of evidence synthesis/integration, presentation of the heatmaps for different streams of evidence (human, in vivo, in vitro) and plan for integration of the in vitro battery data in the heatmap for in vitro.

4.2. EFSA Proposal on the evidence synthesis and integration to establish a putative AOP

EFSA presented a proposal for the synthesis and integration of the evidence in the context of the AOP framework with the intention of postulate an AOP based on the available evidence. The following points were presented and discussed by the WG:

Use the available information to define and characterize the AO/s, if any. Priority will be initially given to the in-vivo experimental evidence. Data from the human observational studies and from the studies conducted on zebra fish will be also included in the process of hazard identification.

The assessment of Key Event Relationships and the overall assessment of the AOP will be based on a probabilistic method by characterizing and listing the uncertainties related to each step (MIEs, KEs, AOs).

EFSA proposed to the experts an approach for the synthesis of human evidence (an evidence table in an excel sheet).

Full probability distribution will be run using Expert Knowledge Elicitation (EKE) methodology for eliciting knowledge from the experts in as unbiased manner as possible. A short practical exercise to illustrate the methodology was conducted during the meeting by the experts WG.

[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

4.3. Actions for the next meeting

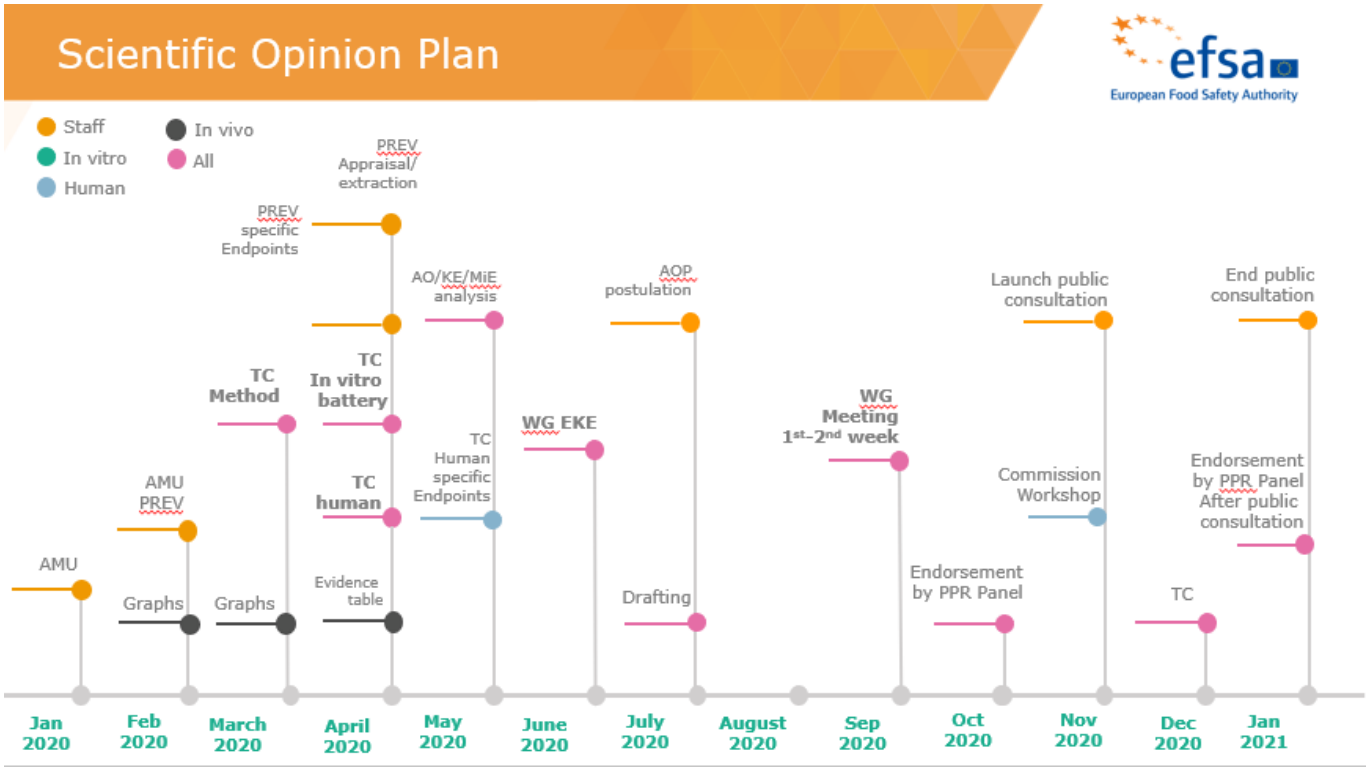
See presentation.

4.4. Meeting plan for 2020

See presentation.

5. Any Other Business

Not Applicable.



PESTICIDE PEER REVIEW UNIT

PPR / Pesticide Peer Review Unit

MINUTES OF THE 12th MEETING OF THE WORKING GROUP ON "Developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity"

Held on 15 January 2020, via teleconference

(Agreed on 26 January 2020)

Participants

- Working Group Members:
  Antonio F. Hernández-Jerez
  Martin Wilks
  Ioanna Tzoulaki
  All have participated in all points of the agenda.

- Hearing Experts:
  Not Applicable

- European Commission and/or Member States representatives:
  Not Applicable

- EFSA:
  Pesticides Peer Review Unit (PREV) : Iris Mangas (Chair)
  Assessment and Methodology Support Unit (AMU): Elisa Aiassa, Irene Guajardo

- Others:
  Not Applicable

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 Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], 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)

Not Applicable

5. Scientific topic(s) for discussion

5.1. Appraisal human observational studies: resolution of the conflicts and results.

Following the re-customisation of the Critical Appraisal Tool for human observational studies, the WG repeated the appraisal for questions 2 and 4 for all the studies. The conflicts of this appraisal were discussed and solved by the experts. The rationale was discussed and included in Distiller and in the Draft Material and Methods section of the Scientific Opinion.

5.2. Human observational studies: endpoints and data extraction model discussion.

The WG decided to extract all the endpoints for human observational studies. The data extraction forms were created by AMU Unit in Distiller and were briefly presented to the WG.

6. Any Other Business

Not Applicable

[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

PPR / Pesticide Peer Review Unit

Minutes of the 11th Meeting of the Working Group on developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity

08 January 2020, via teleconference

(Agreed on 26 January 2020)

Participants

- Working Group Members:
  Susanne Hougaard-Bennekou
  Kevin Crofton
  Antonio F. Hernández-Jerez
  Martin Wilks
  All have participated in all points of the agenda.

- Hearing Experts:
  Not Applicable

- European Commission and/or Member States representatives:
  Not Applicable

- EFSA:
  PREV Unit: Iris Mangas (Chair), Andrea Terron, Luca Martinenghi
  AMU Unit: Elisa Aiassa, Marios Georgiadis, Federica Barrucci

- Others:
  Not Applicable

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 Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], 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)

Not Applicable

5. Scientific topic(s) for discussion

Re-customisation of the Critical Appraisal Tool for human observational studies

Following the WG discussion in the challenge of being consistent when performing the appraisal of experimental studies versus observational studies, the WG discussed the re-customization of the Critical Appraisal Tool for human observational studies. The rational for answering questions 2 and 4 was thoroughly re discussed and modified. For question 2 the WG considered possible confounders the following: maternal age, maternal IQ, sex, ethnicity, socio-economic factors (education level, incomes, occupation), lifestyle (smoking, alcohol consumption, illicit drugs, stress, diet), and co-exposure to other chemicals associated with DNT (e.g. OPs, lead…). For question 4 the WG noted that measurement of specific metabolites in urine does not allow an accurate estimate of exposure to deltamethrin mainly based on the uncertainty in Deltamethrin kinetics, the uncertainty on the correct timing of biomarker collection and the presence of the metabolites in the environment.

A revision of the appraisal was considered necessary for these two questions. The rational was included in Distiller and in the Draft Material and Methods section of the Scientific Opinion.

6. Any Other Business

Not Applicable

[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

PPR / Pesticide Peer Review Unit

Minutes of the 10th Meeting of the Working Group on developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity

6 December 2019, via teleconference

(Agreed on 23 December 2019)

Participants

- Working Group Members:
  Susanne Hougaard-Bennekou
  Kevin Crofton
  Antonio F. Hernández-Jerez
  Martin Wilks
  All have participated in all points of the agenda.

- Hearing Experts:
  Not Applicable

- European Commission and/or Member States representatives:
  Anna Bal-Price (attended all points of the agenda)

- EFSA:
  PREV Unit: Andrea Terron, Iris Mangas, Luca Martinenghi
  AMU Unit: Federica Barrucci, Elisa Aiassa (all points of the agenda)

- Others:
  Not Applicable

1. Welcome and apologies for absence

The Chair welcomed the participants.

2. Adoption of agenda

The agenda was adopted.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], 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)

Not Applicable

5. Scientific topic(s) for discussion

5.1. Results of the appraisal: human observational studies, in vivo and in vitro lines evidences.

The Heatmaps with the results of the appraisal were presented and discussed. Consistency in the appraisal among the different lines of evidence was discussed. The experts acknowledged inconsistency on the appraisal rational of the experimental versus the observational studies.

In regards with humans some difficulties were noted, and a revision is needed, the lack of a common terminology in the studies and the difficulty for classification on the endpoint was highlighted.

6. Any Other Business

Not Applicable

[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

PPR / Pesticide Peer Review Unit

Minutes of the 9th Meeting of the Working Group on developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity

21 November 2019, via teleconference

(Agreed on 16 December 2019)

Participants

- Working Group Members:
  Antonio F. Hernández-Jerez
  Martin Wilks
  Ioanna Tzoulaki
  All have participated in all points of the agenda.

- Hearing Experts:
  Not Applicable

- European Commission and/or Member States representatives:
  Not Applicable

- EFSA:
  PREV Unit: Andrea Terron, Iris Mangas, Luca Martinenghi
  AMU Unit: Elisa Aiassa, Federica Barrucci

- Others:
  Not Applicable

1. Welcome and apologies for absence

The Chair welcomed the participants.

2. Adoption of agenda

The agenda was adopted.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], 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)

Not Applicable

5. Scientific topic(s) for discussion

5.1. Human observational appraisal: resolution of the conflicts

The WG discussed the conflicts resulted from the appraisal in parallel of the human observational studies. The rational was included in the Protocol of the Scientific Opinion.

6. Any Other Business

Not Applicable

[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

PPR / Pesticide Peer Review Unit

Minutes of the 8th Meeting of the Working Group on developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity

20 November 2019, via teleconference,

(Agreed on 16 December 2019)

Participants

- Working Group Members:
  Kevin Crofton (attended all points of the agenda)

- Hearing Experts:
  Not Applicable

- European Commission and/or Member States representatives:
  Anna Bal-Price (attended all points of the agenda)

- EFSA:
  PREV Unit: Andrea Terron, Iris Mangas, Luca Martinenghi
  AMU Unit: Elisa Aiassa

- Others:
  Not Applicable

1. Welcome and apologies for absence

The Chair welcomed the participants.

2. Adoption of agenda

The agenda was adopted.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], 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)

Not Applicable

5. Scientific topic(s) for discussion

5.1. In vitro appraisal: resolution of the conflicts

The WG discussed the conflicts resulted from the appraisal in parallel of the in vitro studies. The consistency among the different groups appraising in vitro studies was also discussed. The rational was included in the Protocol of the Scientific Opinion.

6. Any Other Business

Not Applicable

[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

PPR / Pesticide Peer Review Unit

Minutes of the 7th Meeting of the Working Group on developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity

23 - 25 October 2019, Arona, Italy

(Agreed on 18 November 2018)

Participants

- Working Group Members:

  Susanne Hougaard-Bennekou

  Kevin Crofton

  Ioanna Tzoulaki (through Skype)

  Antonio F. Hernández-Jerez (Chair)

  Martin Wilks

  All have participated in all points of the agenda (except for Ioanna Tzoulaki that attended via Teleconference on the 24th from 13:00 to 18:00)

- Hearing Experts:

  Martin Paparella (attended from the 23rd at 14:00 to the 24th until 17:00)

- European Commission and/or Member States representatives:

  Anna Bal-Price (attended all points of the agenda)

- EFSA:

  PREV Unit: Andrea Terron, Iris Mangas

  AMU Unit: Laura Martino (only days 23rd and 24rd), Elisa Aiassa (all points of the agenda)

- Others:

  Not Applicable

1. Welcome and apologies for absence

The Chair welcomed the participants.

2. Adoption of agenda

The agenda was adopted with the following changes: item 14 and item 11 were included in item 4. Item 13 was included in item 5. For the first- and second-day, break-out sessions were planned (items 7, 8 and 9) with working group (WG) members being divided into small groups based on the need of work on the appraisal. The final agreed agenda was as follows:

1 Welcome and Apologies for absence

2 Adoption of the agenda

3 Declarations of interest

4 Drafting of the Protocol for the SO status. Synthesis, integration and uncertainty analysis of the data.

5 General discussion issues on studies selection: Inclusion of the ADME data in the IATA.

6 Uncertainty analysis methodology, proposal to be discussed (including a preliminary assessment of the uncertainty analysis for the OECD TG 426)

7 In vivo studies: status of the appraisal and resolution of the conflicts.

8 In vitro studies: status of the appraisal and resolution of the conflicts.

9 Human observational studies: tailoring questions in Distiller and piloting.

10 Next meeting agenda, meeting calendar and new tasks assignment.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], 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)

Martin Paparella was invited as a hearing expert to answer the question and discuss point 5.3 of the agenda.

[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. Scientific topic(s) for discussion

5.1. Drafting of the Protocol for the SO status. Synthesis, integration and uncertainty analysis of the data.

The synthesis, integration and data extraction procedure of the available lines of evidences following EFSA Scientific assessment procedure were presented to the working group (WG).

The WG noted that heterogeneity was found in the terminology used for the developmental neurotoxicity (DNT) endpoints in the public literature. This was particularly true for the in vitro and human observational studies.

The WG highlighted the relevance of having a common language for the definition of neurodevelopmental endpoints in the 3 lines of evidence (in vivo, in vitro and human observational studies).

The need to reconcile the heterogenicity and define a common terminology for the endpoints and therefore classify and cluster them in a second step was pointed out by the experts.

For human observational studies it was noted by the WG that the DSM-5 approach has already addressed this issue with the harmonization and classification for neurodevelopmental disorders.

The uncertainty analysis in line with the EFSA Guidance on Expert Knowledge Elicitation was introduced to the WG.

The WG decided not to discuss in detail this point and to postpone the discussion on which methodology will be applied until the appraisal step is finalized and there is a common understanding on the available evidence by endpoints for the different line of evidence.

5.2. General discussion issues on studies selection: Inclusion of the ADME data in the IATA[3]

The need of inclusion of Toxicokinetic data in the IATA case studies was agreed for the WG. For that purpose, the WG proposed to consider the ADME data specifically generated for the substances that will be included in the case study.

It was also noted that Physiologically-Based Pharmacokinetic Model using in vitro data and in vitro to in vivo extrapolation already exists for Deltamethrin (publicly available at Toxicological Sciences, 169(2), 2019, 365–379; https://doi.org/10.1093/toxsci/kfz042).

The WG discussed the inclusion of the zebrafish data in the IATA; the WG agreed that in vitro studies are the ones including embryos of less than 120 hours post fertilization (hpf). Studies will be considered to fall into the in vivo category when the age is more than 120 hpf.

5.3. Uncertainty analysis methodology, proposal to be discussed OECD 426 preliminary work

The WG invited the hearing expert for answering the following question:

How can we map the uncertainties of current guideline in vivo studies and how can we include them in the uncertainty analysis in the IATA case studies?

A draft proposal was presented for the OECD TG 443 and 426 and OPPTS 870.6300 (1998). This work is in progress and it will be consolidated in the next months. The hearing expert will be

[3] http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2019-00100

included in the list of participants for the next meetings in order to continue the debate on this point and define which details will be necessary for the inclusion of this specific uncertainty analysis in the overall uncertainty analysis.

5.4. In vivo studies: status of the appraisal and resolution of the conflicts.

A number of 17 publications were included in the appraisal step for in vivo line of evidence.

The current list of endpoints and cluster was agreed as follows:

Experimental animal studies	
Endpoint category	**Specific endpoints (measurement method)**
1. Physical and developmental landmarks	• Sexual maturation (age) • Clinical observation (visual observation, period) • Functional observation battery
2. Neuropathology endpoints [see OECD TG 426 as a standard reference]	• Brain weight (measure unit, absolute and relative to body weight, period) • Quantitative morphometric evaluation (linear measurement, areal measurements, brain morphometric landmarks, brain regions measured, stereology. Period) • Qualitative neuropathology examination (diagnostic criteria, severity score criteria, standard and special stain used, period) • Neuroimaging (quantitative, e.g. MRI)
3. Behavioural endpoints See OECD TG 426 and NAFTA guidance as a standard reference	• **Behavioural ontogeny**. • **Motor activity**: horizontal direction; other direction, additional fine movements (test system, detection system (computer), period, increase or decrease in: ambulatory counts, ambulatory distance, ambulatory time, vertical movements (rearing), discrete non-ambulatory movements, total activity) • **Auditory startle response** (integrity of a sensory-evoked motor response) **with or without habituation** (learning endpoint): effects on overall startle amplitude, effects on habituation in startle magnitude, comparison between ages of testing, sex differences (period, test method, decrease in response amplitude after repeated startle stimulus presentation during the test session and measurement of latency). • **Learning and memory** (learning is defined as a relatively permanent change in behaviour that is the result of experience. Memory is defined as the retention and use of acquired information about locations, events, or temporal order to modify

Experimental animal studies	
Endpoint category	**Specific endpoints (measurement method)**
	subsequent behaviour. Learning and memory can be inferred from changes in behaviour). The endpoints assessed are test system related: ○ Letter Mazes M, Y, E (Position, Discrimination: latency to escape, errors, trials to criterion). ○ Morris Water Maze (Spatial Learning: latency to escape over trials, path length to locate hidden platform, search parameters during retention probe trials). ○ Passive Avoidance (Associative Learning: latency, trials to criterion). ○ Biel Water Maze (Sequential learning: latency, errors) ○ Cincinnati Maze (Sequential/Egocentric Learning: latency, errors) • **Social behaviour (qualitative or quantitative, tbc test method)** • **Anxiety/Fear** • **Swimming Behaviour** • **Impulsive behaviour** • **Motor coordination (eg., Rotorod)** •
4. Clinical chemistry endpoints	• **Hormones** • **Cholinesterase activity**
5. Neurochemistry	• **Proteins** • **Enzyme activity** • **Genes**
6. Neurophysiology	• **Evoked Potentials** • **LTP (Long term potentiation)** • **EEG** • **Other**
7. Other	• **Ophthalmological** • **Long term potentiation**

The current status of the appraisal was discussed, and conflicts were therefore solved between the two reviewers.

The experts discussed the allocation to TIERS algorithm, it was agreed as follows:

- ✓ TIER 1: All key questions are scored +/++ AND maximum 1 non-key question is scored - or –
- ✓ TIER 2: study does not meet criteria for TIER 1 or TIER 3
- ✓ TIER 3: one (or more) key question is scored -/– OR -/– for the majority of the non-key questions

5.5. In vitro studies: status of the appraisal and resolution of the conflicts.

A number of 30 publications were included in the appraisal step for in vitro stream of evidence. A draft list of endpoints is proposed as follows by the WG.

In vitro studies	
Endpoint category	**Specific endpoints (measurement method)**
8. Proliferation endpoints	• To add (if needed)
9. Apoptosis endpoints	• To add (if needed)
10. Differentiation	• Neurogenesis • Gliogenesis • Oligodendrocyte differentiation • Astrocytic differentiation
11. Migration endpoints	• Neural migration • Radial glia migration. • Glia migration • To add (if needed)
12. Growth/maturation	• Neurite outgrowth • Neuronal morphology • Synaptogenesis • Neuronal cell types • To add (if needed)
13. Network formation/function	• MEA • MFR • Number of bursts • Burst duration • Intervals between bursts • Other to add if needed
14. Cytotoxicity/viability	• MTT assay • LDH level • Neutral red accumulation • Other to add if needed
15. Channels/transporters	• Sodium • Calcium • Chloride • Potassium • Other to add if needed
16. Proteins	• Synaptophysin • SNAP25 • Synaptobrevin • MAP2 • Other to add if needed
17. Receptors	• GABA • NMDA • DA

In vitro studies	
Endpoint category	**Specific endpoints (measurement method)**
	• 5-HT • Other to add if needed
18. Neurotransmitters	• Other to add if needed
19. Enzymatic activity	• Calcineurin • Calmodulin • Dephosphorylation • Other to add if needed
20. Microglia activation	• TNF alpha • IL1-□ • Morphological changes • Other to add if needed
21. Oxidative stress	• ROS production • Nrf2 expression/translocation • Mitochondrial membrane integrity • Other to add if needed
22. Cell organelles integrity	• Nuclear integrity • Lysosomal integrity • Mitochondrial membrane integrity • Other to add if needed
23. NEUROPHYSIOLOGY/patch clamp	• ionic currents in individual neurons • Membrane excitability • Other to add if needed
24. Genomic	• Other to add if needed
25. Behavioural endpoints (in zebrafish)	• Thigmotaxis • Locomotor activity • Spasms • Swimming activity • Other to add if needed
26. Pathology (in zebrafish)	• Craneomorphological effects • Curvature of the body axis • Quantitative morphometric examination (body area, head area, head-body angle) • Qualitative morphometric evaluation • Other to add if needed
27. Genes (in zebrafish)	• Other to add if needed
28. Zebrafish Mortality	• Other to add if needed
29. Other	

A Teleconference was planned to discuss the appraisal and solve the conflicts among the 4 appraisal reviewers (Anna, Kevin, Iris, Andrea).

5.6. Human observational studies: tailoring questions in Distiller and piloting.

A number of 8 publications were included in the appraisal step for epidemiological line of evidence. The list of endpoints needs to be agreed. A draft was proposed by an expert based on DSM-5 classification for neurodevelopmental disorders. The WG separated in two different categories Autism spectrum disorders and Attention-Deficit/Hyperactivity Disorder based on both categories are measured differently in the human observational studies of the literature retrieved (**American Psychiatric Association - Diagnostic and statistical manual of mental disorders, 5th ed., Arlington, VA: American Psychiatric Association; 2013), as follows**.

1. Intellectual disabilities
2. Communication disorders
3. Autism spectrum disorders (ASD)
4. Attention-Deficit/Hyperactivity Disorder
5. Motor disorders
6. Specific learning disorders
7. Other neurodevelopmental disorders

A Teleconference was planned to solve the appraisal conflicts and discuss the endpoints category among the 3 appraisal reviewers (Ioanna, Antonio, Martin) and EFSA Staff. A statistician from EFSA will act as a second reviewer of the statistic question.

5.7. Next meeting agenda, meeting calendar and new tasks assignment

Next meetings were planned as follows:

Two Teleconferences were planned to discuss the appraisal conflicts: (1) for in vitro on the 20th of November (Starting at 14:00 and closing at 18.00) among the experts that conducted the appraisal of the in vitro studies; (2) for human observational studies on the 21st of November (Starting at 14:00 and closing at 17.30) among the experts that conducted the appraisal of the human studies.

One more Teleconference was planned to discuss the results of the appraisal and endpoints on the 6th of December among all the WG experts.

A physical meeting is now planned for February 25 (starting at 14:00) to February 27 (closing at 13:00) at EFSA.

A physical meeting is planned on June 02 (starting at 14:00) to June 04 (closing at 13:00) at EFSA.

6. Any Other Business

Not Applicable

PESTICIDE PEER REVIEW UNIT

PPR / Pesticide Peer Review Unit

Minutes of the 6th Meeting of the Working Group on developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity

21 October 2019 (via teleconference)

(Agreed on 12 November 2019)

Participants

- Working Group Members:
  Ioanna Tzoulaki
  Antonio Hernandez Jerez
  Martin Wilks
  All have participated via teleconference, in all points of the agenda.

- Hearing Experts:
  Not Applicable

- European Commission and/or Member States representatives:
  Not Applicable

- EFSA:
  PREV Unit (Chair): Iris Mangas
  AMU Unit: Elisa Aiassa

- Others:
  Not Applicable

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 Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] 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)

Not Applicable.

5. Scientific topic(s) for discussion

5.1. Structured evidence appraisal: Pilot the Critical Appraisal Toolkit (CAT) for the human observational studies, continuation

The WG discussed the rationale for answering the questions for human observational studies. There was no time to finish and it was decided to continue the discussion during the next physical meeting.

6. Any Other Business

Not Applicable

7. Next meeting(s)

[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

PPR / Pesticide Peer Review Unit

Minutes of the 5th Meeting of the Working Group on developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity

10 October 2019 (via teleconference)

(Agreed on 11 October 2019)

Participants

- Working Group Members:

  Susanne Hougaard-Bennekou

  Kevin Crofton

  All have participated via teleconference, in all points of the agenda.

- Hearing Experts:

  Not Applicable

- European Commission and/or Member States representatives:

  Not Applicable

- EFSA:

  PREV Unit (Chair): Andrea Terron, Iris Mangas

  AMU Unit: Elisa Aiassa, Fulvio Barizzone, Federica Barrucci (participated in all the points of the agenda)

- Others:

  Not Applicable

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 Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], 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)

Not Applicable.

5. Scientific topic(s) for discussion

5.1. Structured evidence appraisal: Pilot the CAT for the In vivo and In vitro strains and evidence

The WG discussed the rational for answer the questions for in vivo and in vitro strain of evidence. The WG pilot the forms on one study for each strain each.

6. Any Other Business

Not Applicable

7. Next meeting(s)

Physical meeting on the 23-24-25th of October.

[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

PPR / Pesticide Peer Review Unit

Minutes of the 4th Meeting of the Working Group on developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity

4 October 2019 (via teleconference)

(Agreed on 11 October 2019)

Participants

- Working Group Members:

  Susanne Hougaard-Bennekou

  Kevin Crofton

  Ioanna Tzoulaki

  Antonio F. Hernández-Jerez

  Martin Wilks

  All have participated via teleconference, in all points of the agenda.

- Hearing Experts:

  Not Applicable

- European Commission and/or Member States representatives:

  Not Applicable

- EFSA:

  PREV Unit (Chair): Andrea Terron (participated only part of the agenda), Iris Mangas

  AMU Unit: Elisa Aiassa, Fulvio Barizzone, Federica Barrucci (participated in all the points of the agenda)

  Laura Martino (participated only part of the agenda)

- Others:

  Not Applicable

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 Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], 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)

Not Applicable.

5. Scientific topic(s) for discussion

5.1. Structured evidence appraisal: Tailoring the Critical Appraisal Tool for the epidemiological studies

Elisa Aiassa presented the OHAT/NTP tool 11 questions organized in 7 domains (Selection bias, counfounding bias, performance bias, attrition/exclusion bias, detection bias, selective reporting bias and other sources of bias).

The WG discussed the rational for answer each of the first 5 questions and tailor the questions to the specific evidence for the human observational studies. The rational was included in the Draft protocol. There was no time to finish.

6. Any Other Business

Not Applicable

7. Next meeting(s)

Teleconference on October 10th.

[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

PPR / Pesticide Peer Review Unit

Minutes of the 3rd Meeting of the Working Group on developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity

26 September 2019 (via teleconference)

(Agreed on 11 October 2019)

Participants

- Working Group Members:

  Susanne Hougaard-Bennekou

  Kevin Crofton

  Ioanna Tzoulaki

  Antonio F. Hernández-Jerez

  Martin Wilks

  All have participated via teleconference, in all points of the agenda.

- Hearing Experts:

  Not Applicable

- European Commission and/or Member States representatives:

  Anna Bal-Price

- EFSA:

  PREV Unit (Chair): Andrea Terron, Iris Mangas

  AMU Unit: Elisa Aiassa, Fulvio Barizzone, Federica Barrucci (all participated in all the points of the agenda), Laura Martino (participated only in the 4 point of the agenda)

- Others:

  Magdalini Sachana: Observer from OECD (participated only in the points from 1 to 4 of the agenda).

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 Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] 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)

Not Applicable.

5. Scientific topic(s) for discussion

5.1. Introduction to the Uncertainty analysis

Laura Martino presented an overview of the Uncertainty in scientific assessments and EFSA harmonised approach to analyse it. The key function played by communication of uncertainty was highlighted. She presented uncertainty definition: "A general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question" and the two main types of uncertainty: the uncertainty affecting the methods and the uncertainty affecting the evidence. It is important to have a process in place to identify systematically the evidence that is relevant for the formulated problem formulation.

The main advantages of the use of structured evidence appraisal using Critical Appraisal Tools (CATs) were presented: Reduce bias and subjectivity if planned upfront; Increase consistency within and across WGs; Increase transparency and Scientifically defensible.

All the experts agreed in using the structured evidence appraisal for the Scientific Opinion. Methods of uncertainty analysis were not discussed, and it was decided by the experts to further discuss this item in the next physical meeting on the 23-24-25th of October.

The WG agreed a to develop Protocol for the Scientific Opinion with the aim of defining as much as possible beforehand the strategy that will be applied for collecting data, appraising the relevant evidence, and analysing and integrating the different strains of evidence. A Draft Protocol is being developed by EFSA Staff and the Working Group and will be published.

[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

5.2. Structured evidence appraisal: Tailoring the Critical Appraisal Tool for the in vivo studies

Elisa Aiassa presented the OHAT/NTP tool 11 questions organized in 7 domains (Selection bias, counfounding bias, performance bias, attrition/exclusion bias, detection bias, selective reporting bias and other sources of bias).

The WG discussed the rational for answer each of the 11 questions and tailor the questions to the specific evidence for the in vivo studies. The rational was included in the Draft protocol.

A Placeholder Teleconference on October 10th from 13:30 to 16:30 was planned for piloting the tool (Parma time).

5.3. Structured evidence appraisal: Tailoring the Critical Appraisal Tool for the in vitro studies

Elisa Aiassa presented the OHAT/NTP tool 11 questions organized in 7 domains (Selection bias, counfounding bias, performance bias, attrition/exclusion bias, detection bias, selective reporting bias and other sources of bias).

The WG discussed the rational for answer each of the 11 questions and tailor the questions to the specific evidence for the in vitro studies. The rational was included in the Draft protocol.

Placeholder Teleconference on October 10th from 13:30 to 16:30 (Parma time).

5.4. Structured evidence appraisal: Tailoring the Critical Appraisal Tool for the epidemiological studies

There was no time for discussion of this point and a Teleconference on October 4th was organized with the aim of tailoring the Critical Appraisal Tool for the human observational studies.

6. Any Other Business

Not Applicable

7. Next meeting(s)

Placeholder Teleconferences on 04th and on 10th of October.

PPR / Pesticide Peer Review Unit

Minutes of the 2nd Meeting of the Working Group on developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity

8-9-10 July 2019

(Agreed on 26 July 2019)

Participants

- Working Group Members:

  Susanne Hougaard-Bennekou

  Kevin Crofton

  Ioanna Tzoulaki (through Skype)

  Antonio F. Hernández-Jerez

  Martin Wilks

  All have participated in all points of the agenda (except for Ioanna Tzoulaki that attended via Teleconference on the 8th full day, on 9th from 9.00 to 12.00 am and on the 10 from 9.00 to 12.00 am.)

- Hearing Experts:

  Not Applicable

- European Commission and/or Member States representatives:

  Anna Bal-Price (attended until the 9th at 12.00 am)

- EFSA:

  PREV Unit: Andrea Terron, Iris Mangas

  AMU Unit: Elisa Aiassa, Irene Munoz-Guajardo (participated only in the last point of the agenda)

- Others:

  Not Applicable

1. Welcome and apologies for absence

The Chair welcomed the participants.

2. Adoption of agenda

The agenda was adopted with the following changes: item 11 was included on the third day based on the need of conducting a structured search, retrieval, selection and appraisal of the evidence in the scientific assessment process at EFSA for the project. The rest of the items (from 4 to 9) were condensed in the previous two days as presented in the minutes. Item 10 was discussed after the discussion with AMU unit.

1	Welcome and Apologies for absence
2	Adoption of the agenda
3	Declarations of interest
4	Problem formulation; finalization
5	Feedback from the tasks assigned, available human data
6	Feedback from the tasks assigned, available experimental in vivo and in vitro data
7	Postulate AOP
8	Next steps; Uncertainty analysis methodology, proposal to be discussed
9	Drafting of the SO, status
10	Next meeting agenda, meeting calendar and new tasks assignment
11	The scientific assessment process at EFSA: focus on evidence retrieval, selection and appraisal by AMU Unit

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], 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)

Not Applicable.

[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. Scientific topic(s) for discussion

5.1. Introduction to the Working Group meeting

Andrea Terron presented the contextualization of the Scientific Opinion. The Scientific Opinion is part of an EFSA effort for the development and use of in-vitro methods for the assessment of developmental neurotoxicity (DNT) hazard of chemicals. The Pesticide Unit submitted a Standard Project Submission Form (SPSF) at the OECD for the preparation of guidance on the application and interpretation of in-vitro DNT assays, led by EFSA, US EPA and Danish EPA with the participation of interested OECD member states. In order to provide an adequate scientific background and facilitate the preparation of OECD guidance, EFSA granted a procurement for the development of the in vitro DNT testing battery, generate data using 120 relevant chemicals and design and employ a data analysis tool. This Scientific Opinion is part of this project and is intended to develop integrated approaches to testing and assessment (IATA) case studies (where the outcome of the in vitro studies will be used as part of the available evidence) that will be used for the development of the OECD guidance. Two substances were selected by the working group, the insecticide Deltamethrin and the herbicide Flufenacet.

5.2. Problem formulation; finalization[3]

Iris Mangas presented some proposals based on previous discussion: if the problem formulation 1) should clearly specify whether the in vitro testing battery gives added value to the DNT Hazard characterization and (2) should include the IATA as a framework for the analysis.

The WG agreed in dividing the problem formulation in two questions based on the 2 steps of the Terms of Reference execution plan:

- How certain are we that the proposed active substance is a developmental neurotoxicant in humans based on the available data in the IATA?
- To what extent does the in vitro testing battery inform the uncertainty on the DNT hazard characterization when it is used in the IATA framework for the proposed active substances?

5.3. Feedback from the tasks assigned, available human data

For Deltamethrin, a WG member presented the status of the compilation and assessment of the epidemiological available data.

The search strategy was as follows:

Key words: Deltamethrin AND (human data OR epidemiological studies) in title or abstract; Database: Pubmed.

The outcome resulted in 9 studies. However, it was noted that the search is preliminary and not exhaustive, and some problems/limitations were noted (e.g. different outcomes for potential DNT effects, different measurement of exposure, quality of the studies could be an issue and should be systematically appraised, exclusion and inclusion criteria should be decided…).

For Flufenacet a WG member presented his search and it was noted that no epidemiological studies are available for this active substance.

A WG member presented his search for deltamethrin. Using the search string "deltamethrin" AND ((developmental neurotox*) OR neurodevelopment* OR neurobehav* OR neurocognit*), a total of 27 publications were retrieved in Pubmed including in vivo in vitro and human data.

[3] http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2019-00100

The WG did not discuss in detail the studies and considered that a more exhaustive and structured search is needed. For that purpose, the WG decided to ask support to the EFSA AMU Unit.

After discussion, the Working Group proposed the following keywords to be sent to the AMU unit as a search string for the epidemiological studies:

Keywords:

((Neurological OR (psychom development) OR (psychol* development) OR behav* OR Attention OR Intelligence OR Neurodevelopment* OR Neurobehav* OR Autism OR neurocognitive OR cognitive) AND child*)*

AND (deltamethrin and synonyms OR pyrethroid) for the search for deltamethrin*

AND flufenacet for the search for flufenacet.

Eligibility criteria and databases were discussed with AMU team (see section 5.8)

5.4. Feedback from the tasks assigned, available in vivo and in vitro data

A WG member presented the status of the compilation and assessment of the in vivo and in vitro available data. The WG did not discuss in detail the studies and considered that a more exhaustive and structured search is needed. For that purpose, the same strategy as for the epidemiological evidence will be used and the WG asked for support to EFSA AMU Unit.

After discussion, the Working Group proposed the following keywords to be sent to the AMU unit for the retrieval of the in vivo studies. The strings are a point of departure and will be reviewed by EFSA staff:

(DNT OR (developmental neuro) OR (behav* development) OR (behav* ontogeny) OR cognit* OR neuro* AND (perinatal OR postnatal OR fetal OR fetus OR foetuses OR foetal OR embryo) OR (Development AND (activity OR growth OR startle OR learning OR memory OR brain OR neuropath* OR morphometric OR neuroanatom* OR brain))*

And NOT – insects

AND Deltamethrin for the search for deltamethrin

AND flufenacet for the search for flufenacet.

After discussion, the Working Group proposed the following keywords to be sent to AMU unit for the search of the in vitro studies:

(In vitro) AND ((Neurite outgrowth) OR (Neural cell differentiation) OR Synaptogenesis OR (Synapse formation) OR (Synaptic pruning) OR Myelinogenesis OR (Myelin formation) OR (Oligodendrocyte differentiation) OR (Astrocyte differentiation) OR (Glial differentiation) OR (Glial migration) OR (Network formation) OR (Neural progenitor) OR Neurosphere OR LUHMES OR (Electrode array))

And NOT – insects

AND Deltamethrin for the search for deltamethrin

AND flufenacet for the search for flufenacet.

The experts noted that a search was conducted recently for the in vitro data for the procurement (see Literature review on in vitro and alternative Developmental Neurotoxicity (DNT) testing methods, EFSA external scientific report., 10.2903/sp.efsa.2015.EN-778).

The strings were:

((((((model[Title/Abstract] OR test[Title/Abstract] OR assay*[Title/Abstract] OR method*[Title/Abstract] OR technique*[Title/Abstract] OR set up[Title/Abstract] OR experiment*[Title/Abstract] OR endpoint*[Title/Abstract] OR prioritization*[Title/Abstract] OR system*[Title/Abstract] OR evaluation*[Title/Abstract] OR exposure*[Title/Abstract] OR testing[Title/Abstract] OR tests[Title/Abstract])))) AND in vitro[Title/Abstract]))) OR ((culture*[Title/Abstract] OR brain slice*[Title/Abstract] OR cell based[Title/Abstract] OR cell line*[Title/Abstract] OR cell model*[Title/Abstract] OR cell system*[Title/Abstract] OR cellular model*[Title/Abstract] OR cellular assay*[Title/Abstract] OR cellular system*[Title/Abstract] OR cellular method*[Title/Abstract] OR cellular technique*[Title/Abstract] OR cellular endpoint*[Title/Abstract] OR cellular exposure*[Title/Abstract] OR immortalised[Title/Abstract] OR immortalized[Title/Abstract] OR IPS cell*[Title/Abstract] OR primary cell*[Title/Abstract] OR InVitro Techniques[MeSH] OR tumor cell line*[Title/Abstract] OR Cells, Cultured[MeSH] OR Astrocyte*[Title/Abstract] ORESC[Title/Abstract] OR glial cell*[Title/Abstract] OR iPSC[Title/Abstract] OR nerve cell*[Title/Abstract] OR neural cell*[Title/Abstract] OR neuroblastoma [Title/Abstract] OR neuronal cell*[Title/Abstract] OR oligodendrocyte*[Title/Abstract] OR pheochromocytoma*[Title/Abstract] OR pluripotent cell*[Title/Abstract] OR schwann cell*[Title/Abstract] OR stem cell*[Title/Abstract]OR teratocarcinoma*[Title/Abstract] OR tumor cell[Title/Abstract] OR microglia[Title/Abstract]))*

It was decided to use both search strategies as starting point for discussion with AMU.

5.5. Postulate the AOP:

EFSA presented the in vitro DNT testing battery assays and how they cover a wide range of key neurodevelopmental processes. The WG discussed whether the data could be consolidated in an existing AOP or a new AOP would be needed.

For deltamethrin, based on its Mode of Action by modulating voltage-gated calcium channels (VGCCs) a Molecular Initiating Event (MIE) for DNT is possible. However, other potential MIEs cannot be discarded.

The WG concluded that they expect development of an AOP to be difficult due to the lack of in vivo key elements between the MIE and the in vivo and epidemiological data. However, this will be discussed once all the evidence for the in vivo, in vitro and epidemiological studies is completed and appraised.

This will be further discussed in the next meeting.

5.6. Next steps, Uncertainty Analysis methodology, proposal to be discussed

A WG member presented the different dimensions of the uncertainty analysis (contextual, substantial and procedural). It was proposed to focus the uncertainty analysis on the substantial dimension. It was noted that the IATA case studies will bring different lines of evidence and methods together to reach a conclusion on hazard characterization. The IATA case studies will contain different layers and the overall uncertainty associated with IATAs is generated as the result of combining uncertainties of the individual IATA components (e.g. in vitro, in vivo, epidemiological studies…). For each step of the IATA, uncertainties characterization is needed by considering the

input data (quality, reliability and relevance of the data) and the extrapolation of the data (interpretation and integration of the data).

The way to do this uncertainty analysis was addressed in a brainstorming discussion between all the experts, including some possible methods. The experts concluded that in principle a quantitative method will be the gold standard, but the experts noted that it is necessary to involve experts in the application of the selected uncertainty analysis methodology.

Experts also agreed to have a hearing consultation with an external expert with practical experience on uncertainty analysis for animal toxicology guideline studies. This is very important when considering the intrinsic limitations of the OECD TG for DNT.

The experts agreed to further discuss this with the external expert and EFSA AMU unit experts on uncertainty analysis.

5.7. Drafting of the Scientific Opinion, Status

This item was not discussed, and it was postponed for the next meeting.

5.8. The scientific assessment process at EFSA: focus on evidence retrieval, selection and appraisal by AMU Unit

AMU evidence retrieval, selection and appraisal at EFSA. Experts agreed on following EFSA process to conduct the scientific assessment and the AMU procedure to conduct the literature review. In order to that, the plan is as follows:

1. Evidence retrieval:

AMU will conduct the literature search in the following Databases: PubMed, Web of Science Core Collection, Toxnet or SciFindern.
For grey literature: thesis will be included.
Experts agreed on the inclusion and exclusion criteria for the epidemiological, in vivo and in vitro studies. AMU will prepare the Distiller forms with the agreed criteria.

2. Study selection:

It will be conducted in two steps. In each step two independent reviewers will perform the selection in parallel. EFSA staff will address the first step checking abstract and title, for the second step (full text) EFSA staff will require experts support.

3. Data extraction EFSA staff will internally discuss with AMU statisticians the methodology and will inform the WG in September by Teleconference.

4. Evidence appraisal

Experts decided to use OHAT/NTP tool, modified if needed.
AMU will train the experts on the OHAT/NTP Critical Appraisal Tool and support the work.
Experts will pilot the tool in the September TC and conduct the evidence appraisal in October. A second placeholder TC by AMU is planned on the 10th of October to clarify doubts on the CAT.

5.9. Next meeting agenda, meeting calendar and new tasks assignment

EFSA presented a proposal for the Homework and next meeting agenda. The WG agreed on the Homework to be conducted and the next meetings dates:

Meeting on 23-24-25 of October (Starting at 14.00 on the 23 and closing the meeting on the 25 at 13.00) with the main scope of discussing the results of the evidence retrieval, selection and appraisal of the data.

Meeting on the week of 23-28 of February. The main aim will be to perform the uncertainty analysis of all the data and presentation of the in vitro testing battery results. The hearing experts will be invited to answer the WG questions.

A complete agenda for the meetings will be circulated later.

6. Any Other Business

Not Applicable

7. Next meeting(s)

Teleconference on the 26th of September (Starting at 13:00 and closing at 19.00). Teleconference on the 10th of October (Starting at 13:00 and closing at 18.00).

Meeting on 23-24-25 of October (Starting at 14.00 on the 23 and closing the meeting on the 25 at 13.00).

Meeting on the week of 24-28 of February.

PPR / Pesticide Peer Review Unit

Minutes of the 1st Meeting of the Working Group on developing Integrated Approaches to Testing and Assessment (IATA) case studies on Developmental Neurotoxicity

20 May 2019, Teleconference

(Agreed on 24 May 2019)

Participants

- Working Group Members:

  Susanne Hougaard-Bennekou, Kevin Crofton, Ioanna Tzoulaki, Antonio F. Hernández-Jerez, Martin Wilks

  All have participated via teleconference, in all points of the agenda (with the exception of Susanne Hougaaard-Bennekou that did not participate to the last two items in the agenda).

- Hearing Experts:

  Not Applicable

- European Commission and/or Member States representatives:

  Anna Bal-Price

- EFSA:

  Andrea Terron (PREV Unit), Iris Mangas (PREV Unit)

- Others:

  Magdalini Sachana (Observer from OECD)

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 Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] 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)

Not Applicable.

5. Scientific topic(s) for discussion

5.1. Scope of the opinion, including the terms of reference and the relevance of the IATA framework[3]

Iris Mangas presented the Scope of the Opinion, including the Term of Reference (ToR). The experts agreed on the ToR and execution plan below for the Scientific Opinion:

ToR: For the Scientific Opinion, the PPR Panel will consider developing Integrated Approaches for Testing and Assessment (IATA) case studies using a developmental neurotoxicity (DNT) risk assessment based problem formulation using all available information (e.g. including epidemiology and in vivo experimental data) on defined pesticide active substances.

The execution plan is to conduct a 2-step analysis for each case-study using the IATA framework in order to answer the problem formulation question. The WG will use the Adverse Outcome Pathway (AOP) concept to inform each IATA case study.

In the first step the WG will evaluate the level of uncertainties associated with the available database (e.g. in vivo test guideline experimental data, epidemiological evidence, public literature data, other relevant data) for characterization of a DNT Hazard for each selected pesticide active substance.

[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
[3] http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2019-00100

In the second step, the WG will integrate the outcome of the in-vitro testing battery for DNT in the AOP-informed IATA case study and provide a new uncertainty analysis.

The Scientific Opinion will include the outcome and discussion of the IATA cases as well as will discuss and conclude in what way the in vitro testing battery may contribute to the DNT hazard characterization for pesticide active substances, and what its limitations are.

5.2. The regulatory problem formulation

Iris Mangas presented a proposal for the regulatory problem formulation. The problem formulation will be further discussed (and agreed) at the next meeting. However, it was agreed that: (1) the problem formulation should clearly specify if the in vitro testing battery gives added value to the DNT Hazard characterization and (2) should include the IATA as a framework for the analysis.

(action for EFSA staff: To prepare a new proposal for the problem formulation considering the discussion above for the next meeting).

5.3. Analysis plan/Outline for the IATA

Iris Mangas presented the analysis plan. This will be used as a starting point for developing the IATA for each case study. More details will be added to the plan once the available dataset compilation is done in the next meeting.

5.4. Weight of evidence/uncertainties analysis methodology

The uncertainty analysis methodology was not discussed, and its discussion is planned for the next meeting.

5.5. How many case studies can we develop in the defined time frame and

5.6. Chemical selection discussion

The two items were discussed together. Andrea Terron presented the timeline and the criteria for the selection of Chemicals: Chemical Class, quality and quantity of available dataset and DNT concern.

The experts discussed several options. After evaluation of the advantages and disadvantages, considering the criteria above and the available timeframe it was concluded:

1. Two case studies can be developed in the available timeframe. In a possible second step the inclusion of a 3rd case study could be evaluated once the first two are in the finalization phase. It was discussed that an organophosphate substance could be included as the 3rd case study.

2. One of the substances should be a substance that was negative in the regulatory DNT in vivo study. This will be very valuable in order to evaluate the advantage of the inclusion of the in vitro testing battery in the DNT Hazard Characterization.

(Action needed: Kevin Crofton and Andrea Terron will internally discuss and send a proposal to the WG for approval).

3. One of the substances should be a pyrethroid, based on the concern for DNT.

Deltamethrin could be the ideal candidate. The ability of this pyrethroid substance to produce the 3-phenoxybenzoic acid (3-PBA) metabolite, used in biomonitoring studies, will be checked. This is a concern because there are multiple pyrethroids with this metabolite, and may reduce the accuracy of a single chemical exposure estimate.

(Action needed Suzanne Hougaard-Bennekou to check if PBA is produced by Deltamethrin).

5.7. Timeline: Organizational issues (timeframe, hearing experts' meetings, meetings calendar)

A proposal for the Timeline was presented by Iris Mangas considering the publication of the Scientific Opinion on June 2020.

There was an agreement that 2 meetings are needed for the first step of the analysis plan and that these should be conducted in 2019. There was an agreement to work in parallel for both case-studies. Next meeting date was fixed on 8-9-10 of July with the main scopes of: (1) compilation and analysis of the epidemiological and experimental lines of evidence for DNT; (2) consolidation of these data in the AOP-IATA and (3) proposal for the uncertainty analysis methodology to be applied in the case studies.

The current plan is to have a total of 3-4 more TC or meetings in 2020 in order to finalize the Scientific Opinion in June 2020.

5.8. Expertise and WG members

Andrea Terron presented the expertise and proposed distribution of work among the members of the WG.

The members of the WG agreed to operationally distribute the work in groups as specified below. One person will be leader of the group and the tasks will be internally divided among the members of each group (see below groups and main output). This approach is intended to facilitate the evaluation of the available evidence, maximize the efficiency of the working group and the drafting of the first version of the case study.

1. Output **In vivo toxicology assessment.**

   Kevin Crofton *leader*

   Susanne Hougaard

2. Output **In vitro neurotoxicology assessment.**

   Kevin Crofton *leader*

   Anna Price *(observer)*

3. Output **Consolidation of the data in the AOP-IATA framework.**

   Susanne Hougaard *leader*

   Sachana Magdalini *(observer)*

   Anna Price *(observer)*

   Kevin Crofton

   (All)

4. Output **Integration of the results in the Regulatory framework.**

   All

5. Output **Evaluation of the Epidemiology evidence.**

   Antonio Hernandez *leader*

   Ioanna Tzoulaki

   Martin Wilks

6. Output **Uncertainties analysis.**
   Martin Wilks *leader*

   (All)

5.9. Outline of the Scientific Opinion

Andrea Terron presented EFSA template for the Scientific Opinion and a proposal for the Outline.

It was agreed to use the OECD template for reporting IATA.

(Action needed to Magdalini Sachanna: to send the OECD template for reporting IATA; action needed to EFSA staff to distribute it to the WG).

5.10. Initial homework in preparation of the next meeting

5.11. Next meeting agenda

Andrea Terron presented a proposal for the Homework and next meeting agenda. The WG agreed on the Homework to be conducted by the next meeting of **8-9-10 of July** (**Starting at 9 am on the 8th and close the meeting on the 10th at 13.00)** as follows:

For Output 1 and 5: Compilation and assessment of all the available data.

The results will be included in the Draft for the Scientific Opinion and will be presented in the next meeting. The results will be discussed and consolidated in the AOP-IATA in the next meeting.

(Action needed to EFSA Staff: to send to the WG members all data available and instructions for the search of the public literature data).

(Action needed for team leaders: to organize among the members of the group the task)

For Output 6: Martin Wilks will present a proposal for the Uncertainty Analysis in the next meeting and it will be discussed by the WG.

A complete agenda will be circulated later.

6. Any Other Business

Not Applicable

7. Next meeting(s)

See point 5.11