PESTICIDE PEER REVIEW UNIT

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

MINUTES OF THE 15TH MEETING OF THE WORKING GROUP ON THE "DEVELOPMENT OF ADVERSE OUTCOME PATHWAYS RELEVANT FOR THE IDENTIFICATION OF SUBSTANCES HAVING ENDOCRINE DISRUPTORS PROPERTIES"

Held on 9th of November 2022 (teleconference)

Agreed on 1st December 2022

Participants

- **Working Group Members:**

  Marina Marinovich (chair)

  Karine Angeli

  Camilla Recordati

- **Observers:**

  Sharon Munn (JRC)

  Niklas Andersson (ECHA)

- **EFSA**:

  PREV Unit: Anna Lanzoni, Martina Panzarea, Ana Cioca

  MESE Unit: Laura Martino

1. Welcome and apologies for absence

The Chair welcomed the WG members. Apologies were received from Majorie van Durseen.

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

The comments received from the appointed PPR Panel reviewers were presented and discussed by the Working Group (WG) members. The comments were addressed and, where needed, the text of the Draft Scientific Opinion and Annexes was amended.

5. Next meeting(s)

None.

[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

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

MINUTES OF THE 14TH MEETING OF THE WORKING GROUP ON THE "DEVELOPMENT OF ADVERSE OUTCOME PATHWAYS RELEVANT FOR THE IDENTIFICATION OF SUBSTANCES HAVING ENDOCRINE DISRUPTORS PROPERTIES"

Held on 20th of October 2022 (teleconference)

Agreed on 4th November 2022

Participants

- **Working Group Members:**

  Marina Marinovich (chair)

  Karine Angeli

  Camilla Recordati

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

  Sharon Munn (JRC)

  Niklas Andersson (ECHA)

- **Observers:**

  Nora Bouftas

- **EFSA**:

  PREV Unit: Anna Lanzoni, Martina Panzarea, Ana Cioca

  MESE Unit: Laura Martino

1. Welcome and apologies for absence

The Chair welcomed the WG members. Apologies were received from Majorie van Durseen.

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

The Working Group (WG) progressed drafting the scientific opinion. The WG discussed the evidence supporting the KERs. Two aspects were mainly discussed:

- assessment of essentiality as part of the KER and/or KE as per the definition reported in the OECD Handbook for AOP developers
- quantification of the KER certainty

The draft Scientific Opinion will be prepared for the review by the appointed reviewers of the PPR Panel.

5. Next meeting(s)

Next meeting is scheduled for **November 9th** (time 10:00 – 17:00 CET) and will be held by TC.

[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

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

MINUTES OF THE 13TH MEETING OF THE WORKING GROUP ON THE "DEVELOPMENT OF ADVERSE OUTCOME PATHWAYS RELEVANT FOR THE IDENTIFICATION OF SUBSTANCES HAVING ENDOCRINE DISRUPTORS PROPERTIES"

Held on 27-28 of September 2022

Agreed on 10 October 2022

Participants

- **Working Group Members:**

  Marina Marinovich (chair)

  Camilla Recordati

  Majorie van Durseen

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

  Sharon Munn (JRC)

- **Observers:**

  Barbara Viviani

- **EFSA**:

  PREV Unit: Anna Lanzoni, Martina Panzarea

  MESE Unit: Laura Martino

  EFSA Observers: Melina Steinbach

1. Welcome and apologies for absence

The Chair welcomed the WG members. Apologies were received from Ms. Angeli.

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. Presentation of the evidence for KERs and collegial quantification of the KERs certainty

An overview of the progress done since the last meeting was presented by EFSA.

The Working Group (WG) was briefed about the purpose of the current meeting, namely presentation of the evidence for Key Event Relationships (KERs) and collegial quantification of the KERs certainty.

MESE Unit presented the approach proposed by EFSA for the evaluation of the KERs certainty for each AOPs developed by the WG and by the external Contractor.

The approach combined a qualitative evaluation of the three criteria (i.e., low, medium, high) for each evidence supporting the KER (i.e., biological plausibility, empirical support, essentiality), as described in the OECD Handbook for AOP developers, and a quantification of the judgments on each criterion using an Expert Knowledge Elicitation (EKE) and the concept of probability.

Supported by MESE Unit, experts evaluate the KERs certainty for the KER included in the following AOPs:

- AOP estrogen metabolism (SULT1E1 inhibition)
- AOP chemically induced imbalance in sex steroid hormones
- AOP from ER activation to Uterine adenocarcinoma

5. Next meeting

Next meeting is scheduled for **October 20th** (time 10:00 – 17:00 CET) and will be held by TC.

[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

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

MINUTES OF THE 12TH MEETING OF THE WORKING GROUP ON THE "DEVELOPMENT OF ADVERSE OUTCOME PATHWAYS RELEVANT FOR THE IDENTIFICATION OF SUBSTANCES HAVING ENDOCRINE DISRUPTORS PROPERTIES"

Held on 14th June 2022 (teleconference)

Agreed on 1st July 2022

Participants

- **Working Group Members:**

  Marina Marinovich (chair)

  Karine Angeli

  Camilla Recordati

  Majorie van Durseen (absent)

- **Observers:**

  Nora Bouftas

- **EFSA**:

  PREV Unit: Anna Lanzoni, Martina Panzarea, Nikolaos Tagaras, Marco Binaglia

  AMU Unit: Elisa Aiassa, Laura Martino (for item 5 of the agenda)

  EFSA's Observers: Steinbach Melina, Aiello Holden Kiara, Smith Nicola, Grossi Marina

1. Welcome and apologies for absence

The Chair welcomed the WG members. Apologies were received from Majorie van Durseen.

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. Scientific discussion on the AOPs development

An overall overview of the progress done since the last meeting was presented by EFSA.

The Working Group (WG) discussed scientific aspects of the two subgroups dealing with early Key Events (KEs) occurring before oestrogen receptor (ER) activation in uterus.

Both the subgroups presented the progress done with the data extraction for the included evidence (i.e. the description of the KEs, biological plausibility, essentiality, and empirical support of the KERs):

- for the description of KEs and KERs biological plausibility, the subgroups used a free text format, in line with the OECD Handbook and template for AOP developers.
- for empirical support, time-dose concordance tables were presented by expert Angeli. A preliminary discussion took place. Specifically, the following points were tackled:
    - Limitations and uncertainties for Empirical Support
    - Possible quantification of the uncertainties with probabilistic approach
    - Usage of a probabilistic threshold for specific stressor (as a tool to evaluate how much change, in terms of % and dose, is needed to trigger the AOPs)

  The WG agreed to further proceed with the inclusion of data in a format of a dose-temporal-concordance table following OECD Handbook and template for AOP developers.

Specific topic for the different subgroups were also discussed as reported in the following lines.

<u>Subgroup 1 i.e., AOPs on estrogen metabolism (data extraction)</u>

The subgroup proceeded and finalised the full-text screening of the references included for the eligibility assessment.

[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

On the bases of the full text screening exercise, the putative AOPs initially identified, namely, AOP1 - binding and inhibition of sulfotransferase 1E1 (SULT1E1), AOP2 - binding and inhibition of 17β-Hydroxysteroid dehydrogenases and AOP3 - Nuclear Receptor activation aryl hydrocarbon receptor (AhR), were modified in their content and name:

- the group decided to not proceed further with the development of the KEs related to the Nuclear Receptor activation aryl hydrocarbon receptor (AhR) considering that the large majority of the studies retrieved and assessed during the full-text screening were related to the DNA damage and therefore not relevant for the development of the current AOP.
- the AOP1 and 2 were renamed as *inhibition of sulfotransferase 1E1* and *inhibition of 17β-Hydroxysteroid dehydrogenases*, respectively.

In addition, the group acknowledged the importance of aromatase in oestrogen metabolism, therefore the WG decided to further investigate the aromatase induction as molecular initiating event (MIE).

Subgroup 2

The subgroup presented an overview of the evidence retrieved for the proposed AOP.

Based on the evidence retrieved the WG decided to re-name the subgroup as *AOP on Reduced availability of GnRH leading to uterine adenocarcinoma via increased estrogen availability at target organ level.*

4.2. Discussion on the drafted Scientific Opinion

It was reminded that the **protocol document** will be incorporated as an Annex in the External Report from the contractor. To avoid duplications, the protocol document will not be annexed to the Plant Protection Products and their Residues (PPR) Panel Scientific Opinion, rather there will be a reference to the contractor's report.

The outline of the Scientific Opinion agreed during the 11th WG meeting was further developed, specific paragraphs were drafted by the WG members as described below.

A preliminary draft of the **methodological approach** was provided by EFSA and presented to the WG for discussion. The specific methodologies developed in each subgroup were tailored on the specific needs (e.g., on the knowledge available - canonical vs non-canonical), this being acceptable and not representing a protocol deviation. The WG agreed that these specific methodologies will be reported as appendices of the Scientific Opinion.

Preliminary drafts on the **relevance of developing AOPs on uterine adenocarcinoma from the regulatory point of view** and **considerations on the pathology of endometrial carcinoma** were presented by the experts Angeli and Recordati, respectively and discussed by the WG for agreement. Regarding the considerations on the pathology of endometrial carcinoma, the WG agreed to keep in the Scientific Opinion a concise summary and include the complete paragraph with the details as Appendix to the Scientific Opinion.

5. Any Other Business

The WG discussed procedural aspects of the current project, including: the review of the draft opinion by the Plant Protection Product and their Residues (PPR) Panel, nomination of the reviewers by the WG members and definitive title of the AOPs. It was acknowledged that the Key Events developed by the two nominated subgroups will be referred to as "early KEs occurring before ER activation in uterus". The contractor provided a summary of the state of the art. It was not possible to discuss this due to the lack of time.

The critical steps that would guide the planned timeframe were defined. In this line, new tasks allocation and deadlines will be sent to the WG members by EFSA and further agreed by email.

6. Next meeting(s)

A two-day physical meeting is scheduled for **September 27th (time 13:00-18:00 CET) - 28th (time 09:00-18:00 CET), 2022**.

PESTICIDE PEER REVIEW UNIT

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

MINUTES OF THE 11TH MEETING OF THE WORKING GROUP ON THE "DEVELOPMENT OF ADVERSE OUTCOME PATHWAYS RELEVANT FOR THE IDENTIFICATION OF SUBSTANCES HAVING ENDOCRINE DISRUPTORS PROPERTIES"

Held on 12-13 of April

Agreed on 10.05.2022

Participants

- **Working Group Members:**

  Marina Marinovich (chair)

  Karine Angeli

  Camilla Recordati

  Majorie van Durseen

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

  Niklas Andersson (ECHA)

- **Observers:**

  Barbara Viviani (Contractor)

- **EFSA**:

  PREV Unit: Andrea Terron, Anna Lanzoni, Martina Panzarea, Nikolaos Tagaras

  AMU Unit: Elisa Aiassa and Laura Martino (for items from 1 to 9 of the agenda), Nicova Klara

1. Welcome and apologies for absence

The Chair welcomed the WG members.

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on 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

A brief introduction was given by EFSA to present the aim and the topics to be discussed in this working group (WG) meeting.

4.1. Update on AOP development progress (data extraction and critical appraisal of the evidence)

The contractor presented the state of the art. Of the six phases foreseen for the AOP development, Phase I (title and abstract screening) and Phase II (full text screening) were concluded; Phase III (data extraction and the appraisal of the evidence) is ongoing.

A scientific discussion took place on specific issues relevant for progressing with the work foreseen for the Phase III:

Strategy to select relevant records as eligible for systematic review

A piloting test was performed to assess the adequateness of the criteria for the inclusion/exclusion of the studies for the systematic review process, including the critical appraisal step.

The selection strategy was discussed and agreed by the WG members, specifically:

Primary research studies that do not include proper controls in the study design will not be included for the appraisal; however, they will be considered for narrative descriptions of the Key Events (KEs) papers including information on the methodology used to measure the key event (KE) will be selected for the appraisal

A proper justification of the approaches used to select the papers as being eligible for the appraisal step will be reported in the protocol.

[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

The WG agreed that the Risk of Bias (RoB) for primary research studies will be assessed using a customized version of the Critical Appraisal Tool (based on the Office of Health Assessment and Translation (OHAT) National Toxicology Program (NTP) tool). Distiller will be used as a tool for conducting the RoB.

AOP refinement

It was noted that the link between the activation of the oestrogen receptor alpha (ERα) and the epigenetic alterations (or viceversa) needs to be further substantiated. The experts underlined the necessity to explain how, and which epigenetic alteration mechanism is triggered by ERα activation.

4.2. Update on early KEs occurring before ER activation in uterus

Subgroup 1 (i.e., AOPs on oestrogen metabolism) and Subgroup 2 (i.e., AOP on Senescence and chemically induced imbalance in sex steroid hormones) presented the progress done since the last meeting on the development of these additional AOPs.

5. Any Other Business

A preliminary outline of the Scientific Opinion was presented by EFSA and agreed by the WG.

The critical steps that would guide the planned timeframe were defined. In this regard, deadlines were agreed, and new tasks were allocated to the WG members and to the EFSA Staff.

6. Next meeting(s)

The next meeting will be held on the **14th of June 2022 (time 10-16 CET)**, by teleconference.

PESTICIDE PEER REVIEW UNIT

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

MINUTES OF THE 10TH MEETING OF THE WORKING GROUP ON THE "DEVELOPMENT OF ADVERSE OUTCOME PATHWAYS RELEVANT FOR THE IDENTIFICATION OF SUBSTANCES HAVING ENDOCRINE DISRUPTORS PROPERTIES"

Held on 23 February 2022 (teleconference)

Agreed on 16 of March 2022

Participants

- **Working Group Members:**

  Marina Marinovich (chair)

  Karine Angeli

  Camilla Recordati

  Majorie van Durseen

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

  Federica Madia (JRC) (absent)

- **Observers:**

  Barbara Viviani

- **EFSA**:

  PREV Unit: Andrea Terron, Anna Lanzoni, Martina Panzarea, Nikolaos Tagaras

  AMU Unit: Elisa Aiassa, Laura Martino, Nicova Klara

1. Welcome and apologies for absence

The Chair welcomed the WG members. Madia's apologies were received.

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on 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. Update on AOP development progress (full-text screening)

The contractor presented the progress done on the development of the postulated AOP since the last meeting.

An overview of the preliminary results obtained after the full-text screening for the human studies was presented: of note, the records retrieved are mainly diagnostic research studies (DRS). Critical appraisal tool for addressing the risk of bias of such studies were discussed and agreed upon.

Preliminary results obtained after the screening of few references on the epigenetic modulation (KE1 of the postulated AOP) were also presented. The group discussed extensively this key event (KE) and the contractor was suggested to include modification in the AOP accordingly.

4.2. Early KEs non-uterine phase

Subgroup 1 (i.e., oestrogen metabolism) (full—text screening and data extraction)

The progress done since the last meeting was presented to the working group (WG). The subgroup proceeded with the full-text screening of the references included for the eligibility assessment.

The data extraction phase was also initiated in parallel for few references and, based on this retrieved information, the group presented a new revision of the postulated key events for the early KEs dealing with oestrogen metabolism.

Subgroup 2 (i.e., AOP on Senescence and chemically induced imbalance in sex steroid hormones)

Due to time constraint the update from the subgroup 2 was postponed to the next meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

5. Any Other Business

Tasks allocation was discussed and agreed upon. The group discussed on the next steps and on the agenda of the next meeting. Intermediate meetings for progress monitoring were also agreed upon.

6. Next meeting(s)

A physical meeting is scheduled for **April 12 (time 09:00-18:00 CET)-13 (time 09:00-18:00 CET)**, 2022.

PESTICIDE PEER REVIEW UNIT

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

MINUTES OF THE 9TH MEETING OF THE WORKING GROUP ON THE "DEVELOPMENT OF ADVERSE OUTCOME PATHWAYS RELEVANT FOR THE IDENTIFICATION OF SUBSTANCES HAVING ENDOCRINE DISRUPTORS PROPERTIES"

Held on 30 November 2021 (teleconference)

Agreed on 21 December 2021

Participants

- **Working Group Members:**
  Marina Marinovich (chair)
  Karine Angeli
  Camilla Recordati
  Majorie van Durseen

- **European Commission and/or Member States representatives:**
  Federica Madia (JRC)

- **Observers:**
  Niklas Andersson (ECHA)
  Terje Svingen (Technical University of Denmark - DTU)
  Barbara Viviani

- **EFSA**:
  PREV Unit: Andrea Terron, Martina Panzarea, Nikolaos Tagaras
  AMU Unit: Elisa Aiassa, Laura Martino, Nicova Klara

1. Welcome and apologies for absence

The Chair welcomed the WG members.

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on 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

An overview of the project was presented to the observers.

The working group aims to develop a series of Adverse Outcome Pathways (AOPs) relevant to the identification of substances having endocrine disruptors properties. The selection of the AOPs to be developed is based on the analysis of the most common EATS and non-EATS endocrine adverse effects as observed through the peer review process of pesticide risk assessment.

In this regard, the working group decided to develop, as first case, an AOP with uterine adenocarcinoma (UA) as adverse outcome (AO). The development of this AOPs is outsourced to an external contractor.

In parallel with the contractor, the working group (WG) is developing a series of Key Events (KEs) likely to occur before the uterine phase and related to 1) oestrogen metabolism and 2) senescence or chemically induced imbalance in sex steroid hormones. The purpose of this parallel work is to identify pivotal nodes (i.e. oestrogen dominance) likely to occur before the uterus events.

4.1. Update on AOP development progress

The contractor presented the progress done on the development of the postulated AOP.

As anticipated during the last meeting of the WG, the full-text screening phase started. An overview of the preliminary results obtained after the full-text screening for the human studies was presented. Differently from what agreed at the beginning, systematic reviews (SRs) were included in the search and will be used to provide support on biological plausibility. However, it was noted that only primary research studies will be selected for further steps.

The next steps in the agreed methodological approach will include the appraisal and the data extraction of the selected papers. The contractor will be guided by EFSA AMU Unit that will provide the support needed throughout the procedure.

Furthermore, experts discussed on the postulated MIE (oestrogen receptor activation) and KE1 (epigenetic modulation) relationship. It was noted that with the current scientific knowledge, it is not possible to define with certainty which KEs come first. However, from the search done by the

[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

contractor, much more empirical evidence was reported for the oestrogen receptor activation leading to epigenetic modulation.

4.2. Early KEs non-uterine phase

Subgroup 1 (i.e. oestrogen metabolism)

Three putative AOPs were postulated by the subgroup and named accordingly.

These AOPs are related to several Molecular Initiating Events (MIEs): 1) AOP1 binding and inhibition of Sulfotransferase 1E1 (SULT1E1), 2) AOP2 binding and inhibition of 17β-Hydroxysteroid dehydrogenases (HSD17β) and 3) AOP3 Nuclear Receptor activation aryl hydrocarbon receptor (AhR). The latter, AOP3, was mainly discussed by the experts. It was noted that DNA damage events, likely to occur after the Nuclear Receptor activation AhR and CYP1B1 induction, should be considered as part of the network and thus their description is necessary.

An overview of the strategy used to retrieve the evidence on the proposed AOPs was also presented.

The total number of the references identified after the literature search was n = 1253. Titles and abstracts screening were performed by 2 reviewers in parallel and relevant papers were selected to be included in the full-text screening phase. The full-text screening will be performed by all the members of the subgroup and a dedicated template will be used to extract the data from the selected papers. According to the agreed plan, the data extraction will be finalized by the end of March 2022.

It was agreed that the AOPs should be linear until the identified common node (i.e. oestrogen dominance).

It was also acknowledged that despite the fact that progesterone plays a key role in the unopposed oestrogen dominance events, its metabolism will be not further considered for the time being.

Subgroup 2 (i.e. AOP on Senescence and chemically induced imbalance in sex steroid hormones)

The subgroup presented an overview of the evidence retrieved for the proposed AOP.

In detail the subgroup collected information on the difference blocks of the putative AOP:

- neuronal control of sexual behavior and hormones i.e. reduced Gonadotropin-releasing hormone (GnRH) neurone activation, deregulation of the kisspeptin release
- ovary and hormonal regulation
- estrous cyclicity

It was acknowledged that the stressor-based approach has many limitations for the AOP development and for the purpose of the project the attention should be focused on the biological plausibility description of the Key Events Relationships (KERs) without considering the AO. The identified stressor (i.e. atrazine) can be used for the empirical support description up to the oestrogen dominance.

It was also underlined that for this AOP the pivotal KE is the disruption of luteinizing hormone (LH) surge.

5. Mini workshop

A workshop was organized with the aim to discuss the scientific ground, the priorities, and the tender specifications to be included in the grant for the development of several AOPs for ED.

An overview of the systematic tools (i.e. systematic mapping and systematic review) and advanced search methodologies (i.e. Machine Learning, DistillerSR) used in the AOP development was presented. These methodologies allowed experts to develop transparent and reproducible AOPs.

An update on FREIA (Female Reproductive toxicity of Endocrine disrupting chemicals (EDCs): a human evidence-based screening and Identification Approach) project and on its impact on the AOP development was presented by Terje Svingen (DTU).

6. Any Other Business

Tasks allocation was discussed and agreed upon.

7. Next meeting(s)

Next meeting is planned for **February 23rd (time 14-18)**, 2022 by teleconference.

PESTICIDE PEER REVIEW UNIT

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

MINUTES OF THE 8TH MEETING OF THE WORKING GROUP ON THE "DEVELOPMENT OF ADVERSE OUTCOME PATHWAYS RELEVANT FOR THE IDENTIFICATION OF SUBSTANCES HAVING ENDOCRINE DISRUPTORS PROPERTIES"

Held on 21 September (teleconference)

Participants

- **Working Group Members:**
  Marina Marinovich (chair)
  Karine Angeli
  Camilla Recordati
  Majorie van Durseen

- **European Commission and/or Member States representatives:**
  Federica Madia (JRC)
  Sharon Munn (JRC)
  Niklas Andersson (ECHA) (absent)

- **Others:**
  Barbara Viviani (observer)

- **EFSA**:
  PREV Unit: Andrea Terron, Martina Panzarea
  AMU Unit: Laura Martino (absent), Irene Munoz

1. Welcome and apologies for absence

The Chair welcomed the WG members. Apologies were received by Niklas Andersson (JRC) and Laura Martino (AMU Unit).

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on 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. Update on AOP development progress

The contractor presented the progresses done on the development of the postulated AOP. The outcome of the analysis conducted with the topic modelling tool was used to populate the putative AOP with additional key events.

In agreement with previous decisions, an update was given on the search strategy regarding the postulated KE1 (epigenetic modulation) and the KE2 (reduced expression of genes involved in DNA-Repair). A thorough description of the approach taken to translate the concepts into search strings was presented. The next steps will include loading the abstracts for KE1 and 2 into Distiller, loading full texts of the selected records and start selecting relevant data to be extracted.

4.2. Early KEs outside the uterus

A series of KEs likely to occur before the uterine phase and related to 1) oestrogen metabolism, 2) senescence or chemically induced imbalance in sex steroid hormones and 3) hormonal imbalance and obesity, were presented to the WG. These KEs will represent additional AOPs to be developed in parallel by the WG members.

The WG was updated on the postulated sequence of KEs expected to occur before the uterine phase. Discussion was focus on modalities associated with several MIEs: binding and inhibition of SULT1E1, Nuclear Receptor activation AhR, aging (and reduced GnRH neurone activation) and deregulation of the kisspeptin release.

The following scheme will be followed for the drafting after postulation of the AOP:

- Description of the KEs
- Description of the biological plausibility of the KERs; list (with no description) what is known for the essentiality and empirical support.

[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

EFSA secretariat informed the WG on the progress on the proposal of launching a Grant for the development of several AOPs for ED.

6. Next meeting(s)

Next meeting is planned for October 28th (9-13), 2021 by teleconference.

PESTICIDE PEER REVIEW UNIT

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

MINUTES OF THE 7TH MEETING OF THE WORKING GROUP ON THE "DEVELOPMENT OF ADVERSE OUTCOME PATHWAYS RELEVANT FOR THE IDENTIFICATION OF SUBSTANCES HAVING ENDOCRINE DISRUPTORS PROPERTIES"

Held on 20 July 2021 (teleconference)

Agreed on 4 August 2021

Participants

- **Working Group Members:**

  Marina Marinovich (chair)

  Karine Angeli

  Camilla Recordati

  Majorie van Durseen

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

  Federica Madia (JRC)

  Sharon Munn (JRC)

- **Others:**

  Barbara Viviani (observer)

- **EFSA**:

  PREV Unit: Andrea Terron, Martina Panzarea

1. Welcome and apologies for absence

The Chair welcomed the WG members. Apologies were received by Niklas Andersson (JRC) and Laura Martino (AMU Unit).

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on 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. Update on AOP development progress

The contractor presented the progress done on the development of the postulated AOP. The outcome of the analysis conducted with topic modelling tool was used to populate the putative AOP with additional key events.

In agreement with previous decisions, discussion was focus on the ED mediated events targeting the uterine mucosa. It was explained that the KE/KERs prioritization was based on biological plausibility and measurability of the events.

The following topics were discussed during the meeting.

- *Specificity of molecular initiating event (MIE)*

Due to its strong biological plausibility, the most suitable MIE to be further considered in the drafting of the adverse outcome pathway (AOP), is the activation of the oestrogen receptor alpha (ERα). Some uncertainties (e.g. why this MIE is selected, why the oestrogen receptor beta is not considered and what are the immediate KEs following activation of the MIE) were noted by the WG and should be addressed in the postulated AOP.

Additionally, although it is well known that oestrogen drives endometrial cell proliferation, the detailed molecular mechanism has not been elucidated yet; it is not clear if oestrogen directly activates the epithelial cells via binding to ERs or if some of the actions on epithelial cells may be mediated by endometrial stroma. However, it is noted that the stromal activation expression of aromatase may be linked through the AOP network. In this regard, the WG suggested the contractor to describe the location of the oestrogen receptor and include further consideration on the stromal compartment, including aromatase activation.

- *Link between MIE and KE1*

The WG proposed to consider additional key events (KEs) (e.g. dimerization of the receptors, overactivation of PI3K) that might occur between the MIE (ERα activation) and the KE1 (epigenetic modulation). In this regard, the AOP wiki will be investigated to search for existing AOP and KE.

- *Molecular fingerprints of type I uterine adenocarcinoma*

[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

It was acknowledged that PTEN (Phosphatase And Tensin Homolog) gene is the most frequently altered gene in Type I uterine adenocarcinoma in humans; however, it is still not clear if this event is occurring, and therefore measurable, in animal models. This uncertainty should be further addressed since it is currently a gap between the in-utero activation of ERα and the relevance of the model used in the regulatory framework. In this regard, the WG suggested the contractor to include in the search string not only the standard strains of animal models (rodents) but also those strains (e.g. Donryu rats) considered sensitive to the Type I uterine adenocarcinoma.

- *Consideration on hyperplasia*

Hyperplasia (non-atypical and atypical) was discussed. The WG considered this KE as having a pivotal role in the AOP; it provides a bridge between morphological changes (AO) and the genetic instability (KEs).

- *Genotoxic and non-genotoxic events*

The WG noted that the downstream events are mostly related to genotoxicity (e.g. lack of DNA repair and accumulation of mutation and uterine cancer), whereas the upstream part of the putative AOP is mostly based on non-genotoxic events. In this regard efforts should be made to develop a bridge between the two sections of the AOP; in addition to this, the WG proposed to build the empirical evidence also using genotoxic substances.

4.2. Early KEs outside the uterus

A series of KEs likely to occur before the uterine phase and related to 1) estrogen metabolism, 2) senescence or chemically induced imbalance in sex steroid hormones and 3) hormonal imbalance and obesity, were presented to the WG. These KEs will represent additional AOPs to be developed in parallel by the WG members.

The WG mainly discussed the AOP dealing with '*senescence and chemically induces imbalance in sex steroid hormones'*. It is noted that human menopausal period and the reproductive senescence in rodents are associated to different mechanisms: in rodents there is a relation with impairment of hypothalamic functionality, whereas in humans with exhaustion of oocytes in the ovaries. While developing the AOP, a distinction should be made between the physiologically senescence in rodents, which is linked to an anticipation of the process caused by oestrogen dominance and what is relevant from an endocrine disruption point of view for human beings (i.e. increase oestrogen and persistent oestrus cycle).

Therefore, the AOP should be further developed focusing the attention on the definition of the adversity (uterine adenocarcinoma) and what is triggering it, keeping in mind that the AOP should inform on endocrine disruption mechanisms relevant to humans.

5. Any Other Business

The WG and the contractor agreed on the next steps and on the implementations to be done.

New action points were allocated to the WG members. The WG members will develop in parallel two AOPs relevant for the early KEs outside uterine phase:

- AOP on Estrogen Metabolism
- AOP on Senescence and chemically induces imbalance in sex steroid

- The following scheme will be followed for the drafting:
- Postulation of the AOPs (agreement on the KEs/KERs)
- Description of the KEs

- Description of the biological plausibility of the KERs; list (with no description) what is known for the essentiality and empirical support.

6. Next meeting(s)

Next meeting is planned for September 21 (9-13), 2021 by teleconference.

PESTICIDE PEER REVIEW UNIT

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

MINUTES OF THE 6TH MEETING OF THE WORKING GROUP ON THE "DEVELOPMENT OF ADVERSE OUTCOME PATHWAYS RELEVANT FOR THE IDENTIFICATION OF SUBSTANCES HAVING ENDOCRINE DISRUPTORS PROPERTIES"

Held on 26 May 2021 (teleconference)

Agreed on 4 June 2021

Participants

- **Working Group Members:**

  Marina Marinovich (chair)

  Karine Angeli

  Camilla Recordati

  Majorie van Durseen

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

  Federica Madia (JRC)

- **Others:**

- **EFSA**:

  PREV Unit: Andrea Terron, Martina Panzarea

  AMU Unit: Laura Martino

1. Welcome and apologies for absence

The Chair welcomed the WG members. Apologies were received from Sharon Munn (JRC) and Niklas Andersson (ECHA).

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. Protocol for approval

A summary on the structure of the protocol was presented to the working group. The **phase 1** (*concluded*) consisted in setting the scope of the assessment, drafting the putative AOPs and defining the problem formulation. The **phase 2** (*currently on going*) consists in the definition of the methods for mapping the evidence to learn and refine the structure of the AOP, in the refinement of the problem formulation questions and definition of the criteria to prioritize the KEs and KERs. The **phase 3** consists in planning the methods to perform the systematic retrieval, in screening papers for relevance (with machine learning methods), in data extraction and appraisal of the evidence (**Distiller will be used as tool**). Then, as second step of the same phase, the evidence will be synthetized and integrated and uncertainties quantified. In the **phase 4** the integration of the evidence and the quantification of the AOP certainty will be used.

Comments made by working group members were addressed throughout the protocol.

The discussion was mainly focused on the criteria for prioritization of KEs for which knowledge is not sufficiently well-established (whereas a simplified approach will be used for the '*well-established*' KEs) and on the criteria for prioritization of stressors to support the assessment of the empirical evidence.

Furthermore, WG members agreed on the eligibility criteria (e.g. study design, population, exposure, endpoints) for selecting *in vitro, in vivo* and human studies.

Dossier data will be included.

5. Update on AOP following application of AI

An overview of the machine learning technique used (i.e. topic modelling) was presented by EFSA AMU Unit; topic modelling allows clustering papers according to the semantic similarity in an automatic way through the artificial intelligence (AI), this would provide topics that can trigger '*discovery*' of MIEs/KEs/AOs relevant for the pathway.

The contractor presented the outcome of the application of AI: it was underlined that the 32% of the clouds were considered further in the analysis. Clouds were discriminated by endpoint category and by subtopics and further analysed to update the postulated putative AOP.

[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

The WG will consider if more upstream KEs (e.g. disruption of the oestrus cycle, persistent oestrus with unopposed oestrogen dominance) will be further developed. In this case, this upstream part will be developed by the WG and not by the contractor.

The WG agreed that, considering the timeframe of the procurement, focus should be given to MIEs that are expected to be activated on the target site (uterine mucosa), for which some critical stressors are likely available (tamoxifen, oestradiol)

6. Any Other Business

New action points were allocated to the working group members.

7. Next meeting(s)

Next meeting is planned for July 20th (9-13), 2021 by teleconference.

PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 5TH MEETING OF THE WORKING GROUP ON "DEVELOPMENT OF ADVERSE OUTCOME PATHWAYS RELEVANT FOR THE IDENTIFICATION OF SUBSTANCES HAVING ENDOCRINE DISRUPTORS PROPERTIES"

Held on 19 March 2021 (teleconference)

Agreed on 12 April 2021

Participants

- **Working Group Members:**

  Marina Marinovich (chair)

  Karine Angeli

  Camilla Recordati

  Majorie van Durseen

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

  Sharon Munn (JRC)

  Federica Madia (JRC)

- **Others:**

  Barbara Viviani

  Elena Bernardini

  Niklas Andersson (ECHA)

- **EFSA**:

  PREV Unit: Andrea Terron, Martina Panzarea

  AMU Unit: Laura Martino, Irene Munoz

1. Welcome and apologies for absence

The Chair welcomed the WG members.

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on 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. Update of the activities done by EFSA since the last WG meeting

The main changes from the last meeting were presented to the experts. A series of document was produced since the last meeting (e.g. list of chemical stressors, initial mapping of the literature, series of putative AOPs).

It was underlined that a key element of the project would be the use of an evidence-based approach to develop transparent and reproducible AOPs.

4.2. Chemical list available from EFSA, initial search done by EFSA

The list of the chemical stressor is currently available in the drafted working protocol.

4.3. Kick off meeting with the awarded contractor: Presentation of the project

A summary of the project including the scope, the terms of reference, the problem formulation and the methodologies that will be applied, were presented by the contractor. The information available and the documentation produced by the WG will be shared with the contractor with the aim to work synergistically during the time frame defined in the tender.

4.4. Systematic review

The contractor presented the methodology to be followed. First, a systematic mapping to identify additional MIEs and KEs will be carried out to refine/integrate the initial AOP. Second, a systematic review will be implemented to provide empirical support.

The challenging points that will be framed within the timeline of the WG are: AOPs prioritization after the initial mapping of KE, MIE versus the postulated AOPs, and the selection of stressors to start the systematic review.

[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

Experts discussed about the most critical aspect of the projects: problem formulation, terminology to be used, aim of the systematic mapping phase and methodology to be followed. The terminology will be reviewed, and a dedicated Glossary created.

4.4.1. Proposal for the eligibility criteria to be used to retrieve and screen the evidence and perform the retrieval and screening of the evidence

The proposal for the eligibility criteria was provided by the contractor. Population's and outcome's eligibility criteria and the terminology to be used were discussed. The final decision about the selection of the studies for inclusion/exclusion will be further agreed with the WG's members.

4.4.2. Proposal for the search string

The aim of the definition of a search strategy will be to 1) Find keywords, 2) Create search strings. The best defined MIEs (i.e. estrogenic activity, increase in situ aromatase activity) will be the starting point to define the search strategy.

The final and definitive search string will be reviewed and forwarded to the WG's experts for further comments.

The entire process will be iterative: through mapping, anchoring, and refining, if additional elements relevant from a biological point of view are found, these will be included as additional KEs.

The results of the search will be collected and managed by using specific tools. The usage of tools for evidence mapping should be further decided between EFSA and the contractor.

4.4.3. Proposal for a critical appraise tool (e.g. OHAT-NTP) to appraise the internal validity of the studies and adapt where needed.

The systematic review process was briefly presented. The critical appraisal tools to be used would be further detailed in the next meeting.

4.4.4. Proposal for a data models to extract the data.

The systematic review process was briefly presented. The models to be used to extract data would be further detailed in the next meeting. Overall, the results of the search will be collected and managed by using specific tools.

4.5. Communication with EFSA and the WG

The communications between the different parts involved will be constant to support the contractor in the process.

4.6. Evidence based AOP, working protocol

EFSA (AMU Unit) presented the structure and the content of the working protocol. The protocol is characterized by four phases, which will be implemented by either the WG or the contractor in consultation with EFSA WG.

The first phase (scope of the assessment, draft of the putative AOPs and of problem formulation) was finalised. The information provided by the contractor was considered enough to finalise the draft of the second phase (definition of the methods for mapping the evidence to learn and refine the structure of the AOP, refinement of the problem formulation questions).

The third and fourth phases (systematic retrieval, screening for relevance, data extraction, appraisal of the evidence, uncertainty analysis and quantification) will be revised soon after the completion of

phase 2. It was underlined that, during the prioritization phase, the KEs considered as scientific dogmas will be left out from the systematic review process. The details about phase 3, OHAT/NTP and EKE will be presented and discussed in the next meeting.

5. Any Other Business

New action points were allocated to the working group members.

6. Next meeting(s)

Next meeting is planned for May 26th, 2021 by teleconference.

PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 4th MEETING OF THE WORKING GROUP ON "DEVELOPMENT OF ADVERSE OUTCOME PATHWAYS RELEVANT FOR THE IDENTIFICATION OF SUBSTANCES HAVING ENDOCRINE DISRUPTORS PROPERTIES"

Held on 26 November 2020 (teleconference)

(Agreed on 17 December 2020)

Participants

- Working Group Members:
  Marina Marinovich (chair)
  Karine Angeli
  Camilla Recordati
  Majorie VanDurseen

- Hearing Experts:
  Not Applicable

- European Commission and/or Member States representatives:
  Sharon Munn (JRC)

- EFSA:
  PREV Unit: Andrea Terron
  AMU Unit: Laura Martino

- Others:
  Niklas Andersson (ECHA)

1. Welcome and apologies for absence

The Chair welcomed the participants. Apologies were received from Majorie VanDurseen.

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. Discuss tender specification for the negotiated procedure

The tender specifications elaborated by EFSA were presented to the working group for feedback. The negotiated procedure will be launched in December and will serve as a background work by the working group for the finalization of ED mediated adverse outcomes in the utero.

The road map for developing the ED AOP was discussed in order to ensure that the working group and the contractor will be able to work synergistically during the time period defined in the tender.

4.2. Meeting plan for 2021

EFSA will provide soon a meetings calendar that will fit with the deliverables of the contract as specified in the tender specifications.

5. Any Other Business

None.

6. Next meeting(s)

To be planned

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 3rd MEETING OF THE WORKING GROUP ON "DEVELOPMENT OF ADVERSE OUTCOME PATHWAYS RELEVANT FOR THE IDENTIFICATION OF SUBSTANCES HAVING ENDOCRINE DISRUPTORS PROPERTIES"

Held on 23 and 24 June 2020 (both days in the afternoon), by teleconference

(Agreed on 20 July 2020)

Participants

- Working Group Members:
  Marina Marinovich (chair)
  Karine Angeli
  Camilla Recordati
  Majorie van Durseen

- Hearing Experts:
  Darlene Dixon (US NTP)
  Richard Judson (US EPA)

- European Commission and/or Member States representatives:
  Sharon Munn (JRC)
  Elise Grignard (JRC)

- EFSA:
  PREV Unit: Andrea Terron, Alfonso Lostia, Martina Panzarea
  AMU Unit: Elisa Aiassa Irene Munoz, Laura Martino

- Others:
  Niklas Andersson (ECHA)

1. Welcome and apologies for absence

The Chair welcomed the participants. Apologies were received from Richard Judson and Niklas Andersson.

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. Selection of chemical stressors

- EFSA presented the preliminary work done to support the selection of chemical stressors to be used to collect existing information for AOPs development on uterine adenocarcinoma. EFSA presented a list of potential chemical stressors as well as the strategy followed to define such list.
- Participants presented also potential chemical stressors following the action agreed in the previous WG meeting.
- Based on the discussion held during the WG meeting, a list of chemical stressors was compiled. The list will be therefore the starting point for the systematic literature search.

4.2. Evidence based approach for AOP development and uncertainty analysis

EFSA presented the methodological protocol for an evidence-based approach for the AOP development. The proposed evidence-based approach aims to collect existing information from literature and from available databases (e.g. EFSA, ANSES, NTP) for the chemical stressors in order to identify relevant data to develop the AOPs. A general strategic scheme was presented and discussed at the WG meeting. The WG members agreed to use the proposed approach.

4.3. Presentation on reproductive aging in women and rodents

The WG member Camilla Recordati gave a presentation on the reproductive aging in women and rodents. The presentation was the basis for discussing how aging plays a role in uterine neoplasms and to contextualise when uterine neoplasm is a result of an oestrogen dominance consequent to a variation in the occurrence of the normal reproductive senescence or due to an endocrine disruption mechanism. WG members agreed that

[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

changes in the oestrous cycle, when treated related, should be considered adverse. However, when changes in the oestrus cycle are impacting the age of reproductive senescence, it remains difficult to establish a link with an endocrine mode of action, when the only information is available in the carcinogenicity study. In both human and rat, oestrogen dominance remains the most relevant cause and an in-depth analysis of the evidence is necessary to conclude on endocrine disruption.

5. Any Other Business

ACTION LIST:

Circulate the list of chemical stressors.

Prioritise chemical stressors to be used for literature search: not genotoxic chemicals will be prioritised.

Define the searching strategy to collect existing information for the prioritised chemical stressors.

Map of available AOPs in the wiki.

Distribute the current AOP table to the WG members for collecting feedback.

6. Next meeting(s)

The next meeting will be held during the 4Q of 2020 and it will be a virtual meeting.

PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 2nd MEETING OF THE WORKING GROUP ON "DEVELOPMENT OF ADVERSE OUTCOME PATHWAYS RELEVANT FOR THE IDENTIFICATION OF SUBSTANCES HAVING ENDOCRINE DISRUPTORS PROPERTIES".

Held on 25 - 26 March 2020 by teleconference

(Agreed on 06 April 2020)

Participants

- Working Group Members:
  Marina Marinovich (chair)
  Karine Angeli
  Camilla Recordati
  Majorie van Durseen

- Hearing Experts:
  Not Applicable

- European Commission and/or Member States representatives:
  Sharon Munn (JRC)
  Elise Grignard (JRC)

- EFSA:
  PREV Unit: Andrea Terron, Alfonso Lostia
  AMU Unit: Elisa Aiassa, Irene Munoz, Laura Martino

- Others:
  Niklas Andersson (ECHA)

1. Welcome and apologies for absence

The Chair welcomed the participants. Apologies were received from Sharon Munn and Elise Grignard.

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. Morphological changes in the uterus; definition of adverse Outcome (AO)

A detailed presentation on uterine neoplasms was discussed by the working group. Point of discussion included:

- the role of unopposed oestrogen as a common key event (KE) in mammal's uterine adenocarcinoma,
- the human Type I uterine adenocarcinoma as a model for an endocrine mediated AO in human,
- the uterine adenocarcinoma as a rodent model to reflect the AO in the standard regulatory experimental toxicological studies, particularly the rat carcinogenesis,
- the existence of a continuum in the rat uterine adenocarcinoma characterized by the glandular hyperplasia leading to adenocarcinoma,
- the specificity of mouse model for the vaginal and cervix clear-cell carcinoma as a model of the human neoplasm induced by DES,
- the existence of multiple scenario and possibly different mechanisms depending on the window of exposure and consideration on the cover of all sensitive populations in the context of the current data requirements in Europe for the different jurisdictions,
- the relevance of the reproductive senescence as a sensitive time; difference between the human menopausal period and the reproductive senescence in rodents need further exploration to better assess the changes in hormonal balance and their potential different impact across species,
- key hormones that are considered in the pathological process are oestrogens and progesterone; though, the working group discussed the complexity of the prolactin mediated pathway in the process of uterine neoplasms and the impact of potential differences between human and rat in the function of prolactin on reproductive functions and related pathologies,

[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

- different animal models were presented, including transgenic models, they will be duly considered, particularly if evidence is provided by these models to support KEs essentiality,
- molecular patterns where also described in brief; there is however a recognition that the mechanistic understanding of the molecular mechanisms in uterine neoplasms pathology remain uncertain,
- models based on pharmaceutical medicines were also presented and further consideration for using medicines as a model of the AO are needed,
- the working group recognises that it is more complex to postulate AOPs for non-oestrogen mediated MIEs i.e. chemicals that can bound and transactivate the E receptor/s.

4.2. Putative AOPs for uterine neoplasms and list of potential chemical stressors

Several putative AOPs with rodent uterine adenocarcinoma were presented and discussed at the working group. Although some common KEs could have been recognized across the different AOPs, more work is needed to come to a more developable hypothesis. A list of possible chemical stressors was presented; however, the WG concluded that more work is necessary to explore potential additional chemical stressors, including pharmaceuticals and hormones.

4.3. Evidence based approach for AOP development and uncertainty analysis

The working group discussed the EFSA proposal to develop, where possible, an evidence based AOP with inclusion of a structured uncertainty analysis. A preliminary methodological protocol was presented and discussed.

The scope of the work (problem formulation) is so far the following:

to develop AOPs relevant for the identification of substances having ED properties leading to a uterine adenocarcinoma as AO, applying, where possible and applicable, an evidence-based approach including structured uncertainty analysis.

4.4. Literature search, appraisal of existing literature; overall strategy

A possible strategy and structure of the literature search was discussed; a more structured proposal will be done by EFSA.

5. Any Other Business

ACTION LIST:

Investigate additional database for the retrieval of additional chemicals that can be used as a stressor for the empirical support of the KERs.

Investigate the available literature for the retrieval of additional chemicals that can be used as a stressor for the empirical support of the KERs. This would also include the evaluation of hormones as stressors.

Consider the available AOPs and populate/delete based on expert knowledge i.e. add MIE/KEs.

Provide expert feedback on physiological differences between human and rodents (rat and mouse) in reproductive senescence and impact on hormonal derangement.

Search strategy proposal.

Map of available AOPs in the wiki.

Initial contact with the US-EPA for understanding of key players in the field.

Update DMS

6. Next meeting(s)

6.1 Meeting plan for 2020

A teleconference will be set for June second half.

A physical meeting will be set for the second half of September.

PESTICIDE PEER REVIEW UNIT

MINUTES OF THE 1st MEETING OF THE WORKING GROUP ON "DEVELOPMENT OF ADVERSE OUTCOME PATHWAYS RELEVANT FOR THE IDENTIFICATION OF SUBSTANCES HAVING ENDOCRINE DISRUPTORS PROPERTIES".

Held on 12 November 2019, by video-conference

(Agreed on 13 November 2019)

Participants

- Working Group Members:
  Marina Marinovich (chair)
  Karine Angeli
  Camilla Recordati

- Hearing Experts:
  Not Applicable

- European Commission and/or Member States representatives:
  Sharon Munn (JRC)
  Elise Grignard (JRC)

- EFSA:
  PREV Unit: Andrea Terron, Alfonso Lostia
  AMU Unit: Elisa Aiassa

- Others:
  Niklas Andersson (ECHA)

1. Welcome and apologies for absence

The Chair welcomed the participants. Apologies were received from Sharon Munn and Elise Grignard.

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. Scope of the working group/mandate: The secretariat of EFSA illustrated the Terms of References as proposed by the PPR Panel and agreed by EFSA.

4.2. The AOP framework: The secretariat illustrated the key concepts for the development of an AOP. For the development of AOPs the OECD guidance on AOP development will be used.

4.3. Evidence based development of AOPs: EFSA (AMU Unit) presented the possibility of using an evidence-based approach for the development of AOPs. The working group will discuss this option in detail and decision will be taken at the next working group meeting.

4.4. Actions for the next meeting: EFSA to prepare putative AOPs for uterine neoplasms based on biological plausibility; EFSA will prepare a proposal for an evidence based approach; expert to prepare a presentation on adverse effects in the uterus based on morphological changes. The analysis should consider diagnostic criteria that are in line with the expected nomenclature used in the experimental toxicology with a comparative reference to human and should consider any potential pathology continuum based on time concordance.

4.5. Meeting plan for 2020

5. Any Other Business

None.

6. Next meeting(s)

25 – 27 March 2020

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf