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