

Scientific Panel on Plant Protection Products and their Residues

Minutes of the 6th meeting of the Working Group on Scientific Opinion of the PPR Panel investigating experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia

Held on 28-29 January 2016, Parma (Italy)

(Agreed on 12 April 2016)

Participants

- **Working Group Members:**

Susanne Hougaard Bennekou (chair), Karine Angeli, Antonio F. Hernandez-Jerez, Ellen Fritsche, Marcel Leist, Alberto Mantovani, Pablo Menendez, Anna Price, Barbara Viviani

- **Hearing Experts¹:**

Florianne Tschudi-Monnet

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

Not Applicable

- **EFSA:**

Pesticides Unit: Andrea Terron

- **Others:**

Not Applicable

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

1. Welcome and apologies for absence

The Chair welcomed the participants.

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes² and the Decision of the Executive Director on Declarations of Interest³, EFSA screened the Annual Declaration of Interest and the Specific Declaration of Interest filled in by the working group members invited for the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process or at the Oral Declaration of Interest at the beginning of this meeting.

4. Agreement of the minutes of the 5th Working Group meeting held on 17-18 November 2015, Parma.

The minutes of the 5th Working Group meeting held on 17-18 November 2015 were agreed on 28 January 2016 and were published on the EFSA website.⁴

5. Hearing Expert

Prof. Florianne Tschudi-Monnet was invited to present her views on the role of neuroinflammation in Parkinson's disease of the present meeting.

6. Scientific topics for discussion

- 6.1.** The following title of the second AOP on Parkinsonian motor deficits was agreed: "Mitochondria-dependent ROS overproduction in nigra-striatal neurons induced by redox cycling leading to parkinsonian motor deficits". The WG agreed that the overall assessment for the proposed AOP can be prepared to be reviewed at the next WG meeting.

² <http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf>

³ <http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014.pdf>

⁴ <http://www.efsa.europa.eu/sites/default/files/assets/Epidem1.pdf>

- 6.2.** The WG discussed the draft material intended to be submitted in the Wiki for the AOP on Inhibition of mitochondrial complex I. This AOP will use Rotenone and MPTP/MPP+ as tool compounds.
- 6.3.** The WG discussed the tool compounds to be selected for the proposed AOP on Infant Leukaemia and agreed that data should be collected for Etoposide.
- 6.4.** The WG discussed on the similarities of the proposed pathway for the AOP on childhood leukaemia with the two hit carcinogenicity model. It was agreed to include the KE "Clonal expansion" laterally to KE2 (Delayed Infection (postnatal). Considering the limited data available to fill essentiality and empirical support, the WG suggested to maximise the biological plausibility.

7. Any Other Business

Not Applicable

8. Next meetings

The next meeting will be held in Parma on 12-13 April 2016.

Minutes of the meeting of the Working Group on Scientific Opinion of the PPR Panel investigating experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia with Industry

Held on 16 March 2016, New Orleans (US)

Participants

- **Working Group Members:**

Susanne Hougaard Bennekou (Chair), Alberto Mantovani, Karine Angeli, Marcel Leist, Barbara Viviani, Ellen Fritsche, Anna Price, Antonio Hernandez-Jerez, Pablo Menendez

- **Hearing Experts¹:**

Breckenridge Charles, Daniel Minnema, Mark Butt, Jeffrey Wolf, Richard Smeyne representing the agrochemical company Syngenta.

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

Not Applicable

- **EFSA:**

Pesticides Unit: Andrea Terron

- **Others:**

Not Applicable

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

1. Welcome and apologies for absence

The Chair welcomed the participants.

Apologies were received from Olavi Pelkonen, Pablo Menendez, Karine Angeli and Alberto Mantovani.

2. Adoption of agenda

The agenda was adopted without changes.

The agenda included one single item: Technical hearing dedicated to the presentation by Industry of stereology, biochemistry and pathology data on the herbicide Paraquat in neurotoxicity studies.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes² and the Decision of the Executive Director on Declarations of Interest³, EFSA screened the Annual Declaration of Interest and the Specific Declaration of Interest filled in by the working group members invited for the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process or at the Oral Declaration of Interest at the beginning of this meeting.

4. Scientific topic(s) for discussion

4.1. Technical hearing.

Industry presented data from a number of studies conducted to investigate the potential neurotoxicity of the herbicide Paraquat. Paraquat induced neurotoxicity is controversial in the literature and multiple elements contribute to this complex argumentation e.g. host susceptibility, dose regimen and scheduling, investigative methods applied in the different studies published in the scientific literature. Data from a number of complementary studies replicating the most common experimental design proposed for Paraquat or following the regulatory toxicology study design were presented.

² <http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf>

³ <http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014.pdf>

The methodological approach used to evaluate the stereology of the substantia nigra was given in detail.

The participants asked a number of technical questions which were promptly addressed by the presenters.

Additionally to stereology, a number of pathology results were presented. Pathology investigation included the evaluation of the silver degeneration stain, vital stain, and a number of markers of neuroinflammation.

In one of the study presented there was a marginal statistically significant decrease in the number of TH positive cells in the substantia nigra of mice treated i.p. with Paraquat at the dose of 15 mg/kg administered weekly for 3 times. This was not accompanied by a decrease in the total number of neuronal nuclei in the substantia nigra and the observation was not accompanied by a decrease in striatal dopamine. Similar changes were observed in animals treated with the positive control MPTP where however a clear drop in striatal dopamine was observed. This was not replicated in a subsequent study at the same and higher dose (3 X 25 mg/kg weekly i.p.). The finding was also not replicated in Smeyne (unpublished data) at dose of 10 mg/kg i.p. administered 6 times or at 20 mg/kg i.p. administered 3 times. The effect was considered by Industry linked to a perturbation of TH rather than consequent to a decrease in number of TH positive neurons

Biochemistry data on striatal dopamine content and dopamine turnover were also presented.

All the studies presented were considered negative by Industry while the investigations conducted with the positive control MPTP, a known toxicant of the nigrostriatal pathway, were considered in line with the expectations. The Industry concluded that Paraquat is not inducing a change in the number of dopaminergic neurons in the substantia nigra and no changes indicative of neurodegeneration or neuroinflammation were observed at pathology investigation. Industry also concluded that biochemical investigation was indicative that Paraquat is not inducing any change in dopamine and/or dopamine turnover in mice.

All the data presented are available in the public literature or close to be published.

EFSA thanks Industry representatives for the very detailed presentation given to the working group and for having answered the multiple questions posed by the working group members.

Minutes of the 5th meeting of the Working Group on Scientific Opinion of the PPR Panel investigating experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia

Held on 17 and 18 November 2015, Parma (Italy)

(Agreed on 28 January 2016)

Participants

- **Working Group Members:**

Susanne Hougaard Bennekou (chair), Alberto Mantovani, Karine Angeli, Marcel Leist, Barbara Viviani, Ellen Fritsche, Anna Price, Antonio Hernandez-Jerez, Pablo Menendez

- **Hearing Experts¹:**

Florianne Tschudi-Monnet

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

Not Applicable

- **EFSA:**

Pesticides Unit: Andrea Terron

- **Others:**

Not Applicable

1. Welcome and apologies for absence

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

The Chair welcomed the participants.
Apologies were received from Antonio Hernandez-Jerez.

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes² and the Decision of the Executive Director on Declarations of Interest³, EFSA screened the Annual Declaration of Interest and the Specific Declaration of Interest filled in by the working group members invited for the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process or at the Oral Declaration of Interest at the beginning of this meeting.

4. Agreement of the minutes of the 4th Working Group meeting held on 6-7 October 2015, Konstanz.

The minutes of the 4th Working Group meeting held on 6-7 October 2015 were agreed on 17 October and were published on the EFSA website.⁴

5. Hearing Expert (s)

Prof. Florianne Tschudi-Monnet was invited to present her views on the role of neuroinflammation in Parkinson's disease of the present meeting.

6. Scientific topic(s) for discussion

6.1. A preliminary AOP on "Binding of inhibitor to the Complex I of the mitochondrial Electron Transport Chain in dopamine neurons of nigrostriatal pathway might lead to motor deficit typical of Parkinsonism" was presented and discussed by the WG⁵.

6.2. The WG discussed the plan for the submission of the AOP to the Wiki.

6.3. The WG discussed the second AOP on "Chemically induced ROS generation leading to motor deficit of Parkinsonism".

² <http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf>

³ <http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014.pdf>

⁴ <http://www.efsa.europa.eu/sites/default/files/assets/Epidem1.pdf>

⁵ <http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2014-00480>

6.4. The WG finalized the issue on how to integrate neuroinflammation in the context of these AOPs.

6.5. The WG discussed the draft AOP on Infant Leukaemia and possible data gaps.

6.6. The WG discussed the draft AOP on childhood leukaemia.

7. Any Other Business

Not Applicable

8. Next meeting(s)

Next meeting will be held in Parma on the 28th and 29th of January 2016.

Minutes of the 4th meeting of the Working Group on Scientific Opinion of the PPR Panel investigating experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia

Held on 6 and 7 October 2015, Konstanz (Germany)

(Agreed on 17 October 2015)

Participants

- **Working Group Members:**

Susanne Hougaard Bennekou (Chair), Alberto Mantovani, Karine Angeli, Marcel Leist, Barbara Viviani, Ellen Fritsche, Anna Price, Antonio Hernandez-Jerez, Pablo Menendez.

- **Hearing Experts:**

Florianne Tschudi-Monnet

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

Not Applicable

- **EFSA:**

Pesticides Unit: Andrea Terron

- **Others:**

Not Applicable

1. Welcome and apologies for absence

The Chair welcomed the participants.

The Chair welcomed Pablo Menendez as a new expert of the working group.

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes¹ and the Decision of the Executive Director on Declarations of Interest², EFSA screened the Annual Declaration of Interest and the Specific Declaration of Interest filled in by the working group members invited for the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process or at the Oral Declaration of Interest at the beginning of this meeting.

4. Agreement of the minutes of the 1st Working Group meeting held on 14 April 2015, Paris.

The minutes of the 1st Working Group meeting held on 14 December 2015 were agreed.

5. Hearing Expert (s)

Prof. Florianne Tschudi-Monnet was invited to present her views on the role of neuroinflammation in Parkinson's disease at the present meeting.

6. Scientific topic(s) for discussion

- 6.1.** Scientific Opinion of the PPR Panel investigating experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia³.
- 6.2.** The WG discussed the title of the AOPs linked to the tool substances MPTP and Rotenone.
- 6.3.** The WG discussed and agreed the AOPs Key Events and AOP Key Events relationship.

¹ <http://www.efsa.europa.eu/en/keydocs/docs/independencypolicy.pdf>

² <http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014.pdf>

³ <http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2014-00480>

6.4. The WG discussed the role of neuroinflammation in Parkinson's disease. Appreciation from the WG was expressed for the scientific input received from Florianne Tschudi-Monnet.

6.5. A comprehensive presentation of the regulatory data requirements for genotoxicity and cancerogenicity hazard exploration and blood related hazard exploration for pesticides was made and discussed in the context of the childhood leukaemia AOP. A draft AOP scheme for this adverse outcome was discussed.

7. Any Other Business

Not Applicable

8. Next meeting

The next meeting will be held in Parma on the 17th and 18th of November 2015.

Minutes of the 3rd meeting of the Working Group on Scientific Opinion of the PPR Panel investigating experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia

Held on 14 April 2015, Paris (France)

(Agreed on 6 October 2015)

Participants

- **Working Group Members:**

Susanne Hougaard Bennekou (Chair), Alberto Mantovani, Karine Angeli, Marcel Leist, Barbara Viviani, Ellen Fritsche, Anna Price, Antonio Hernandez-Jerez

- **Hearing Experts:**

Not Applicable

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

Not Applicable

- **EFSA:**

Pesticides Unit: Andrea Terron, Arianna Chiusolo

- **Others:**

Not Applicable

1. Welcome and apologies for absence

The Chair welcomed the participants.

Apologies were received from Antonio Hernandez-Jerez.

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes¹ and the Decision of the Executive Director on Declarations of Interest², EFSA screened the Annual Declaration of Interest and the Specific Declaration of Interest filled in by the working group members invited for the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process or at the Oral Declaration of Interest at the beginning of this meeting.

4. Agreement of the minutes of the 1st Working Group meeting held on 19 February 2015, Paris.

The minutes of the 1st Working Group meeting held on 14 December 2015.

5. Hearing Expert (s)

None

6. Scientific topic(s) for discussion

6.1. Scientific Opinion of the PPR Panel investigating experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia³.

6.2. The WG discussed the proposal on text on Interpretation of the Terms of Reference. The WG discussed the data requirements in the pesticide regulations for the exploration of neurotoxicity and developmental neurotoxicity³.

6.3. The WG discussed the introduction of the Scientific Opinion.

¹ <http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf>

² <http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014.pdf>

³ <http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2014-00480>

6.4. A scheme summarizing the key mechanistic steps of PD was presented and discussed. The scheme was considered a valid tool and will be considered for the chemical specific AOPs.

6.5. The WG agreed that a hearing expert on the role of neuroinflammation in Parkinson disease is necessary.

6.6. The WG agreed that an additional expert with specific competence in the Childhood Leukaemia is necessary.

7. Any Other Business

Not Applicable

8. Next meeting(s)

The next meeting will be held in Konstanz on the 6th and 7th of October 2015.

Minutes of the 2nd meeting of the Working Group on Scientific Opinion of the PPR Panel investigating experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia

Held on 19 February 2015, Paris (France)

(Agreed on 14 April 2015)

Participants

- **Working Group Members:**

Susanne Hougaard Bennekou (chair), Alberto Mantovani, Karine Angeli, Marcel Leist, Barbara Viviani, Ellen Fritsche, Anna Price, Antonio Hernandez-Jerez

- **Hearing Experts:**

Not Applicable

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

Not Applicable

- **EFSA:**

Pesticides Unit: Andrea Terron, Arianna Chiusolo

- **Others:**

Not Applicable

1. Welcome and apologies for absence

The Chair welcomed the participants.

Apologies were received from Antonio Hernandez-Jerez.

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes¹ and the Decision of the Executive Director on Declarations of Interest², EFSA screened the Annual Declaration of Interest and the Specific Declaration of Interest filled in by the working group members invited for the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process or at the Oral Declaration of Interest at the beginning of this meeting.

4. Agreement of the minutes of the 1st Working Group meeting held on 14 December 2014, Parma

The minutes of the 1st Working Group meeting held on 14 December 2015 were agreed.

5. Scientific topic(s) for discussion

- 5.1.** Scientific Opinion of the PPR Panel investigating experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia³.
- 5.2.** The WG discussed the outcome of the stakeholder workshop on the use of epidemiological data in the context of regulatory risk assessment. The working group observed that the use of AOP was generally understood as a relevant approach to define the biological plausibility as part of the hypothesis. The WG also observed that the concept of AOP needs to be properly communicated and that the potential strengths and benefits of introducing the AOP concept in the regulatory context are still poorly understood.
- 5.3.** The problem formulation (i.e. interpretation of the terms of reference) should clearly specify that exposure is understood as

¹ <http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf>

² <http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014.pdf>

³ <http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2014-00480>

toxicokinetics and exposure to pesticide, as understood in the epidemiological context is not part of this mandate.

5.4. The WG discussed the data requirements in the pesticide regulations for the exploration of neurotoxicity and developmental neurotoxicity.

5.5. An initial discussion was made on the tool substances to be used in the building of AOPs.

6. Any Other Business

Not Applicable

7. Next meeting

The next meeting will be held in Paris on 14 April 2015

Scientific Panel on Plant Protection Products and their Residues

Minutes of the 1st meeting of the Working Group on preparation of a Scientific Opinion of the PPR Panel investigating experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia

Held on 04 (afternoon) and 05 (morning).12.2014 Parma, EFSA

(Agreed on 19/01/2015)

Participants

- **Working Group Experts:**

- Susanne Hougaard Bennekou (Chair), Alberto Mantovani, Antonio Hernandez-Jerez, Karine Angeli, Marcel Leist, Barbara Viviani, Ellen Fritsche.

- **EFSA:**

Pesticides Unit: Andrea Terron, Arianna Chiusolo.

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

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests, EFSA screened the Annual Declaration of interest and the Specific Declaration of interest filled in by the experts invited for the present meeting. No conflicts of interests related to the issues discussed in this meeting have been identified during the screening process or at the oral Declaration of interest at the beginning of this meeting.

4. Agreement of the minutes of the 5th Working Group meeting held on 07-08 10 2014

There was no minute to approve.

5. Scientific topic(s) for discussion

Preparation of a Scientific Opinion of the PPR Panel investigating experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia (EFSA-Q-2014-00480).

The following items were presented and discussed by the Working Group:

Activities, roles and responsibilities of EFSA, the Pesticide Unit, PPR Panel and Working Group members.

Presentation of the Epidemiology project following the publication of the External Scientific report on systematic reviews of epidemiological studies linking pesticide exposure to human health outcomes carried out by the University of Ioannina Medical School in Greece (2013), with particular emphasis on the two mandates of the PPR Panel.

A feedback from the AOP/IATA workshop (OECD) was presented and discussed.

The ANSES Opinion following the INSERM report was presented and discussed.

The rapporteur for the Working Group was nominated.

The agenda of the stakeholder workshop planned for February 2015 was presented and discussed.

The Working Group was informed that EFSA launched procurement for a systematic literature review on Parkinson's disease and childhood leukaemia and mode of actions for pesticides.

The Working Group discussed the construction of the Adverse Outcome Pathways (AOP) and multiple examples were presented.

6. Any other business

Tasks were allocated.

7. Next Meeting

19 February 2015 in Paris.