Oslo, 22-23 May

SCIENTIFIC COMMITTEE

Minutes of the 11th meeting of the Working Group on Biological Relevance

Held on 22-23 May, Oslo

(Agreed on 10 July 2017)

Participants

- **WG Experts:**
  Jan Alexander (Chair), André Penninks, John Griffin, Robert Luttik, Josef Schlatter, Hendrik van Loveren, Johannes Westendorf.
- **EFSA:**
  SCER Unit: Nikolaos Georgiadis, Bernard Bottex

  AMU Unit : Fulvio Barizzone

1. Welcome and apologies for absence

The Chairman welcomed the participants.

Apologies received by Giuseppe Ru, Susanne Hougaard Bennekou, Wopke van der Werf, Rudolf Antonius Woutersen, Antoine Messean, Jean-Louis Bresson and Jan Arend Stegeman.

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 Processes[1] and the Decision of the Executive Director on Declarations of Interest[2], 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 were identified during the screening process or at the Oral Declaration of Interest at the beginning of this meeting.

[1] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[2] http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014.pdf

4. Scientific topic(s) for discussion

4.1 Address of the received comments during the public consultation

It was highlighted that the overall feedback from the comments that were received during the public consultation, which lasted from 6 March to 1 May 2017, was positive. The members discussed and addressed the comments and an amended final version of the guidance document was prepared in order to be sent to the EFSA SC for adoption in the July plenary.

4.2 Next steps and timeframe

The members will work on the last agreed amendments and send their input via emails to the secretariat before the document is sent to the SC.

5 AOB

None.

6 Next meeting(s)

Teleconference 12 June 2017

Parma, 10-11 January 2017

SCIENTIFIC COMMITTEE

Minutes of the 10th meeting of the Working Group on Biological Relevance

Held on 10-11 January 2017, Parma

(Agreed on 25 January 2017)

Participants

- **WG Experts:**
  Jan Alexander (Chair), André Penninks, John Griffin, Robert Luttik, Josef Schlatter, Hendrik van Loveren, Johannes Westendorf, Antoine Messean, Jean-Louis Bresson and Jan Arend Stegeman.
- **EFSA:**
  SCER Unit: Nikolaos Georgiadis

  AMU Unit : Fulvio Barizzone[1]

1. Welcome and apologies for absence

The Chairman welcomed the participants.

Apologies received by Giuseppe Ru, Susanne Hougaard Bennekou, Wopke van der Werf, Rudolf Antonius Woutersen.

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 were identified during the screening process or at the Oral Declaration of Interest at the beginning of this meeting.

[1] Present on the 1st day
[2] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[3] http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014.pdf

4. Agreement of the minutes of the 9th Working Group meeting held on Parma 12 – 13 October 2016, Parma

The participants reviewed the draft minutes of the 9th working group meeting held on 12 – 13 October 2016 in Parma and they were adopted.

The minutes will be published on the EFSA website.

5. Scientific topic(s) for discussion

5.1 Finalisation of the guidance document

The members were updated on the outcome of the EFSA Scientific Committee (SC) comments, which were received during the November EFSA SC plenary. It was highlighted that the overall feedback was positive and that most of the received comments (submitted orally or written) have already been addressed. Some remaining issues raised by these comments were discussed during the current WG meeting, and an amended version of the guidance document was prepared.

5.2 Next steps and timeframe

See above for next steps.

6 AOB

None.

7 Next meeting(s)

The next working group meeting will be held via teleconference on 21 February 2017, only if it is considered appropriate following comments received during the next EFSA SC.

Parma, 12-13 October 2016

SCIENTIFIC COMMITTEE

Minutes of the 9th meeting of the Working Group on Biological Relevance

Parma, 12-13 October 2016

(Agreed on 10 January 2017)

Participants

- **WG Experts:**
  Jan Alexander (Chair), André Penninks, John Griffin, Giuseppe Ru[1], Robert Luttik, Josef Schlatter, Hendrik van Loveren, Johannes Westendorf, Antoine Messean and Jean-Louis Bresson.
- **EFSA:**
  SCER Unit: Nikolaos Georgiadis

1. Welcome and apologies

The Chairman welcomed the participants.

Apologies received by Jan Arend Stegeman, Susanne Hougaard Bennekou, Wopke van der Werf, Rudolf Antonius Woutersen.

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[2] and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests[3], 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 were identified during the screening process or at the Oral Declaration of interest at the beginning of this meeting.

[1] Present on the 1st day
[2] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[3] http://www.efsa.europa.eu/en/keydocs/docs/independencerules.pdf

4. Adoption of the minutes of the 8th Working Group meeting

The participants reviewed the draft minutes of the 8th working group meeting held on 22 – 24 August 2016 in Parma and they were adopted.

The minutes will be published on the EFSA website.

5. Draft guidance document on Biological Relevance

The members discussed the remaining issues raised from the comments received by the SC members during the September plenary. All the comments were addressed appropriately and an amended version of the guidance document was prepared.

Actions:

A. *The members agreed to provide their inputs before the document is sent to the SC members for a new revision and discussion.*

B. *The draft will be amended and distributed according to the discussions.*

6. Next steps and timeframe

See above for next steps.

The next working group meeting will be held in Parma on 10-11 January 2017.

7. AOB

None

Parma, 22-24 August 2016

SCIENTIFIC COMMITTEE

Minutes of the 8th meeting of the Working Group on Biological Relevance

Parma, 22-24 August 2016

(Agreed on 12 October 2016)

Participants

- **WG Experts:**
  Jan Alexander[1] (Chair), John Griffin, Wopke van der Werf[2], Robert Luttik, Rudolf Antonius Woutersen, Giuseppe Ru, Josef Schlatter, Susanne Hougaard Bennekou, Hendrik van Loveren, Johannes Westendorf, Antoine Messean
- **EFSA:**
  SCER Unit: Bernard Bottex, Nikolaos Georgiadis

1. Welcome and apologies

Due to the absence of Jan Alexander on the 1st day, Josef Schlatter kindly accepted to chair the meeting.

The Chairman welcomed the participants.

Apologies were received from Jean-Louis Bresson, André Penninks and Jan Arend Stegeman.

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[3] and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests[4], 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 were

[1] Not present on the 1st day
[2] Present on the 1st day
[3] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[4] http://www.efsa.europa.eu/en/keydocs/docs/independencerules.pdf

identified during the screening process or at the Oral Declaration of interest at the beginning of this meeting.

4. Adoption of the minutes of the 7th Working Group meeting

The participants reviewed the draft minutes of the 7th working group meeting held on 23–24 May 2016 in Parma and they were adopted.

The minutes will be published on the EFSA website.

5. Draft guidance document on Biological Relevance

The members presented their amended examples following the decision tree to set specific decision criteria on whether an effect is biologically relevant. The experts discussed further improvements needed to shape the final form of the document following the WG comments.

Actions:

A. *The members agreed to develop their examples according to the received comments.*

B. *The draft will be amended and distributed according to the discussions.*

6. Next steps and timeframe

See above for next steps.

The next working group meeting will take place in Parma on 12-13 October.

7. AOB

None

Parma, 23-24 May 2016

SCIENTIFIC COMMITTEE

Minutes of the 7th meeting of the Working Group on Biological Relevance

Parma, 23-24 May 2016

(Agreed on 22 August 2016)

Participants

- **WG Experts:**
  Jan Alexander (Chair), Jean-Louis Bresson, John Griffin, Andrew Hart[1], Robert Luttik, André Penninks, Giuseppe Ru, Josef Schlatter, Jan Arend Stegeman, Hendrik van Loveren, Johannes Westendorf
- **EFSA:**
  AMU Unit: Fulvio Barizzone
  GMO Unit: Anna Lanzoni
  SCER Unit: Bernard Bottex, Nikolaos Georgiadis

1. Welcome and apologies

The Chair welcomed the participants. Apologies received by Wopke van der Werf, Rudolf Antonius Woutersen, Susanne Hougaard Bennekou.

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[2] and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests[3], 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 were identified during the screening process or at the Oral Declaration of interest at the beginning of this meeting.

[1] Present on the 2nd day
[2] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[3] http://www.efsa.europa.eu/en/keydocs/docs/independencerules.pdf

4. Adoption of the minutes of the 6th Working Group meeting

The participants reviewed the draft minutes of the 6th working group meeting held on 29 February – 1 March 2016 in Parma and they were adopted.

The minutes will be published on the EFSA website.

5. Draft guidance document on Biological Relevance

Following the Scientific Committee (SC) plenary held in April, the members were updated on the comments received by the members of the SC aimed at improving the draft. The working group discussed the further steps needed to shape the final form of the document following the SC comments.

Actions:

A. The members agreed to develop their examples according to the agreed structure.

B. The draft will be amended and distributed according to the discussions.

6. Next steps and timeframe

See above for next steps.

The next working group meeting will take place in Parma on 22 August (starting at 13.30h), 23 August and 24 August (finishing at 16.00h).

7. AOB

None

Parma, 29 February-1 March 2016

SCIENTIFIC COMMITTEE

Minutes of the 6th meeting of the Working Group on Biological Relevance

Parma, 29 February-1 March 2016

(Agreed on 23 May 2016)

Participants

- **WG Experts:**
  Jan Alexander (Chair), Jean-Louis Bresson, John Griffin, Andrew Hart[1], Susanne Hougaard Bennekou, Robert Luttik, André Penninks, Giuseppe Ru, Josef Schlatter, Jan Arend Stegeman[2], Wopke van der Werf, Hendrik van Loveren, Johannes Westendorf, Rudolf Antonius Woutersen
- **EFSA:**
  AMU Unit: Fulvio Barizzone
  GMO Unit: Anna Lanzoni
  SCER Unit: Bernard Bottex, Nikolaos Georgiadis

1. Welcome and apologies

The Chair welcomed the participants. No apologies were received.

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[3] and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests[4], 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 were identified during the screening process or at the Oral Declaration of interest at the beginning of this meeting.

[1] Day 1 only
[2] Day 1 only
[3] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[4] http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014.pdf

4. Adoption of the minutes of the 5th Working Group meeting

The participants reviewed the draft minutes of the 5th working group meeting held on 14-15 January 2016 in Parma and they were adopted.

The minutes will be published on the EFSA website.

5. Draft guidance document on Biological Relevance

5.1 Review of the contributions

Following to the discussion on examples from the various EFSA areas of activities during the last meeting, the members agreed to restructure the examples according to the following structure:

a. Problem formulation – Definition of the question to answer

b. Collection and selection of the biologically relevant data

c. Reviewing dimensions of biological relevance for each data set

5.2 Further drafting

The working group discussed on the further steps needed to shape the final form of the document.

Actions:

A. The members agreed to revise and comment on the update version according to the agreed structure. The draft will be amended and distributed according to the discussions.

B. The updated version will be provided to the SC for a first round of comments.

6. Next steps and timeframe

See above for next steps.

7. Next meeting dates

The next working group meeting will take place in Parma on 23 May (starting at 13.30h) and 24 May (finishing at 16.00h).

Parma, 14-15 January 2016
EFSA/SC/2057

SCIENTIFIC COMMITTEE

Minutes of the 5th meeting of the Working Group on Biological Relevance
Parma, 14-15 January 2016
(Agreed on 29 February 2016)

Participants

- **WG Experts:**
  Jan Alexander (Chair), Jean-Louis Bresson, John Griffin, , André Penninks[1], Giuseppe Ru, Josef Schlatter, Jan Arend Stegeman[2], Johannes Westendorf, Rudolf Antonius Woutersen, Andrew Hart
- **EFSA:**
  AMU Unit: Fulvio Barizzone
  GMO Unit: Anna Lanzoni
  SCER Unit: Bernard Bottex, Nikolaos Georgiadis

1. Welcome and apologies

The Chair welcomed the participants.

Apologies received from Robert Luttik, Wopke van der Werf, Susanne Hougaard Bennekou and Hendrik van Loveren.

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[3] and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests[4], 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 were identified during the screening process or at the Oral Declaration of interest at the beginning of this meeting.

[1] Present on the 2nd half of the 1st day and the entire 2nd day
[2] Participation via teleconference
[3] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[4] http://www.efsa.europa.eu/en/keydocs/docs/independencerules.pdf

4. Adoption of the minutes of the 4th Working Group meeting

The participants reviewed the draft minutes of the 4th working group meeting held on 30 November – 1 December 2015 in Parma. The minutes were then adopted and will be published on the EFSA website.

5. Draft guidance on Biological Relevance

5.1 Review of the contributions

Following the discussion on examples from the various EFSA areas of activities during the last meeting, the members agreed to restructure the examples according to the following structure:

1. Problem formulation

2. Relevance of the evidence/data

3. Nature and size of the effect

4. Overall relevance taking into account the exposure

Some of the members brought new examples to the attention of the working group or even updated their existing ones according to the comments received during the 4th meeting. More specifically:

- ANS Assessment

An example with Aspartame (E591) as a food additive was presented to the group.

- AHAW assessment

The examples related to the assessment of the risk of entry and establishment into the Mediterranean countries neighbouring the EU of an infectious agent (the Rift Valley Fever Virus) and the gas stunning and unconsciousness at slaughter were further expanded following the comments of the previous meeting.

- BIOHAZ assessment

A case study on the zoonotic potential of classical and atypical scrapie was presented. One of the main questions in relation to the animal TSEs is their ability to infect humans; a number of criteria, based on the Bradford-Hill criteria, have been used by the BIOHAZ Panel to assess the zoonotic potential of TSE agents. The example discussed the use of specific test systems (humanised transgenic mice) and their relevance for human infection assessment. The biological relevance considerations in relation to TSE infectivity for humans was illustrated. It was also highlighted which Bradford-Hill criteria are useful to decide on the relevance of the available evidence.

- FEED assessment

A case for a feed additive containing a mixture of essential oils and herbs to improve the performance of chicken for fattening: the evaluation of the biological relevance of an effect under consideration includes adverse (unwanted) effects and positive (wanted) effects on different species was developed and presented to the WG.

- CEF assessment

The CEF Panel example was presented, related to the evaluation of the toxicity of BPA for humans considering all relevant toxicological information available and characterization of the human health risks taking into account specific groups of the population (e.g. pregnant women, infants and children, etc.).

- GMO assessment

Another example was presented from last time. More specifically, a Scientific Opinion on application (EFSA-GMO-NL-2007-45) for the placing on the market of the herbicide-tolerant genetically modified soybean MON 87708 × MON 89788 for food and feed uses, import and processing under Regulation (EC) No 1829/2003 from Monsanto.

5.2 Biological Relevance considerations and uncertainty characterisation

A new proposal was presented on a conceptual framework for consideration of "relevance". The working group commented and further developed it to make it more fit for purpose.

In general, the WG agreed that the guidance will be drafted according to the below structure:

a. Problem formulation – Definition of the question to answer

- Definition of adverse/benefit
- Population of interest
- Endpoints
- Protection goal

b. Clarify whether the assessment is standardised (regulatory driven or not)

c. Collection of the data accordingly or evaluation of the provided data in the case of the standardised assessment

d. Relevance and reliability of the evidence/data for the assessment

- Relevance of the effect
- Size and nature of the effect Magnitude of the effect (is it statistically significant or bigger than the critical effect level?)
- Power of the studies
- Models (parameters)

e. Relevance of the effect

- Exclusion from the assessment
- Mode of Action, Adverse Outcome Pathways
- Critical Effect Level
- Uncertainties

Further drafting

The working group discussed the subsequent steps needed to shape the final form of the document.

Actions:

A. The members agreed to revise and comment on the update version according to the agreed structure.

B. The members will ensure that their examples follow the agreed structure

6. Next steps and timeframe

See above for next steps.

7. Next meeting dates

The next working group meeting will take place in Parma on 29 February 2016 (starting at 14:00) and 1 March 2016 (finishing at 18.00).

Parma, 9 December 2015
EFSA/SC/2032

SCIENTIFIC COMMITTEE

Minutes of the 4th meeting of the Working Group on Biological Relevance
Parma, 30 November – 1 December 2015
(Agreed on 14 January 2016)

Participants

- **WG Experts:**
  Jan Alexander (Chair), Jean-Louis Bresson, John Griffin, Robert Luttik, André Penninks, Giuseppe Ru[1], Josef Schlatter, Jan Arend Stegeman, Wopke van der Werf, Hendrik van Loveren, Johannes Westendorf, Rudolf Antonius Woutersen
- **EFSA:**
  AMU Unit: Fulvio Barizzone, Laura Martino
  GMO Unit: Anna Lanzoni, Claudia Paoletti
  SCER Unit: Bernard Bottex, Nikolaos Georgiadis, Jean-Lou Dorne

1. Welcome and apologies

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[2] and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests[3], 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 were identified during the screening process or at the Oral Declaration of interest at the beginning of this meeting.

[1] Present on Day 2 only
[2] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[3] http://www.efsa.europa.eu/en/keydocs/docs/independencerules.pdf

4. Adoption of the minutes of the 3rd Working Group meeting

The participants reviewed the draft minutes of the 3rd working group meeting held on 7-8 September 2015 in Parma.

Due to a number of corrections to be incorporated, the minutes will be circulated to the working group after the meeting for adoption by written procedure. They will then be published on the EFSA website.

5. Draft guidance on Biological Relevance

Review of the contributions

Following the discussion on examples from the various EFSA areas of activities during the last meeting, the members of the working group tried further to capture commonalities and specific aspects with regard to biological relevance consideration in EFSA's assessments.

- **NDA assessment (Health claim)**

Efficacy assessments performed by NDA differ from the chemical risk assessments by the level of uncertainty associated with the evidence provided that the Panels are ready to accept. Whilst in chemical risk assessment, evidence from any test system may be considered for possible relevance and used to perform the assessment (with the use of safety factors), for NDA, only human data can be considered as sufficient to conclude on efficacy. All other types of evidence may be considered as relevant and supportive for the assessment but they will never be considered as sufficient evidence. The consequence is that in practice, any dossier that lacks human evidence will be rejected, without considering whether the other types of evidence that have been provided are relevant or not.

An example illustrating biological relevance considerations in relation to human data used for efficacy assessment (relation biomarker and endpoint) was presented. In this particular example, a statistically significant variation in the response was considered as a biologically meaningful effect size.

- **NDA assessment (Dietary Reference Values)**

Recommended dietary allowances (RDA), i.e. the amount of individual nutrients (e.g. calcium, protein, etc.) which should be consumed daily by a healthy population to ensure that the nutritional requirements of 97.5% of its members be met are primarily designed for implementation at the scale of populations. They are now known as dietary reference values (DRV) in Europe.

Dietary reference values rely on data bases of highly variable quality, from consistent experimental data to simple extrapolation from dietary surveys. These very different levels of uncertainties are overlooked in practical life.

A specific example (Vitamin D) will be used to illustrate the above issues (relevance of the data for the target population group).

- **FEED assessment**

An example was presented where the evaluation of the biological relevance of an effect under consideration includes adverse (unwanted) effects and positive (wanted) effects on different species.

The proposed feed additive of the example contains essential oils derived from steam distillation of plants. One of these essential oils contains the alkenyl-benzene derivative estragole in considerable concentrations. The feed additive also contains a mixture of crushed herbs, containing among others cayenne pepper that may lead to acute adverse effects in some population groups.

- **AHAW assessment**

The example related to the assessment of the risk of entry and establishment into the Mediterranean countries neighbouring the EU of an infectious agent (the Rift Valley Fever Virus) listing all the biological effects of interest was further discussed.

The second example, related to gas stunning and unconsciousness at slaughter, illustrates biological relevance considerations in animal welfare assessment.

- **CEF assessment**

An example on bisphenol A discusses the biological relevance of the mammary gland proliferation and morphological observations made in the mammary gland following exposure to BPA in rodent studies in respect to the development of breast cancer in humans.

- **BIOHAZ assessment**

A case study on the zoonotic potential of transmissible spongiform encephalopathies (TSEs) was presented. One of the main questions in relation to the animal TSEs is their ability to infect humans; a number of criteria, based on the Bradford-Hill criteria, have been used by the BIOHAZ Panel to assess the zoonotic potential of TSE agents. The example discussed the use of specific test systems (humanised transgenic mice) and their relevance for human infection assessment. The example also highlights which Bradford-Hill criteria are useful to decide on the relevance of the available evidence.

- **Pesticides assessment**

An example on pesticides having an effect on the thyroid system was presented. The effect of relevance for the assessment will differ depending on whether one considers a single substance assessment or a pesticides group assessment.

- **GMO assessment**

The GMO example illustrates the need and the difficulty to characterise natural variability in order to decide on what is relevant for the assessment.

- **Chemical risk assessment**

Cadmium (Cd) was chosen as an example for chemical risk assessment. The example illustrates the use of mode of action considerations to decide on the relevant effect on which to base the assessment. The example is also specific in the sense that it is based on human data.

- **ERA Assessment**

Protection goals are normally set to protect populations. In some cases (e.g. vertebrates), protection goals are also set to protect individuals. The example presented illustrated the differences between an environmental risk assessment on birds and on insects and how the adversity of various endpoints and sizes of effect were considered. The example also shows that in many cases it will be difficult to point out what the biological relevant threshold of an endpoint will be.

- **PLH assessment**

The PLH example illustrates relevance considerations linked to modelling, i.e. how the Panel decides that the outcome of a model is relevant for the assessment.

6. Further drafting

The working group discussed the structure of the guidance and the further steps needed to shape the final form of the document.

7. Next meeting dates

The next working group meeting will take place in Parma on 14 January 2016 (starting at 09:00h) and 15 January 2016 (finishing at 13.00h).

Parma, 9 December 2015
EFSA/SC/2005rev1

SCIENTIFIC COMMITTEE

Minutes of the 3rd meeting of the Working Group on Biological Relevance
Parma, 7-8 September 2015
(Agreed on 5 January 2016 by written procedure)

Participants

- **WG Experts**:
  Jan Alexander (Chair), Jean-Louis Bresson, John Griffin[1], Susanne Hougaard Bennekou, Robert Luttik, André Penninks, Jan Arend Stegeman, Wopke van der Werf, Hendrik van Loveren[2] and Johannes Westendorf
- **EFSA:**
  AMU Unit: Fulvio Barizzone, Laura Martino[2]
  GMO Unit: Anna Lanzoni[1], Claudia Paoletti[1]
  SCER Unit: Bernard Bottex, Jean-Lou Dorne

1. Welcome and apologies

The Chair welcomed the participants and in particular Dr. Jean-Louis Bresson (NDA Panel) who replaces Dr. Ambroise Martin, and Dr. Wopke van der Werf (PLH Panel) who replaces Dr. Michael Jeger following the renewal of the EFSA Panels and Scientific Committee in July 2015.

Apologies were received from Dr. Josef Schlatter and Dr. Rudolf Antonius Woutersen.

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[3] and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests[4], 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

[1] Present on Day 1 only
[2] Present on Day 2 only
[3] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[4] http://www.efsa.europa.eu/en/keydocs/docs/independencerules.pdf

issues discussed in this meeting were identified during the screening process or at the Oral Declaration of interest at the beginning of this meeting.

4. Adoption of the minutes of the 2nd Working Group meeting

The participants reviewed the draft minutes of the 2nd working group meeting held on 26-27 May 2015 in Brussels. The minutes will be published on the EFSA website.

5. Workshop on increasing robustness, transparency and openness of scientific assessments

The working group was provided with a summary of the workshop on increasing robustness, transparency and openness of scientific assessments that took place on 29-30 June 2015 in Brussels. Comments and suggestions made by the workshop participants will be considered by the working group when developing the guidance document. The draft summary report of the workshop will be circulated, together with these notes, to the working group.

6. Draft guidance on Biological Relevance

Members of the working group discussed a number of examples from the various EFSA areas of activities to try and capture commonalities and specific aspects with regard to biological relevance consideration in EFSA's assessments. When discussing these examples, the working group noted that panels use different approaches to decide on relevant data on which to base their assessment. A number of recommendations will be proposed for the consideration of the Scientific Committee.

- **AHAW assessment**

A first example related to the assessment of the risk of introduction of an infectious agent (the Rift Valley Fever Virus) in Europe was discussed. This example is of particular interest because the basic reproduction ratio of the virus can be considered as a critical effect size for biological relevance. It also discusses biological relevance whether you look at individual level or population level.

The second example, to be further expanded, will illustrate biological relevance considerations in animal welfare assessment. The example that was chosen (gas stunning before slaughter) will be helpful to discuss how an EFSA Panel decides on what is harmful. This example was considered as interesting by the working group as it used a rather well defined biological threshold value (time before unconsciousness) for welfare, as compared to other examples for which the concept of "welfare" is much more debated.

- **ANS assessment**

The working group discussed the proposal to have an example on aspartame where the developmental toxicity observed in animals was attributed to phenylalanine. A text will be prepared for the 5th working group meeting.

- **BIOHAZ assessment**

A case study on the zoonotic potential of transmissible spongiform encephalopathies (TSEs) was introduced. One of the main questions in relation to the animal TSEs is their ability to infect humans; a number of criteria, based on the Bradford-Hill criteria, have been used by the BIOHAZ Panel to assess the zoonotic potential of TSE agents. The example will further expand on the use of specific test systems (humanised transgenic mice) and their relevance for human infection assessment.

The working group underlined the usefulness of this example to illustrate the importance of test system considerations and the need to further identify which Bradford-Hill criteria relate more to biological relevance discussion and which relate more to weight of evidence considerations.

- **FEED assessment**

Assessments performed by the FEEDAP Panel raise a number of specific issues with regard to biological relevance considerations:

- The assessment usually consists of an efficacy assessment, as well as a safety assessment for target animals, users, consumers and the environment. Biological relevance therefore needs to be considered at different population group levels.
- When it comes to genotoxic compounds, the biological relevance will depend on the animal considered and its lifespan: genotoxicity data will not be considered as relevant for species with a short lifespan (e.g. a chicken killed after 42 days), while they will be considered as relevant for pets / companion animals.
- Authorisations for claims are usually required for all animal species. Regulation however sets that testing a substance on three major species allows then to extrapolate the outcome of the assessment to all species. Statistical significance (rather than biologically relevant effect size) is used as main relevance criteria when it comes to efficacy assessment.

- **GMO assessment**

Comparative assessments made in the GMO area were introduced. The comparative assessment requires the simultaneous application of two complementary tests: the test of difference and the test of equivalence. The test of difference is used to verify whether the GM plant, apart from the introduced genetic modification(s), is different from its comparator and might therefore be considered a hazard (potential risk) which, depending on the type of identified difference, in combination with extent and pattern of exposure, may require further safety evaluation. The test of equivalence is used to verify whether the agronomic, phenotypic and compositional characteristics of the GM plant fall within the normal range of natural variation. Such a range of natural variation is estimated from a set of non-GM reference varieties with a history of safe use and therefore allows comparisons of the GM plant with a similar food or feed produced without the help of genetic modification and for which there is a well-established history of safe use. Such assessment should address both intended and unintended effects.

The working group emphasized the need for an example highlighting the need and the difficulty to characterise natural variability in order to decide on what is relevant for the assessment.

- **NDA assessment**

Efficacy assessments performed by the NDA Panel differ from the chemical risk assessments by the level of uncertainty associated with the evidence provided that the Panels are ready to accept. Whilst in chemical risk assessment, evidence from any test system may be considered for possible relevance and used to perform the assessment (with the use of safety factors), for NDA, only human data can be considered as sufficient to conclude on efficacy. All other types of evidence may be considered as relevant and supportive for the assessment but they will never be sufficient. The consequence is that, in practice, any dossier that lacks human evidence will be rejected, without considering whether the other types of evidence that have been provided are relevant or not. It was explained that in this particular case, it is the legislation that sets the kind of threshold for what is relevant to base the assessment on. It was noted that this issue is borderline with weight of evidence considerations.

The working group asked for an example illustrating biological relevance considerations in relation to human data used for efficacy assessment (relation biomarker and endpoint).

- **Pesticides assessment**

The working group decided to use an example of pesticides having an effect on the thyroid system. Whether one considers a single substance assessment or a pesticides group assessment, the effect of relevance for the assessment will differ. In the first instance, because of the definition of an endocrine disruptor, a biologically relevant effect will consist of a variation of thyroid hormones levels and an adverse effect in an intact organism, while for grouped pesticides assessment, a statistically significant change in thyroid hormones will be considered as a relevant effect for the grouping. This example is also interesting as homeostasis in rats is very different compared with humans; in addition to illustrating the fact that the question to answer may set what is relevant for the assessment, it also covers the concepts of homeostasis and relevance of the test species when discussing biological relevance.

- **PLH assessment**

The working group identified that pest risk assessments are very similar to those done in the animal health area, except that PLH uses more modelling in their assessments. A practical example will be presented at the next working group meeting.

- **Environmental risk assessment**

Environmental risk assessment usually follows fixed protocols aimed at deriving an overall NOEC for various endpoints (e.g. 15 endpoints for bird studies). The NOEC is then compared to the environmental concentration. The consideration of adversity of effects/endpoints therefore comes later as compared to chemical risk assessment for humans where a NOAEL is derived and subsequently a health based guideline value is established. It was also explained that the population of interest varies depending on the type of environmental risk assessment. When done on birds and mammals, the effects at individual level

are taken into account, while assessments on aquatic organisms and insects are rather done at population levels, taking into account other aspects such as recovery.

The working group suggested developing an example illustrating the differences between an environmental risk assessment on birds and on insects. For the latter, it was suggested to use bees, as a threshold for recovery is currently under discussion. The examples should also illustrate how the adversity of various endpoints and sizes of effect has been considered.

It was clarified that all examples for the guidance document are for illustration purposes and therefore there is no need to enter into specific chemical considerations, or use specific data submitted in dossiers to EFSA.

- **Chemical risk assessment**

The participants agreed on having a joint example to illustrate how to address effects other than clear-cut effects, making use of mode of action or adverse outcome pathways considerations to understand how these effects are linked to the adverse effect. Before starting working on the joint example, the working group asked for a simple example to try and map possible specific considerations related to biological relevance considerations in chemical risk assessment. The previous EFSA assessment of cadmium will be used as a "simple" example.

- **Interpretation of the Terms of Reference**

In line with the new EFSA template for opinions, a section will be drafted to clarify the interpretation of the terms of reference by the working group, i.e. making it clear that this guidance document will discuss not only concepts to decide whether an effect is adverse, or beneficial, or relevant for the assessment, but also criteria and concepts to be considered and whether a dataset is relevant to be used as evidence for the assessment (e.g. adequacy of the test system, power of the study) etc.

- **Introduction section**

The working group came back to its previous idea to structure the guidance document according to the risk assessment paradigm and agreed with the proposal to organise the document according to the Prometheus Deliverable 1 report.

- **Biological Relevance and Uncertainty**

Members of the working group were invited to keep track of possible sources of uncertainties related to biological relevance considerations when drafting their contributions / examples. A member of the SC Working Group on Uncertainty will be invited to the January 2016 meeting to help with this exercise.

7. Next steps and timeframe

The working group members identified for drafting a contribution (see previous section) will provide their contribution by 15 October 2015.

The updated draft guidance will then be circulated to the whole working group who will then review all sections and provide possible comments / additional drafting suggestions to the Secretariat by 16 November 2015.

8. Next meeting dates

The next working group meeting will take place in Parma on 30 November (starting at 13.30 h) and 1 December 2015 (finishing at 16.00 h).

Parma, 24 August 2015
EFSA/SC/1969

SCIENTIFIC COMMITTEE

Minutes of the 2nd meeting of the Working Group on Biological Relevance Brussels, 26-27 May 2015 (Agreed on 7 September 2015)

Participants

- **WG Experts**:
  Jan Alexander (Chair), André Penninks, Josef Schlatter, Jan Arend Stegeman[1], Hendrik van Loveren, Johannes Westendorf and Rudolf Antonius Woutersen[2]
- **EFSA:**
  AMU Unit: Fulvio Barizzone
  GMO Unit: Anna Lanzoni[3]
  SCER Unit: Bernard Bottex

1. Welcome and apologies

The Chair welcomed the participants. Apologies were received from John Griffin, Susanne Hougaard Bennekou, Michael John Jeger, Ambroise Martin and Robert Luttik.

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[4] and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests[5], 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 were identified during the screening process or at the Oral Declaration of interest at the beginning of this meeting.

[1] Present on Day 1 only
[2] Via Conference call on Day 2
[3] Via Conference call
[4] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[5] http://www.efsa.europa.eu/en/keydocs/docs/independencerules.pdf

4. Adoption of the minutes of the 1st Working Group meeting

The participants reviewed the draft minutes of the 1st working group meeting held on 17 April 2015 in Brussels. The minutes will be published on the EFSA website

5. Draft guidance on Biological Relevance

The members of the working group reviewed the contributions received regarding definitions and concepts associated with biological relevance (see notes of the 1st working group meeting). In a second step, the working group discussed how these definitions and concepts should be organised in the draft guidance document. As a result of the discussion, a decision was made to organise the guidance document following the risk assessment paradigm, as it could be adapted for all EFSA areas of activity. A detailed outline of the guidance document was prepared.

6. Workshop on increasing robustness, transparency and openness of scientific assessments

On the basis of the draft outline for the guidance document, the meeting participants identified the following questions / issues that would require clarifications from the participants of the above-mentioned workshop:

Q1: do the definitions and concepts developed in the guidance document capture all relevant assessment fields? Are there different definitions and concepts associated with biological relevance that you would like to bring to the attention of the SC Working Group on Biological Relevance?

Q2: Discussion on thresholds in relation to effect sizes and cut-off size (Josef's discussion paper will be tabled for the workshop's breakout groups). Do the participants agree that a biologically relevant effect size does not indicate a dose below which any response is zero, but a dose below which the response is considered to be irrelevant for the assessment? The critical question is, therefore, "when does a biological effect (physiological change) become adverse/beneficial?"

Q3: Apart from the target population, the protection goals and cut-off values for pre-identified biologically relevant effects, do you see any other aspects related to the discussion of biological relevance worth clarifying between the risk assessors and the risk managers before starting the actual assessment?

Q4: In some cases, a weight of evidence approach will have to be conducted to establish relevance. It could be applied at two different levels: integrate various pieces of information to conclude on the relevance of a given effect (e.g. in vitro + in vivo data). Or integrate different evidence to conclude on the relevance of the effect for the target species (e.g. relative increase of an organ weight + modification of serum composition). How should this be addressed in the guidance on weight of evidence?

Q5: Are there other tools or concepts apart from those already identified to set up the critical effect size? The breakout groups are invited to discuss the use of resilience, recovery; homeostasis to set up the cut off value. Is the cut-off value set-up only by expert judgement or are there some quantitative approaches?

Would it be appropriate/feasible/worth listing (default) cut-off values for specific endpoints/target species, reviewing previous assessments?

Q6: Apart from a) uncertainty in the mode of action in the test species, b) extrapolation of the effect to the target species, c) set-up of the cut-off value, what are the key sources of uncertainty to be considered in the context of discussing biological relevance? How should this uncertainty be taken into account? Any impact on the draft guidance on uncertainty characterisation?

7. Next steps and timeframe

The working group members identified a section of the draft guidance that requires expansion and will provide their contribution by 15 July 2015.

The updated draft guidance will then be circulated to the whole working group who will then review all sections, considering whether possible specific needs or considerations linked to their Panel/Unit area of expertise are covered. Proposals for changes will be sent to the Secretariat by end of August at the latest

8. Next meeting dates

The **next working group meeting** will take place **in Parma on 7 September (starting at 14.00) and 8 September 2015 (finishing at 16.00)**. The purpose of the meeting will be to review the outcome of the workshop on increasing robustness, transparency and openness of scientific assessments, and to work further on the draft guidance document.

A doodle survey will be circulated to the working group members to identify the dates for another meeting in November or early December 2015.

9. Any Other Business

The working group was informed about the launch of a procurement by EFSA in relation to the ongoing revision by the PPR Panel of its guidance documents for aquatic and terrestrial ecotoxicology. This procurement aims at collecting information on "biological relevance of effects (considering mortality, sub-lethal and reproductive effects) and magnitude of effects observed in laboratory studies and population level effects on amphibians and reptiles in the field". It is expected that results from this procurement will be available in the second half of 2016.

Parma, 13 May 2015
EFSA/SC/1919

SCIENTIFIC COMMITTEE

Minutes of the 1st meeting of the Working Group on Biological Relevance Brussels, 17 April 2015 (Agreed on 26 May 2015)

Participants

- **WG Experts**:
  Jan Alexander (Chair), John Griffin, Susanne Hougaard Bennekou, Michael John Jeger, Robert Luttik, Ambroise Martin[1], André Penninks, Josef Schlatter, Jan Arend Stegeman, Hendrik van Loveren, Johannes Westendorf and Rudolf Antonius Woutersen
- **EFSA:**
  AMU Unit: Fulvio Barizzone
  GMO Unit: Anna Lanzoni
  SCER Unit: Bernard Bottex

1. Welcome and apologies

The Chair welcomed the participants. Members of the working group were invited to introduce themselves during a tour-de-table. The purpose of the first meeting was to agree on the terms of reference and on "how far" the guidance document should go.

The working group was informed that a workshop on increasing robustness, transparency and openness of scientific assessment will be organised on 29-30 June 2015 in Brussels, with the objective of collecting relevant information / previous work from sister agencies and other organisations to be considered by the working group for this opinion.

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[2] and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests[3], EFSA screened the Annual Declaration of interest and the Specific Declaration of interest filled in by the experts invited for the

[1] Via conference call
[2] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[3] http://www.efsa.europa.eu/en/keydocs/docs/independencerules.pdf

present meeting. No conflicts of interests related to the issues discussed in this meeting were identified during the screening process or at the Oral Declaration of interest at the beginning of this meeting.

4. Increasing robustness, transparency and openness of scientific assessments

Members of the working group were introduced to EFSA's activities on Prometheus (PROmoting METHods for Evidence Use in Scientific assessments), weight of evidence, characterisation of uncertainty in risk assessment and biological relevance, and how these four topics relate to each other.

The working group discussed the terms of reference for the specific activity on biological relevance and confirmed that the guidance should provide a list of criteria and generic issues to decide on biological relevance for the assessment, addressing all EFSA's remit of activities, i.e. human health, animal health, plant health and environmental risk assessment, and covering both adverse and positive effects.

The working group started the discussion from the definition given in the SC opinion on statistical significance and biological relevance (EFSA, 2011). In this opinion, a biologically relevant effect can be defined as "*an effect considered by expert judgement as important and meaningful for human, animal, plant or environmental health. It therefore implies a change that may alter how decisions for a specific problem are taken*".

Once the biological relevance of a specific dataset has been considered, together with the uncertainty around the data, and the statistical significance of the results (reliability of the data), then the issue of what weight to give to this piece of evidence for the ongoing assessment can be considered.

The working group noted that the concept of biological relevance is associated with a number of other concepts and tools that will need to be further discussed in the guidance document: adverse (effect), adaptive, harm, benefit, homeostasis, transient effect (as opposed to sustained effect), resilience, (ecological) recovery, biological threshold, mechanism of action, mode of action, adverse outcome pathway, statistical significance, critical effect size, statistical power, protection goals, test system, experimental model use, nature of an effect, risk factor for a disease, field trials and equivalence, *in silico* data and biological relevance and toxicological relevance

Members of the working group will draft some text describing further these concepts and tools, for further discussion at the next working group meeting. Members of the working group were also invited to think of a possible outline for the guidance document.

5. Next meeting dates

Doodle Polls will be sent shortly after the meeting to identify possible dates for two meetings: one in May/June 2015, before the EFSA workshop on increasing robustness, transparency and openness of scientific assessments, and the second one at the end of August/early September 2015.