Scientific Committee

Minutes of the 6th meeting of the Working Group on Benchmark Dose

Held on 21 & 22 April 2016, Parma

(Agreed on 30 May 2016)

Participants

- **Working Group Members:**

  Marc Aerts, Laurent Bodin, Allen Davis[1], Lutz Edler, Ursula Gundert-Remy[2], Salomon Sand, Josef Schlatter (Chair) and Wout Slob

- **EFSA:**

  AMU Unit: Jose Cortinas Abrahantes

  SCER Unit: Bernard Bottex, Georges Kass

1. Welcome and apologies for absence

The Chair welcomed the participants. Apologies were received from Daniele Court Marques and Christophe Rousselle.

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[3] and the Decision of the Executive Director on Declarations of Interest[4], EFSA screened the Annual Declaration of

[1] Via conference call, 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

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.

4. Agreement of the minutes of the 5th Working Group meeting held on 20 & 21 January 2016, Parma.

The minutes of the of the 5th Working Group meeting held on 20 and 21 January 2016 were agreed[5].

5. Update of the guidance on Benchmark Dose

The participants went through the various sections of section 5 of the document. The flow chart to derive the BMD confidence interval and the criteria for selecting the models to use for the BMD analysis were further clarified. Modifications have been inserted directly in the draft guidance. The new version resulting from this working group's discussion was circulated after the meeting. Sections to be updated and persons responsible for the update have been highlighted directly in the draft guidance.

The US EPA will provide written comments on the approach proposed for BMD analysis and the recommended models. Members of the working group with specific expertise in statistics will review these comments and discuss whether there is a need to amend the guidance.

6. Next steps

The draft guidance will be proposed for endorsement for public consultation at the 79th SC Plenary meeting (6-7 July 2016); the public consultation will then run until mid-September 2016.

7. Next meeting(s)

The following dates for the meetings in 2016 were identified:

- **30 May 2016**, conference call from 14.00 to 16.00 h to finalise the guidance document before it goes to the Scientific Committee for possible endorsement for public consultation.
- **5-6 October 2016**, Parma. The meeting (which will start at 14.00 h on the 5th and finish at 16.00 h on 6th October) is to review the

[5] https://www.efsa.europa.eu/sites/default/files/assets/benchmarkwg.pdf

comments received during the public consultation and finalise the guidance document.

Scientific Committee

Minutes of the 5th meeting of the Working Group on Benchmark Dose

Held on 20 & 21 January 2016, Parma

(Agreed on 21 April 2016)

Participants

- **Working Group Members:**

Marc Aerts, Laurent Bodin, Lutz Edler[1], Ursula Gundert-Remy, Alicja Mortensen, Salomon Sand[2], Josef Schlatter (Chair) and Wout Slob

- **EFSA:**

AMU Unit: Jose Cortinas Abrahantes

SCER Unit: Bernard Bottex, Georges Kass

1. Welcome and apologies for absence

The Chair welcomed the participants. Apologies were received from Daniele Court Marques, Allen Davis and Christophe Rousselle.

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[3] and the Decision of the Executive Director on Declarations of Interest[4], 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

[1] Day 2 only
[2] Via webconference, 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

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. Agreement of the minutes of the 4th Working Group meeting held on 4&5 November 2015, Amsterdam.

The minutes of the of the 4th Working Group meeting held on 4&5 November 2015 were agreed. The minutes will be published on the EFSA website (http://www.efsa.europa.eu/sites/default/files/assets/benchmarkwg.pdf).

5. Update of the guidance on Benchmark Dose

The participants went through the various sections of the document. Most of the discussion focussed on the flow chart to derive the BMD confidence interval and the criteria for selecting the models to use for the BMD analysis. Modifications have been inserted directly in the draft guidance. The new version resulting from this working group's discussion has been circulated together with these notes. Sections to be updated for the next working group meeting and persons responsible for the update have been highlighted directly in the draft guidance.

In order for the group to get a chance to review the full draft guidance prior to the next working group meeting (30-31 March 2016), **all contributions will be sent to the Secretariat by 15 March 2016 at the latest**.

6. Next steps

Simulations to test the proposed flow chart will be done on different types of datasets. The modellers and statisticians of the working group will review the outcome among themselves. In case of an issue that cannot be resolved among this subgroup and that would require the involvement of the whole working group, a **tentative date** has been blocked **for a conference call: 15 February 2016 from 10.00 to 12.00 h**

The objective is still to have the guidance document endorsed for publication at the 78th SC Plenary meeting (April 2016); the public consultation will then run for 6 weeks in May and June 2016.

7. Next meeting(s)

The following dates for the meetings in 2016 were identified. The meeting place will be confirmed later.

- **15 February 2016**, conference call from 10.00 to 12.00 h. **Tentative date** depending on the outcome of the simulations done with the proposed flow chart.
- **30-31 March 2016**, starting at 10.00 h on the 30th and finishing at 17.00 h on the 31st. Brussels or Amsterdam
- **24-25 August 2016**, meeting starting and ending time, and meeting place to be determined

SCIENTIFIC COMMITTEE AND EMERGING RISKS UNIT

Scientific Committee

Minutes of the 4th meeting of the Working Group on Benchmark Dose

Held on 4 & 5 November 2015, Amsterdam (The Netherlands)

(Agreed on 20 January 2016)

Participants

- **Working Group Members:**

  Marc Aerts, Laurent Bodin, Allen Davis[1], Lutz Edler, Ursula Gundert-Remy, Alicja Mortensen, Salomon Sand, Josef Schlatter (Chair) and Wout Slob

- **Observer:**

  Christophe Rousselle (DG Health and Consumers SCCS)

- **EFSA:**

  AMU Unit: Jose Cortinas Abrahantes

  SCER Unit: Bernard Bottex

1. Welcome and apologies for absence

The Chair welcomed the participants. Apologies were received from Daniele Court Marques.

2. Adoption of agenda

The agenda was adopted without changes.

[1] Via conference call

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes[2] and the Decision of the Executive Director on Declarations of Interest[3], 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.

4. Agreement of the minutes of the 3rd Working Group meeting held on 21&21 September 2015, Brussels.

The minutes of the of the 3rd Working Group meeting held on 21&22 September 2015 were agreed. The minutes will be published on the EFSA website (http://www.efsa.europa.eu/sites/default/files/assets/benchmarkwg.pdf).

5. Update of the guidance on Benchmark Dose

The participants went through the various sections of the document, agreeing on the contents of the updates to be inserted for the next working group meeting. The new version resulting from this working group's discussion will be circulated together with these notes. Sections to be updated for the next working group meeting and persons responsible for the update have been highlighted directly in the draft guidance.

A section "interpretation of the terms of reference" will be added to explain what the working group has done and which sections were modified.

In order for the group to get a chance to review the full draft guidance prior to the next working group meeting, **all contributions will be sent to the Secretariat by 7 January 2016 at the latest**. The Secretariat will then circulate the new version of the guidance document, to be discussed during the January working group meeting, by 11 January 2016 at the latest.

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

6. Next steps

The Working Group acknowledged that the update needed for the guidance document is more significant than initially anticipated and that it will not be possible to have the document ready for publication by the end of this year. An extension of the deadline will be requested to the Scientific Committee and EFSA, with the objective to have the document finalised during the 2nd half of 2016.

The working group reorganised its working calendar (see next section) in order to:

- Have the guidance document endorsed for publication at the 78th SC Plenary meeting (April 2016); the public consultation will then run for 6 weeks in May and June 2016
- Have the guidance document adopted at the 80th SC Plenary meeting (September 2016)

7. Next meeting(s)

The following dates for the meetings in 2015 were identified. The meeting place will be confirmed later.

- **20 November 2015,** conference call from 14.00 to 16.00 **cancelled**
- **20-21 January 2016**, starting at 9.00 on the 20th and finishing at 13.00 on the 21st. Parma
- **30-31 March 2016**, starting at 10.00 on the 30th and finishing at 17.00 on the 31st. Brussels or Amsterdam
- **24-25 August 2016**, meeting starting and ending time, and meeting place: to be determined

SCIENTIFIC COMMITTEE

Minutes of the 3rd meeting of the Working Group on Benchmark Dose

Held on 21 & 22 September 2015, Parma (Italy)

(Agreed on 4 November 2015)

Participants

- **Working Group Members:**

  Marc Aerts, Laurent Bodin, Allen Davis[1], Lutz Edler, Ursula Gundert-Remy, Alicja Mortensen, Salomon Sand, Josef Schlatter (Chair) and Wout Slob

- **EFSA:**

  AMU Unit: Jose Cortinas Abrahantes[2]

  SCER Unit: Bernard Bottex and Georges Kass

1. Welcome and apologies for absence

The Chair welcomed the participants. Apologies were received from Daniele Court Marques and Christophe Rousselle

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[3] and the Decision of the Executive Director on Declarations of Interest[4], 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

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

meeting were 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 2nd Working Group meeting held on 28 & 29 May 2015, Brussels.

The minutes of the of the 2nd Working Group meeting held on 28 & 29 May 2015 were agreed. The minutes will be published on the EFSA website (http://www.efsa.europa.eu/sites/default/files/assets/benchmarkwg.pdf).

5. Update of the guidance on Benchmark Dose

The participants went through the various sections of the document, agreeing on the contents of the updates to be inserted in the guidance document for the next working group meeting.

Sections 1, 2, 3, 3.1, 3.2, 3.3, 3.4, 4, 4.1, 4.2, 4.4 and 4.5 of the 2009 guidance document remain unchanged.

Section 4.3 (Potency comparison) was only modified by adding the Bosgra et al (2009) reference.

6. Issues to be addressed by the update

6.1. Selection and specification of the BMR (Sections 3.5 and 5.2)

Most of what is currently section 3.5 will be moved to section 5.2 (specification of BMR) to avoid duplication. Section 3.5 will only consist in a couple of key sentences explaining what a BMR is about so that the reader can understand Figure 1 and the examples developed in section 3.4

For quantal data, the recommendations remain unchanged compared with the 2009 guidance document: a default BMR of 10% is recommended

For continuous data, the starting point remains the default value of 5%. The working group disagreed with the proposal to use for BMR one Standard Deviation (SD) from the control group, as the value will depend on the quality of the experiment.

The guidance document will make it clear that it is possible to deviate from the 5% default. The working group discussed the possible use of clinical reference values or normal values from historical controls. Any deviation from the default 5% BMR will have to be explained and documented. It will be made very clear that in principle, the value for the BMR (whether one decides to go for the default value, or to modify it on the basis e.g. of biological meaning) should be decided before starting the BMD analysis, and not reconsidered afterwards because one does not like the outcome e.g. the confidence interval around the BMD. The value of the BMR should also not depend on the specific dose-response dataset considered.

6.2. Specification of type of dose-response data (section 5.1)

The first paragraph related to non-significant trend will be moved to the section on model fitting (5.4), explaining that existing software for BMD analysis compare the dose-response with the no-response model, which is equivalent to doing a trend test.

6.3. Selection of candidate dose-response models (section 5.3)

A short paragraph on the distribution to be assumed (log-normal by default, based on empirical evidence) will be inserted. The text from Marc proposed for the second meeting of the working group, and annexed to these notes, will be used as a starting point. The section will flag that there may be cases where another assumption for the distribution may be needed. Criteria to decide when to move away from the default log-normal distribution, e.g. outcome of a Q-Q Plot test should be provided in the section.

The figure in slide 44 from lecture 2 of the advanced training on BMD will be inserted in the guidance document to better explain the meaning of the a, b, c and d parameters of the models.

7. Continuous data:

The list of properties for the models to be used has been updated. The use of model averaging will be recommended as well for analysing continuous data. Table 3 and accompanying text will be updated accordingly.

8. Quantal data:

Table 3 and accompanying text will be updated considering that the default approach will be model averaging with quantal data. For the LMS family, the one-stage, two-stage and three-stage models will remain in the table, since the BIC will be used to weigh the goodness-of-fit of the three different models of the LMS family and select the one to be used for model averaging.

9. Model constraints

The section is fine as it is, with the text explaining why the previous recommendation that the slope should be constrained in some cases, has changed in the updated guidance

9.1. Fitting and accepting models

The general rule in the new guidance document will be to go for model averaging, using the BIC for weighing the various models, based on their fitting properties. Some text will therefore be needed on the reasons why we change the approach as compared to the previous guidance document, and to explain in simple words what model averaging is, what this BIC criteria is and what is meant by weighing the various models according to their goodness-of-fit. The report on model averaging from the US EPA, to be published by the end of this

year, will be cross-referenced. The section will also explain the impact of using model averaging as compared to the previous approach (go for the lowest BMDL from the models with an accepted fit).

The decision to use the BIC instead of the AIC criteria was made to align with the choice made by the US EPA and ensure consistent use of the model averaging approach between Europe and the US.

The section will explain that the software for doing model averaging on quantal data is already available. All models in Table 3 should be used, unless there is a good reason for excluding a model, e.g. it is not converging. Any exclusion of a model from the list of default models to be used (Table 3) should be explained and documented. In case of models from the same family (e.g. LMS family), only one (the one with the lowest BIC) can be used for the model averaging.

A few lines about what should be looked at for accepting/not accepting models will be added.

Regarding continuous data, the software is not ready yet. When it will be, model averaging will be done on the Hill and the Exponential models. The Working Group does not agree with the US EPA approach to also use the Power and the Polynomial models because of their property to allow for negative response values, which is not possible from a biological point of view. The guidance document will recommend extending the family of candidate models for model averaging of continuous data.

The section should also describe the approach to be used during the transition period, with the softwares currently available (BMDS, Proast, R). Most of the currently existing text in the section "fitting and accepting models" will be recycled. The working group agreed to go for the minimal approach and to stick to the Exponential and Hill models as default for modelling continuous data. In case these models lead to BMDLs differing by more than one order of magnitude, the guidance will recommend that the assessor consults a specialist in BMD modelling. Possible solutions consist of adding new models (complying with the above-mentioned properties), or the use of the maximal approach (see text from Wout, page 31-32, as a starting point – reference needed). Any deviation from the default approach (using the Exponential and Hill models) will have to be explained and documented.

Further discussion about when to go for the maximal approach, or when to add new models, and how often the default approach will not be possible, is still needed, i.e. the minimal approach using the Hill and Exponential models.

9.2. Estimating the BMD, and establishing the BMDL as the Reference Point

The section will have to be redrafted based on the new approach (model averaging). It will still contain some guidance on how to proceed with continuous data during the transition period until the software for model averaging becomes available.

The section will make it clear that no dataset or model can be excluded just on the criteria that it leads to a broad [BMDL-BMDU] confidence interval. What uncertainty is acceptable or not is a risk management issue and not a statistical

one. The following recommendations will be made, in order of preference: 1) explore the possibility to get better data, 2) consider historical data / previous information to make better use of the data, 3) increase the value of the BMR, discussing what would be the meaning of such an increase from a biological point of view. In all cases, the information about the low level of information contained in the dataset should be passed to the risk manager.

For continuous data and in the absence of model averaging software, in case the BMDLs resulting from the Exponential and the Hill model differ by one order of magnitude or more, which reflects a large model uncertainty, the recommendations in the current guidance document ("several options are available and should be considered on a case-by-case basis, e.g. reconsidering whether the dataset contains relevant information, re-evaluating the set of models, increasing the BMR") will be kept.

The section will better underline that the BMDL should not be extrapolated outside the observation range. This issue will arise when the BMDR is lower than the lowest response, i.e. the first dose tested that was chosen has been too high. In such a situation, an additional uncertainty factor will be needed, as is done when a LOAEL is used to derive a health-based guidance value.

The recommendation section will stress again the fact that using the same number of animals in experiments but with more dose levels would be more informative for estimating the "true" dose-response curve.

9.3. BMD approach and covariates

A specific section discussing the use of the BMD approach for analysing the effect of covariates on the dose response will be inserted before section 5.7 (specific issues of human dose-response data). The text in track changes mode under the current section 4.3 will be used for this new section. It is possible to combine datasets related to the same endpoint.

Paragraphs of section 5.7 discussing the issue of covariates with human data will link with the new independent section on covariates.

A suggestion was made to annex an example showing the results when combining and not combining datasets, and the impact on the resulting BMDs, BMDLs and BMDUs.

9.4. Reporting a BMD analysis

The working group agreed that the current section "illustration", will be merged with the section "reporting a BMD analysis"

The section will start with the list of the information that should be provided (points A to G in the current guidance document to be eventually updated). A table format template for reporting this information for both quantal and continuous data will be prepared. The general message is that people should be able to trace back what has been done during the BMD analysis.

Following these general considerations, two illustrations will be provided.

The first one on quantal data, using model averaging. The dataset on rats (50 animals per dose group) showing thyroid epithelial vacuolisation (page 50 of the current guidance document) will be used.

For the continuous data illustration, the working group will check if it is feasible to mock up model averaging with the 2-year study on deoxynivalenol (DON) in mice (page 48 of the current guidance document). The same example will be updated, using the minimal approach with the latest version of Proast, and inserting the BMDUs as well.

9.5. Conclusion/Recommendation section

The following recommendations will be inserted:

- increase the number of dose levels without changing the total number of animals used in the experiment
- develop more models for continuous data, to be used when the Hill and the Exponential models lead to different BMDLs
- Develop trainings on model averaging, once the softwares are available
- Create a technical report where difficult situations are illustrated. Consider going back to datasets used in past EFSA opinions
- Create a standing working group (or other structure deemed more appropriate by EFSA) to address BMD analysis issues that cannot be addressed by in-house expertise and that would require consensual agreement on how to address it in a harmonised manner.
- Develop guidance on the use of the BMD approach with human data.

10. Next steps

The next meeting will be used to prepare a clean version of the updated guidance document. The document will then be presented to the Scientific Committee at the 11-12 November Plenary meeting and proposed for endorsement for public consultation (decision now postponed). A conference call will be organised with the working group immediately after to address possible comments from the Scientific Committee. The objective is to put the document for public consultation before Christmas. A targeted consultation of the relevant panels will be organised in parallel. The consultation will last 6 weeks (Christmas break excluded).

11. Next meeting(s)

The following dates for the meetings in 2015 were identified. The meeting place will be confirmed later.

- 4-5 November 2015, starting at 10.00h on the 4th and finishing at 17.00h on the 5th. Amsterdam Schiphol Airport
- 20 November 2015 (conference call from 14.00h to 16.00h);

- 30-31 March 2016, starting at 10.00h on the 30th and finishing at 17.00h on the 31st. Brussels or Amsterdam

Parma, 24 August 2015
EFSA/SC/1972

SCIENTIFIC COMMITTEE

Minutes of the 2nd meeting of the Working Group on Benchmark Dose

Held on 28 & 29 May 2015, Brussels (Belgium)

(Agreed on 21 September 2015)

Participants

- **WG Experts:**
  Marc Aerts, Laurent Bodin, Allen Davis[1], Lutz Edler, Ursula Gundert-Remy[2], Alicja Mortensen[3], Josef Schlatter (Chair) and Wout Slob
- **Observers:**
  Christophe Rousselle (DG SANTE SCCS)
- **EFSA:**
  AMU Unit: Jose Cortinas Abrahantes[4]
  FIP Unit: Georges Kass
  SCER Unit: Bernard Bottex[2]

1. Welcome and apologies

The Chair welcomed the participants. Apologies were received from Daniele Court Marques and Salomon Sand.

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[5] and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests[6], 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] Via conference call
[2] Participated on Day 1 only
[3] Participated via conference call on Day 2 only
[4] Participated on Day 2 only
[5] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[6] 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 1st meeting

The participants reviewed the draft minutes of the 1st working group meeting held on 15 April 2015 in Amsterdam. The minutes will be published on the EFSA website.

5. General considerations regarding the update of the SC Guidance on Benchmark Dose

Having reviewed the various contributions provided by the members of the working group for this meeting, it was agreed that the purpose of the exercise was to adjust/amend the existing SC Guidance (2009), keeping it as concise and simple as possible. The participants noted that it is mostly section 5 of the existing guidance document that requires amendments.

6. Issues to be addressed by the update

a. Model constraints

Following a presentation from Wout Slob, the working group concurred that an infinite slope at the 0-dose is a difficult concept as it depends primarily on the scale used and is, therefore, not a valid argument for being the rationale for constraining models; there is therefore no rationale for systematically constraining models leading to an infinite slope at the 0-dose.

An initial review of the slope parameter (called "d" in Proast) for the Exponential and Hill models, using historical data showed that this parameter is comprised most of the time between 0.5 and 2 or 3. The working group acknowledged that this review has been done so far on a limited number of endpoints and should be further looked at. Still a "d"-parameter value far outside of the above-mentioned range could be considered as unrealistic on the basis of this preliminary review and require to consider whether the use of this model is acceptable for the assessment purpose.

In BMDS, the slope (d-parameter) has been fixed arbitrarily to $d \geq 1$ to protect against extreme modelling decisions.

The working group discussed two different ways to look at the constraint issue:

- Do not constrain the model, then discuss whether the resulting "d-value" is acceptable compared to the historical range values for the slope parameter
- Or constrain in a first step, then look at whether the dose-response curve is very different compared to the non-constrained one. If it is different, then the d-parameter should be further considered, as well as the appropriateness of the dataset under consideration.

b. Model Selection (see decision trees annexed)

The working group discussed whether to use maximal or minimal models for benchmark dose analysis; Wout Slob explained that 4 parameters are needed to explain biology: 1) the background response parameter "a", 2) the potency parameter "b", 3) the maximum response parameter "c" and 4) the steepness

parameter "d". A review of historical datasets with a larger number of dose-groups (Slob and Setzer) showed that using an Exponential or Hill model with 4 parameters always fit these historical datasets and captures the model uncertainty. It is recommended to use at least 2 models in particular when data are limited (e.g. few doses).

From a software point of view, it was noted that Proast uses the Hill and Exponential models for continuous data as default pre-loaded models. BMDS has a couple of additional pre-loaded models. Some working group members underlined the fact that other models that fit appropriately the data could be used for dose-response modelling as well. The working group stressed the importance of providing the EFSA experts with a tool as user friendly and simple to use as possible, while ensuring appropriate derivation of the reference point.

Based on the above discussion, the working group agreed to use by default the Hill and Exponential models with 4 parameters and to take the lowest BMDL as reference point.

If these two models give different BMDL values ("different" still to be quantified), or result in a big [BMDL-BMDU] range (here again, an appropriate rage should be quantified), then more models may need to be explored for the dataset. The three restrictions for considering additional models will be added to the guidance document

The working group noted that for quantal data, several models are already pre-loaded both in Proast and BMDS.

The working group agreed that the AIC criteria and weighing of the models will be used to decide which models among the ones with an acceptable fit should be still considered for deriving the BMDL. Further explanations will be inserted in the guidance document.

When more than one model results in an acceptable fit but gives different BMD/BMDL values, the working group will recommend deriving the reference point by calculating the BMD and BMDL-BMDU range by model averaging.

Allen Davis informed the working group that the US EPA has been working on developing model averaging for continuous data only up to now. There is no indication if/when model averaging will be considered for quantal data.

Other members of the working group indicated that an R-based tool has been developed where prior distributions are already set for model averaging.

If deemed useful for EFSA's needs, an example illustrating how to use this tool to perform model averaging will be annexed to the guidance document. A recommendation will also be inserted that EFSA spends money to make this R-based software on model averaging more user friendly.

The working group identified the need to further clarify a number of specific cases in the guidance document:

- Cases where there is a large confidence interval [BMDL-BMDU]. One solution to solve the issue will be to increase the BMR. The importance of communicating to the Risk Manager that the resulting health based guidance value is based on a larger effect size will be underlined.

- In cases where none of the models appropriately fit the data, this should be a signal for the risk assessor to look for anomalies in the data or check the adequacy of the statistical model. This aspect will be further expanded in the guidance document

The working group should also check whether the examples currently described in the guidance document fit the new proposed approach; they will be reworked if needed.

c. Selection of the BMR

The BMR has traditionally been set to 5% for continuous and 10% for quantal data; this approach is currently followed in the SC Guidance on BMD. EPA is currently favouring the use of one standard deviation (1SD) as BMR. In his presentation, Wout Slob identified drawbacks in the use of 1SD to set the BMR, primarily because the 1SD value is dependent on the study (e.g. quality of the study) and is affected by errors (e.g. sampling errors). Likewise, the use of a fixed 5% value for the BMR (for continuous data) does not take into account the maximum response and group variability which both are a characteristic of the endpoint. It was noted that when the 5% value for continuous data is linked to the maximum response, this value comes close to the 1SD value.

The working group proposed to consider the default value of 5% for continuous data as a starting point for setting the BMR. Deviations from the 5% default value can be considered when based on biological or toxicological relevance or maximum response or on the distribution of the data, on condition that the rationale and arguments for deviation from the default values are provided.

The working group agreed that the 10% default value remained acceptable for setting the BMR for quantal data.

The working group emphasised the importance of considering future opportunities in the area such as the availability of 1SD values for individual endpoints or the percentile distribution for setting BMRs.

The section should be expanded to also cover in vitro and omics data.

d. Non-significant trends

The issue of modelling approaches versus statistical approaches, when the evidence for a biological or toxicological response is not in the data, was discussed. The working group agreed on the following approach. First a trend test using defined models should be applied to the data. If no trend is identified, this should be recorded and no further action is to be taken. A technical methodology section could be drafted as an appendix to the main document.

e. Combining datasets

The issue of whether datasets from males and females from the same species and same experiment or even from different species can be combined was discussed. The approach proposed by the working group is to perform a covariate analysis on the datasets to identify differences between sexes or species. In the absence of differences in response, the datasets should be combined for the BMD analysis. A suggestion for future work was to explore the feasibility of generating sound databases of critical endpoints with historical data

that could be used to combine with experimental datasets. This could help where the data generate large confidence intervals, the rationale being that for specific endpoints, the maximal response and the shape of the curve tend to be similar.

2. Next meeting dates

The following dates for the meetings in 2015 were identified (the meeting place will be confirmed later):

- **21-22 September 2015** (2 full days)**;**
- **4-5 November 2015** (2 full days)**;**
- **11 December 2015** (conference call)**.**

Parma, 13 May 2015
EFSA/SC/1916

SCIENTIFIC COMMITTEE

Minutes of the 1st meeting of the Working Group on Benchmark Dose

Held on 15 April 2015. Amsterdam (Netherlands)

(Agreed on 28 May 2015)

Participants

- **WG Experts:**
  Marc Aerts, Laurent Bodin, Allen Davis[1], Lutz Edler, Ursula Gundert-Remy[2], Salomon Sand, Josef Schlatter (Chair) and Wout Slob
- **Observers:**
  Christophe Rousselle (DG SANTE SCCS)
- **EFSA:**
  AMU Unit: Jose Cortinas Abrahantes
  FIP Unit: Georges Kass
  PRAS Unit: Daniele Court Marques
  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. Apologies were received from Alicja Mortensen.

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] Via conference call, whole day
[2] Via conference call, morning
[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. Discussion on the Mandate and Terms of Reference

The Chair introduced the history of the development of the benchmark dose approach, the 2009 SC guidance on the use of the benchmark dose approach in risk assessment, as well as the terms of reference and timeframe described in the mandate.

The participants agreed to go further than the five issues identified in the terms of reference as requiring further guidance and listed the points below to be addressed in the update of the 2009 opinion. In order to facilitate the discussion during the next meeting, responsible persons (names indicated in brackets) for the various issues will draft some text or prepare a presentation on the points to be addressed (core points, possible options, what should be the conclusions).

The format of the update (either an addendum or a revision) of the 2009 opinion will be agreed later, depending on the amount of amendments needed.

5. Issues to be addressed by the update

a. Model selection

- Recommendation of models to be used by default depending on the type of data (quantal/continuous). Clarify that it is possible to deviate from these default models as long as the reason for this is described. In practice, any model with an acceptable fit can be considered for benchmark dose modelling.
- Draft a couple of lines discussing assumed distributions.
- Use of nested models (Hill/Exponential): do we go for the model with an accepted fit and the lowest number of parameters, or should we go directly for the Exponential/Hill model with four parameters?
- Should models allowing for non-monotonic dose-response modelling be included?

b. Selection of the BMR

When to use a (default) percent change in the response, when to use one or several standard deviations as the basis for the BMR? The update will underline that default values for BMR (5% for continuous data, 10% for quantal data) are based on in vivo data and should therefore be reconsidered when analysing non-animal data.

c. Selection of the reference point (point of departure)

Should it be the lowest BMDL? Or the BMDL from the model with the best fit? Or should it result from model averaging calculation? See section 5.5 of the 2009 SC guidance on benchmark dose.

A US EPA report looking at possible methodologies for model averaging is currently under review. US EPA kindly accepted to share this report "in confidence" with the working group members.

d. Model constraints

The 2009 opinion recommends constraining models when leading to an infinite slope of the dose-response close to "0" dose, as an infinite slope is not "biologically" plausible. Latest publications claim that such constraints are not needed. The issue will be further discussed at the next meeting of the working group.

e. Criteria for accepting datasets for BMD modelling

- Interpretation of the computer output – standard errors on the parameters of the model.
- 1 order of magnitude between BMDLs from models with an acceptable fit? Distance BMD/BMDL? Distance BMDL/BMDU? Review the ranges that were accepted in the past.
- Number of dose groups.

The issue of BMD analysis of studies with no significant dose response trend (e.g. weak genotoxic and carcinogenic compound leading to very few tumours incidences) was put on hold by the working group. Depending on the case considered, one could indeed advise for reformulating the question to answer, or modify the experiment so that it has enough power, or if one knows e.g. from read-across that an effect for the substance considered can be expected, still calculate a BMDL with this dataset

A proposal was made to attach to the update a couple of examples illustrating that the BMD approach really makes a difference with "poor" datasets.

f. Rules for combining datasets

Explain the difference between combining datasets (e.g. males + females from the same experiment) and pooling datasets (data from two different experiments). Further guidance should be provided on when to do a covariate analysis: do the two datasets follow the same dose response? If they vary, at what level? Just the background response? Make a recommendation that covariate analysis should be included as an option in the BMDS software

g. BMD and litter effects

What could be suitable model(s) and how should they be parametered?

h. Softwares

- Different versions of the same software may lead to different results when there is a change in the executables. A couple of lines will be drafted to explain these differences and to highlight the importance of reporting the software used and the model version number.
- Recommend changing the default distribution to log-normal distribution for continuous models in the BMDS software.
- Underline that the Hill models are different in Proast and BMDS.

- The update will explain that, when deciding to deviate from the recommended "basic" models, any software (e.g. R, Matlab) can be used.

i. BMD analysis reporting

- The main points to be reported are already listed in the 2009 guidance document but a template could be useful to ensure standardisation of the reporting.
- Define/confirm what needs to be reported.
- A BMDS Excel macro allows for the automatic generation of a report according to US EPA standards.
- A suggestion has been made to look at the interval between the BMDL and BMDU (uncertainty around the BMD), rather than the interval between the BMD and BMDL.
- Make a recommendation to update BMDS so that BMDUs are reported for all models. Discuss the use of reporting BMDs (central estimates): some consider them as still needed for comparing potencies.

j. Increasing BMD acceptance and implementation (Recommendation section)

- Importance of investing in training, not only for EFSA Panels but also for Member States Competent Authorities and outsourced test labs.
- A suggestion was made to gather feedback from Panels on the reason why they had difficulties in applying the BMD approach in their assessments.
- Parameters of interest will be extracted from the EFSA opinion where the BMD approach has been used with animal data.
- EFSA Pesticides Unit has outsourced the comparison of NOEC values to EC10/EC20 values, including confidence values, in aquatic and terrestrial ecotoxicological risk assessment. The database to be considered is exclusively related to the environment, and doesn't include any analysis of mammalian toxicity studies.
- Review of the NTP database is currently on-going. Further information will be uploaded in the DMS.

k. Review of the 2009 guidance document

All members of the working group to go through the 2009 opinion and identify what needs to be rewritten because outdated or wrong.

The following issues were considered by the working group as too resource-demanding to be addressed in this update and will be recommended for further development:

- Use of the BMD approach with epidemiological data
- Use of the BMD approach with categorical data (low, mild, high…)
- Use of the BMD approach with mixtures

- Use of the BMD approach for comparing relative potencies when dealing with the same effects (briefly addressed in section 4.3 of the 2009 guidance document)

6. Next meeting dates

The following dates for the meetings in 2015 were identified. The meeting place will be confirmed later.

- **28 May** (full day) **– 29 May 2015** (9.00-13.00 or 9.00-17.00 depending on the meeting place)
- **21-22 September 2015** (2 full days)**;**
- **4-5 November 2015** (2 full days)**;**
- **11 December 2015** (conference call)**.**