METHODOLOGY AND SCIENTIFIC SUPPORT UNIT

2nd Working Group meeting on Benchmark Dose Modelling

13 May
09.00-13:00
MINUTES - Agreed on 26 May 2025

Location: EFSA - Parma (Meeting Room 00/03)/Webconference

Attendees:

- Working Group Members:
Gundert-Remy Ursula (UG), Thomas Tietz (TT), AERTS Marc (MA), Salomon Sand (SS), Þórhallur Ingi Halldórsson (ÞH), Ron Hoogenboom (RH)
- Hearing Experts[1]:
Not Applicable
- European Commission and/or Member States representatives:
Not applicable
- EFSA:
MESE unit: José Cortinas Abrahantes (JCA, chair), Efisio Solazzo (ES, coordinator), Molle Arnaud (MA)

  Tauriainen Tuuli (FFEDCO), Al Harraq Zainab (FIP), Neri Franco Maria (NIF), Civitella Consuelo (FIP), Albert Océane (NIF), Binaglia Marco (PREV), Alberto Linguadoca (PLANTS)
- Others:
From NIF unit: Laganaro Marcello, Rossi Annamaria, Favata Areti, Magani Maura, Beneventi Elisa, Pieger Anna Maria, Nuin Irene, Kass Georges

I. Welcome and apologies for absence

The Chair welcomed the participants.
Apologies were received from P. Craig.
B. Bokkers did not participate as unavailable for this date.

II. Adoption of agenda

The agenda was adopted without changes.

III. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence[2] and the Decision of the Executive Director on Competing Interest Management[3], EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting.

For further details on the outcome of the screening of the Annual Declarations of Interest, please refer to Annex (delete Annex II, delete the roman number in Annex I). Oral Declaration(s) of Interest were asked at the beginning of the meeting and no additional interest was declared.

[1] As defined in Article 34 of the Decision of the Executive Director concerning the selection of members of the Scientific Committee, the Scientific Panels, and the selection of external experts to assist EFSA with its scientific work: http://www.efsa.europa.eu/en/keydocs/docs/expertselection.pdf

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

IV. Scientific topic(s) for discussion

JC illustrated a recent application of BMD modelling in the context of in-vitro micro-nuclei (MN) assays study, with specific application to Neotame. The current BMD guidance does not cover modelling of data collected during in-vitro experiments, thus the opinion of the WG was solicited with respect to the procedure to adopt when facing these types of studies.

Considering that the frequencies of MN cells observed are rather small, the extra risk definition of the BMD has been adjusted to ensure that BMD definition does not correspond to the added risk, and the relative definition used for continuous outcomes was the preferred option. Considering that the implementation only provides the extra risk definition, derivations were used to define the corresponding extra risk BMR that align with the desired relative definition.

$$(1)\ BMR_C = \frac{\pi(BMD) - \pi(0)}{\pi(0)} = \frac{\pi(BMD)}{\pi(0)} - 1$$

$$(1 + BMR_C) \cdot \pi(0) = \pi(BMD)$$

$$(2)\ BMR_Q \cdot \big(1 - \pi(0)\big) + \pi(0) = (1 + BMR_C) \cdot \pi(0)$$

Consensus was reached on the following steps when dealing with micro-nucleus (MN) studies (aneugenicity and clastogenicity) conducted with in-vitro experiments:

- When available, use of historical control data to support the definition of a BMR:
    - Derive from the historical control data the parameters (mode, means and alpha and beta) characterizing the Beta distribution that represents the probability of observing micronucleate cells
    - Determine the likelihood of observing values outside the historical control values (observed minimum and maximum proportions, as well the probability of being outside the 95th CI ranges provided, in order to assess the adequacy of the Beta distribution derived from mean and standard deviations reported). BMR is derived as the ratio of the difference between $\boldsymbol{\tau}$(defining a potential threshold that is considered to be representing values outside the control ranges) and $\boldsymbol{\mu}$ (the most likely value of the Beta distribution), and $\boldsymbol{\mu}$: $\boldsymbol{BMR} = \frac{\boldsymbol{\tau}-\boldsymbol{\mu}}{\boldsymbol{\mu}}$. The threshold needs to be determined on biological basis (this process will be endpoint and study dependant).
- If no historical data can be retrieved for the endpoint under investigation, the control of the experiment can be used, using the observed standard deviations (study and endpoint dependant, decisions need to be made in terms of how many sds would be sufficient to represent the appropriate threshold) to define a BMR sufficiently outside the control range. Note that this option should be considered as last resort to define an appropriate BMR in this content.
- The BMR from the beta distribution is replaced in the above equation by the BMR_C and the mode is substituted by $\boldsymbol{\pi(0)}$ to derive the appropriate BMR_Q
- Investigate if there is a plate effect by means of cluster analysis (for example, cells from same plate exhibits similar response than from cells from between plates). If no significant correlation can be determined, then the cell counts of the plates can be pulled as they can

be considered independent. If a significant correlation is detected, then the analysis considering clustering effect could be used to estimate BMD and its credible interval.

- Estimate BMC (Benchmark concentration) and its credible interval adopting the BMR_Q derived from the procedure above.

Next, JC presented a recent application of BMD analysis related to dioxin exposure and sperm count in humans. This is another example of an application not currently covered by existing guidance. The specific data and analysis shown have not been included in, nor adopted by, any formal opinion; rather, they are intended to illustrate the methodology that could be followed in similar epidemiological cases.

The dataset in question presents several challenges: the data are not uniformly distributed across exposure levels, do not follow a monotonic trend, do not include a zero-exposure group (i.e. lack a control group, which is necessary for defining the BMD), and contain extreme values that may or may not be considered outliers for exclusion in the analysis.

The question posed to the WG was how to approach BMD modelling under such conditions, particularly regarding:

- Sparsity of data and unbalanced distribution across exposures: possible approaches include the analysis considering all observations or subsetting the data to the lower exposure scale (the region of interest), but this might bias the overall fit;
- Use of spline-based methods for curve fitting (smoothing methods that allow for flexible model curves) and extrapolation to zero-dose level;
- Treatment of outliers, including whether and how they should be excluded.

The WG acknowledged that epidemiological data inherently show large variability, which affects both the presence of outliers and the reliability of estimates in the absence of a clear control. Historical data could potentially inform zero-exposure ranges through informative priors, but they also are likely to have a high variability. The lack of contextual information—such as confounders (e.g. age, lifestyle factors)—and the absence of a control group significantly hinder the reliability of any conclusions drawn from the analysis. Moreover, the feasibility of extrapolating to a zero-exposure level is highly dependent on the specific study design, including the minimum exposure level observed, and cannot be generalised across studies.

The development of methodological guidance for addressing such cases will require further discussion.

Next, the NIF unit of EFSA presented the BMD analysis conducted with the support of JC. The analysis was conducted using studies from different laboratories and different rat strains. The studies were conducted following GLP and OECD guidelines and were appraised to be of good quality studies. Each of the studies considered a different dose spacing and ranges, focusing on their specific uses. Considering Bayesian principles, analysis can be conducted based on specific study that could be used to inform the priors for specific parameters (e.g. the BMD parameter) to analyse the other studies, making the estimation of that specific parameter in principle more accurate considering that the default prior is a weakly informative prior, representing in principle a non-informative prior in the non-linear model context. This way of dealing with several studies could be a way to estimate the parameter of interest for all studies considered relevant. However, the selection of the study to be used to inform the prior distribution for other studies is not straight forward and several criteria could be considered. In this specific case the study with the larger dose ranges was used to build informative prior for the other studies, this was done by considering

as well that two strains were used in the five studies selected. Results from this procedure did not show major improvement or differences with the resulting BMD estimation when the non-informative prior was used. In principle the procedure proposed to deal with such situation was to consider a covariate analysis where studies and strains are considered as covariates and derive from this analysis BMD and credible interval for each level of the covariates included. Then this could be complemented by this other procedure where Bayesian principles can be used to derive informative priors. Considering the results in this specific case and the procedure to select the study to be used to generate informative priors not to be straight forward, the WG agreed to use the covariate analysis (considering laboratory and strain as covariate variables) in such context. If studies were conducted in chronological order, the Bayesian principle could be of used.

The final point discussed concerned the preparation of a document, in the form of a Letter to the Editor, in response to a recent paper published in the *Critical Reviews in Toxicology* journal by RIVM and collaborators. The WG had been informed by EFSA about the planned preparation of this document during the previous meeting held on 11 March 2025, and a draft was circulated on 2 May. All WG members present at the meeting agreed to contribute to the draft and to be listed as co-authors. ES will share a link to the document to be commented on by the 31st of May.

1st Working Group meeting on Benchmark Dose Modelling

11 March 2025
13:30-17:30
MINUTES - Agreed on 20 March2025

Location: EFSA - Parma (Meeting Room 00/04)/Webconference

Attendees:

- Working Group Members:
Gundert-Remy Ursula (UG), Thomas Tietz (TT), Aerts Marc (MA), Craig Peter (PC), Bas Bokkers (BB), Salomon Sand (SS), Þórhallur Ingi Halldórsson (ÞH)
- Hearing Experts[1]:
Not Applicable
- European Commission and/or Member States representatives:
Not applicable
- EFSA:
MESE unit: José Cortinas Abrahantes (JCA, chair), Efisio Solazzo (ES, coordinator)

  TAURIAINEN Tuuli (FFEDCO), AL HARRAQ Zainab (FIP), NERI Franco Maria (NIF), CIVITELLA Consuelo (FIP), ALBERT Océane (NIF), BINAGLIA Marco (PREV), ACKERL Reinhard (NIF)
- Others:
Not applicable

I. Welcome and apologies for absence

The Chair welcomed the participants.
Apologies were received from R. HOOGENBOOM.
B.Bokkers did not participate in agenda point 11 due to a conflict of interest being identified for this agenda item.

II. Adoption of agenda

The agenda was adopted without changes.

III. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence[2] and the Decision of the Executive Director on Competing Interest Management[3], EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting.

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

IV. Scientific topic(s) for discussion

ES gave a presentation outlining the mandate of the WG, its composition, and recent activities related to BMD modelling, including scientific developments, updates to the webtool, and training initiatives.

JC followed with a presentation on the current BMD guidance, emphasizing its mandate and describing the key technical aspects, the Bayesian approach, decision flows, and uncertainty assessment.

JC also provided an update on the ongoing discussions between EFSA and RIVM following a bilateral meeting held on February 11, 2025. He contextualized the meeting by briefly recapping the history of discussions between EFSA and RIVM on BMD-related topics. The bilateral meeting was specifically scoped to address divergences that led RIVM to issue an Article 30 procedure (diverging scientific opinions) regarding the BMD guidance. EFSA's perspective on RIVM's position was presented to the WG.

JC then outlined the progress made during the bilateral meeting, highlighting points on which a way forward was agreed: i) Operating under an inclusive Bayesian framework – A user manual will be developed to guide users in making choices based on prior knowledge of distributions, models, and parameters, which foresees as well the inclusion of sensitivity analysis including all distributions and models in order to assess potential deviation in the data from the expected historical knowledge, also in case that no historical knowledge is available about the endpoint, inclusion of all models and distributions was considered the way forward, ii) Reformulating models using natural parameters to improve clarity and consistency, iii) Enhancing the BMD tool's output by including the model-averaged estimates and credible intervals of all natural parameters.

Moving on to the next agenda item, ES presented an overview of a scientific manuscript that RIVM and some external collaborators have submitted for publication. The manuscript was accepted and is now in the proof-reading stage before publication. The manuscript summarizes RIVM's perspective on BMD modelling and practice and includes several criticisms of EFSA's BMD guidance, the Bayesian BMD tool and US-EPA suite of models. WG members were invited to share their views on the content, having received an electronic copy of the manuscript before the meeting.

A dedicated session followed to draft EFSA's response to the manuscript, addressing the criticisms raised against the guidance and webtool. BB left the meeting during this discussion due to a conflict of interest. MA then presented an analysis of the manuscript's critical and unclear points.

The meeting concluded with all WG members agreeing to evaluate co-authorship of the response document, which EFSA will draft and distribute for review.

Annex I

Interests and actions resulting from the screening of Annual Declarations of Interest (ADoI)

CONFLICT OF INTEREST: In the Annual Declaration of Interest submitted by Mr Bas Bokkers, the following interest has been declared: Interests – Employment - National Institute for Public Health and the Environment (RIVM) (ongoing). In accordance with EFSA's Policy on Independence[4] and the Decision of the Executive Director on Competing Interest Management[5], and taking into account the specific matters discussed at the meeting in question, the interest above was deemed to represent a Conflict of Interest.

This resulted in the exclusion of the expert from any discussion, voting or other processing of item 11 by the concerned scientific group.

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