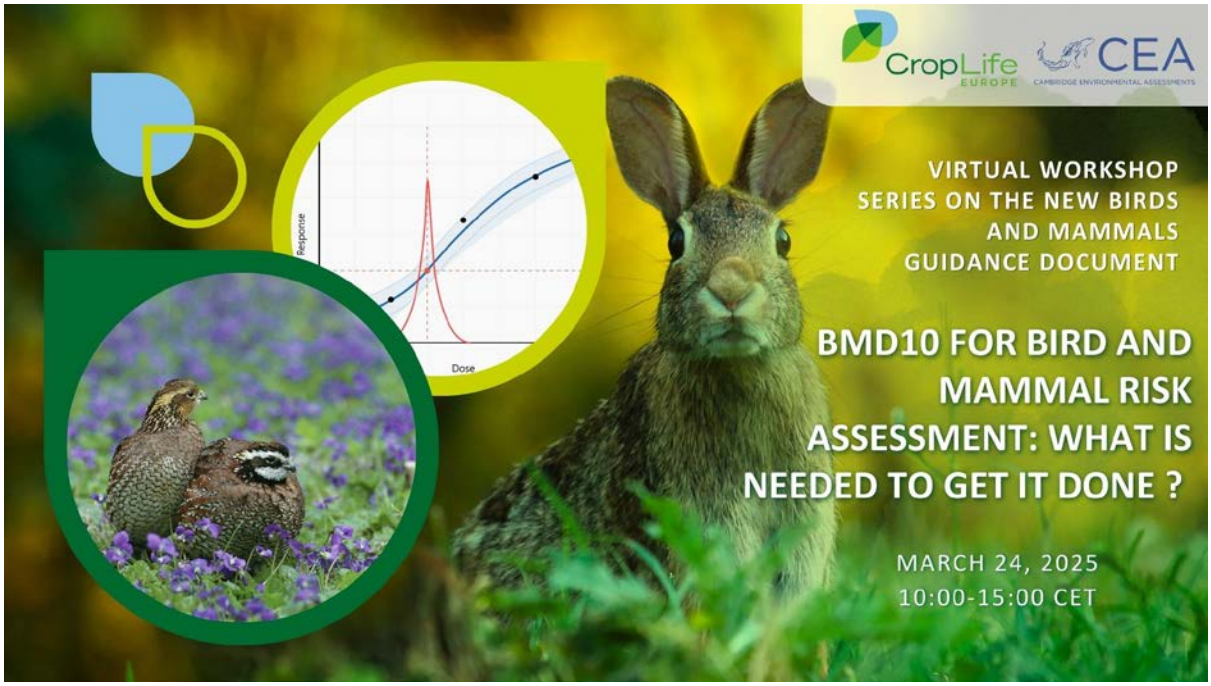

Workshop Minutes

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Introduction

The revised EFSA guidance document for the risk assessment for birds and mammals was published in Spring 2023. It includes new requirements for higher tier studies but remains vague in the practical implementation of some aspects. In order to discuss changes to the risk assessment and higher tier refinement options for birds and mammals in the EU, a series of virtual workshops on was initiated by CropLife Europe.

The second workshop in this series focussed on the generation and use of BMD_{10} endpoints, instead of NOAELs, was organized by Cambridge Environmental Assessments (CEA) and took place on 24th March 2025. Stakeholders from industry, CROs, regulators and academia were in attendance and invited to join in the exchange of ideas. The focus of the workshop was to address procedural and technical challenges, including data selection and processing, with the aim of contributing to the development of procedures that will aid in transitioning to a focus on BMD_{10}s when the EFSA GD 2023 will be implemented in the European Union later in 2025.

The virtual workshop was designed to cover three key aspects surrounding the implementation of BMD_{10}; the regulatory hurdles that need to be addressed, a "cookbook" proposal, designed to create a simplified, stepwise approach to implementing BMD_{10}, and a statistics session that was intended to cover the procedural steps of the calculations. Each of these sessions had a short plenary talk from one of the experts in the area, followed by a discussion with all participants, either in breakout groups or held as a Q&A session. In total, 125 participants joined the virtual workshop on 24th March 2025.

It was suggested at the end of the workshop that a working group be developed to move forwards with some of the findings and suggestions from this virtual workshop, and to engage with key stakeholders, including EFSA. If you would like to be involved in this process please contact manousos.foudoulakis@corteva.com or steven.kragten@syngenta.com

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Topic 1: Regulatory Hurdles

Overview

Two key aspects were presented in this topic:

1. Navigating the Bird and Mammal dossier development and requirements
2. EFSA BMD_{10} tool updates and the impact on regulatory submission

The current understanding is that accurate BMD_{10} estimation is crucial to set agreed endpoints for Tier 1 risk assessment according to EFSA (2023) It provides a more precise estimate of dose-response (when properly performed) and implementation will require re-evaluation at the RMS level and then extend to the zonal level

The current status of BMD_{10} in the regulatory environment is that it will be enforced for a.i. and product submissions after 1st October 2025. Adoption of the new guidance varies across EU MS as the guidance may be implemented fully, partially or not at all according to different MS.

Multiple challenges were highlighted, including:

- Issues if confirmation of BMD_{10} requirement is received late in the process.
- A lack of technical-level pre-submission engagement with RMS
- No clear proposal for completed and ongoing submissions
- Time and resource expensive
- Requires high-level expertise.
- EFSA online BMD Tool is not user friendly and lacks version control.
- Issues with reproducibility and reliability of results
- Need for a harmonised and agreed approach to implementation; a critical topic especially for zonal submissions.

Overall, it was concluded that the whole process needs to be streamlined, with early stakeholder engagement and clear timelines. That there needs to be EU level agreement on the zonal submissions process for the endpoint to be used, or MS will continue to use their own interpretation and significant confusion will occur. Lastly, that the EFSA BMD tool is not sufficiently tested, there is a lack of version control, and it is not ready for regulatory use.

Breakout group discussions

The general consensus across all of the breakout rooms was in agreement that the current situation has many challenges, that harmonisation is needed, and that version control of the tool is paramount, but severely lacking.

The following 4 topics were listed for discussion across the breakout sessions:

- What is the proposed process regarding the evaluation of BMD_{10} values and justification for use of fTWA in Art. 33/43 if they have not yet been evaluated on EU level?

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- In the absence of an agreed LoEP which endpoint should be used for regulatory zonal submissions?
- Do we need a fully tested, reliable, stable and validated regulatory version of the EFSA BMD online tool for EU and product submissions?
- How can the current process be optimized to ensure timely expert input while maintaining the quality and rigor of assessments?

Process for the evaluation of BMD_{10} values

It was highlighted that different evaluators/MSs etc. coming to different conclusions on the BMD would lead to having several potentially conflicting endpoint evaluations for the same active substance and this should be avoided. Zonal harmonisation of the process is clearly needed but will be challenging.

Some participants thought that consultations with the zRMS should be used to define the endpoints, whereas others felt that BMD_{10} evaluation should not be left to the zRMS, but that EU agreed endpoints are the preferred option.

Which endpoint should be used for regulatory zonal submissions?

Currently the LoEP is defined late in the process, however, it was queried how early agreement would work in practice. Timelines were highlighted as a particular challenge, if an authority will not agree on an endpoint based on e.g. presentations at pre-submission meetings, how to ensure there is the time needed to properly evaluate the data?

Several interim processes were also proposed in the discussions. These included continuing on a zonal level with the current EU-agreed list of endpoints and to implement the new BMD endpoints once there has been an evaluation at EU level. The potential to continue with the NOAELs and to start in parallel a process to re-evaluate the endpoints according to the new guidance on EU level was also put forward. As well as the idea of a two-stage dossier submission process intended to allow the time for data evaluation.

However, it was also noted that not having an agreed BMD may impact on the ability to perform art. 33/43 assessments in line with EFSA (2023), for example for the fTWA assessment.

EFSA BMD online tool

It was highlighted that the current BMD_{10} situation is similar to the situation at the start of FOCUS development where version control was also lacking. Are there any lessons learned from that process that could be utilised here?

The view was shared across all groups that a reliable regulatory version is indeed required. Currently the difference in calculated BMD values that are resulting from differences in the version used made participants question if this is a tool ready to use at all.

Specifically, it was stated that it is difficult to use because of version changes by EFSA, resulting in less transparency and different results. The calculator is viewed as more a black box than a

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clear tool. Whilst the tool is handy, with quick calculations, more help is needed to interpret data and for the input of data. More examples and special cases/exceptions need to be given, and pre-testing is needed (standard testing different to the guidance document).

Process optimisation

The general consensus here was that a filtering process to indicate which studies/data to use was essential.

There were several queries relating to application of the guidance to actives and formulations:

- Is it coming into force for actives and products at the same time?
- What to do with a multiple active formulation where one or more actives has an agreed BMD assessment, and one or more actives has an old assessment and therefore no BMD assessment?

Data quality and access were also key issues here. Applicants do not necessarily have access to the actual study reports and raw data that are required for running the BMD analysis. Therefore, is it possible to calculate an accurate BMD when the raw data are not available? Additionally, how to overcome the potential that the outcome of a BMD assessment can differ, depending on the quality of the underlying data?

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Topic 2: BMD "cookbook"

Overview

This topic identified three key challenges in the practical implementation of the BMD_{10}:

- The volume of data
- The relevance of study designs
- The relevance of the study endpoints

It was highlighted that the avian and mammalian data packages are very comprehensive and running the BMD_{10} for all available endpoints would be extremely time expensive, and unnecessary for endpoints that would be considered irrelevant. The extraction of data, particularly from old studies, is also challenging. In addition, these studies are not generally designed for the derivation of BMD_{10} (or EC_x values) as they were intended for NOAEL derivation. Lastly, there are many parameters measured in these toxicity studies that have little, or no, relevance to the protection goals for birds and mammals (e.g., effects on the liver, blood chemistry, etc.).

The "cookbook" that was presented in this session was intended at a first attempt to streamline the process of selecting suitable studies, filtering data and identifying viable endpoints for BMD_{10}, providing a stepwise approach to reduce time input and unnecessary evaluations.

In brief, the stepwise process followed a flow chart with 4 main steps:

1. Select only studies with ecotox relevance.
2. From these studies, identify the relevant endpoints for BMD_{10} (e.g., apical endpoints vs interim effects, ecologically relevant effects, 10% threshold of effects)
3. Further exclusion of studies where endpoints are not expected to drive the BMD_{10} (e.g., those where the dosing levels would not result in the lowest endpoint)
4. Run the BMD calculations.

Full details of the filtering steps proposed are given in the slides from this session, as well as worked examples of the process.

Breakout group discussions

Overall, it was considered that the cookbook, as presented, was a good starting point to attempt to streamline the process of calculating useful BMD_{10} values and was appreciated for its practical and resource-saving benefits. It was thought that this needed to be discussed with regulators, expanded on, and ideally implemented into the GD when refined and optimised.

The following 3 areas were listed for discussion across the breakout sessions:

- Is a stepwise approach needed for the derivation of a BMD (as proposed here) to save significant resources? Is the 'cookbook' approach a suitable way to prioritise data for BMD calculation?

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- Based on the examples presented, do you believe that apical endpoints are considered more relevant than intermediate effects for the ecotox assessment and if so, could a list of BMD-relevant apical endpoints be developed amongst stakeholders as a working document to help the evaluation process?
- Do you believe that the filtering approach used for the BMD cookbook could be acceptable? How could acceptability of this approach be increased?

Suitability of the cookbook

In general, the approach was met with cautious optimism that this could facilitate harmonized and transparent ecotoxicological assessments. It was understood that this was not a fully prescriptive guidance on how to do BMD_{10} calculations, merely a starting point which can be discussed and refined. It was also agreed that the authorities need to be included in the discussions in order to implement such an approach.

There was some evident concern in a few key areas of the cookbook. These included:

- Deciding on what is a "relevant" study and/or endpoint, is it somewhat subjective?
- Justification would be needed as to why studies/effects are filtered out.
- Interim effects still have value, and a WoE approach has merits.
- Transient effects in Tier 1 might not be transient in a wild population.
- Data quality: few dose levels is not conducive to the calculation (NOAEL needs more animals per dose level, BMD_{10} needs more dose levels; acknowledged a trade off with animal welfare), often high variability in controls.

Apical endpoints

Overall, the premise of just applying BMD_{10} to apical endpoints was met with tentative agreement. There was some concern that the exclusion of interim effects would lose information and that the approach may not be easily accepted by regulatory authorities. However, it was agreed that the use of apical endpoints makes a lot of sense and is in line with the B&M GD, so there should be an effort to agree on relevant apical endpoints for the different study types among stakeholders, alongside alignment of how to consider the intermediate effects. One proposal was to only calculate BMD_{10} for the apical endpoint(s) and check that this is reflected in the intermediate effects. Another proposal was to define the apical endpoint according to the outcome of an Adverse Outcome Pathway.

One of the main discussion points that arose from this question was to do with when an apical endpoint has borderline effects. For example, when the calculation shows effects are just < 10%. Some suggest that you should try to calculate BMD anyway, others cautioned that extrapolations bear tremendous uncertainty, particularly when data is already highly variable. It was also questioned whether 10% was the appropriate threshold for all parameters, e.g. body weight data.

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Whilst a list of apical endpoints was considered as a useful tool, on the whole, there were concerns over it being too prescriptive and that this is not a black and white approach, therefore, a case-by-case approach is likely to be more appropriate.

Acceptability

It was unanimous that discussions with regulators would be very important for acceptability and, essentially, more guidance on applying the guidance is required. Whilst it was noted that a lot of the elements of the cookbook (e.g. relevant study designs) are already included in the EFSA (2023) guidance, it was evident that presenting a clear decision path and justification behind decisions for regulators would be crucial. To this end, the cookbook should cover general principals, but there might be exceptions, and additional endpoints and considerations should be included on a case-by-case basis.

Positively, it was concluded that participants, across all stakeholder groups, were interested in further developing a filtering approach. That a group of relevant people should be formed and the discussion continued, with clear objective setting. This workshop has the intention to make this happen and all participants were strongly encouraged to reach out to the Organising Committee regarding this.

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Topic 3: BMD Statistics

Overview

This session covered the statistical steps used in the BMD_{10} calculations, including data formatting, the dose-response evaluation, how to set up and run the BMD tool and assess outputs.

It was highlighted that there is a requirement for biological expertise to reflect back on the calculated endpoints. It was also acknowledged that there remains an issue surrounding version control and that no standard approach is in place for when a BMD cannot be calculated.

The objective of this session was to open dialogue on what is still needed to develop a regulatory version of the EFSA BMD online tool that meets the needs of modelers and regulators.

Statistics Q&A

Question 1: Does it make sense to push a frequentist approach based method on practical level to find the EC10/BMD10 value for bird/mammal studies in the context of ERA until the BMD tool by EFSA is ready for use (as they might historically be more established and could perhaps result in better acceptance)? As Bayesian based modelling does not add much value if no useful prior data is available

Answer: Ultimately, EFSA are driving the direction of BMD analysis and the current position and that of the BMD Guidance (EFSA, 2022) is of using a Bayesian approach as contained within the Bayesian BMD EFSA online tool.

Question 2: Have you come across issues when analysing count data, which are usually approximated with a Poisson or negative binomial distribution? Count data can be approximated by a normal distribution at each dose (if the mean count is sufficiently large). But the variance depends on the mean in a particular way, and the mean depends on dose, implying that homogeneity of variance and homogeneity of coefficient of variation does not hold, which are assumptions made in the implemented models in the application.

Answer: On this topic, the BMD Guidance (EFSA, 2022) states:

"Two 'withingroup' distributions are considered:

- *The normal distribution (as a convenient representative of the family of all symmetric distributions).*
- *The log-normal distribution (as a convenient representative of the family of all rightskewed distributions).*

It is assumed that left-skewed distributions are rare for toxicological data. "

EFSA's expectation is that the log-normal distribution will be a suitable approximation for count data. In practice, we have come across issues, particularly with smaller counts. We are not aware

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of any formal assessment of the suitability of the log-normal distribution in BMD analysis of count data.

Question 3: How reliable are BMD calculations for count data that are actually Poisson distributed (assumption in the tool: normally or log-normally distributed)?

Answer: see Q2 response

Question 4: How should a sensitivity analysis be used when the assumption of homoscedasticity is violated?

Answer: In accordance with the BMD Guidance (EFSA, 2022), when homoscedasticity is violated, the BMD platform produces three BMDs based on the smallest standard deviation, the largest observed standard deviation, and the pooled standard deviation. We are not aware of any clear guidance on what should be reported.

Note that if homoscedasticity is violated for only one of the normal or long-normal distributions, models from the violating distribution gets a lower posterior probability and are automatically weighted low during model averaging and the BMD analysis can continue.

Question 5: Should Bridge Sampling be the default method as it is described the most accurate method in the BMD Guidance (2022)?

Answer: The BMD guidance document (section 2.5.3, EFSA, 2022) is clear that Laplace would be the default approach, but permits Bridge sampling, especially where estimation failures occur. It also reports that Laplace produces reliable results comparable to the most accurate method of Bridge sampling. Furthermore, the experience of those running BMDs has resulted in cases where Laplace outperforms Bridge sampling, so it is not always the case that Bridge sampling is the most accurate method.

Question 6: You said that transformation has not yet been investigated, are there plans to do this in future?

Answer: Zero values are known to cause an issue in the BMD platform. One option we have found is to use summary data instead of individual data. This should work when there are no zero values in the summary data (i.e. means are non-zero). An alternative is to work with the individual data but add a small constant to the zero values. We acknowledge this is not statistical best practice. It should be noted that these are practical work arounds that we have found.

EFSA is aware of the issues where BMD fails to run without transformations and it is hoped that they will address these issues as they are the result of the current limitations of the online tool. At the moment we are not aware of any formal investigation into transformation and further work by EFSA is needed on the tool.

Question 7: How do you run the current version of BMABMDR on a local R instance if it is not provided on Zenodo? Is it available somewhere else?

Answer: The current, or any previous, version of BMABMDR is provided on the main developer's personal GitHub; https://github.com/cecilekremer/BMABMDR. This GitHub is maintained by the

developer, Cécile Kremer of University Hasselt who is acting as the EFSA affiliate for developing BMABMDR. The R version can be installed by following the installation instructions on that page.

Question 8: Can previous versions of the EFSA BMD be used at a later point in time (e.g., to answer regulator questions)?

Answer: Yes, but currently only with the R versions available from the developer's personal GitHub (https://github.com/cecilekremer/BMABMDR). Previous versions of the EFSA Online Tool are not archived on the EFSA statistical models portal (EFSA statistical models). EFSA has committed on improving the version control process as discussed in the November 2024 Ad hoc stakeholder meeting with CropLife Europe (Ad hoc stakeholder meeting with CropLife Europe | EFSA).