EXPERIENCE TO DATE DERIVING ENDPOINTS FOR BIRDS AND MAMMALS USING THE EFSA UPDATED GUIDANCE 2023

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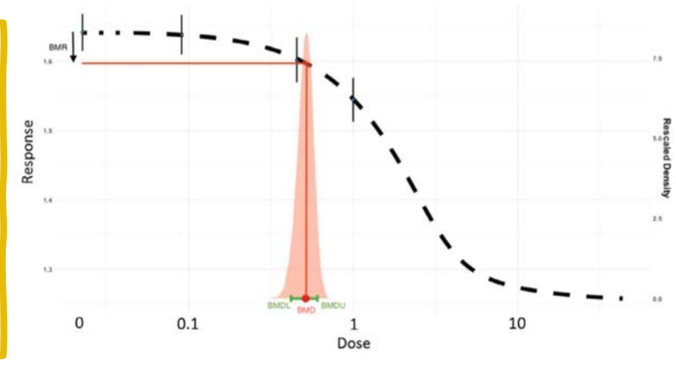
In 2021 the European Food Safety Authority (EFSA) released the draft of an updated bird and mammal guidance[1], followed by the release of the revised guidance in 2023[2]. Deriving ecologically relevant toxicity endpoints for birds and mammals requires reviewing the effects observed in the toxicity studies to determine which are population relevant and which aren't, with the guidance providing some advice on how to make these decisions. Additionally, benchmark dose modelling must now be performed to determine whether valid 10% effect levels (BMD_{10}) can be calculated and used in the risk assessment. This poster aims to summarise our experiences to date, the challenges faced, and the uncertainties still present in the light of the updated guidance.

BMD modelling: key points

- Required for both B&M where possible to calculate.
- EFSA 2023 recommends use of **median BMD_{10}** (EFSA 2021 recommended $BMDL_{10}$).
- EFSA 2023 recommends using a **Bayesian approach** – can be calculated using the new EFSA tool[3]
- EFSA performed an online workshop on the use of the BMD approach and the new tool[4]



Experience/challenges

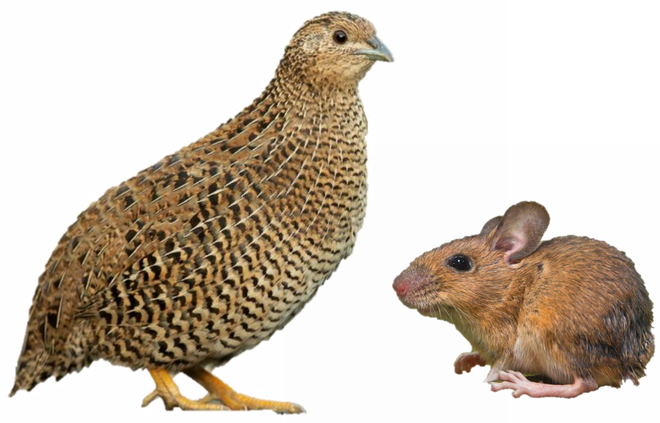
- Standard studies not designed for determining effect level, only NOAELs. More doses would allow a better curve to be fitted – something acknowledged by ESFA in 2023 guidance.
- CEA have practical experience running BMDs using EFSA tools. It is easy to get 'an answer', but careful consideration needed when entering data/selecting options/evaluating results.
- Workshop somewhat useful, but avoided discussing risk assessment context, leaving questions unanswered e.g. which endpoints to model (all of them or just the critical ecorelevant endpoint..?)
- Bird data can be very different to mammals (e.g. proportional endpoints). Workshop provided an example.
- Extracting/reviewing data from (older) studies can be time consuming – best done alongside fTWA consideration
- Need input from Tox experts to interpret mammalian studies
- Best done at earliest opportunity to investigate impact on endpoints and therefore B&M RA.

Uncertainties

- BMD for ecotox and especially new Bayesian tool – very new to everyone. Each submission will be a learning curve!
- Unclear if expertise will be available for 'difficult' cases – what about for regulators?
- Unclear how much 'common sense' can be used to discount BMD – e.g. where little effects or effects only at highest concentration, still need to run BMD? Or run all data regardless?
- EFSA workshop – EFSA stated that BMD tool should only be run once per data set. Not clear how practical/useful this is?
- What to do if BMD validity assessment doesn't pass and point #3 of flowchart in ch. 5.2.7.1. fails: "Additional data may be required, or additional methods explored (e.g. DEBtox modelling) to predict a reliable reference point for the reproductive effect assessment". Also recommends calculating NOAEL according to Green et al. (2022). So further consideration of NOAEL needed where BMD not appropriate?

Ecological relevance: key points

- Main change in EFSA (2023) compared to EFSA (2021) seems to be move from $BMDL_{10}$ to BMD_{10}
- NOAEL may be selected if this estimate isn't considered suitable.
- For mammals, there is a list of behavioural endpoints from developmental neurotox studies (Table C.1.): all effects at least *possibly* ecologically relevant.
- Ch. 5.2.6.1. discusses biological relevance: effects don't have to be statistically significant to be relevant, but also that statistically significant effects may not be relevant (e.g. <10% effects). Also discusses historical control data, outliers, dose-response.



Experience/challenges

- Easier to reject effects <10% (without additional argumentation). But effects ≥10% always considered biologically relevant. Criteria given when arguing against this. What about eggshell thickness <18%?
- Additional guidance given in EFSA (2023) for requirements when supporting endpoints e.g. when using historical control data.
- Guidance for the reporting of the mammalian endpoints is provided (ch. 5.2.6.5.). Focus on magnitude and prevalence of effects. Some examples given e.g. body weight effects 10% considered relevant, body weight gain less relevant. Less/non-relevant endpoints are few.
- Different effect types weighted equally in terms of population level effects, though unlikely to be the case in reality (e.g. pup weight vs. pup survival: unlikely to have similar impacts on populations).

Uncertainties

- Guidance still focusses on requirement for specific cases/data to support ecological (ir)relevance of observed effects (≥10%). As a first-step, guidance can be reviewed for reference to the specific effect observed but failing this the approach would be similar to EFSA (2009) – case-by-case arguments supported by relevant data.
- Guidance briefly mentions rabbits/rats showing different sensitivities to substances, but not clear if a species-specific endpoint can be chosen e.g. rodents for seed treatments.
- Guidance for bird endpoints less detailed.

References:
1 European Food Safety Authority (EFSA). 2021. Draft risk assessment for birds and mammals. https://connect.efsa.europa.eu/RM/s/publicconsultation2/a0l1v00000E7Zev/pc0090
2 EFSA (European Food Safety Authority), Aagaard A, Berny P, Chaton PF, Antia AL, McVey E, Arena M, Fait G, Ippolito A, Linguadoca A, Sharp R, Theobald A and Brock T, 2023. Guidance on the risk assessment for Birds and Mammals. EFSA Journal 2023;21(2):7790, 300 pp. https://doi.org/10.2903/j.efsa.2023.7790
3 EFSA statistical models. Bayesian Benchmark Dose. https://r4eu.efsa.europa.eu/app/bmdbayesian
4 Workshop on EFSA's updated Guidance on the use of the benchmark dose approach in risk assessment. https://www.efsa.europa.eu/en/events/workshop-efsas-updated-guidance-use-benchmark-dose-approach-risk-assessment