BMD “Cookbook” decision scheme

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What is the problem?

Volume of data

Why not run the BMD_{10} for all available endpoints? With the avian and mammalian (particularly) data packages, this can be very **time consuming** and include **unnecessary work** (irrelevant endpoints). Also, **extracting data from old studies** can be an issue. Different evaluators may filter data differently

Study relevance

Avian and mammalian studies are not designed in a way that is intended for deriving BMD/ECx values, they are designed for NOAEL derivation. Carcinogenicity and 28/90day studies are generally considered less relevant according to EFSA (2023). Dose level/spacing should also be considered

Endpoint relevance

Some **parameters** measured in the toxicity studies have **little or no relevance to the protection goals for wild birds and mammals** e.g. effects on liver, blood chemistry, reproductive effects <10% etc.

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Resource estimate for B&M BMD assessment

Based on collected resource estimates, anywhere from 150 – 1800+ hrs for an evaluation (depending on situation).

On average: 646 hrs.

This is likely already accounting for some level of data filtering before running BMDs, which will be different depending on the person performing the evaluation.

What is the solution?

We propose a pragmatic approach ("cookbook") for endpoint selection and consecutive BMD_{10} calculation in order to make effort manageable for both applicants and evaluators.

The focus is on:

- **Selection of relevant <u>studies</u> for BMD analysis**
- **Selection of relevant <u>endpoints</u> for BMD analysis**

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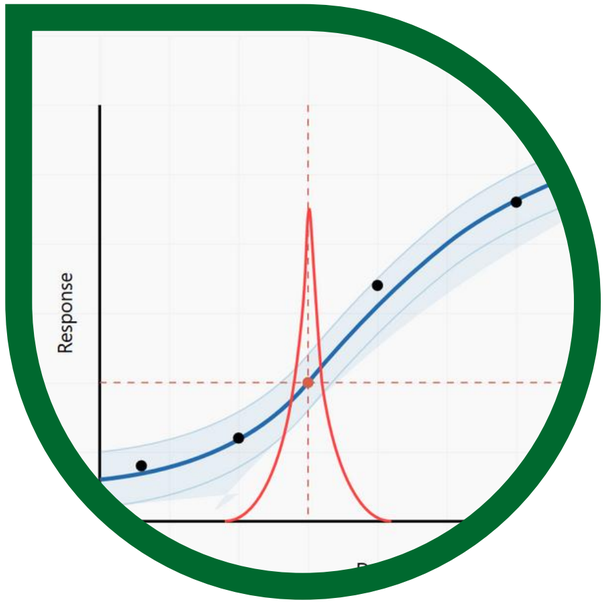
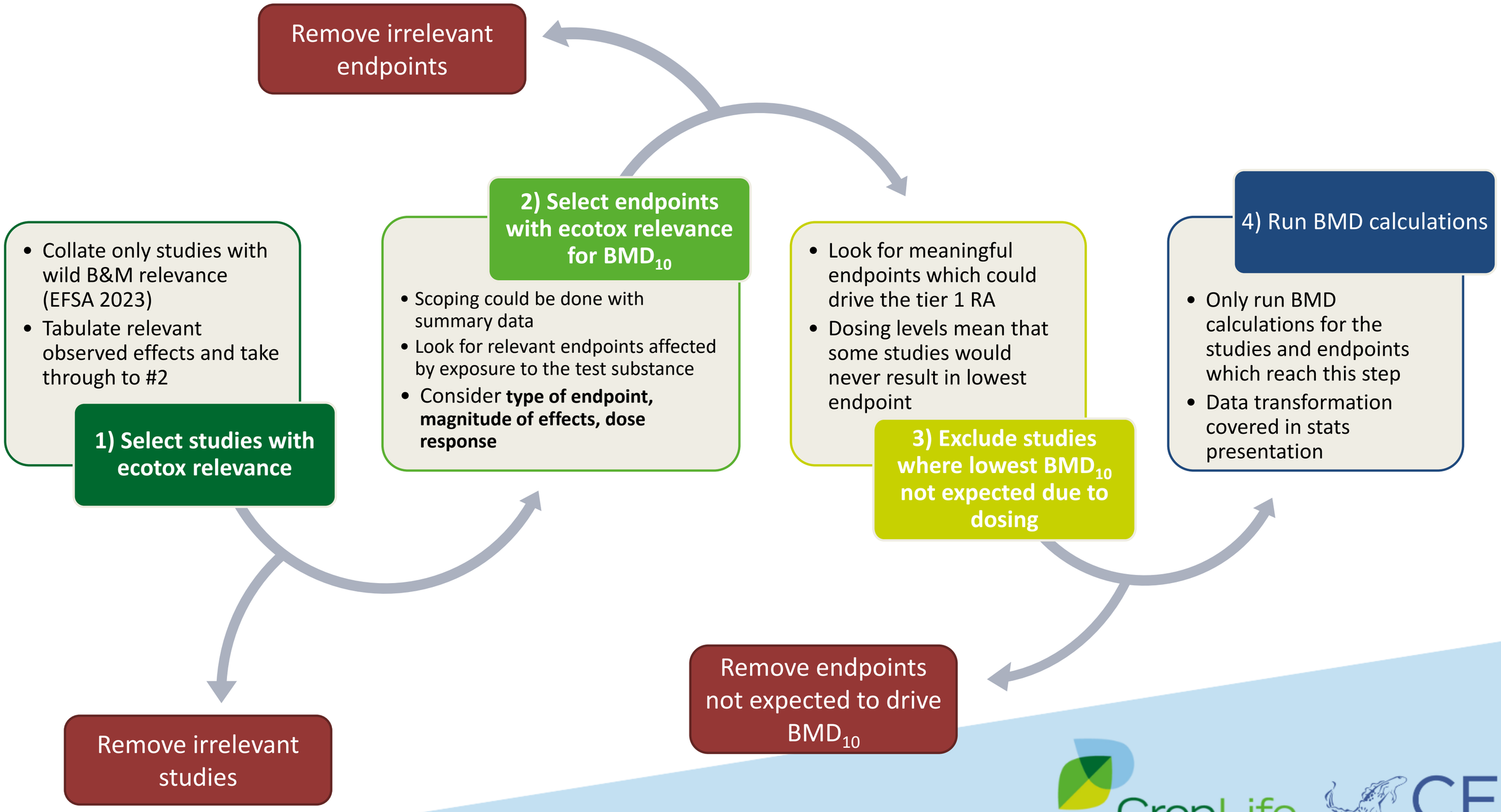


Flow chart of cookbook

We will present a visual representation of the “cookbook” methodology for filtering data

Worked example

We will present a worked example of how to filter data using this methodology


Remove irrelevant endpoints
2) Select endpoints with ecotox relevance for BMD10
• Scoping could be done with summary data
• Look for relevant endpoints affected by exposure to the test substance
• Consider type of endpoint, magnitude of effects, dose response
• Look for meaningful endpoints which could drive the tier 1 RA
• Dosing levels mean that some studies would never result in lowest endpoint
3) Exclude studies where lowest BMD10 not expected due to dosing
4) Run BMD calculations
• Only run BMD calculations for the studies and endpoints which reach this step
• Data transformation covered in stats presentation
Remove endpoints not expected to drive BMD10
• Collate only studies with wild B&M relevance (EFSA 2023)
• Tabulate relevant observed effects and take through to #2
1) Select studies with ecotox relevance
Remove irrelevant studies

01

Select studies with ecotox BMD_{10} relevance

- Bird reproduction studies OECD 206/OCSPP 850.2300. Most endpoints potentially ecologically relevant. Include all studies.
- For mammals, EFSA (2023) gives guidance on potentially relevant study types.
- Carcinogenicity studies less relevant due to dosing (life-long exposure), strain (specific for detection of oncogenic effects), and low relevance of cancer to wild animals.
- 28 & 90-day toxicity studies less relevant due to test duration and life stage, and endpoints are usually also available in acute/chronic/repro tests.
- See EFSA (2023) Ch.5.2.6 and Appendix C for full details.

NB: Studies dropped at this stage may still be useful for contextualising results later

Non-relevant mammal study designs to remove at step 1	Relevant mammal study designs to take through to step 2
Screening tests	Multi-generation study OECD 416
28-day study OECD 407	Extended one-generation reproduction study OECD 443
90-day studies OECD 408, OECD 409	Developmental study OECD 414
Carcinogenicity studies OECD 451, OECD 452, OECD 453	Developmental neurotox (DNT) OECD 426
	90-day neurotoxicity study (OECD 424)

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02

Select endpoints with ecotox relevance for BMD_{10}

- Check if effects are **treatment related and considered adverse** (rather than transient) as evaluated by tox, in studies with relevant study designs.
- Are these endpoints **potentially ecologically relevant**?
- EFSA (2023) provides guidance as to what is considered an ecologically relevant effect
- **Remove endpoints** considered **not-ecologically relevant**: Biomarkers and clinical chemistry; non-reproductive/brain organ effects; feed consumption; bodyweight gain (covered by body weight); variations
- Some endpoints are less clear and **may need to be considered on a case-by-case** basis e.g. developmental malformations; clinical signs; behavioural effects
- Keep endpoints considered potentially ecologically relevant: **Body weight***; **Reproductive endpoints**; **Developmental tox endpoints**; **Neurotox endpoints**
- Remove endpoints with **<10% effects** compared to the control
- Remove endpoints which **do not demonstrate a dose response** as reported in the study report

*Except if resulting from reduced food consumption caused by ↓palatability

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02

Apical endpoints vs. Interim effects

- **Select Apical endpoints with ecotox relevance for BMD_{10}**
- **Apical endpoint**: An observable outcome in a **whole organism**, such as a clinical sign or pathologic state, that is indicative of a state that can result from exposure to a toxicant. I.e. directly measured, whole-organism outcomes of exposure in *in vivo* tests, generally: **death**, **reproductive failure**, or **developmental dysfunction.***
- **Interim/other endpoint**: These are measured outcomes other than apical endpoints. They may be measurements performed during the study, e.g. interim weight measurements, or reproductive measurements which may or may not impact populations.
- **Primary focus should be on apical endpoints and not on interim effects**.

*https://www.ecetoc.org/technical-report-130/2-definitions/

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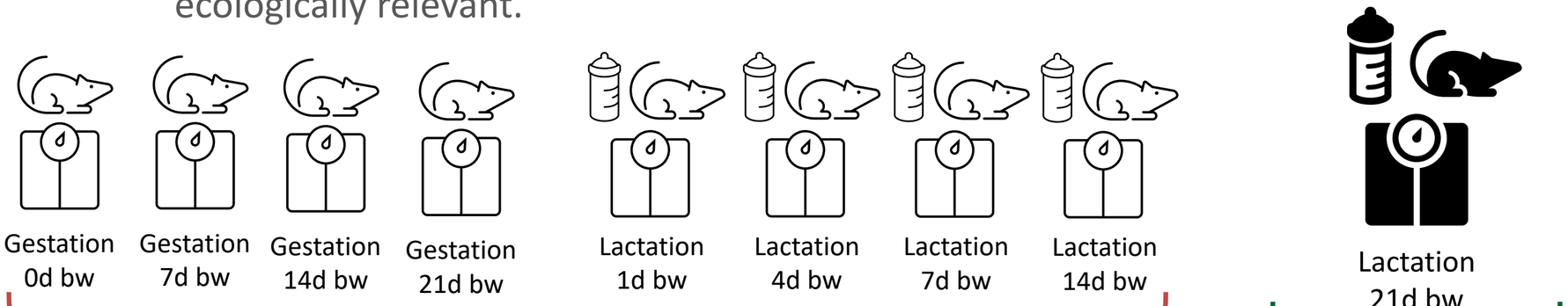
02

Apical endpoints vs. Interim effects

E.g. Maternal body weight in Multi-generation study OECD 416

- This is measured at least every 7d during gestation, and ca. days 1, 4, 7, 14, and 21 of lactation.
- A sig. red. in weight at an **isolated point** e.g. on day 14 of gestation, but not thereafter **is unlikely to be ecologically relevant**.
- The **apical endpoint** is that which is **most likely to impact reproductive output** and **therefore populations**. In this case, weight at 21d lactation is considered the most ecologically relevant.



Intermediary measurements of weight feed into the apical endpoint and are considered less ecologically relevant than the apical endpoint. Transient weight reductions are unlikely to result in population-level effects.

This is the Apical endpoint – effects here are considered the most ecologically relevant as they are most likely to impact repro output and therefore populations.

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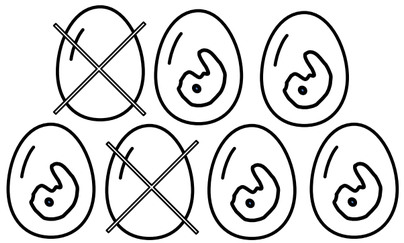
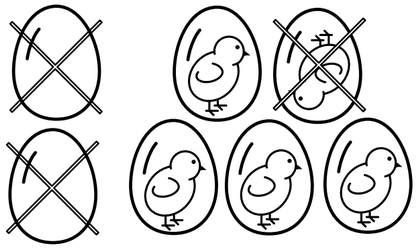
Apical endpoints vs. Interim effects

E.g. Surviving offspring in Avian reproduction test OECD 206

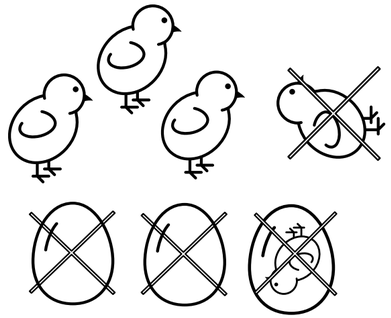
- There are many measurements of **egg and offspring viability** built into the design of OECD 206.
- Many of these can also be viewed as **interim measurements**, **feeding into the most relevant apical endpoint** of 'surviving offspring'.
- Instead of running all endpoints, **focus should be on the apical ones**. Interim measurements can **assist in interpreting effects** where they do occur in the apical endpoints.



Viable embryos of eggs set (%)

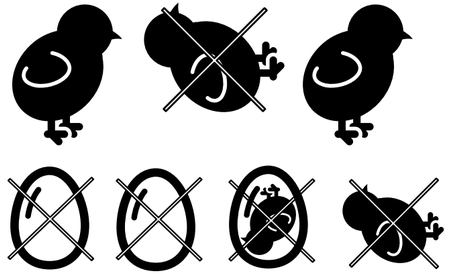


Live 3-week embryos of eggs set (%)



Hatchlings of eggs set (%)

Intermediary measurements of offspring viability feed into the apical endpoint of chick survival and are considered less ecologically relevant than the apical endpoint.



14-day old survivors of eggs set

This is the Apical endpoint – effects on the ultimate number of surviving offspring are considered the most ecologically relevant to populations.

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03

Exclude studies where low BMD_{10} not expected due to dosing

- Due to their **design**, studies may be p**erformed at high dose rates** and result only in **effects at high doses**
- It may technically be possible to calculate a BMD_{10} from a study like this, but it **will never be the lowest BMD_{10}** if studies performed at much lower doses demonstrated relevant effects
- It is proposed to **exclude studies** where the concluded **NOAEL is a factor 5 higher** compared to the lowest available NOAEL for mammals
- The factor chosen is **arbitrary** but is more worst-case than the factor of 3 used in EFSA (2023) for TWA assessment. It is therefore considered a protective approach.

> *"If the lowest ecologically relevant endpoint allows the use of the fTWA, it should also be checked whether a higher ecologically relevant endpoint (within 3x of the lowest endpoint) would not be appropriate with the fTWA, and if so, in that case a risk assessment should be presented using each Endpoint"*. – EFSA (2023)

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04

Run BMD_{10} calculations

- The filtering to this point provides the best chance at **maximizing meaningful BMD_{10} values**
- Consider any **transformations** which need to be performed on the raw data and how it should be inputted into BMD calculations
- Consider whether **litter effects** should be included
- The above will be considered in more detail in the next presentation!

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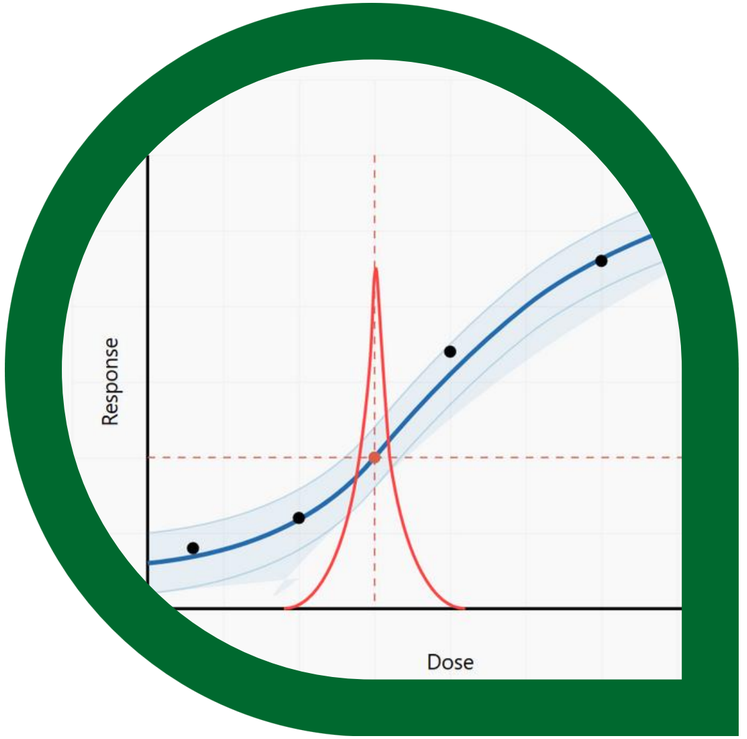
Worked example



01

Case Study: Select studies with ecotox BMD_{10} relevance

- Bobwhite Quail Repro OECD 206
- Mallard duck Repro OECD 206
- Repeated Dose 90-Day rat OECD 408
- Repeated Dose 90-day dog OECD 409
- Rat 2-generation OECD 416
- 2-year rat feeding study OECD 451
- Rat developmental toxicity study study OECD 414
- Rabbit developmental toxicity study OECD 414

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01

Case Study: Select studies with ecotox BMD_{10} relevance

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- Rabbit developmental toxicity study OECD 414

Not relevant study designs or findings from these studies for ecotox -remove

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02 Case Study: Select endpoints with ecotox relevance for BMD_{10}

Study type*	NOAEL (mg/kg bw/d)	Treatment-related Effects	Ecotox relevant effects (Y/N)	>10% effect (Y/N)	Dose response** (Y/N)
Bobwhite Quail Repro OECD 206	261	Eggs laid/hen	Y	Y	Y
		No. of hatchlings/eggs set (no effects on 14-day old survivors of eggs set)	**N**		
Mallard duck Repro OECD 206	261	Eggs laid/hen	Y	Y	Y
		Live 3-week embryos of viable embryos/eggs set	**N**		
		14-day old survivors/eggs set	Y	Y	Y
Rat developmental toxicity study OECD 414	237	**Maternal diarrhoea/urinary incontinence**	**N**		
		Maternal Food consumption	**N**		
		Maternal reduced bodyweight gain	**N**		
		Bodyweight parental Gestation 14d (no other bw effects)	**N**		
Rat 2-generation OECD 416	711	Bodyweight parental 21d lactation	Y	Y	Y
		Bodyweight F1	Y	**N**	
		Bodyweight F2	Y	Y	**N**
		Thymus weight F1	**N**		
Rabbit developmental toxicity study OECD 414	107 (mat. tox)	Bodyweight parental 21d lactation	Y	Y	Y
		Food consumption	**N**		
		Implantation loss	Y	Y	Y
	328 (devmt.)	**Open eye**	**Possibly**		
		Fused sternebrae	**Possibly**		

*OECD Guideline or equivalent (if pre-OECD guideline); ** As reported in the study report

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03

Case Study: Exclude studies where low BMD_{10} not expected due to dosing

Study type*	NOAEL (mg/kg bw/d)	Treatment-related Effects	Ecotox relevant effects (Y/N)	>10% effect (Y/N)	Dose response (Y/N)
Bobwhite Quail Repro OECD 206	261	Eggs laid/hen	Y	Y	Y
Mallard duck Repro OECD 206	261	Eggs laid/hen			Y
		14-day old survivors /eggs set			Y
Rat 2-generation OECD 416	**711**	**Bodyweight parental 21d lactation**			Y
Rabbit developmental toxicity study OECD 414	**107** (mat. tox)	Bodyweight parental 21d lactation			Y
		Implantation loss			Y
	328 (devmt.)	Open eye	Possibly		
		Fused sternebrae	Possibly		

Lowest endpoint = 107.
107*5 = 535.
711 is > 535 therefore remove.
This study will not result in the lowest BMD_{10}

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04

Case Study: Run BMD_{10} calculations

Run BMD_{10} for these endpoints. In the following session we will discuss how to do this

Study type*	NOAEL (mg/kg bw/d)	Treatment-related Effects	Ecotox relevant effects (Y/N)	>10% effect (Y/N)	Dose response (Y/N)
Bobwhite Quail Repro OECD 206	261	Eggs laid/hen	Y	Y	Y
Mallard duck Repro OECD 206	261	Eggs laid/hen	Y	Y	Y
		14-day old survivors/eggs set	Y	Y	Y
Rabbit developmental toxicity study OECD 414	107 (mat. tox)	Bodyweight parental 21d lactation	Y	Y	Y
		Implantation loss	Y	Y	Y
	328 (devmt.)	Open eye	Possibly		
		Fused sternebrae	Possibly		

Some endpoints need further consideration of ecotox relevance

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Using the proposed Cookbook to 'filter' data potentially saves both applicants and regulators a great amount of time/resource

Resource estimate for B&M BMD assessment without filtering

- Based on collected resource estimates, anywhere from 150 – 1800+ hrs for an evaluation (depending on situation).

On average: 646 hrs.

- No standardized guidance for filtering data – potential for different conclusions.

Resource estimate for B&M BMD assessment with filtering

Based on worked example:

- 3/9 studies removed from evaluation.
- From remaining studies 10/18 endpoints removed from evaluation.
- Potential to reduce resource required by 1/2 → 2/3, or more!
- Average assessment reduced to 215-323 hrs.
- Not only is the process more streamlined, but it would also be more standardized across different people performing the same evaluation.

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Overview:

What is the problem?

The BMD approach is welcomed, but EFSA 2023 is vague in the specifics of performing a BMD assessment. Performing BMD_{10} for all available endpoints is impractical and not useful. It would take a lot of time both for applicants and evaluators.

What is the solution?

Here we propose the BMD 'cookbook': a step-by-step process for filtering data and endpoints for the BMD assessment. The process is relatively simple and has the potential to massively reduce unnecessary workload and the time taken to conclude a BMD_{10} for the B&M risk assessment.

Future activities?

Further consideration needed regarding: Agreement with approach? Working document(s)? Apical Vs. intermediate endpoints? Eco-relevance of development effects?

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Break-out group discussion topics

- Is a step-wise approach needed for the derivation of a BMD (as proposed here) in order to save significant resources? Is the ‘cookbook’ approach a suitable way to prioritise data for BMD calculation?
- 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?

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THANK YOU

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