Workshop on the update of the BMD guidance

Brussels 15 - 16 February 2023

EUROPEAN FOOD SAFETY AUTHORITY

USE OF THE BMD APPROACH IN RISK ASSESSMENT

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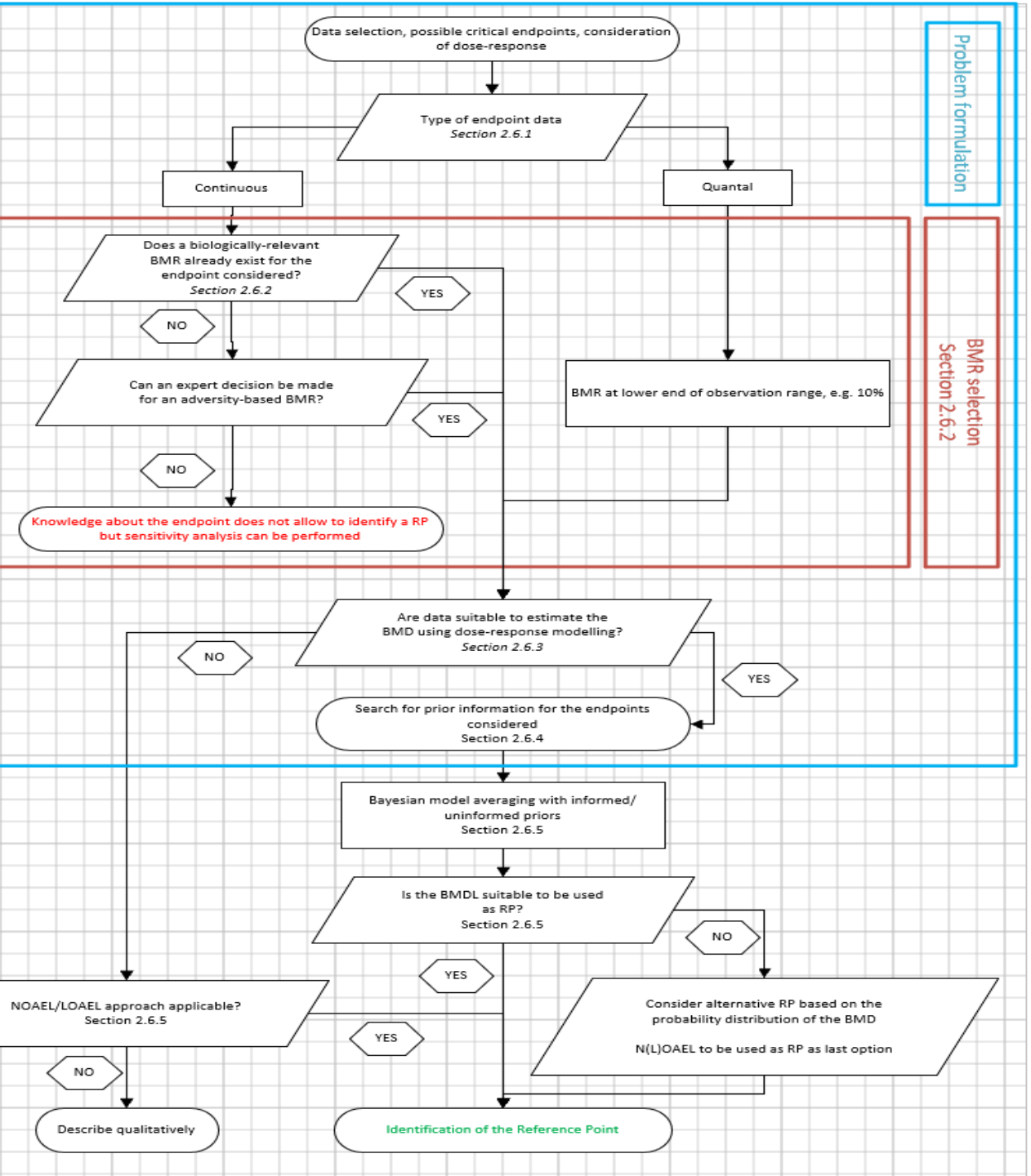
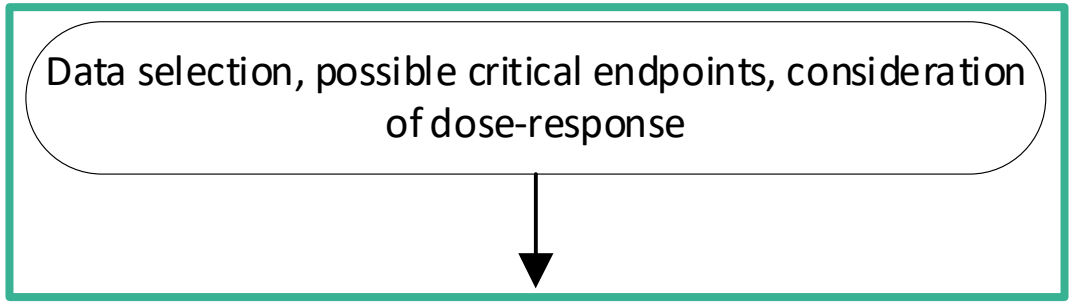
EUROPEAN FOOD SAFETY AUTHORITY



Problem Formulation

PROBLEM FORMULATION 1/4

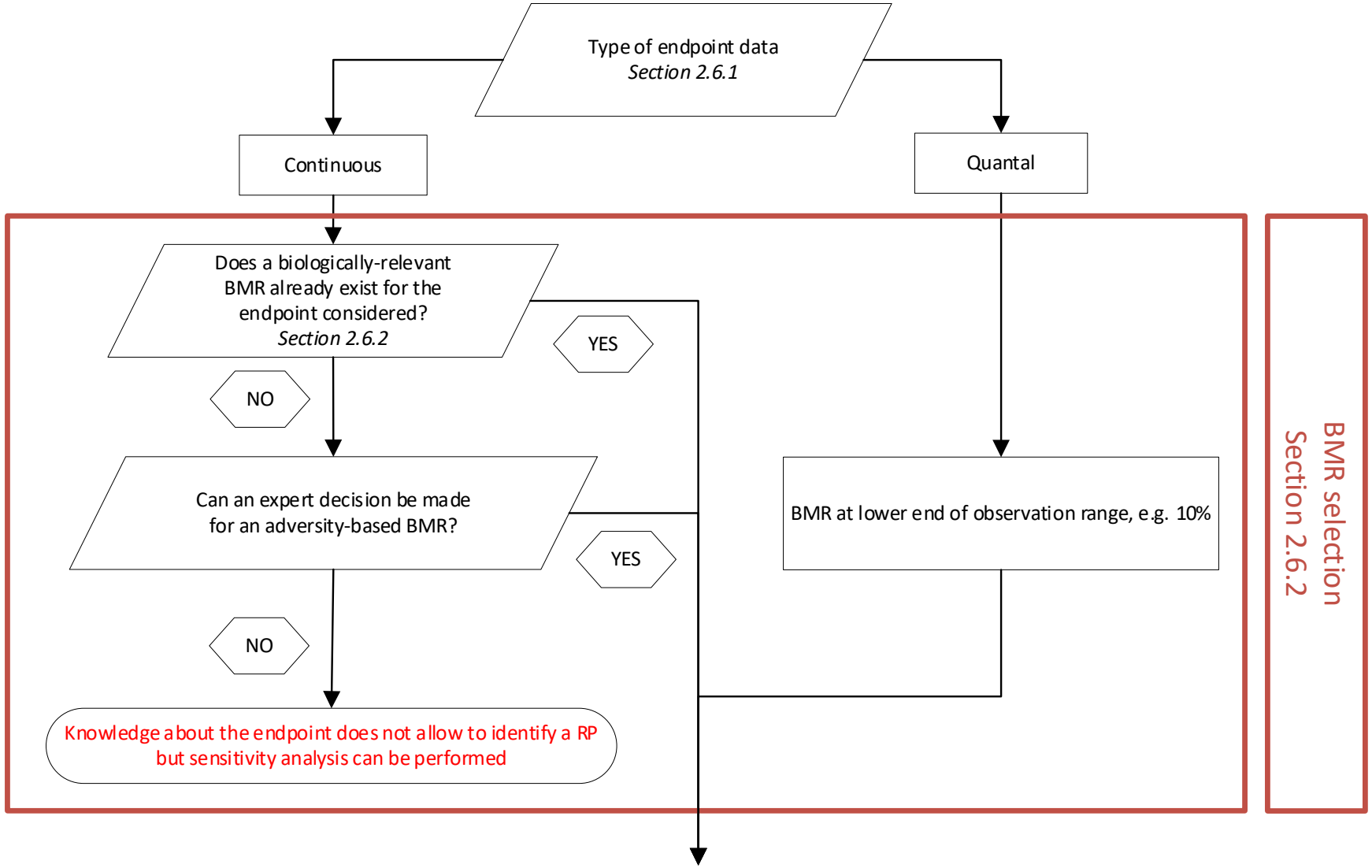


- Potential endpoints to derive my reference point?
- Any indication for sex, age groups or other population characteristics differences, or several studies with similar experimental conditions? -> **covariate analysis**
- Any indication on potential litter effects that should be taken into account? -> **litter effect to be included in the analysis**
- Biological or statistical arguments to reject the Normal or Log-normal distribution of the response for the data considered?

SELECTION OF THE BMR

$$BMR = \frac{Med(BMD) - Med(0)}{Med(0)}$$

PROBLEM FORMULATION 2/4



PROBLEM FORMULATION 2/4

Continuous data

BMR: degree of change that defines a level of response in a specific endpoint that is measurable, considered relevant to humans or to the model species, and that is used for estimating the associated dose (the "true" BMD)

- The BMR should reflect the dose where an effect becomes adverse and, therefore, depends on the nature of the endpoint selected
- A level of adversity can be identified, even though the minimal degree of adversity may not be known. Thus, biologically relevant BMRs may also be represented by a range rather than by a single point
- The increase/decrease defined by the BMR should be a value within the observed range of experimental response. If outside the observed response range, considerations must be made whether the study is suitable to derive a RP
- **If it is not possible to provide an argument for a specific biologically relevant BMR** (or range of biologically relevant BMRs) for the endpoint considered**, this endpoint should not be used to establish a HBGV** -> sensitivity analysis

PROBLEM FORMULATION 2/4

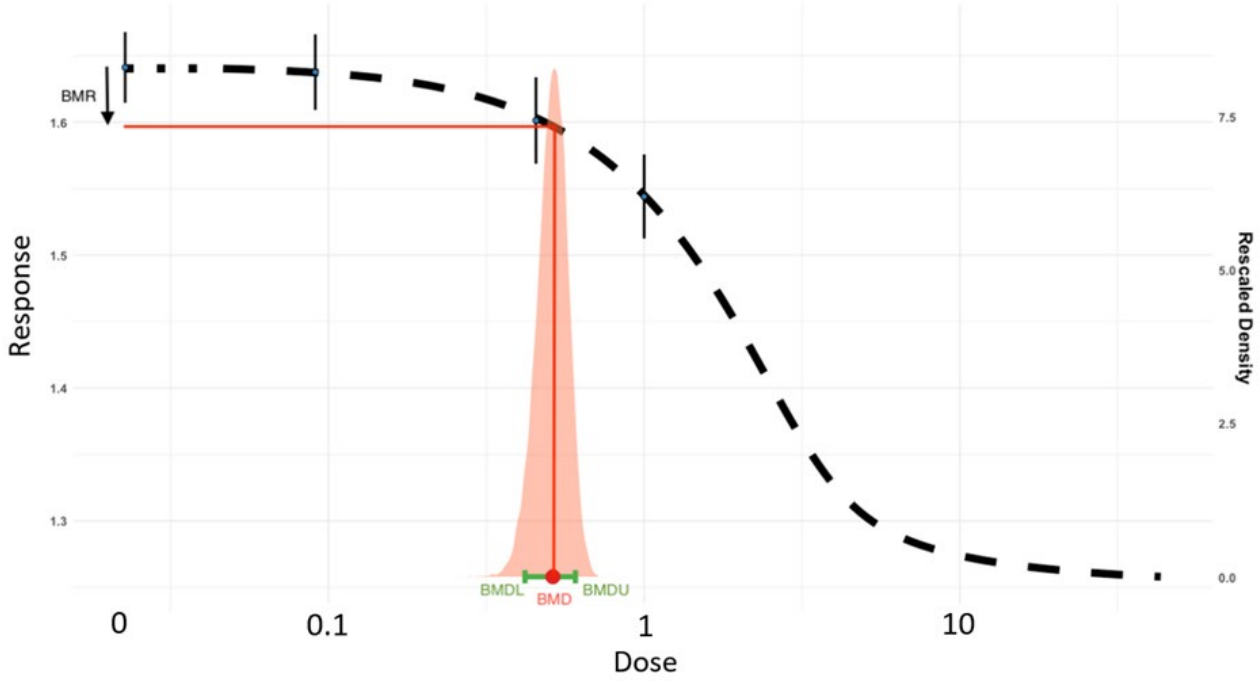
Quantal data

- The BMR is defined in terms of an increase in the incidence of the lesion/response scored, compared with the background incidence (extra risk).

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

- The BMR should be a value within the observed range of experimental response. In case (unlikely) the increase defined by the BMR is outside the observed response range, considerations must be made whether the study is suitable to identify a RP
- A **BMR of 10%** is the lowest statistically significant increased incidence that can be measured in most **animal** studies, and would normally require little or no extrapolation outside the observed experimental data. Any decision to deviate from this proposed value should be explained and documented.

SUITABILITY FOR MODELLING



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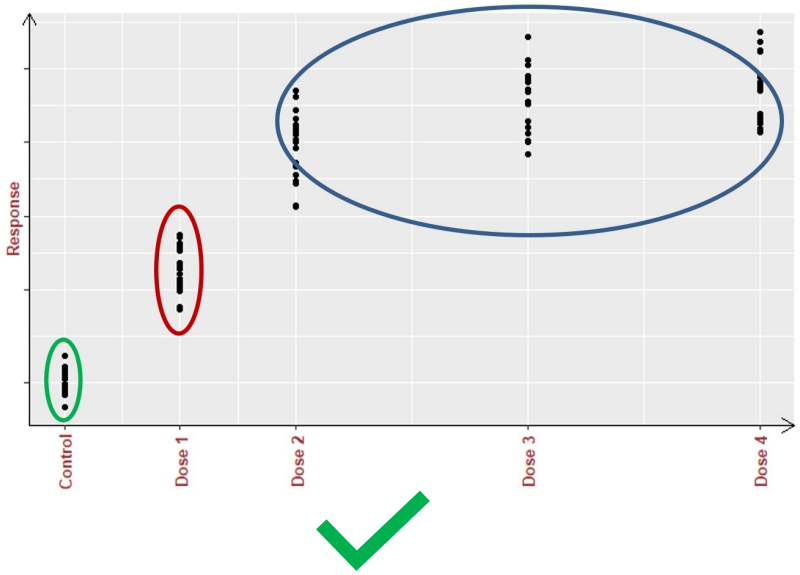
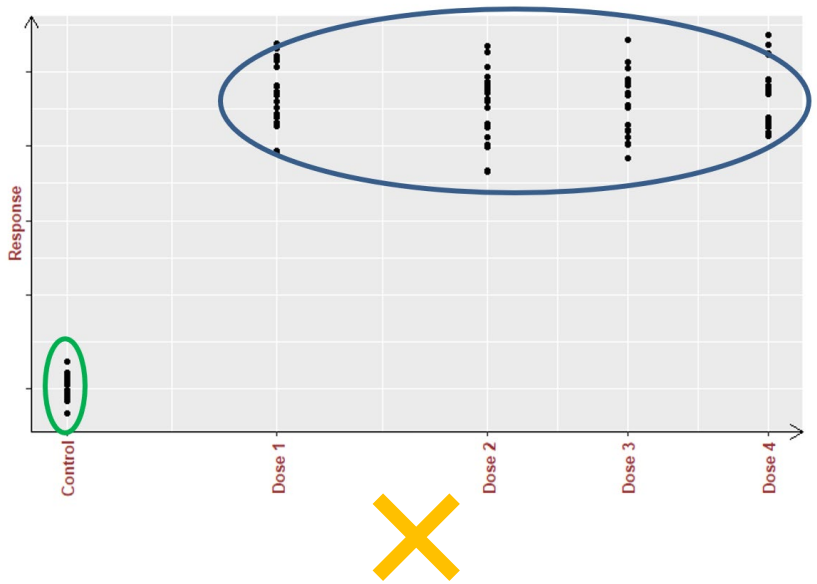
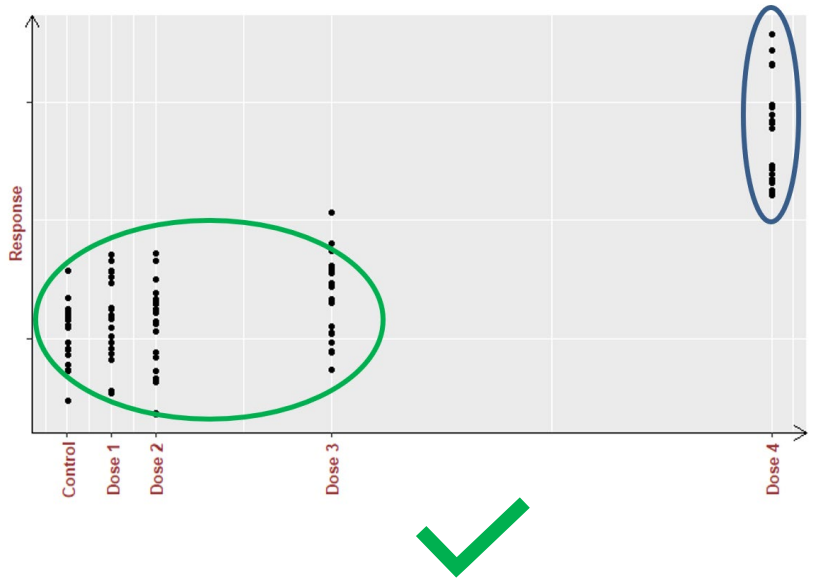
PROBLEM FORMULATION 3/4







X: Expected to produce small BMDL values as not enough small doses have been tested in the experiment conducted, and the BMD will certainly be estimated to be below the first dose tested and it is expected a wide credible interval. Although the data could be modelled, the available information might not be sufficient for estimating the BMD. (**no stopping rule**, use to **flag** potential issues)

If data not showing a dose response effect, consider whether N(L)OAEL approach is applicable

PROBLEM FORMULATION 3/4

High Dose Impact

- Where high dose data are available for the effect of interest, but clearly influenced by another type of effect or mode of action, then it may be justifiable (on biological basis) to exclude the high dose data (recommended to perform analysis with and without). **If there is no indication of an overlaying mode of action, data should not be excluded**.
- If the maximum response is not reached at the highest dose, then the assessor should consider whether it is possible to use an informed prior on the maximum response.
- Decision to exclude one (or several) point(s) from the dose response modelling should always be justified and documented and a sensitivity analysis should be provided considering the observation included and excluded.

PROBLEM FORMULATION 3/4

Absence of non-exposed controls

- The greater the difference between the zero dose and the lowest exposure, the higher the uncertainty
- If the dose-response function is flat at the lower dose range the uncertainty due to extrapolation is generally small. In all other cases extrapolation to zero dose becomes more uncertain, and it depends on the steepness

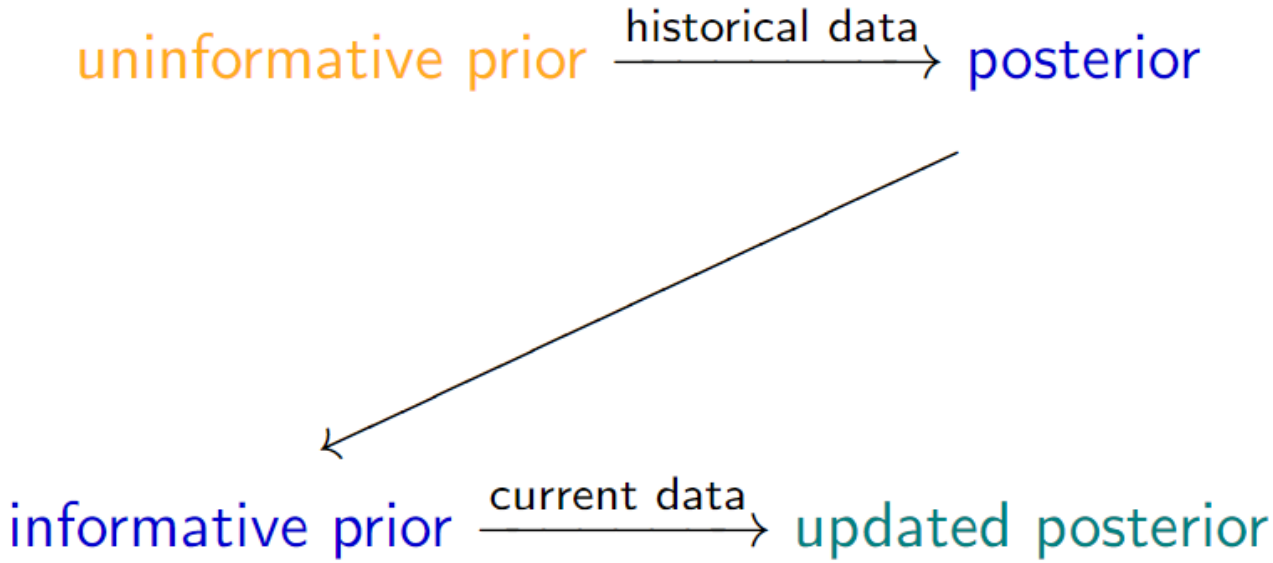
  -> make assumptions on the expected value of the outcome under consideration at zero exposure (via priors)

  -> nutrients where a certain exposure level is required to remain healthy: one would need to use a "background" response value around a pre-defined exposure level

Few practical examples of application of BMD modelling in the absence of non-exposed controls exist -> consult a specialist (e.g. EFSA Standing Working Group on BMD)

The more widespread use of the BMD methodology may highlight the need to update the guidance

PRIOR INFORMATION



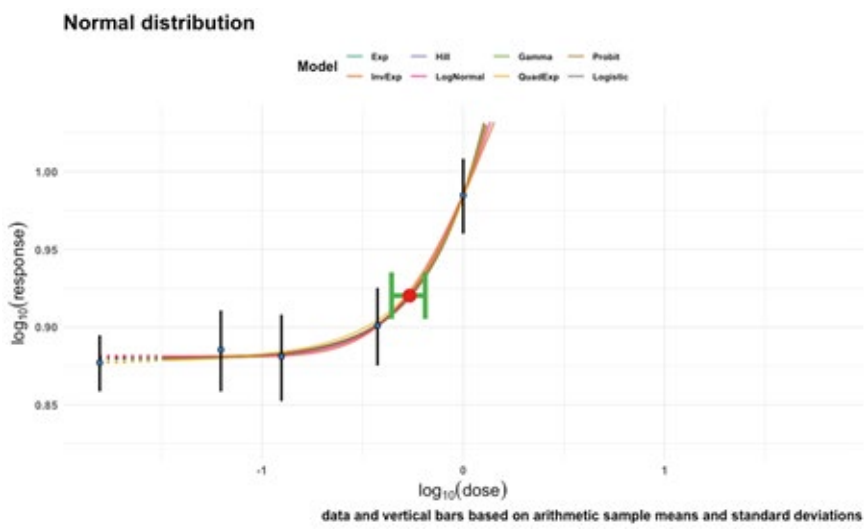
PROBLEM FORMULATION 4/4

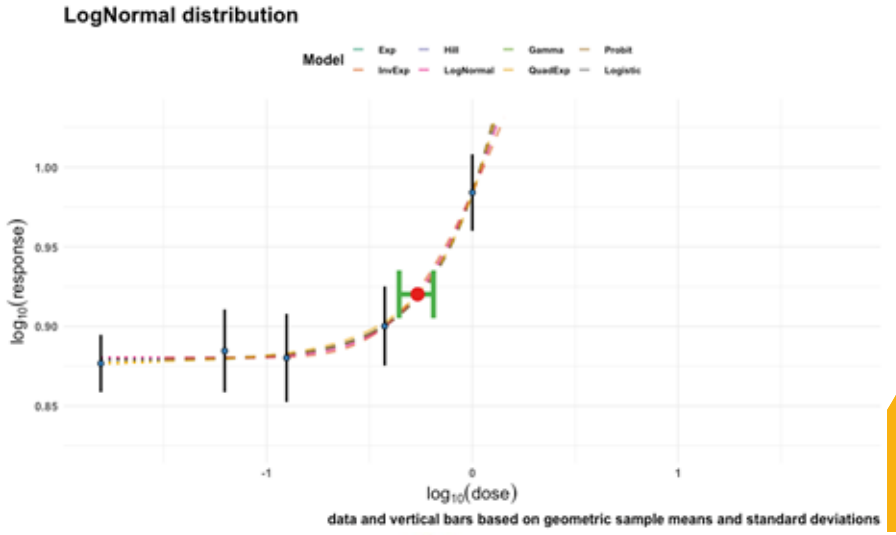
- Uninformative (the default) and informative (as recommended option) priors can be assigned to the natural parameters (background, maximum/minimum response and BMD)
- Weakly uninformative priors have been assigned to technical parameters (d, σ^2)

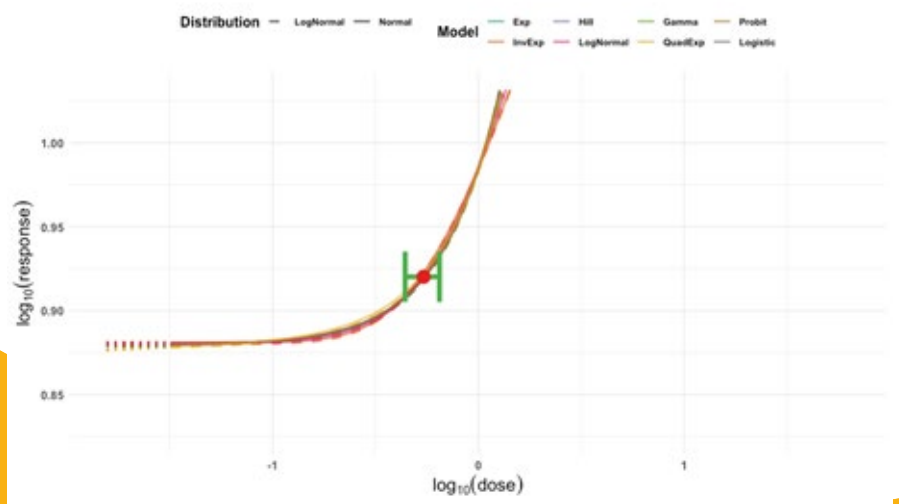
2 Types of prior distribution

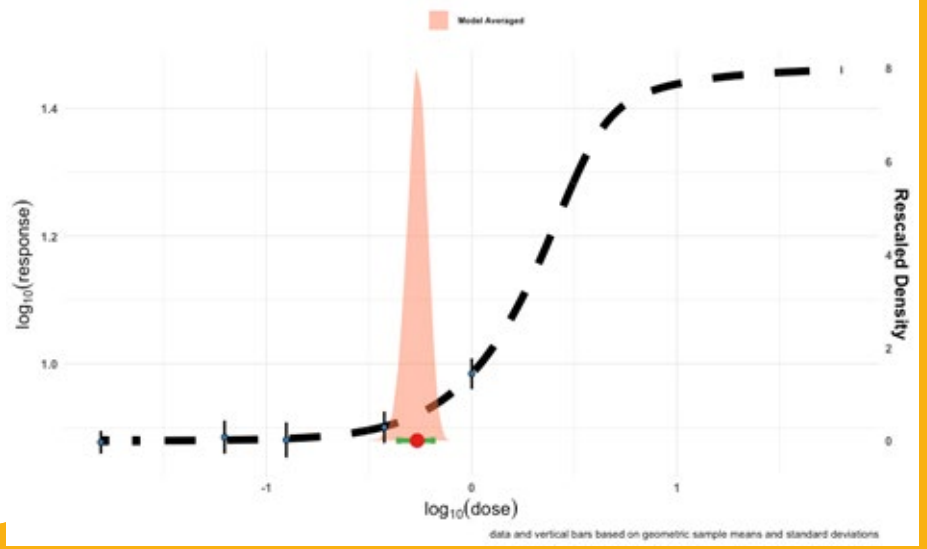
- Normal:
  - Considering US-EPA priors proposed specifically for the curvature (d) and variance of the distributional assumption made (slightly modified)
  - Informative priors based on historical data no straightforward
  - Instability in specific settings
- PERT:
  - defined based on minimum, maximum and mode
  - Easier to set for background, maximum response and BMD
  - Difficulties to build multivariate version

DOSE-RESPONSE MODELLING









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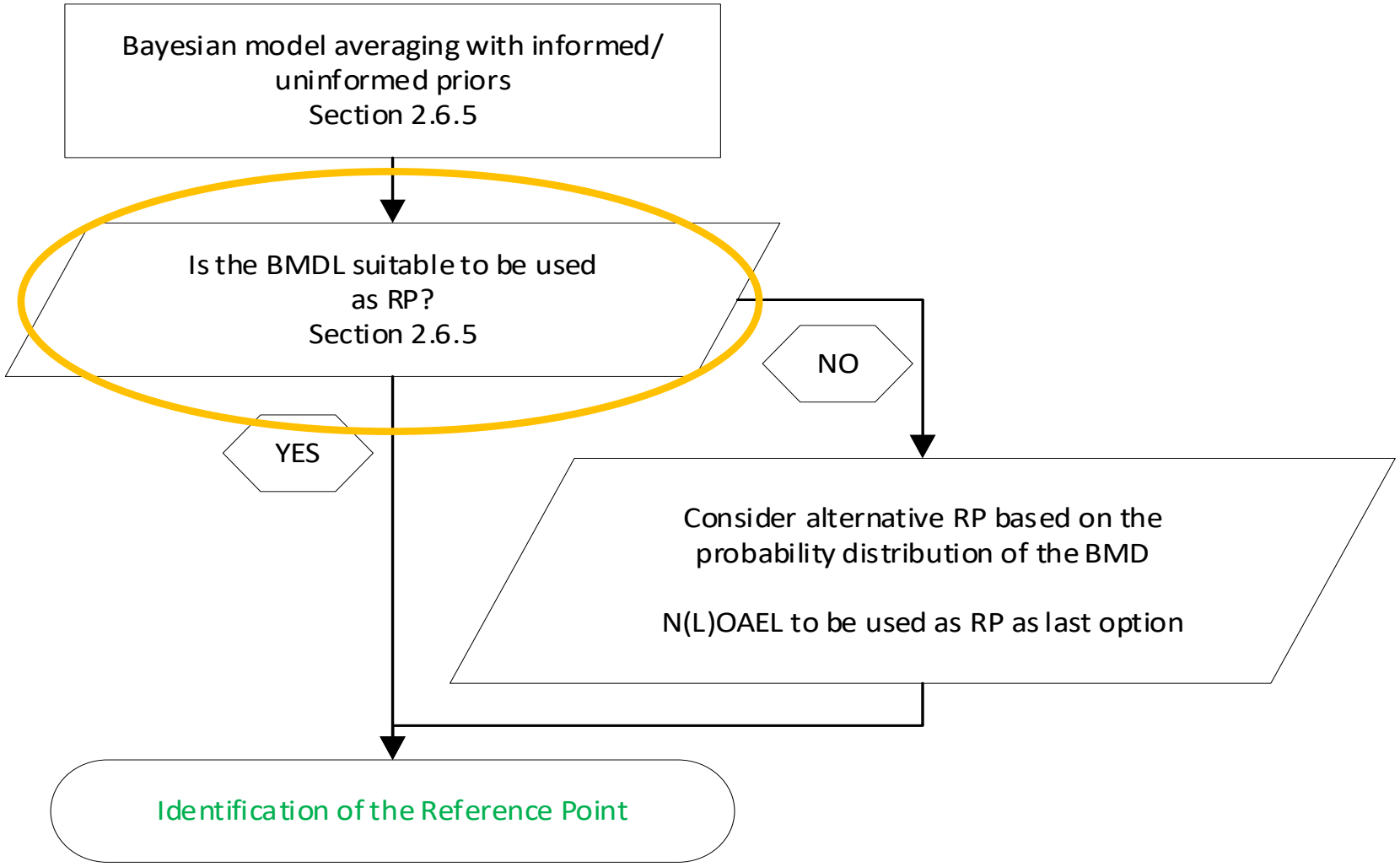
SUITABILITY OF THE BMD MODELLING OUTCOME



SUITABILITY OF THE BMD OUTCOME

- None of the candidate models fit the data sufficiently well
- BMD/BMDL > 20, or
- The BMD is 10 times lower than the lowest non-zero dose , or
- BMDU/BMDL > 50

Post-hoc modification of some parameters of the modelling to obtain a more suitable BMDL are not recommended

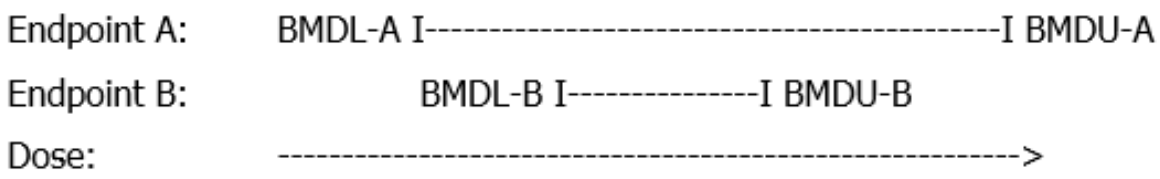
1. Use the probability distribution of the BMD to compare the most likely BMD (mode of the posterior distribution) with the various experimental doses tested
   - If most likely BMD < N(L)OAEL –> most likely BMD as RP
   - If most likely BMD > N(L)OAEL –> N(L)OAEL as RP
   - the most likely BMD should not be lower than 10 times the lowest non-zero dose

2. If the data are considered suitable for BMD modelling and the use of the most likely BMD is considered unreliable, the last option is to use a N(L)OAEL as the Reference Point.

Should the decision be made to use the most likely BMD, or the N(L)OAEL as a RP,
the BMD credible interval should be communicated together with the value selected for the RP.

DETERMINATION OF THE RP FOR A GIVEN SUBSTANCE

- Endpoint with the lowest BMDL
- Consider other aspects:
  - the HBGV is based on a BMDL with a wide credible interval, and is much higher than the exposure estimate, or the MOE is much larger than the minimal value considered necessary, then the high uncertainty in the RP has no consequence for the risk characterization
  - if lowest BMDL concerns an effect that is linked to other endpoints that resulted in much smaller credible intervals but with higher BMDLs
  - If two endpoints are not related to each other, and their biological consequences differs, the risk assessor may give preference to one endpoint rather than another, irrespective of the width of the credible interval



REPORTING OF THE BMD ANALYSIS

A. A summary table of the data for the endpoint(s) for which the BMD analysis is reported.

B. The value of the BMR chosen, and the biologically-based rationale for such a choice

C. The software used, including version number

D. Settings and statistical assumptions in the model fitting procedure when they deviate from the recommended defaults in this opinion, together with the rationale for doing so.

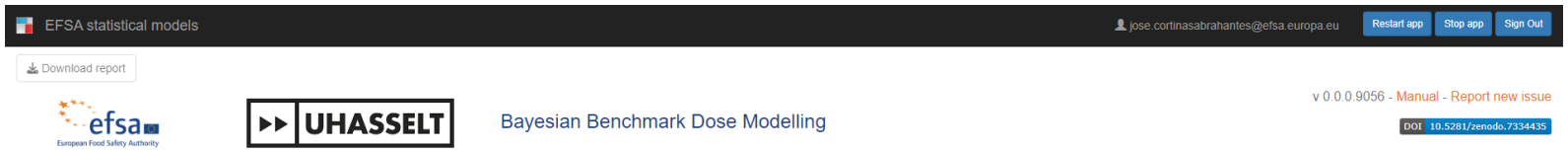
E. A table presenting the models used, and the priors used for the endpoint(s) considered;

F. The BMD estimate(s) and its/their BMDL-BMDU credible interval(s); values should be reported with two significant figures.

G. Plots of the fitted models.

H. Conclusion regarding the selected BMDL to be used as a RP

Template implemented in the EFSA Platform when retrieving the BMD analysis results

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