Statistical framework for BMD

Tom Sinclair

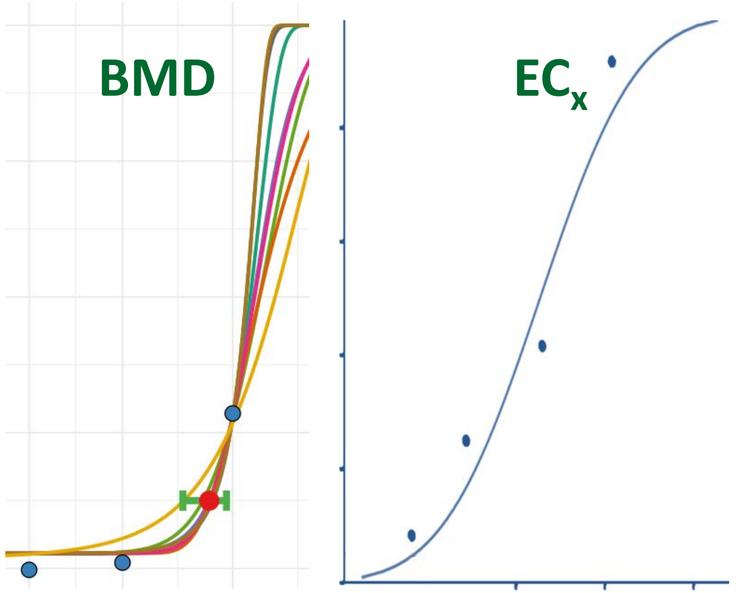
24th March 2025

Key Discussion Points

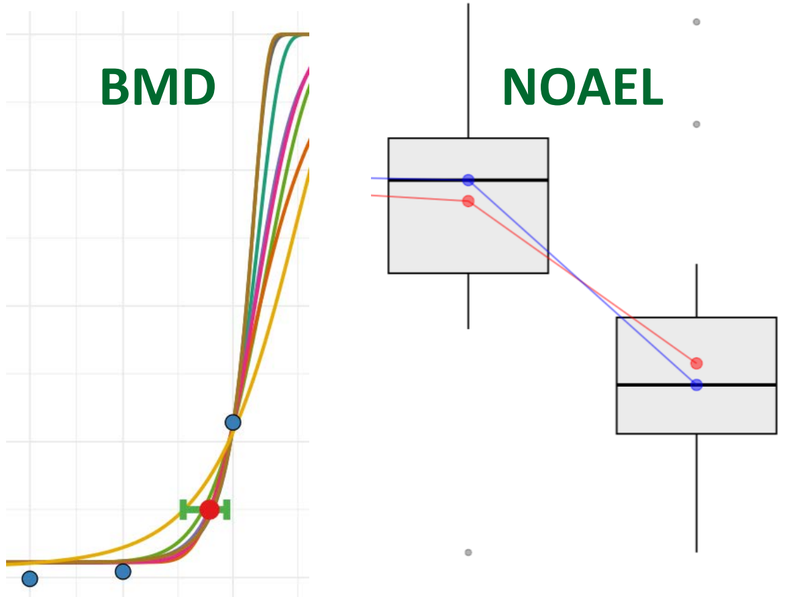
- What are your experiences running and understanding both BMDs and the EFSA Bayesian BMD tool?

- What steps are needed to develop a regulatory version of the EFSA BMD online tool that meets the needs of modelers and regulators?

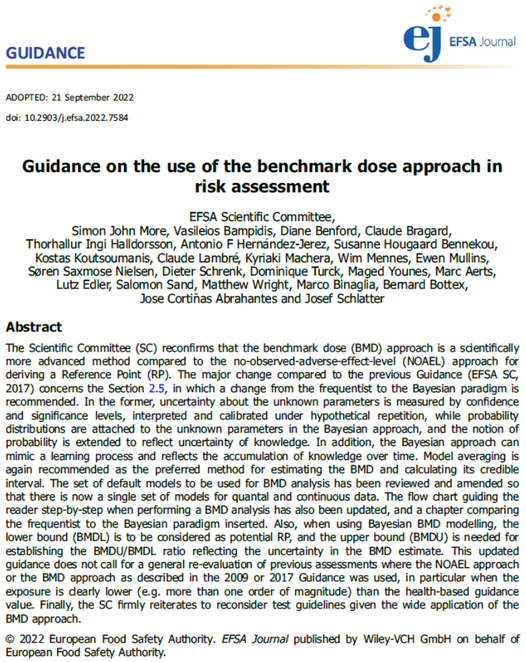
What are BMDs?



A type of dose response analysis that assesses the size response (BMR), and produces BMD_{10} values for risk assessment through a process similar to EC_x dose responses



Makes the full use of the data available when deriving the endpoint, representing complete scientific use of the data



GUIDANCE

EFSA Journal

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Guidance on the use of the benchmark dose approach in risk assessment

EFSA Scientific Committee,
Simon John More, Vasileios Bampidis, Diane Benford, Claude Bragard, Thorhallur Ingi Halldorsson, Antonio F Hernández-Jerez, Susanne Hougaard Bennekou, Kostas Koutsoumanis, Claude Lambré, Kyriaki Machera, Wim Mennes, Ewen Mullins, Søren Saxmose Nielsen, Dieter Schrenk, Dominique Turck, Maged Younes, Marc Aerts, Lutz Edler, Salomon Sand, Matthew Wright, Marco Binaglia, Bernard Bottex, Jose Cortiñas Abrahantes and Josef Schlatter

Abstract

The Scientific Committee (SC) reconfirms that the benchmark dose (BMD) approach is a scientifically more advanced method compared to the no-observed-adverse-effect-level (NOAEL) approach for deriving a Reference Point (RP). The major change compared to the previous Guidance (EFSA SC, 2017) concerns the Section 2.5, in which a change from the frequentist to the Bayesian paradigm is recommended. In the former, uncertainty about the unknown parameters is measured by confidence and significance levels, interpreted and calibrated under hypothetical repetition, while probability distributions are attached to the unknown parameters in the Bayesian approach, and the notion of probability is extended to reflect uncertainty of knowledge. In addition, the Bayesian approach can mimic a learning process and reflects the accumulation of knowledge over time. Model averaging is again recommended as the preferred method for estimating the BMD and calculating its credible interval. The set of default models to be used for BMD analysis has been reviewed and amended so that there is now a single set of models for quantal and continuous data. The flow chart guiding the reader step-by-step when performing a BMD analysis has also been updated, and a chapter comparing the frequentist to the Bayesian paradigm inserted. Also, when using Bayesian BMD modelling, the lower bound (BMDL) is to be considered as potential RP, and the upper bound (BMDU) is needed for establishing the BMDU/BMDL ratio reflecting the uncertainty in the BMD estimate. This updated guidance does not call for a general re-evaluation of previous assessments where the NOAEL approach or the BMD approach as described in the 2009 or 2017 Guidance was used, in particular when the exposure is clearly lower (e.g. more than one order of magnitude) than the health-based guidance value. Finally, the SC firmly reiterates to reconsider test guidelines given the wide application of the BMD approach.

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Recommendations are provided within EFSA 2022 guidance document

EFSA Scientific Committee, More SJ, Bampidis V, Benford D, Bragard C, Halldorsson TI, Hern´andez-Jerez AF, Bennekou SH, Koutsoumanis K, Lambr´e C, Machera K, Mennes W, Mullins E, Nielsen SS, Schrenk D, Turck D, Younes M, Aerts M, Edler L, Sand S, Wright M, Binaglia M, Bottex B, Corti ˜nas Abrahantes J and Schlatter J, 2022. Guidance on the use of the benchmark dose approach in risk assessment. EFSA Journal 2022;20(10):7584, 67 pp. https://doi.org/10.2903/j.efsa.2022.7584

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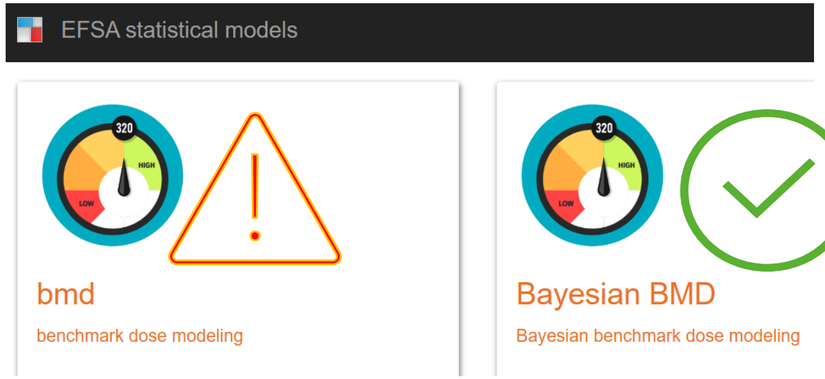
EFSA Bayesian BMD



A Bayesian based online tool for calculating BMD values available at: [EFSA statistical models](https://r4eu.efsa.europa.eu/) (https://r4eu.efsa.europa.eu/)

Uses the BMABMDR package to run the BMDs. The BMABMDR package version must be reported

Those with experience with R can also run BMABMDR outside of the EFSA tool to calculate BMDs

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Version control

Development is ongoing and is reflected with the frequent changes to versions and there is currently no regulatory version

Version	BMD_{10}
0.0.0.9063	x
0.0.0.9065	1.9x

Version	BMD_{10}
0.1.5	36.56
0.0.0.9082	30.67
0.0.0.9075	Version is corrupted
0.0.0.9071	36.57
0.0.0.9060	36.54

Knowing the version is important as different version can affect the BMD

Timeline of EFSA Versions

Version 1
2022-11-16
BMABMDR: v.0.0.0.9042
https://zenodo.org/records/7334435

Version 2
2023-02-16
BMABMDR: v.0.0.0.9057
https://zenodo.org/records/7646997
Incorrectly reported as using BMABMDR v.0.0.0.9042 and dated Nov 16, 2022

Version 3
2023-03-22
BMABMDR: v.0.0.0.9057
https://zenodo.org/records/7759037
Incorrectly reported as using BMABMDR v.0.0.0.9042 and dated Nov 16, 2022

Version 4
2023-05-30
BMABMDR: v.0.0.0.9060
https://zenodo.org/records/7986184
Incorrectly dated Nov 16, 2022

Version 5
2023-12-06
BMABMDR: v.0.0.0.9071
https://zenodo.org/records/10275881
Current version incorrectly links here

Version 6
2024-01-17
BMABMDR: v.0.0.0.9075
https://zenodo.org/records/10523648
This BMABMDR version is corrupted and cannot be installed

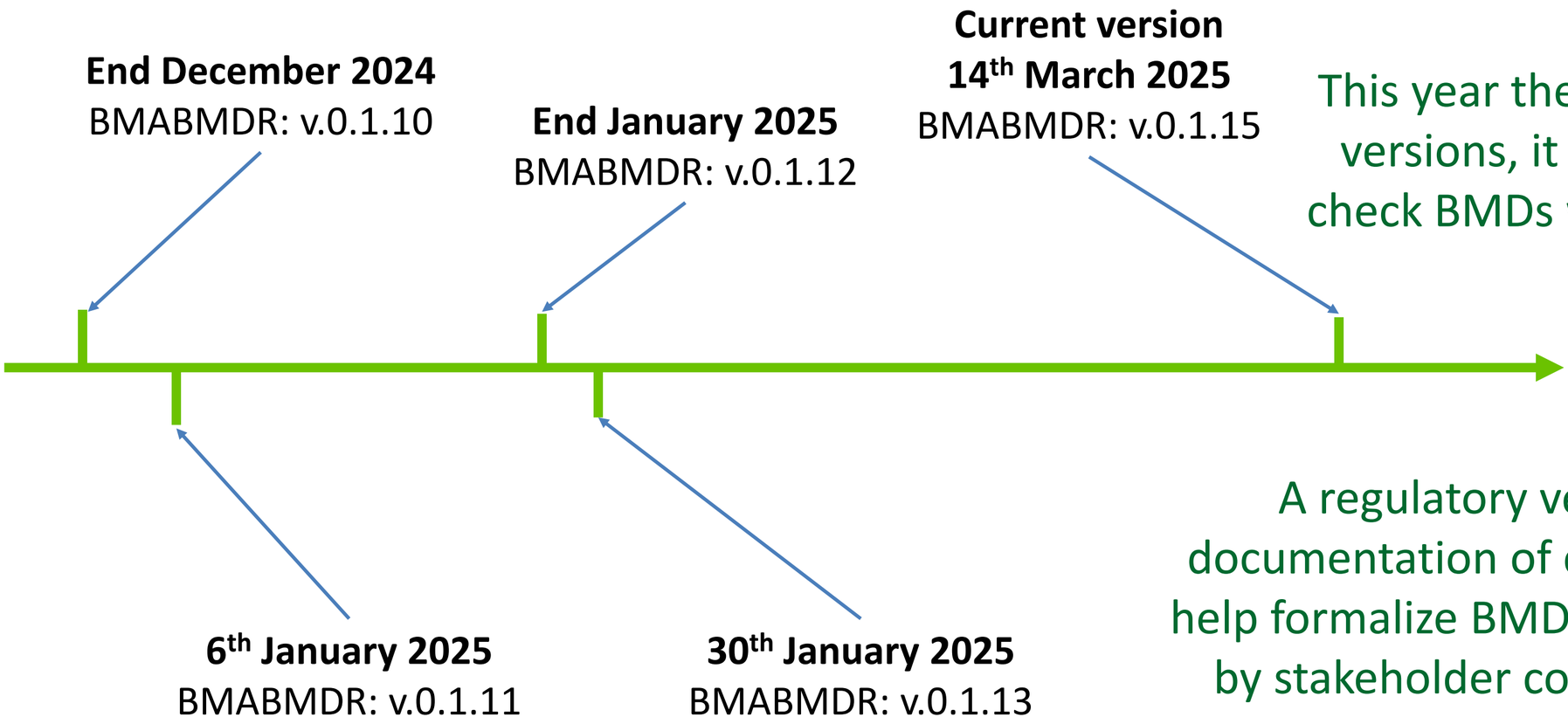
Early 2024
BMABMDR: v.0.0.0.9082
Not available on Zenodo

Mid 2024
BMABMDR: v0.1.5
Not archived on Zenodo and it is not known when it was updated

Current Version
March 2024
BMABMDR: v0.1.1.15
Current version is not archived on Zenodo

January 2025
BMABMDR: v.0.1.10
BMABMDR: v.0.1.11
BMABMDR: v.0.1.12
BMABMDR: v.0.1.13
Not available on Zenodo

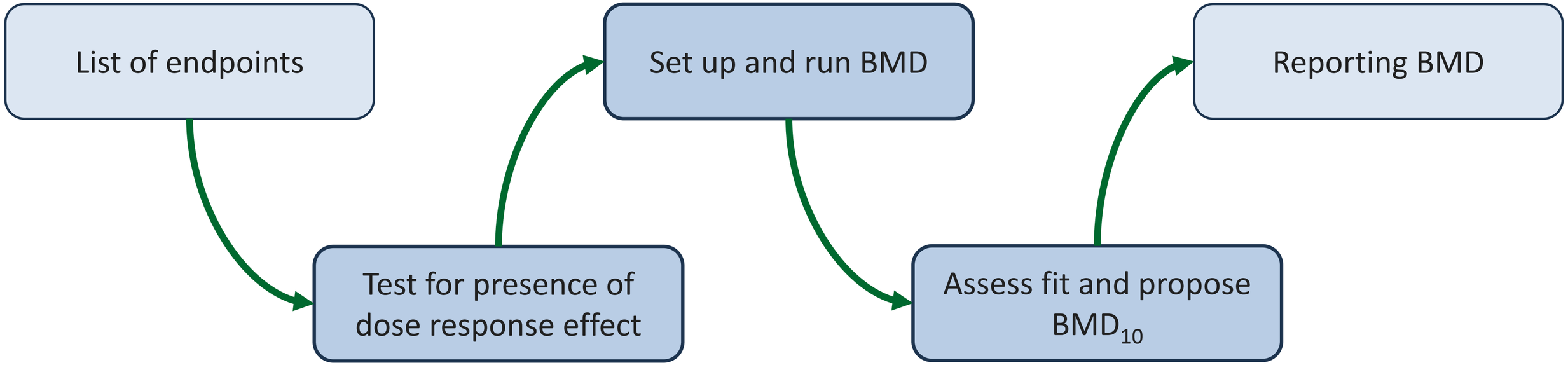
Timeline of EFSA Versions



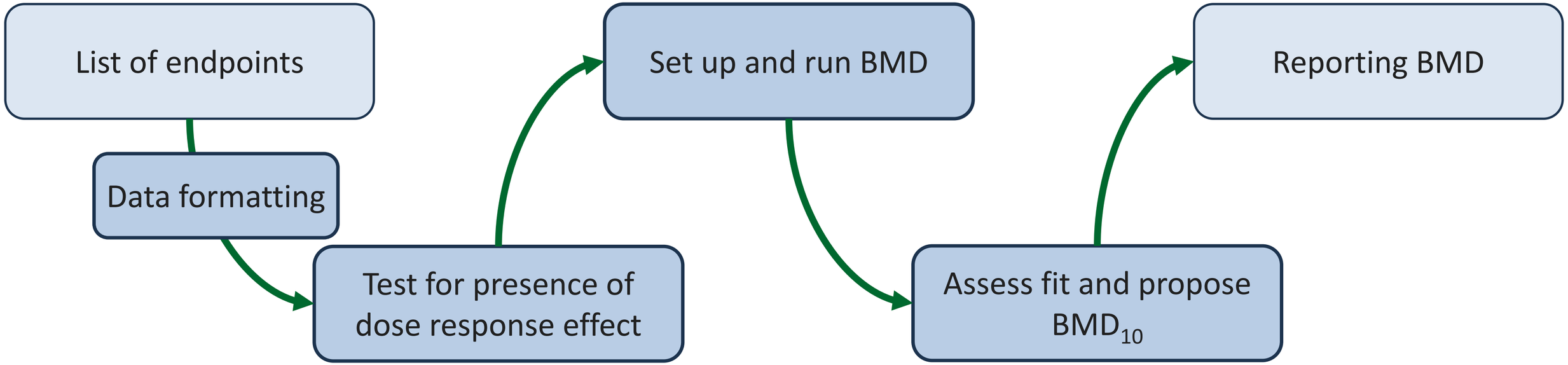
This year there have been five versions, it is not feasible to check BMDs with every version

A regulatory version and documentation of changes would help formalize BMDs, further aided by stakeholder communication

Statistical steps in BMD

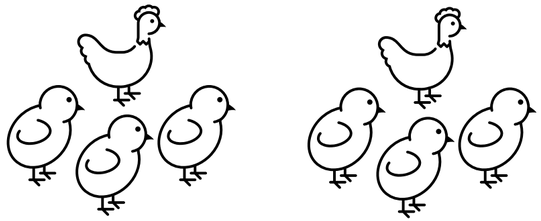


Statistical steps in BMD



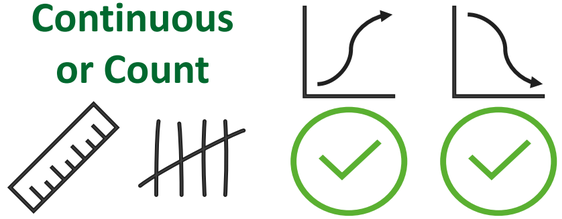
Data Formatting

Litter 1 **Litter 2**



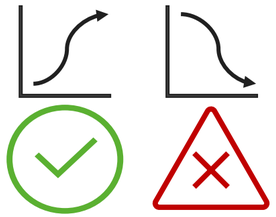
Summary data can be used, except for litter effects.
Litter effects must be individual data and require a separate column with litter number

Continuous or Count



Quantal

1010
1010



Quantal (binomial) data must be transformed to exhibit a positive dose-response relationship

Continuous data: Eggshell thickness
Count data: Eggs laid per hen
Quantal data: Viable embryos of eggs set

No zeros or negatives allowed in the data

- Zeros must be transformed to be marginally non-zero
- Convert negatives to be a ratio
  e.g. negative weight gain becomes a proportion of initial weight

Presence of dose response

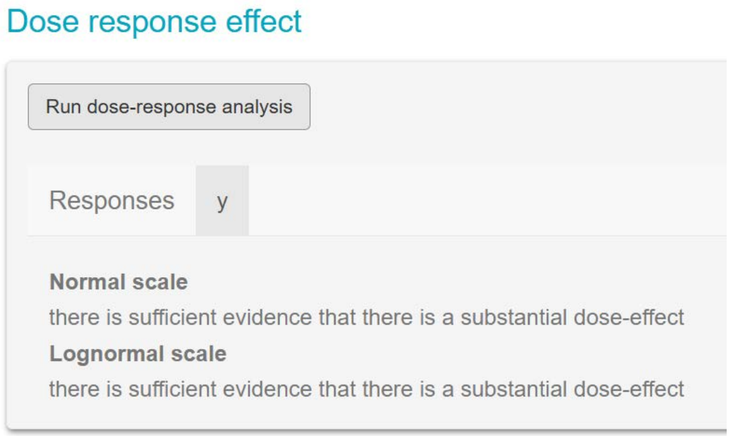
Continuous or Count

Normal scale **Log-normal scale**

Quantal

Quantal test

Needs to be present in at least one of normal or log-normal scales for continuous or count data, and must be present for quantal data



The online tool shows this as dose response effect for both normal and log-normal scales

```
# A tibble: 6 × 4
  group1 group2 p.value direction
   <dbl>  <dbl>   <dbl> <chr>
1      1      0   0.702 less
2      2      0   0.609 less
3      2      1   0.383 less
4      3      0   0.280 less
5      3      1   0.111 less
6      3      2   0.172 less
```

Can also be done frequentist approach e.g. pairwise t-tests

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Setting up the BMD calculator

BMD_5

Default is 0.05 not 0.10

Make sure it is set to calculate a BMD_{10} the tool defaults to a Critical Effect Size (CES, i.e. the Benchmark Response (BMR)) of 0.05/5% (i.e. BMD_5)

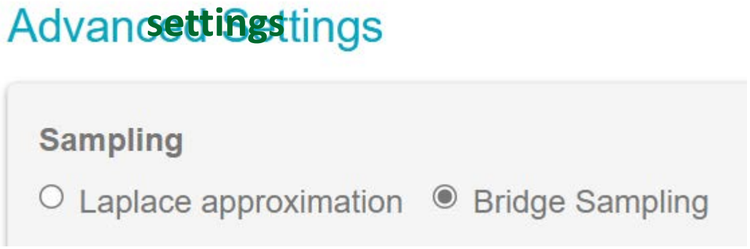
BMD_{10}

Continuous or Count

Normal scale **Log-normal scale**

Select the models in line with the correct normal and log-normal distributions for continuous and count data

N.B. Click on Advanced Settings to see the settings



Default in tool is Bridge Sampling not Laplace

Laplace approximation is faster than Bridge Sampling, and is considered the default approach (EFSA 2022), but Bridge Sampling is an option for estimation failures

EFSA Scientific Committee, More SJ, Bampidis V, Benford D, Bragard C, Halldorsson TI, Hern´andez-Jerez AF, Bennekou SH, Koutsoumanis K, Lambr´e C, Machera K, Mennes W, Mullins E, Nielsen SS, Schrenk D, Turck D, Younes M, Aerts M, Edler L, Sand S, Wright M, Binaglia M, Bottex B, Corti ˜nas Abrahantes J and Schlatter J, 2022. Guidance on the use of the benchmark dose approach in risk assessment. EFSA Journal 2022;20(10):7584, 67 pp. https://doi.org/10.2903/j.efsa.2022.7584

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Assess fit and propose BMD

Statistical and goodness of fit tests: Example

Fitted Models

Full Laplace

Model Averaged BMD

Download ▼

	Model	Type	BMDL	BMD	BMDU
default	Model Averaged	LP	15	20	30

Showing 1 to 1 of 1 entries Previous 1 Next

: None of the tests (Bartlett, Levene and Shapiro-Wilk) have been rejected

: At least one test has been rejected

This BMD appears to fail due to rejected tests

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Statistical and goodness of fit tests: Example

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Showing 1 to 1 of 1 entries Previous 1 Next

: None of the tests (Bartlett, Levene and Shapiro-Wilk) have been rejected

: At least one test has been rejected

This BMD appears to fail due to rejected tests

Check for constant variance coefficient of variation

Bartlett test

Original scale

distributional assumption of constant variance is met, Bartlett test p-value is 0.7324

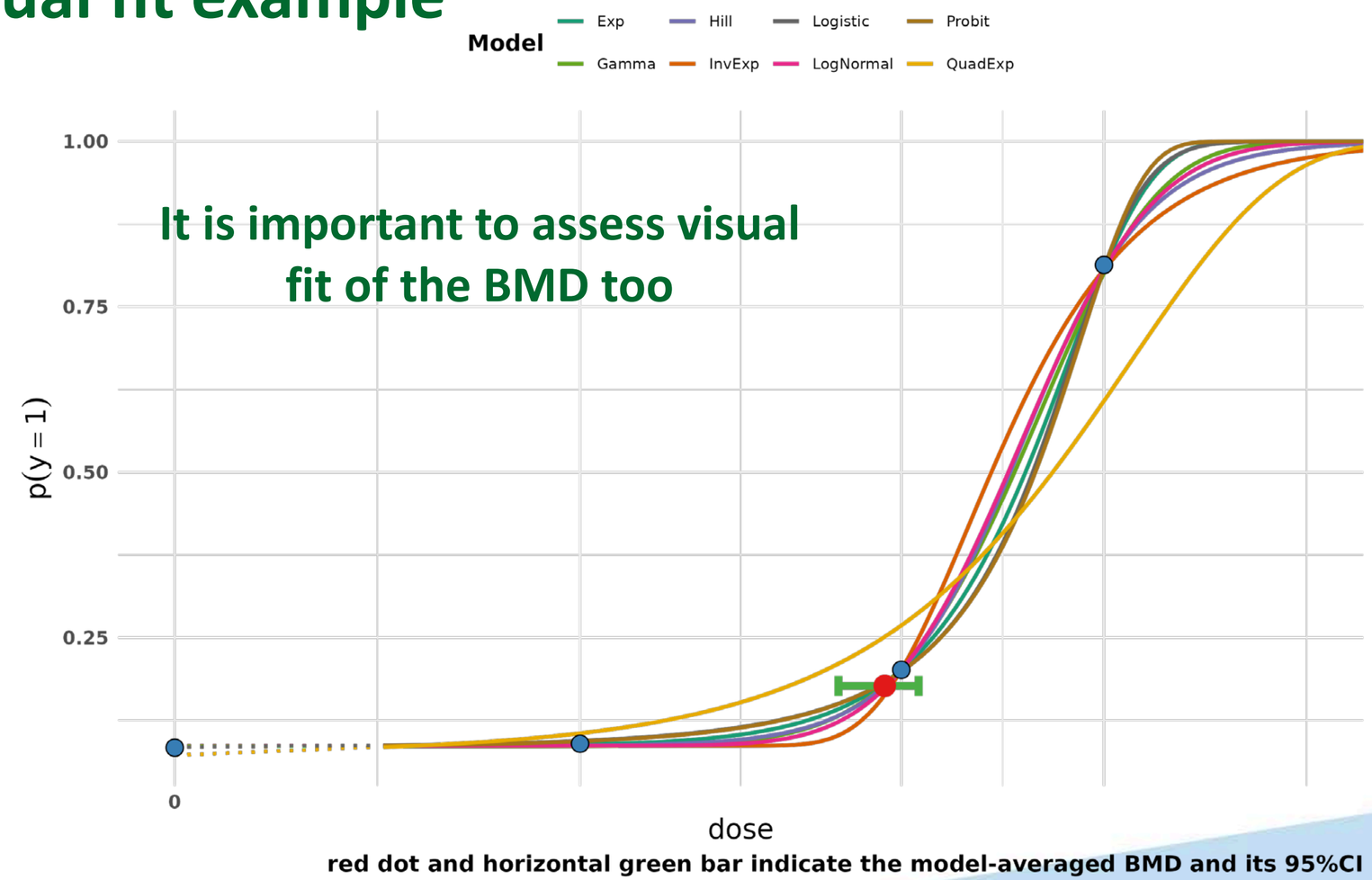
Log-scale

distributional assumption of constant variance (on log-scale) is not met, Bartlett test p-value is 0.0000

However, only the log-normal scale rejects the test, the normal scale passes and therefore the **BMD is reliable**

Assess fit and propose BMD

Visual fit example



red dot and horizontal green bar indicate the model-averaged BMD and its 95%CI

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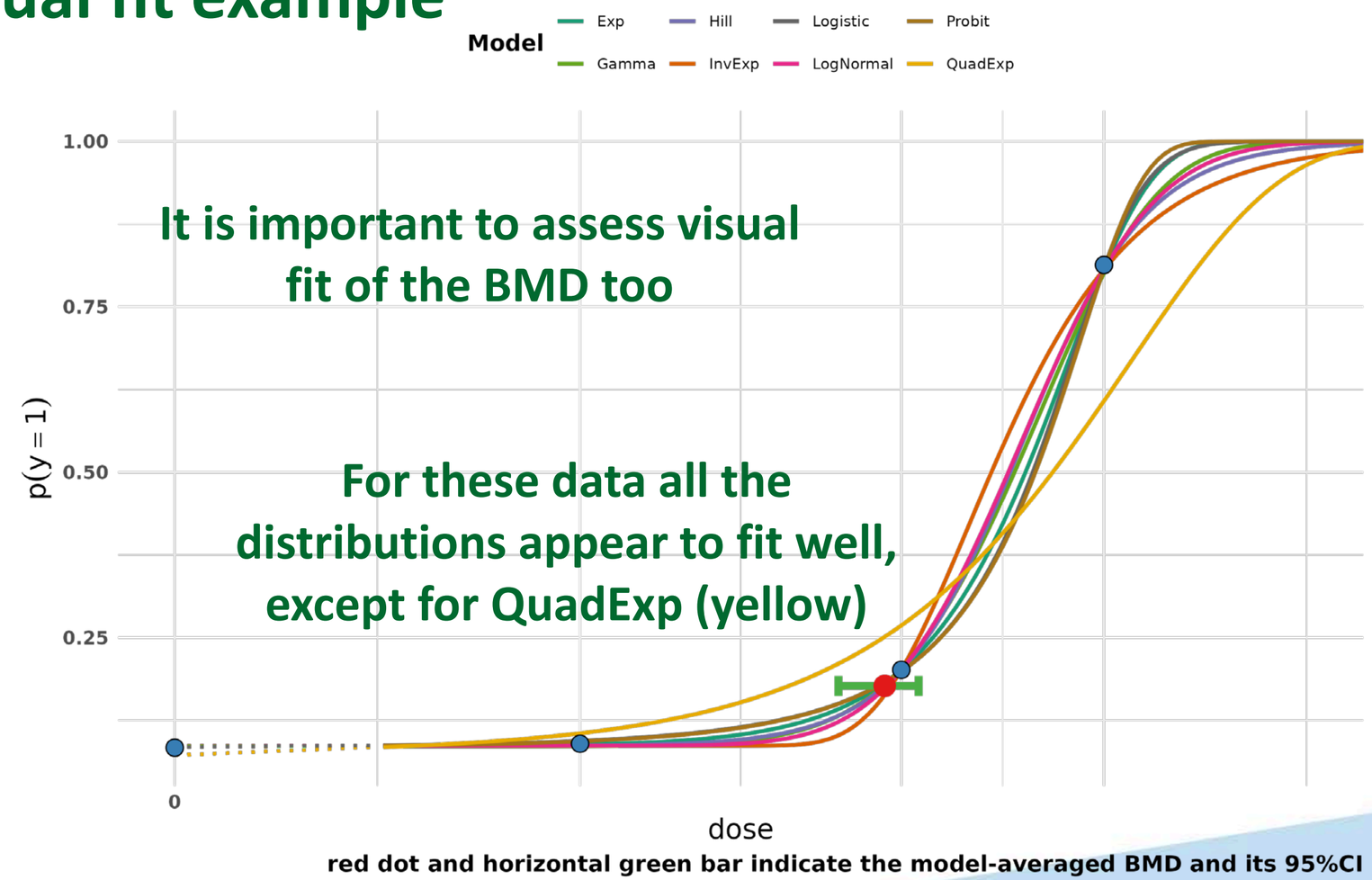
Assess fit and propose BMD

Visual fit example



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Assess fit and propose BMD

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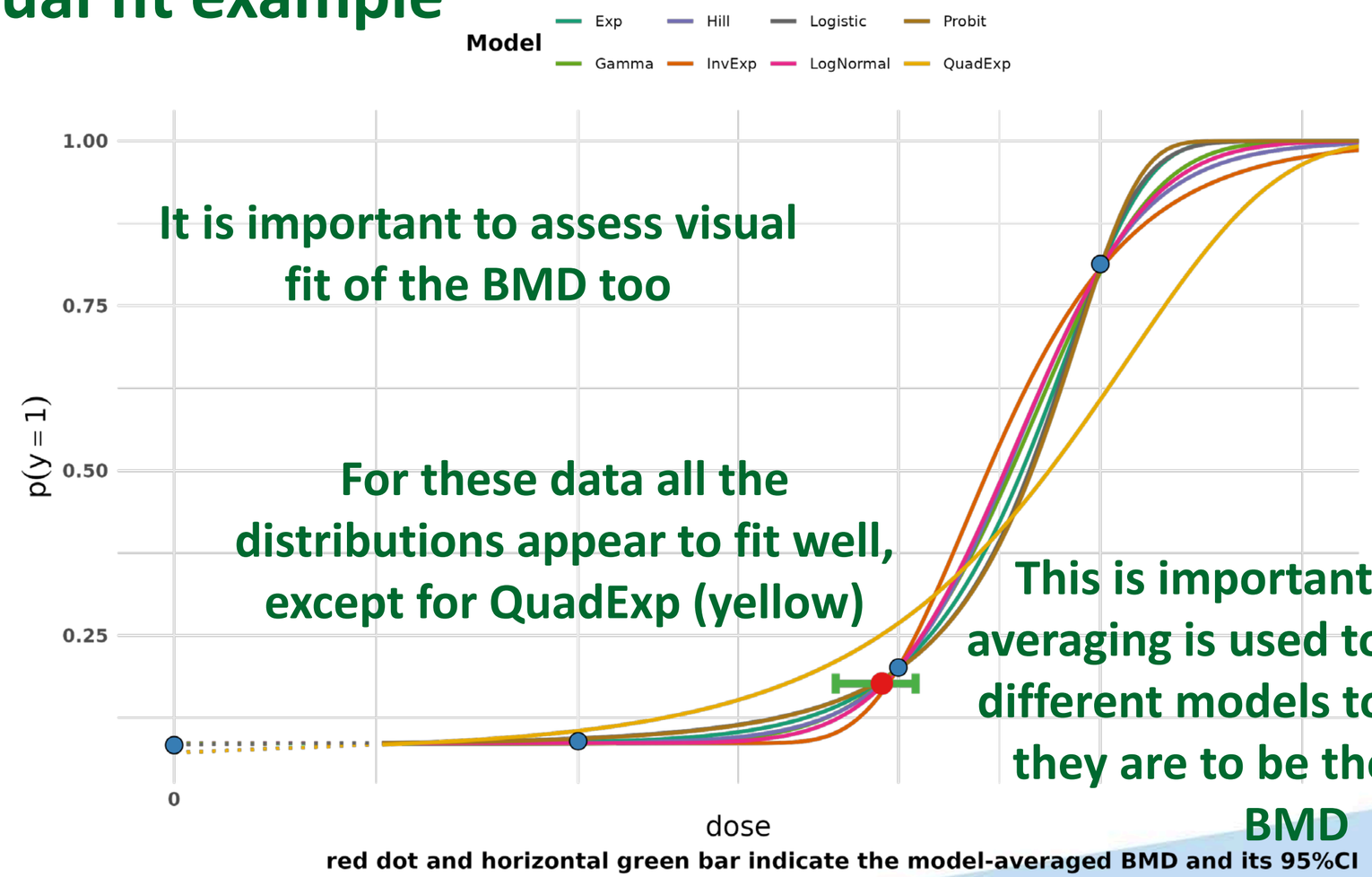

It is important to assess visual fit of the BMD too

For these data all the distributions appear to fit well, except for QuadExp (yellow)

This is important as model averaging is used to weight the different models to how likely they are to be the relevant BMD

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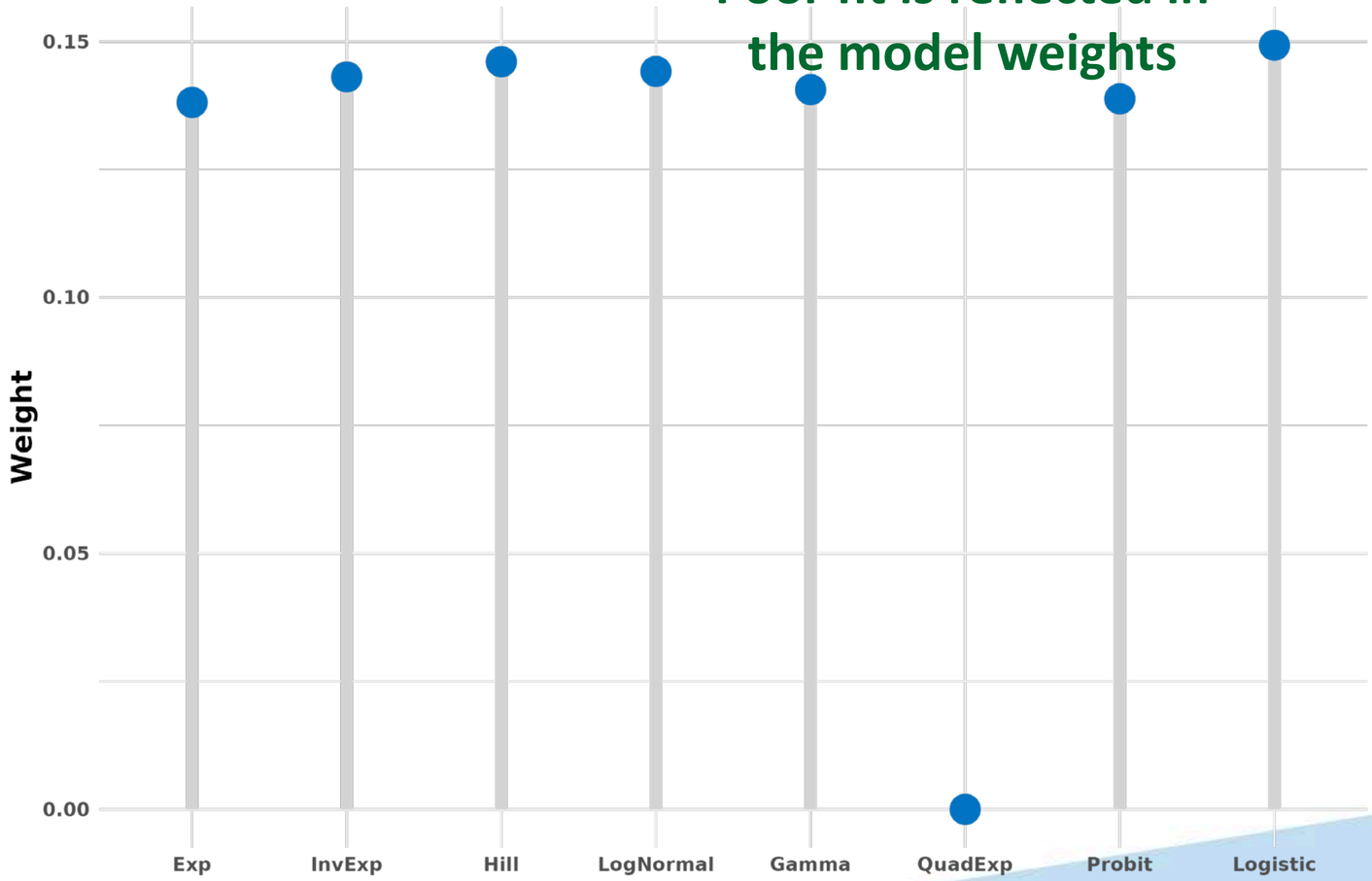
Assess fit and propose BMD

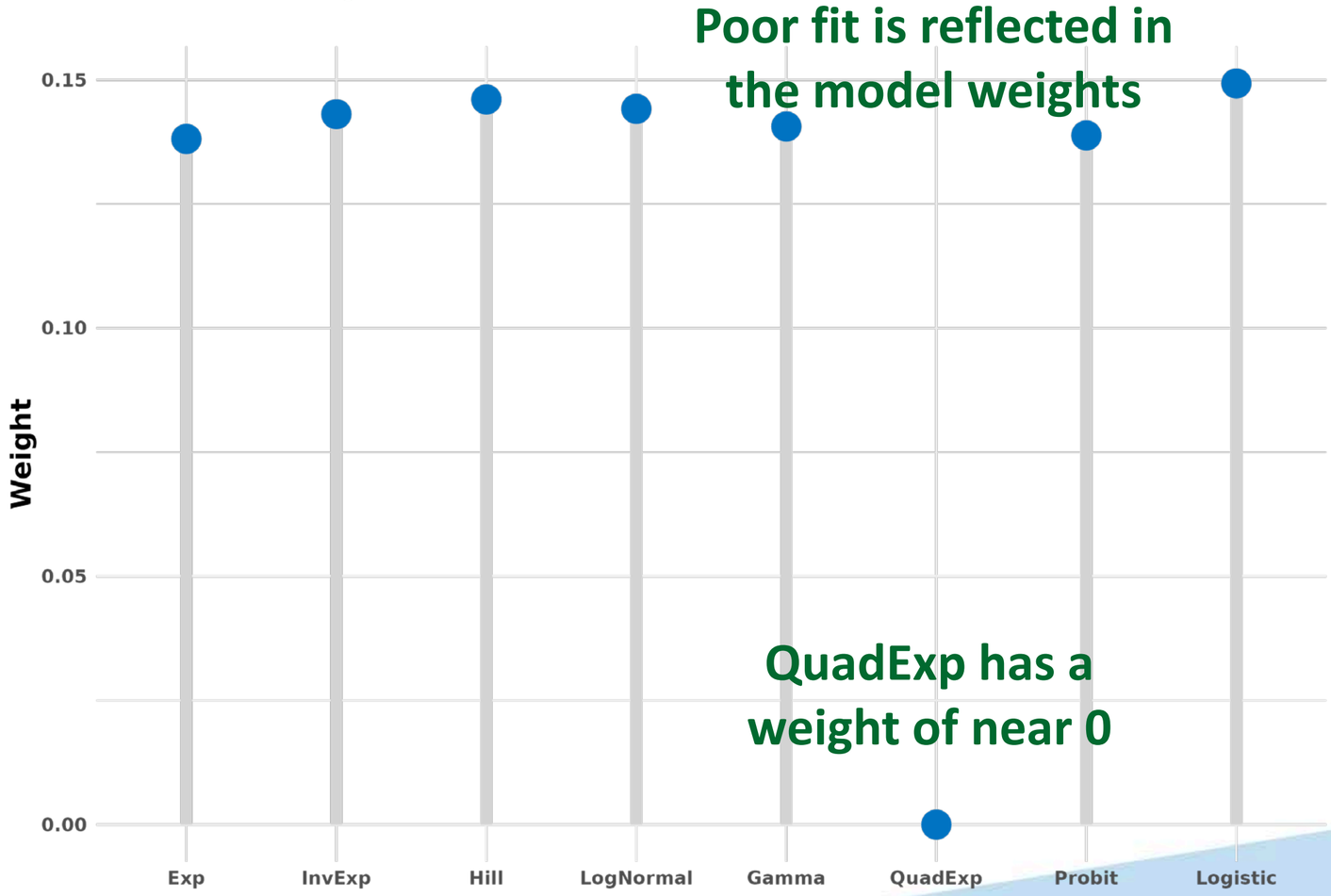
Visual fit example

Poor fit is reflected in the model weights



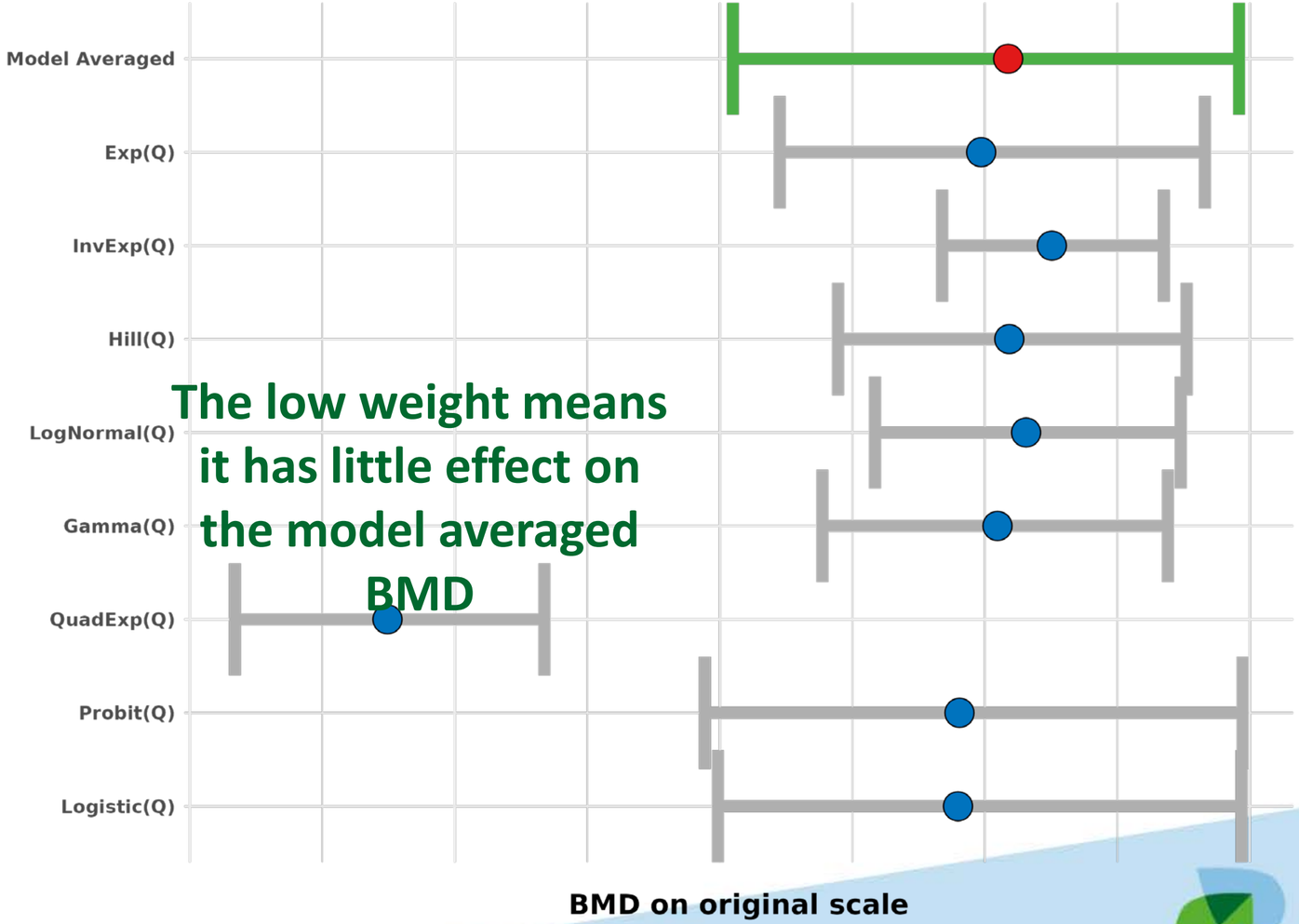
Assess fit and propose BMD

Visual fit example



Assess fit and propose BMD

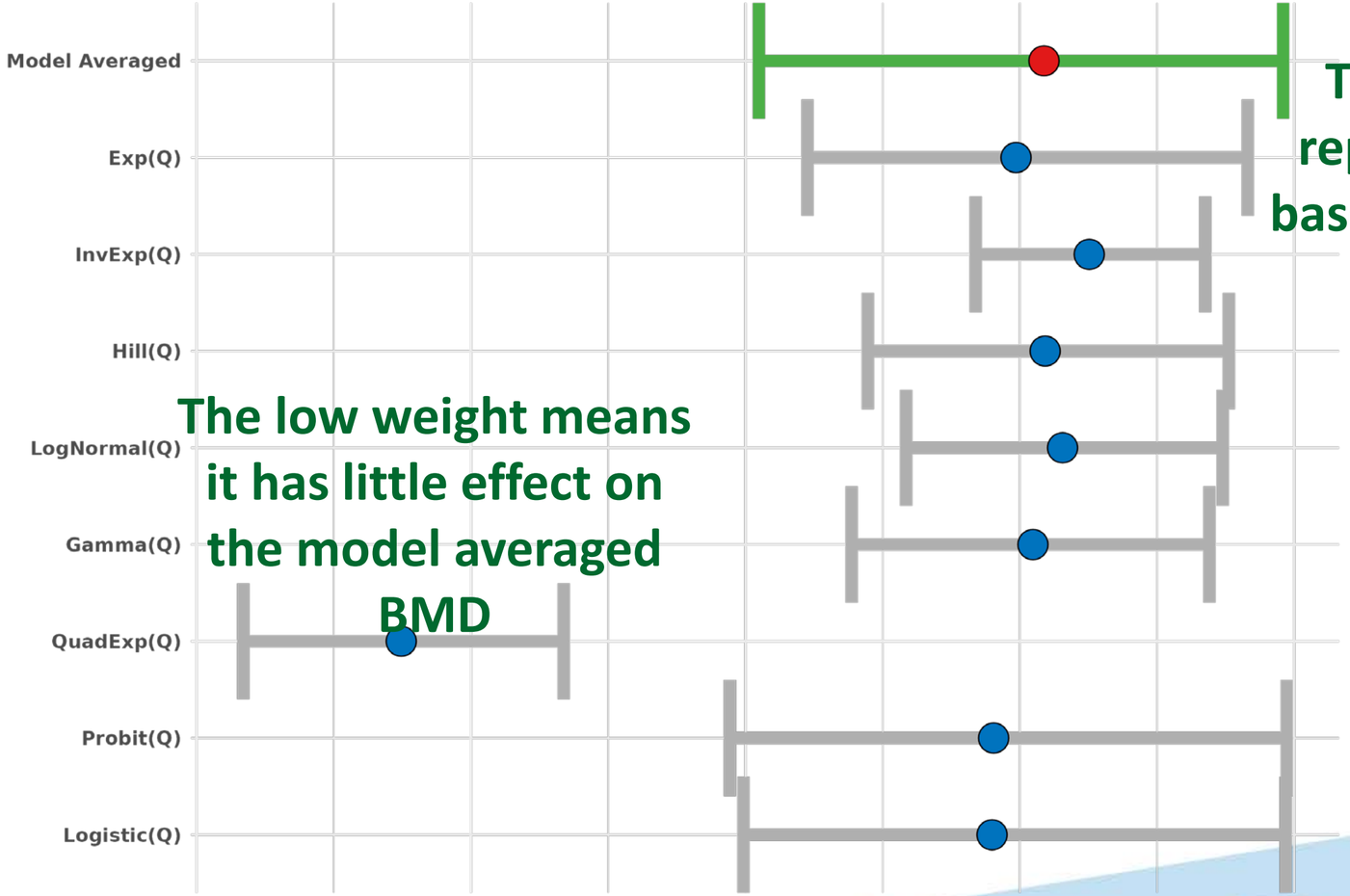
Visual fit example



The low weight means it has little effect on the model averaged BMD

Assess fit and propose BMD

Visual fit example

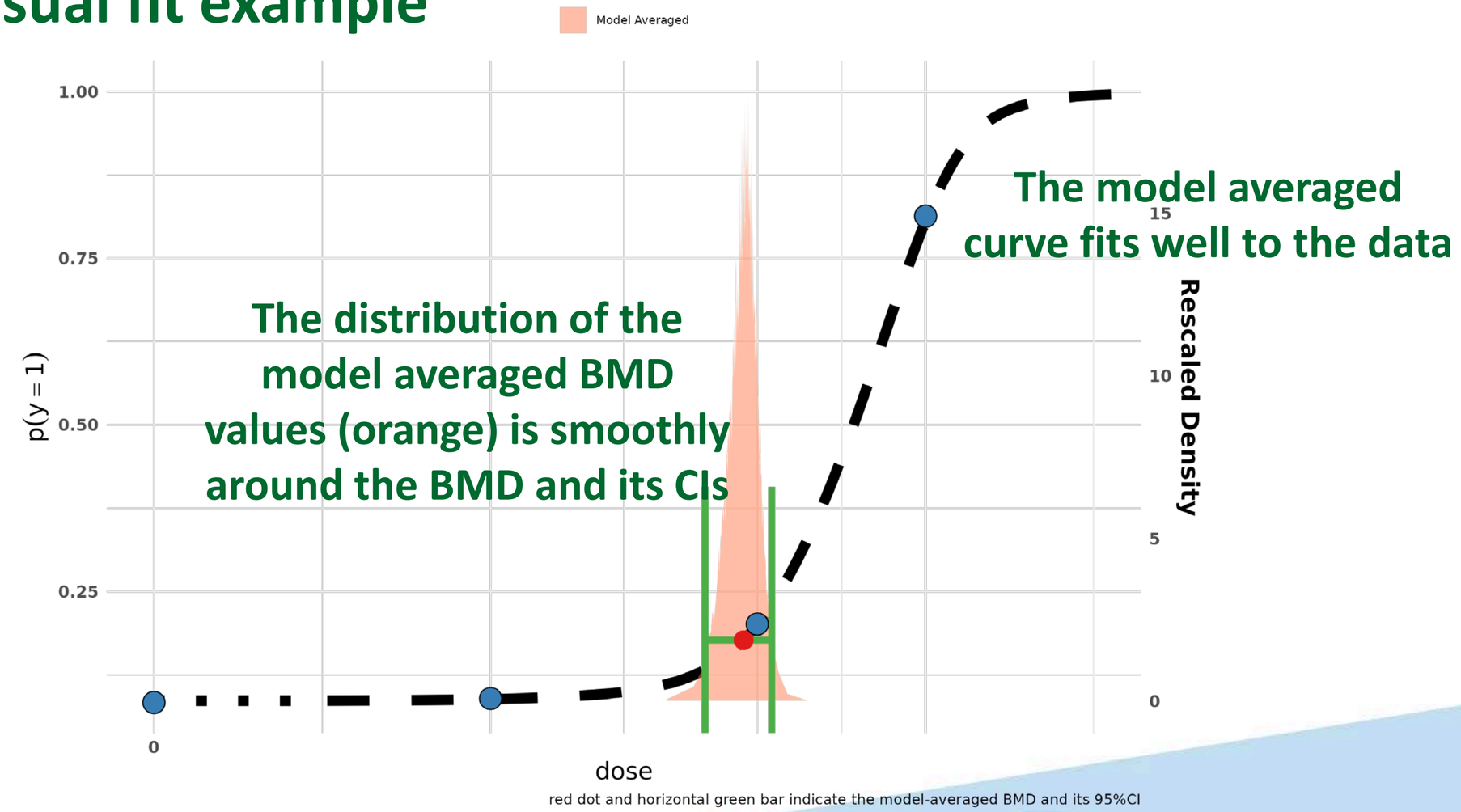


The model averaged BMD represents the most reliable based on the different weights

The low weight means it has little effect on the model averaged BMD

Assess fit and propose BMD

Visual fit example



The distribution of the model averaged BMD values (orange) is smoothly around the BMD and its CIs

The model averaged curve fits well to the data

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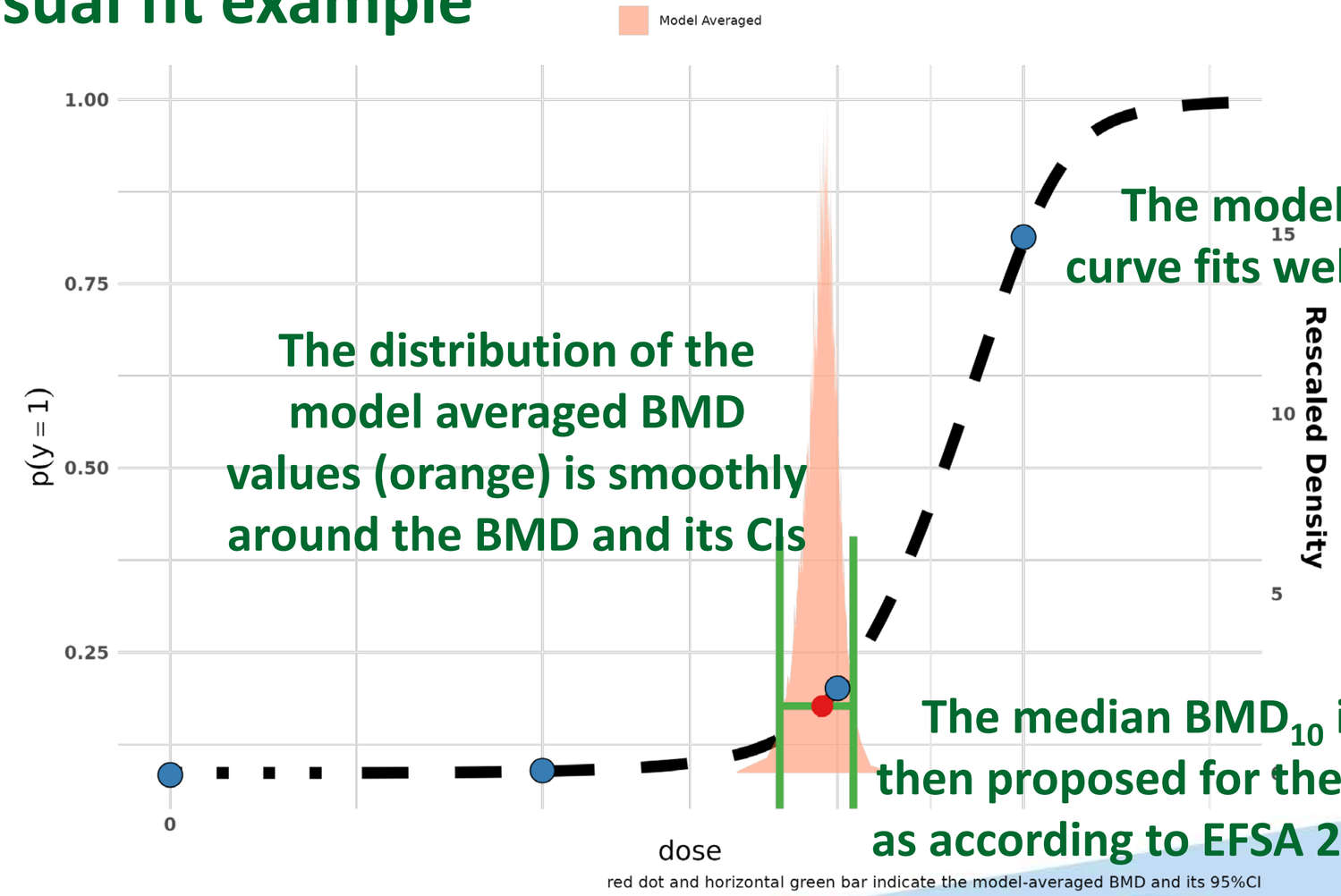
Assess fit and propose BMD

Visual fit example



The model averaged curve fits well to the data

The distribution of the model averaged BMD values (orange) is smoothly around the BMD and its CIs

The median BMD_{10} is then proposed for the RA as according to EFSA 2022

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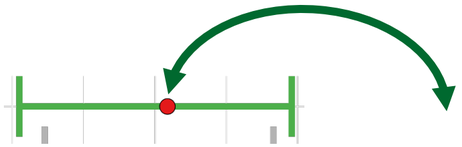
BMD unacceptability criteria

Criteria in EFSA 2022 based of EPA criteria

Goodness of Fit

Best fitting model fits sufficiently well (Bayes factor is 1.29e+00).

None of the candidate models
fit the data sufficiently well



LNZD

LNZD/BMD > 10
The BMD is 10 times lower than
the lowest non-zero dose (LNZD)

BMD/BMDL > 20
The lower credible interval (CI) is
20 times lower than the BMD

BMDU/BMDL > 50
The lower CI is 50 times lower than
the upper CI of the BMD

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Reality Check

- BMDs use the entire data set and therefore represent a scientific improvement upon NOAELs statistically when BMDs are appropriate
- Statistics used throughout the BMD process, and need to reflect back on endpoints with biological expertise
- Considerations and limitations when performing BMDs, especially with the current online tool:
  - Version control remains an issue as no standard regulatory version exists
  - There is no agreed standard approach when a BMD cannot be calculated
  - The median BMD is the relevant endpoint risk assessments
- Communication is key and has been positive so far, and will be the way to improve the tool and establish what is the regulatory version

THANK YOU

Tom Sinclair
thomas.sinclair@basf.com

Internal

Key Discussion Points

- What are your experiences running and understanding both BMDs and the EFSA Bayesian BMD tool?

- What steps are needed to develop a regulatory version of the EFSA BMD online tool that meets the needs of modelers and regulators?

Internal