- Workshop on the update of the BMD guidance
- Brussels 15 - 16 February 2023

EUROPEAN FOOD SAFETY AUTHORITY

EFSA'S USE OF THE BMD APPROACH: THE PAST (2005 - 2022)

Josef Schlatter

EUROPEAN FOOD SAFETY AUTHORITY

THE ORIGIN OF THE USE OF THE BMD APPROACH IN EFSA

2005

The EFSA Journal (2005) 282, 1-31

Opinion of the Scientific Committee on a request from EFSA related to

A Harmonised Approach for Risk Assessment of

Substances Which are both Genotoxic and Carcinogenic

(Request No EFSA-Q-2004-020)

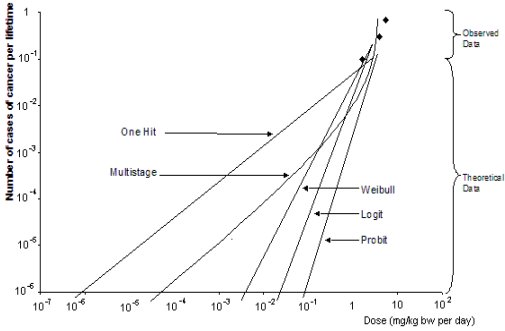
(ADOPTED ON 18 OCTOBER 2005)

- Up to 2005, risk assessment of substances that are both genotoxic and carcinogenic followed the ALARA principle
  → Risk management, **no basis for setting priorities**

- Non-thresholded MOA assumed

i.e. there is no dose without "appreciable" risk

→ Conceptually, there is **no NOAEL**
→ **ADI approach not applicable**



- Low-dose extrapolation?

Math. modeling reveal outcomes differing in orders of magnitude !!!
→ SC had serious reservations

THE ORIGIN OF THE USE OF THE BMD APPROACH IN EFSA

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(Request No EFSA-Q-2004-020)

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The SC recommends using :

- the margin of exposure (MOE) approach
- **the benchmark dose (BMD) approach to obtain the MOE**
  i.e. mathematical modelling within the observed range of experimental animal data to obtain the $BMDL_{10}$
  (estimate of the lowest dose which is 95% certain to cause no more that a 10% cancer incidence)

$$\textbf{MOE} = \frac{\text{BMDL10}}{\text{human exposure dose}}$$

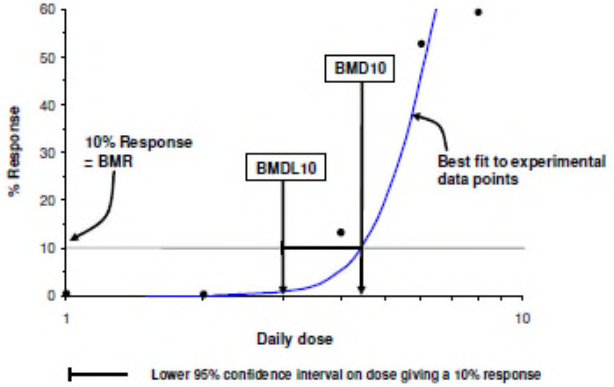
- …for substances not deliberately added to foods
  → in EFSA, the BMD approach initially mostly used for unavoidable contaminants and for quantal data

THE FIRST APPLICATIONS

…The Scientific Committee is currently of the opinion that the use of the BMDL, calculated for a BMR of 10% ($BMDL_{10}$), is an appropriate reference point for substances that are **both genotoxic and carcinogenic**. Such a value is the lowest statistically significant increased incidence that can be measured in most studies, and would **normally require little or no extrapolation outside the observed experimental data**.

- $BMDL_{10}$ represents a small but measurable response

  BMD software was available on the internet, developed by US EPA in 2004 (BMDS)



…The whole BMD approach as such will be subject to further work by the EFSA Scientific Committee.

The first EFSA guidance document 2009

THE FIRST EFSA BMD GUIDANCE DOCUMENT

efsa European Food Safety Authority **2009**

The EFSA Journal (2009) 1150, 1-72

SCIENTIFIC OPINION

Use of the benchmark dose approach in risk assessment[1]

Guidance of the Scientific Committee

(Question No EFSA-Q-2005-232)

Adopted on 26 May 2009

PANEL MEMBERS

Susan Barlow, Andrew Chesson, John D. Collins, Albert Flynn, Anthony Hardy, Klaus-Dieter Jany, Ada Knaap, Harry Kuiper, John-Christian Larsen, David Lovell[2], Pierre Le Neindre, Jan Schans, Josef Schlatter, Vittorio Silano, Staffan Skerfving, Philippe Vannier.

SUMMARY

Considering the need for transparent and scientifically justifiable approaches to be used when risks are assessed by the Scientific Committee and the Scientific Panels of EFSA, the Scientific Committee was requested by EFSA to assess the existing information on the utility of the benchmark dose (BMD) approach, as an alternative to the traditionally used NOAEL approach, and to make recommendations on whether EFSA should use the BMD approach and under which circumstances this use would be appropriate. The Scientific Committee was also asked to provide some guidance on how to use the BMD approach for analysing dose-response data from experimental studies, and to look at the possible application of this approach to data from observational epidemiological studies. Finally, the Scientific Committee was asked to advise on whether the selection of appropriate uncertainty factors are needed when using the BMD approach for deriving the Reference Point.

[1] For citation purposes: Guidance of the Scientific Committee on a request from EFSA on the use of the benchmark dose approach in risk assessment. *The EFSA Journal* (2009) 1150, 1-72

[2] External expert of the EFSA Scientific Committee

1. Assess the existing information on the utility of the benchmark dose (BMD) approach, as an alternative to the traditionally used NOAEL approach
   → *BMD approach is a scientifically more advanced method to the NOAEL approach for deriving a Reference Point, since it makes extended use of available dose-response data and it provides a* ***quantification of the uncertainties*** *in the dose-response data*
2. Provide recommendations on whether EFSA should use the BMD approach and under which circumstances this use would be appropriate
   → *BMD approach is* ***applicable to all chemicals in food****, irrespective of their category or origin, e.g. pesticides, additives or contaminants*
3. Advise on whether the selection of appropriate uncertainty factors are needed when using the BMD approach for deriving the Reference Point
   → *default values for uncertainty factors currently applied remain appropriate and there is* ***no need for any additional UF***
4. Introduction to the BMD approach and provide guidance on how to use it

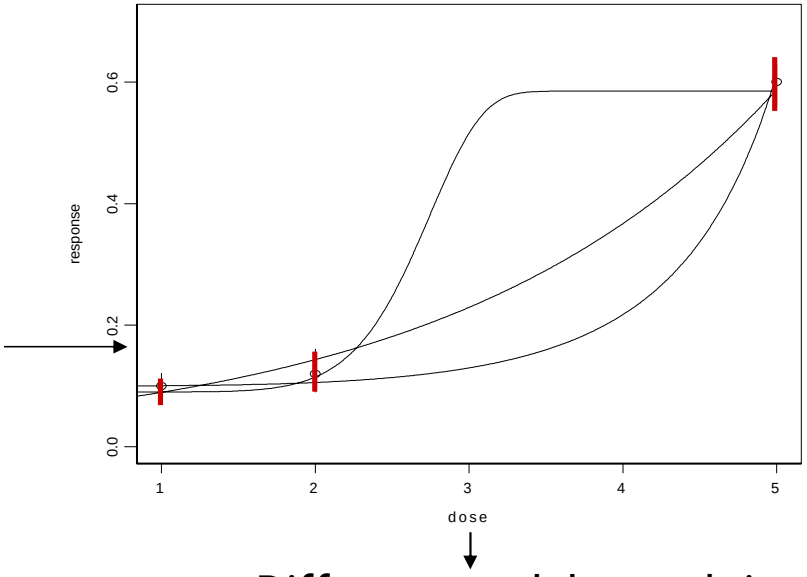
BMD APPROACH VS NOAEL APPROACH

- The NOAEL approach aims at finding the highest experimental dose for which no adverse health effects can be (statistically) detected using the predefined (i.e. tested) doses
  → The NOAEL is therefore not necessarily a 'no adverse effect' dose but a dose where effects were not observable by statistical testing
  → critically dependent on the choice of dose intervals made and the number of subjects at the chosen doses
- The BMD approach uses the same experimental data but, instead of focussing on the predefined doses, it aims at finding a dose corresponding to a predefined response, the benchmark response (BMR)
  → uses all the dose-response data
- The confidence interval for the BMD accounts for the statistical uncertainty in the estimate of the BMD
- Limited number of doses is often examined.
  →This implies model uncertainty. Different models compatible with the data may result in different BMDLs

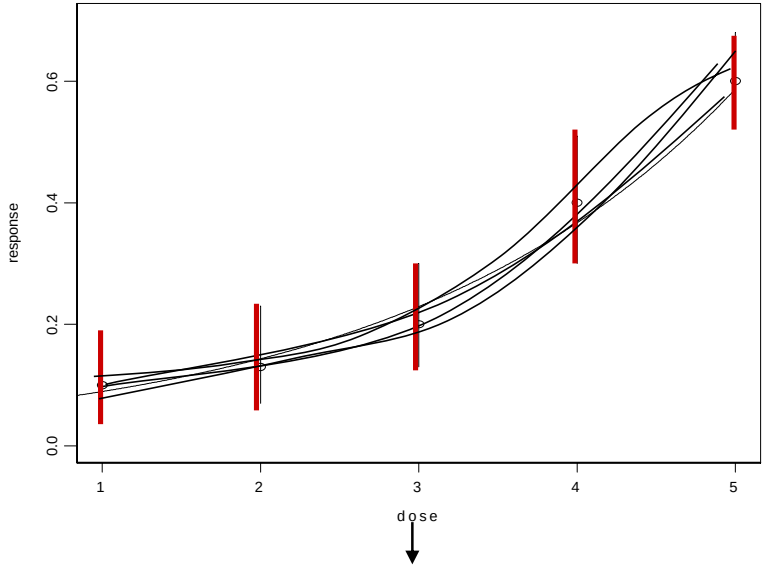
PROBLEMS WITH UNINFORMATIVE DATA

2. Not all doses are tested → *model uncertainty*

BMR



Different models result in *different* BMD(L)s



Different models result in *similar* BMD(L)s

- the ranges of BMDL values obtained may be wide
- Criteria to judge the adequacy of the dose-response data on the basis of the range of BMDL values obtained were not established

UNINFORMATIVE DATA

Two situations that indicate that the data are not informative enough to derive an RP:

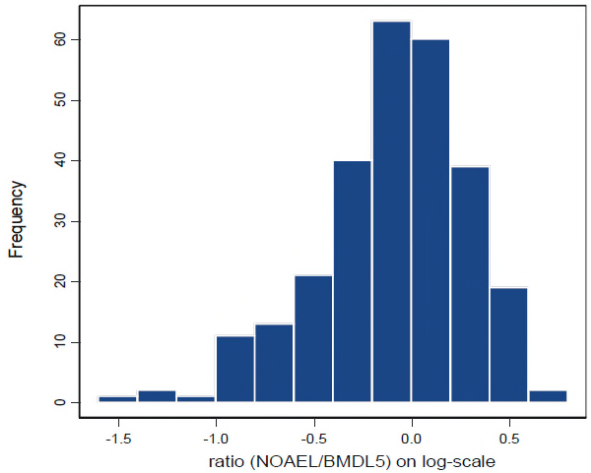
- Ratios BMDU/BDML (or BMD/BMDL) for the individual models are very large
- BMDLs among models are very different (data with high model uncertainty)

As a general rule dose response data should not result in a range of BMDL values that substantially exceeds **one order of magnitude** or are **far below** (or far above) the **observed dose range**

The BMD approach not only provides a RP, it also evaluates the quality of the data and the uncertainty in the estimated RP

→Weaker methods cannot solve weaknesses in data !

BMD APPROACH VS NOAEL APPROACH



Histogram of 395 NOAEL/$BMDL_{05}$ ratios (log_{10}-scale) for the same dose-response data in rat and mouse NTP studies

- BMDL has, on average, the same level of protection as NOAEL
- The traditional uncertainty factors can therefore be applied

BUILDING EXPERTISE ON THE USE OF BMD MODELLING


efsa
European Food Safety Authority

2010

EN-113

TECHNICAL REPORT

Use of BMDS and PROAST software packages by EFSA Scientific Panels and Units for applying the Benchmark Dose (BMD) approach in risk assessment[1]

European Food Safety Authority[2, 3]

- EFSA workshop in December 2010 in Parma to train EFSA Panel experts and EFSA staff
- Application of the BMD approach to **quantal and continuous** data from animal studies

Introduction to two BMD software packages:

- ► BMDS - U.S. Environmental Protection Agency (U.S. EPA)
- ► PROAST - National Institute for Public Health and the Environment, Netherlands (RIVM).

consider all models that are compatible with the data, i.e. those with an acceptable fit

- ➢ not aiming at finding the single statistically best estimate of the BMD
- ➢ Use all plausible values that are compatible with the data

⟹ The lowest BMDL is often used as reference point

THE BMD APPROACH (SUMMARY)

- The BMD approach is applicable to **all toxicological effects**.
- It makes use of all of the dose-response data to estimate the shape of the overall dose-response relationship for a particular endpoint.
- The BMD is a dose level, derived from the estimated dose-response curve, associated with a **specified change in response**, the Benchmark Response (**BMR**).
- The BMDL is the BMD´s lower confidence bound, and this value is normally used as the RP
- The BMD approach provides a formal quantitative evaluation of data quality

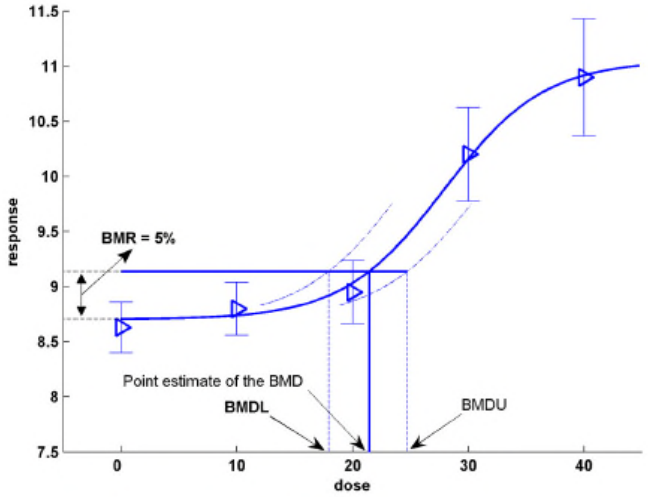


Figure 1: Key concepts for the BMD approach, illustrated by using hypothetical continuous data.

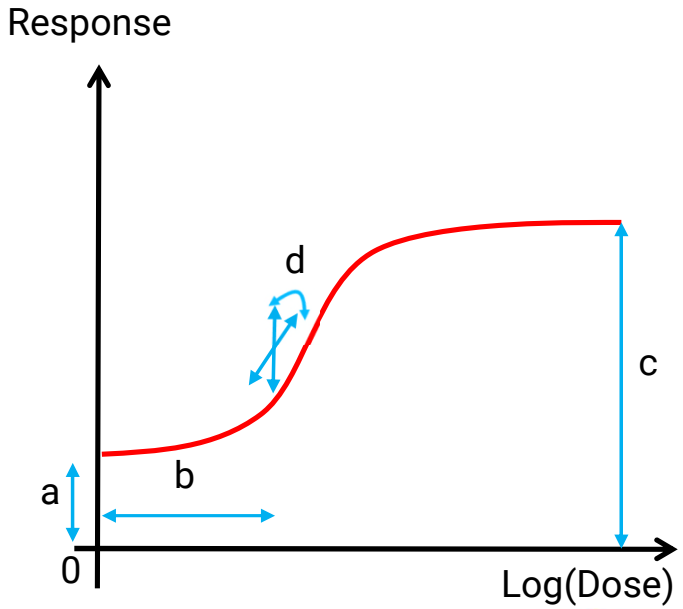
1. Specification of type of dose-response data (quantal or continuous)
2. Specification of a (biologically relevant) BMR
3. Selection of candidate dose-response model(s)
4. Identification of acceptable models
5. Estimating the BMD, and establishing the BMDL as the RP

DOSE-RESPONSE ASSESSMENT

1. For each potentially critical endpoint, apply the proposed set of models
2. Determine the lowest BMDL for each endpoint from the range of acceptable models
3. Determine the lowest BMDL from all these endpoints, which will then be the overall BMDL

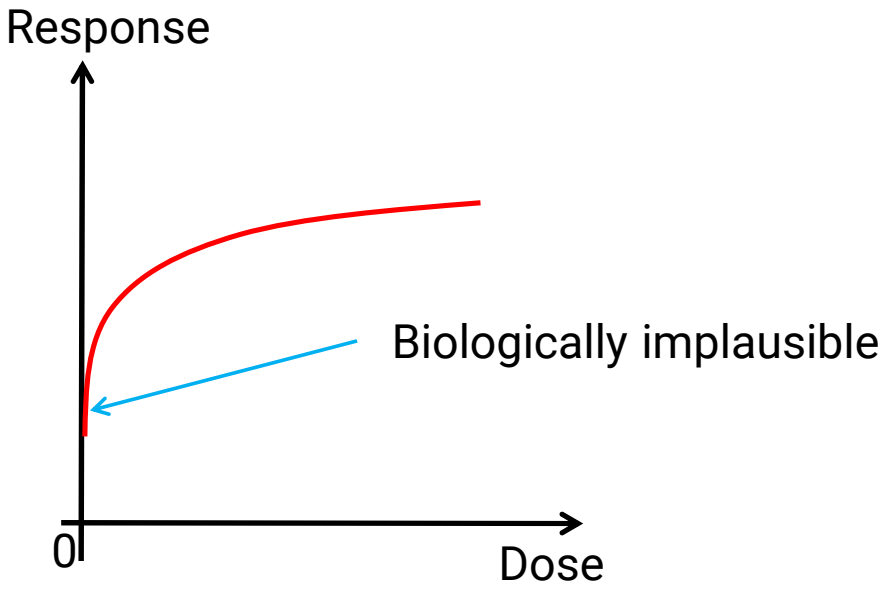
- **Use of the lowest BMDL**
  → until more advanced methods, such as "**model averaging**" have been fully developed and validated.
  Model averaging accounts for model uncertainty
  → preferable to the single model approach

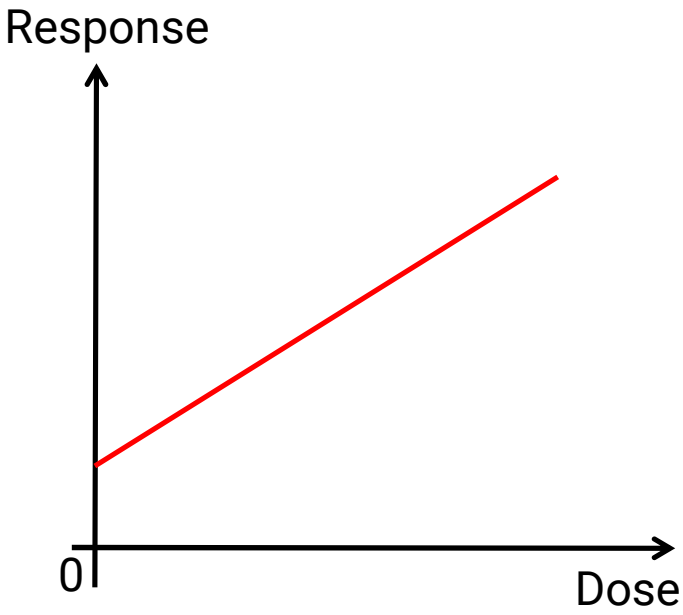
- To avoid the models having undesirable properties, certain **constraints** are imposed on the model parameters previously interpreted as:
  a: background
  b: potency
  c: maximum response (**Quantal** models maximum response is considered to be 1)
  d: steepness/shape



RESTRICTING PARAMETER D

- Model should not have ***infinite slope*** at dose **0**





- Thus parameter d should be **greater** than **1**

EXAMPLE: 3-MCPD MODELLING

- Diverging results especially when dealing with **poor data**

Table 1. Comparison of the results obtained from the BMD modelling of the incidence of renal tubular cell hyperplasia in rats caused by 3-monochloropropane-1,2-diol by EFSA (EFSA CONTAM Panel, 2016) and JECFA (FAO/WHO, 2016).

Study	Sex	EFSA $BMDL_{10}$-BMD_{10} (mg/kg bw per day)	JECFA $BMDL_{10}$-BMD_{10} (mg/kg bw per day)	JECFA $BMDL_{10}$-BMD_{10} model averaging (mg/kg bw per day)	EFSA $BMDL_{10}$-$BMDU_{10}$ model averaging (mg/kg bw per day)
Cho et al (2008)	M	0.077-0.54	0.87-1.21	0.89-1.29	0.20-1.95 (no covariate - 2017) 0.33-1.88 (sex covariate - 2020)
	F	14-27	14.4-23.5	20.4-28.0	20-36 (no covariate - 2017) 13.5-56.2 (sex covariate - 2020)

Table D.2: Male kidney hyperplasia

Incidence data		
Dose (mg/kg bw per day)	**N**	**Effect**
0	50	1
2	50	11
8.3	50	21
29.5	50	36

- choice of the BMR
- Use of different models
- Constraining the steepness parameter "d"

- **EFSA: selected the unconstrained model with the lowest BMDL**
- **JECFA selected the constrained log-logistic model.** *→unrealistically low $BMDL_{10}$ for all unconstrained models*

THE UPDATED EFSA BMD GUIDANCE DOCUMENT

GUIDANCE **2017** EFSA Journal

ADOPTED: 17 November 2016

doi: 10.2903/j.efsa.2017.4658

Update: use of the benchmark dose approach in risk assessment

EFSA Scientific Committee,
Anthony Hardy, Diane Benford, Thorhallur Halldorsson, Michael John Jeger, Katrine Helle Knutsen, Simon More, Alicja Mortensen, Hanspeter Naegeli, Hubert Noteborn, Colin Ockleford, Antonia Ricci, Guido Rychen, Vittorio Silano, Roland Solecki, Dominique Turck, Marc Aerts, Laurent Bodin, Allen Davis, Lutz Edler, Ursula Gundert-Remy, Salomon Sand, Wout Slob, Bernard Bottex, Jose Cortiñas Abrahantes, Daniele Court Marques, George Kass and Josef R. Schlatter

Abstract

The Scientific Committee (SC) reconfirms that the benchmark dose (BMD) approach is a scientifically more advanced method compared to the NOAEL approach for deriving a Reference Point (RP). Most of the modifications made to the SC guidance of 2009 concern the section providing guidance on how to apply the BMD approach. Model averaging is recommended as the preferred method for calculating the BMD confidence interval, while acknowledging that the respective tools are still under development and may not be easily accessible to all. Therefore, selecting or rejecting models is still considered as a suboptimal alternative. The set of default models to be used for BMD analysis has been reviewed, and the Akaike information criterion (AIC) has been introduced instead of the log-likelihood to characterise the goodness of fit of different mathematical models to a dose-response data set. A flowchart has also been inserted in this update to guide the reader step-by-step when performing a BMD analysis, as well as a chapter on the distributional part of dose-response models and a template for reporting a BMD analysis in a complete and transparent manner. Finally, it is recommended to always report the BMD confidence interval rather than the value of the BMD. The lower bound (BMDL) is needed as a potential RP, and the upper bound (BMDU) is needed for establishing the BMDU/BMDL per 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 SC guidance was used, in particular when the exposure is clearly smaller (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 expected wide application of the BMD approach.

Keywords: benchmark dose, BMD, BMDL, benchmark response, NOAEL, dose-response modelling, BMD software

Requestor: EFSA

Question number: EFSA-Q-2014-00747

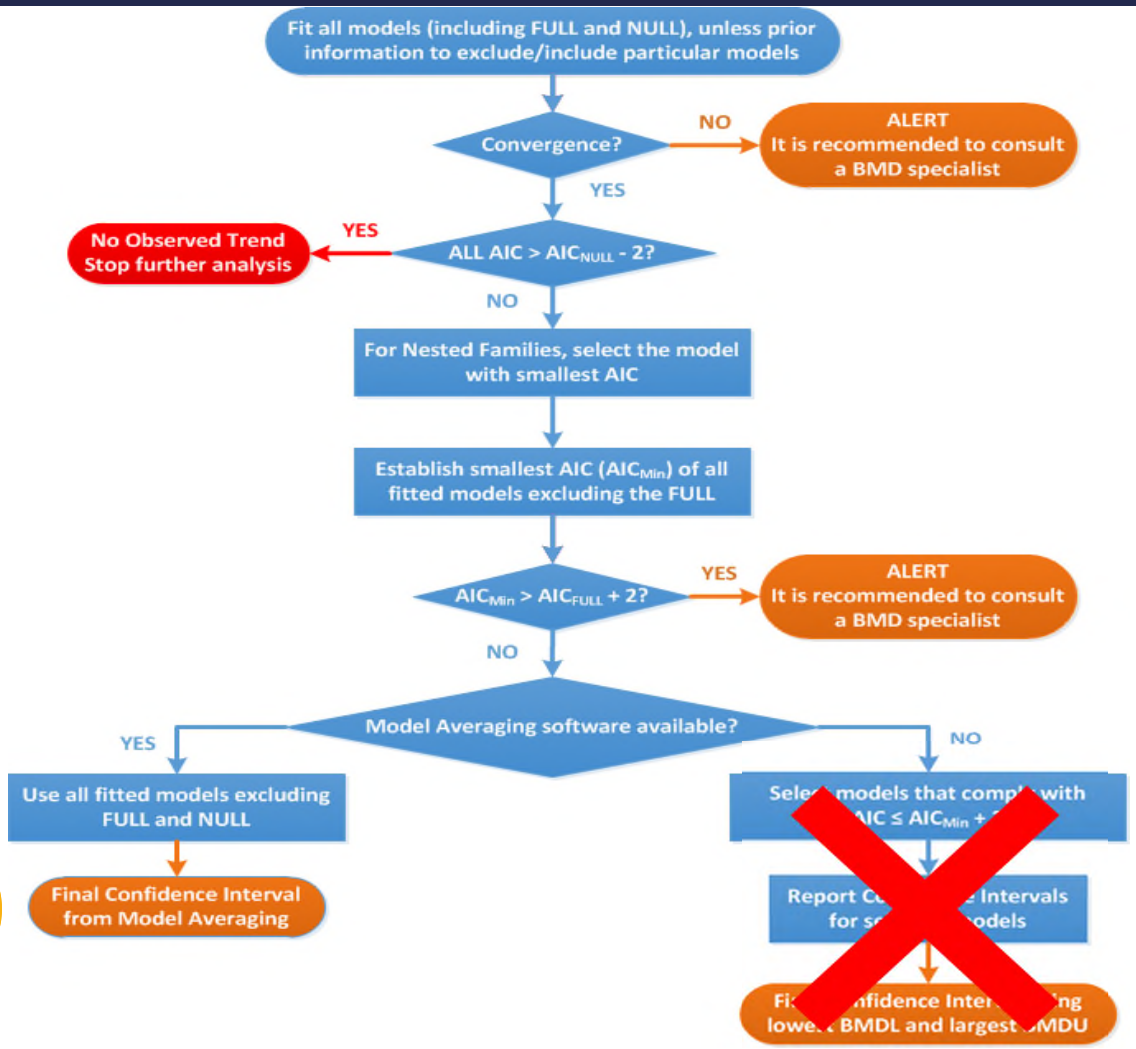
Correspondence: sc.secretariat@efsa.europa.eu

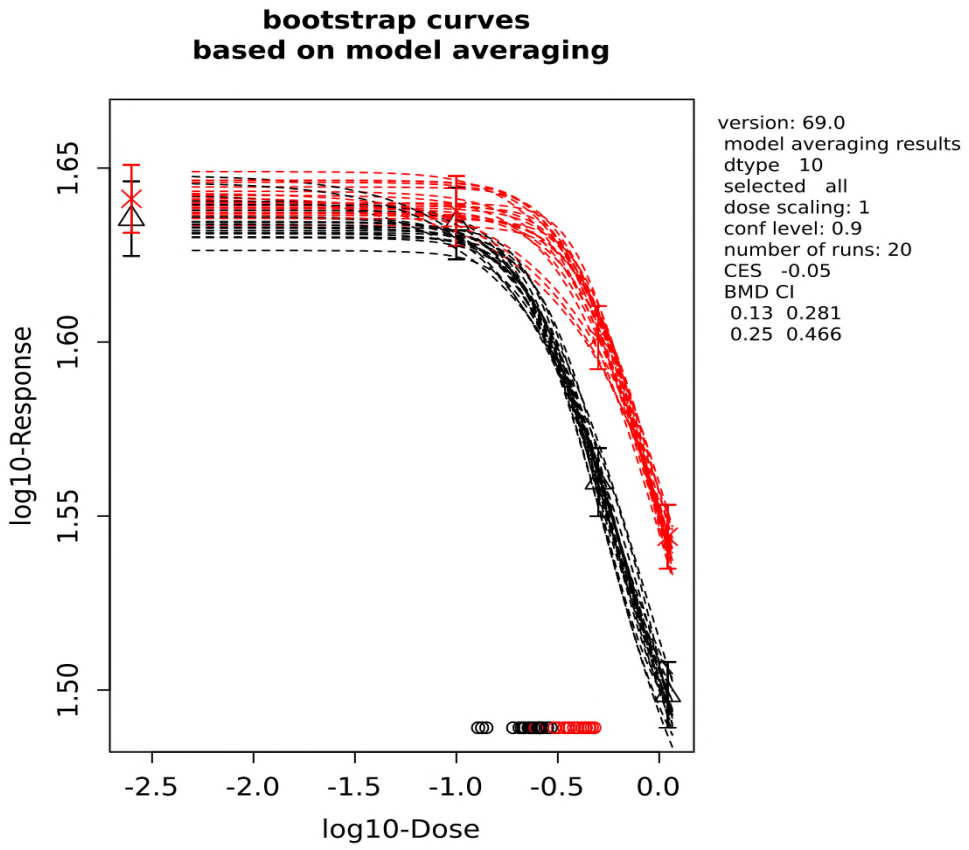
Takes account of the experience accumulated in BMD analysis over the last 7 years

Most of the modifications made concern the section providing guidance on how to apply the BMD approach in practice

- Selecting or rejecting models is considered as suboptimal.
  →***Model averaging is recommended*** *as the preferred method for calculating the BMD confidence interval, acknowledging that the respective tools are still under development and may not be easily accessible to all*
  → individual model results are combined using weights, with higher weights for models that fit the data better
- The Akaike information criterion (AIC) has been introduced instead of the likelihood ratio test to assess the goodness of fit of the models
  (to compare the fit of different models, the AIC is a convenient criterion as it directly integrates the log-likelihood and the number of model parameters in one single value)
- A flowchart has been inserted to guide the reader step-by-step
- Chapter on the distributional part of dose–response models
- Template for reporting a BMD analysis

THE FLOW-CHART



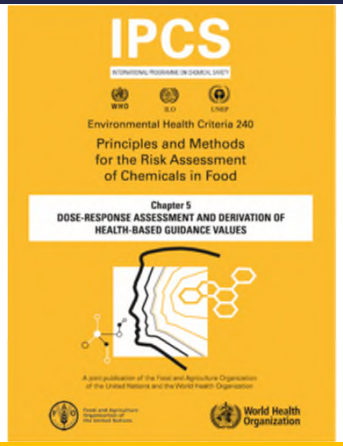


SOME ‘PROBLEMS’ REMAINED

- **Choice of a BMR that is biologically relevant**
- **Constraing model parameters?**
  - **Reduces** the number of curves that could be fitted to the data
  - **Might** also **discard** curves that are compatible with the data
  - In **general** results in **narrower CIs**
  - Resulting in **larger BMDL** values
- **Different sets of models for quantal and continuous data?**
  - extension and unification of the suite of models for continuous and quantal endpoints
- Use of the normal distribution, next to the Log-normal distribution default assumption?
- Parameter interpretation might not be adequate (parameter d)

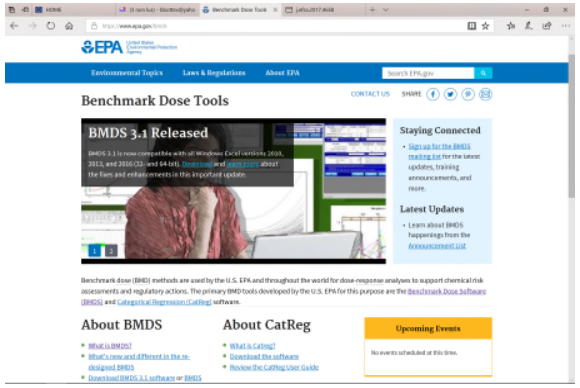
→APPROACHING INTERNATIONAL CONSENSUS ON BMD CONCEPTS

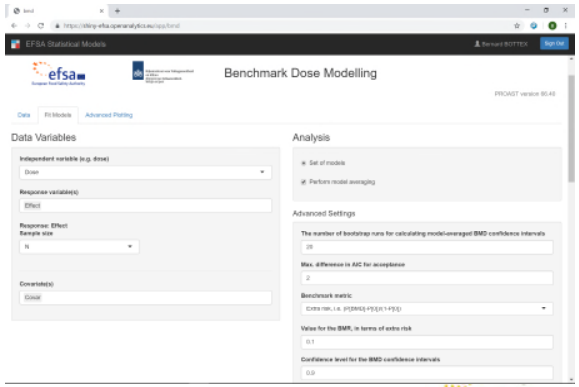
US EPA



WHO IPCS EHC240, 2020

EFSA

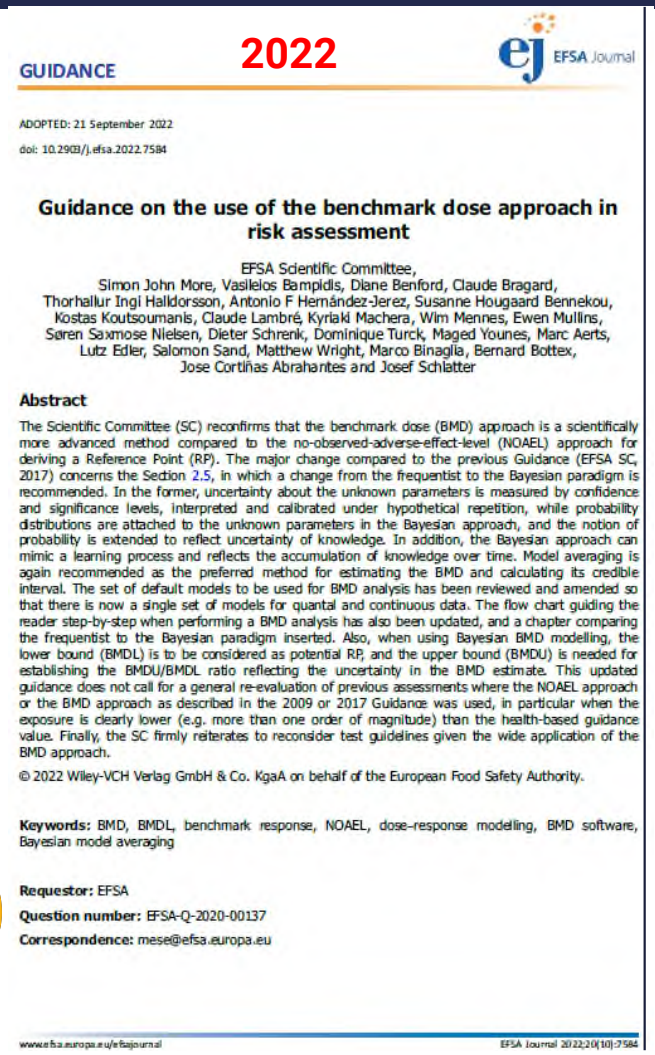




"Align" North America-Europe guidance for dose response assessment / BMD analysis

Harmonisation of the softwares used by EFSA and US agencies for BMD analysis

EFSA GUIDANCE DOCUMENTS



GUIDANCE 2022

EFSA Journal

ADOPTED: 21 September 2022

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

EFSA Scientific Committee,
Simon John More, Vasilelos 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.

Keywords: BMD, BMDL, benchmark response, NOAEL, dose–response modelling, BMD software, Bayesian model averaging

Requestor: EFSA

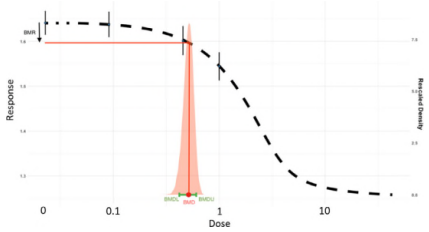
Question number: EFSA-Q-2020-00137

Correspondence: mese@efsa.europa.eu

Harmonise the statistical background and theoretical insights between EFSA and other national and international organisations such as WHO (EHC240 Chapter 5) and US EPA (BMDS)

- Change from the frequentist to the **Bayesian paradigm**.
- set of default models to be used for BMD analysis has been amended so that there is now a **single set of models** for quantal *and* continuous data

Subject of the following presentations



Thank you for your attention!