Probabilistic Bayesian Benchmark Dose (BMD) Analysis for Decision Support

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Introduction on Bayesian BMD (BBMD) Modeling System

The benchmark dose (BMD) methodology has been recommended as a replacement to the traditional No (or Lowest) Observed Adverse Effect Level (NOAEL/LOAEL) method in quantitative human health risk assessment. Comparing to the NOAEL/LOAEL method, the BMD method is a more scientifically rigorous and transparent dose-response modeling approach regarding its quantitative definition of adversity, adequate use of dose-response data, and plausible quantification of uncertainties in modeling process, etc.

As the mainstream of regulatory risk assessment is moving towards a probabilistic assessment framework, a standardized tool to perform both probabilistic BMD estimation and low-dose extrapolation is of urgent need. A core idea in probabilistic dose-response analysis is that the risk of having adverse effects at a specified dose level or the dose causing a certain level of risk should be probabilistically quantified and expressed in terms of distribution. The online BBMD system is designed to achieve those goals. This system is established primarily based on Bayesian statistical analysis featuring Markov Chain Monte Carlo (MCMC) algorithms in Stan Library for model fitting, parameter and quantity of interest (e.g., BMD level) estimation. After distributional BMD is estimated, Monte Carlo (MC) simulation is employed for low-dose extrapolation to derive probabilistic RfD.

This system has **many features that are superior than the current Excel-based BMDS** software published by the US Environmental Protection Agency.

Features of the BBMD System

The BBMD system includes the following six important features: (1) Cross platform; (2) Adaptability for diverse data types; (3) Probabilistic estimation; (4) Reliability and robustness; (5) Advanced BMD estimation; (6) Probabilistic low-dose extrapolation in support of decision making

Cross Platform

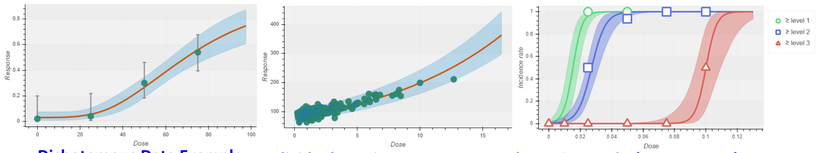
The BBMD system is a web-based computational system with cross-platform accessibility (i.e., not limited by Operation System, Windows, Mac or Linux) anytime and anywhere.

Available at https://benchmarkdose.org

EPA's BMDS is an Excel-based app that requires Windows operation system and 64-bit Excel 2016 or above

Adaptability for Diverse Data Types

- BBMD is capable of analyzing dichotomous data, summary continuous data, individual continuous data (especially for epidemiological study data), and categorical data



Dichotomous Data Example | **Individual Continuous Data Example** | **Categorical Data Example**

EPA's BMDS cannot perform BMD analysis for individual continuous data or categorical data.

Probabilistic Estimation

Weibull fit summary

Pystan version: 2.17.0.0

Power parameter lower-bound: 1

- Full Bayesian Analysis featuring the use of Markov Chain Monte Carlo (MCMC)
- Textual and graphical output of parameter estimation

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Inference for Stan model: anon_model_c080672f617d0e7adea9de34dd07fac8.
1 chains, each with iter=30000; warmup=15000; thin=1;
post-warmup draws per chain=15000, total post-warmup draws=15000.

       mean se_mean     sd  2.5%   25%   50%   75% 97.5%  n_eff   Rhat
a      0.03  2.0e-4   0.02 4.4e-3  0.02  0.03  0.04  0.08  10355    1.0
b      2.93  7.8e-3   0.75  1.71   2.42  2.85  3.34  4.63   9176    1.0
c      0.82  1.7e-3   0.16  0.54   0.71  0.81  0.92  1.15   8338    1.0
lp__ -83.84    0.02   1.33 -87.32 -84.44 -83.48 -82.87 -82.34   5413    1.0

Samples were drawn using NUTS at Tue Dec  5 12:34:58 2017.
For each parameter, n_eff is a crude measure of effective sample size,
and Rhat is the potential scale reduction factor on split chains (at
convergence, Rhat=1).
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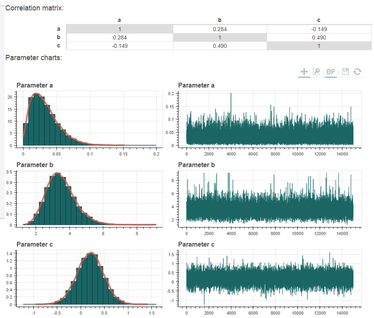
Correlation matrix:

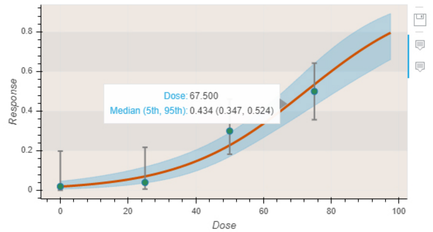
	a	b	c
a	1	0.284	-0.149
b	0.284	1	0.490
c	-0.149	0.490	1

Parameter charts:



- Probabilistic BMD estimation for individual models and model averaged BMD

- Interactive dose-response plot for visual inspection



EPA's BMDS can only provide point estimates instead of distributional estimation.

Reliability and Robustness

- BBMD & BMDS (3.1.2) are thoroughly tested using 518 dichotomous and 108 continuous datasets
- BMD & BMDL were estimated and compared

Dichotomous Models (out of 2,072 BMD estimates)			Continuous Models (out of 216 BMD estimates)		
	BBMD	BMDS 3.1.2		BBMD	BMDS 3.1.2
Quantal-linear	0; 0; (1.2~2.5)	276; 276; (1.1~10.9)	Linear	0; 0; (1.1~2.3)	6; 11; (1.1~24.9)
Logistic	0; 0; (1.1~2.2)	276; 277; (1.1~5.9)	Power	0; 0; (1.1~4.5)	6; 32; (1.0~24.8)
Probit	0; 0; (1.1~2.1)	276; 276; (1.1~6.5)	Hill	1; 1; (1.1~11)	7; 43; (1.0~17.1)
Weibull	0; 0; (1.1~4.4)	276; 283; (1.0~7.8)	Exponential 2	0; 0; (1.1~2.2)	6; 10; (1.0~15.4)
Multistage 2	0; 0; (1.2~2.6)	276; 276; (1.1~7.9)	Exponential 3	0; 0; (1.1~5.7)	6; 51; (1.0~17.4)
LogLogistic	0; 0; (1.1~5.4)	276; 276; (1.1~56.2)	Exponential 4	0; 0; (1.2~23)	6; 31; (1.0~16.0)
LogProbit	0; 0; (1.1~3.8)	276; 356; (1.1~2.6e5)	Exponential 5	0; 0; (1.1~33)	6; 73; (1.0~217.7)
Dich Hill	0; 0; (1.2~191)	281; 623; (1.1~1.4e6)	Note: e.g 623/2072 & 73/216 are two failure rates		

- The table reports: (1) the number of failed BMD estimates, (2) the number of failed BMDL estimates; and (3) the 95th percentile interval of the BMD/BMDL ratio given the default BMR definition

Advanced BMD Estimation

- For dichotomous data, BMD estimates are calculated based on BMR definitions of extra risk & added risk
- For continuous data, various definitions of BMR are used for BMD estimation, including absolute and relative change in central tendency (i.e., median), and hybrid approach based on tails of a distribution
- For categorical data, extra risk & added risk BMD estimates are calculated for specified category
- Model averaged and individual model BMD estimates are calculated for all data types
- User can specify prior weight for selected models for model averaged BMD calculation
- User can specify priors for parameters in dichotomous dose-response models to improve model fitting and BMD estimation

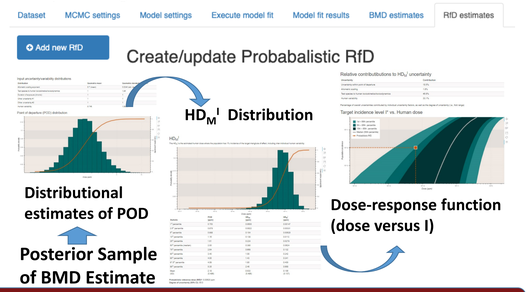
Probabilistic Low-dose Extrapolation

- The posterior sample of BMD estimates is used as the POD for probabilistic low-dose extrapolation
- These uncertainties and variabilities are assumed to be lognormally distributed; and samples are generated using Monte Carlo simulation
- HD_{50}, estimated human dose at which 50% of the population has effects greater than or equal to the target magnitude (M) of effect is estimated
- HDMI, estimated human dose where the population has *I* % incidence (including inter-individual human variability) with effects greater than or equal to target magnitude (M)
- The contribution of each uncertainty/variability factor to overall uncertainty is calculated
- Target Incidence Level I* vs Human Dose plot is produced to show the confident intervals of human dose that can achieve targeted protection goals

Uncertainty contributions

Ratio of 95th percentile to 5th percentile in HDMI: 41.5

Uncertainty	Contribution
Variability within point of departure	0.672%
Allometric scaling	2.04%
Test species to human toxicokinetics/toxicodynamics	57.5%
Duration of exposure	-
Other uncertainty #1	-
Other uncertainty #2	-
Human variability	39.8%



Discussion and Conclusion

- BBMD is a Bayesian and probabilistic BMD modeling system with many advanced features
- BBMD can provide probabilistic estimates for important quantities of interest in dose-response assessment which greatly facilitates the current needs for conducting probabilistic risk assessment