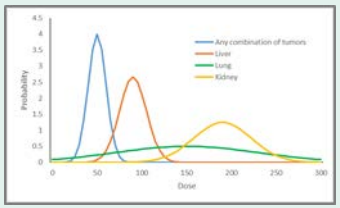
Recent Developments

MS-Combo Model

- MS-Combo model calculates the probability of developing any combination of multiple tumors observed in a bioassay

$$P(d) = 1 - \exp\{-(\beta_0 + \beta_1 d + \beta_2 d^2 + \cdots)\}$$

- Implemented at the recommendation of the NRC



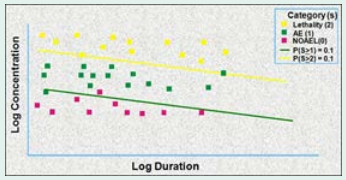
BMDS Wizard

- Excel workbook that simplifies BMD modeling by providing a structured interface to maintain all inputs, outputs, and decisions made in the modeling process

CatReg

- Allows for the meta-analysis of toxicity data from multiple studies, endpoints, and test species
- Estimates the probability that a response of a severity level (s) or greater occurs, given a concentration (C) and duration (t):

$$P(Y \geq s|C,t) = H[\alpha_s + \beta_{1s} * C + \beta_{2s} * t]$$



Risk Assessment Impacts

- Human Health assessments – implementing scientifically sound dose-response methods ensures that EPA (IRIS and PPRTV) assessments reflect the strongest science possible
- Modernizing risk assessment methods – developing new dose-response methods advances the practice of dose-response analysis in EPA, allowing for the better characterization of uncertainty and variability, quantifying incremental risk, and addressing susceptibility

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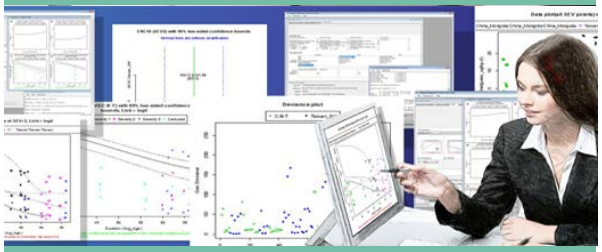
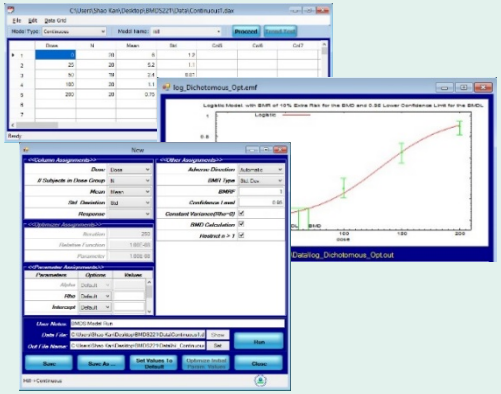
EPA's Benchmark Dose Software (BMDS)



EPA's Benchmark Dose Software is the primary dose-response tool for use in human health risk assessments within the EPA and globally. Currently, there are over 5,000 registered users across 90 countries. BMDS supports the use of BMD methods by Agency partners and a wide array of stakeholders, including international, federal and state regulatory agencies, industry, scientific organizations, academia, and others.

Benchmark Dose Modeling

- Accepted as a default dose-response modeling approach by US EPA
- National Center for Environmental Assessment (NCEA) built and supports Benchmark Dose Software (BMDS, current version 2.7.0.4) to facilitate BMD analyses
- Currently, BMDS supports the modeling of dichotomous, nested dichotomous, continuous, repeated measure, and concentration × time data

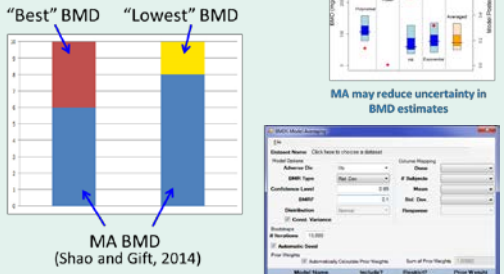


Terminology

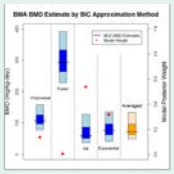
- Benchmark Response (BMR) – a change in response relative to background response in controls
- Benchmark Dose (BMD) – the dose associated with a selected BMR
- Benchmark dose lower confidence level (BMDL) – a one-sided confidence interval on the BMD, usually 95%

Model Averaging

- NCEA and NIOSH developing *draft* Bayesian model averaging method to address model uncertainty
- Estimates a weight-averaged BMD/BMDL from all models being considered
- Uses maximum a posteriori methods and Laplace approximation-based model weights



MA may enhance accuracy of BMD estimates



MA may reduce uncertainty in BMD estimates

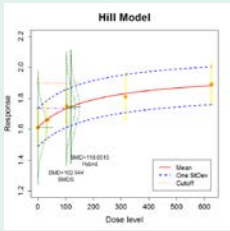
New GUI under development

- Allows for assignment of model parameter priors and model weights, allowing for incorporation of biological or other prior information
- For example, information of a particular endpoint's mode of action may support weighing non-linear models more heavily than linear ones

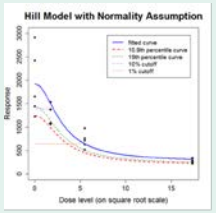
Future Directions and User Support

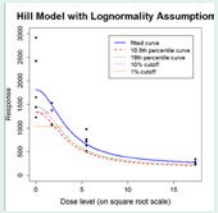
Future Directions

- Hybrid approach – characterizes continuous risk using the percentage change of a popu-lation in the tail of the distribution



- Log-normal distribution – allows for the user to assume responses are log-normally distributed.





- Probabilistic dose-response methods have been proposed (NRC, 2008; 2013) to assist risk management decisions
- Meta-analysis tools using Bayesian statistics and hierarchical modeling will be used to support future EPA health assessments

User Support

- BMDS features a graphic user interface that facilitates efficient modeling, interpretation of results and reporting capabilities.
- The BMDS website (**epa.gov/bmds**) contains a full suite of training materials, including a Quickstart guide, numerous training webinars, and links to currently BMD technical guidance documents.