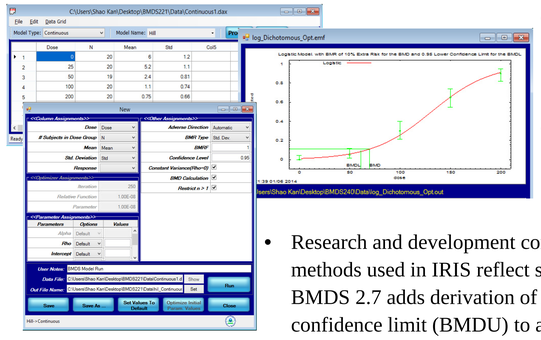
EPA Dose-Response & Related Software - New & Future Developments

J. Allen Davis[1], Jeff Gift[2], David Farrar[1], Jay Zhao[1], and Matt Wheeler[3]

[1] US EPA, Office of Research and Development, National Center for Environmental Assessment - Cincinnati
[2] US EPA, Office of Research and Development, National Center for Environmental Assessment – Washington
[3] National Institute for Occupational Safety and Health, Risk Evaluation Branch – Cincinnati, OH

Benchmark Dose Software (BMDS 2.7 released 8/17)

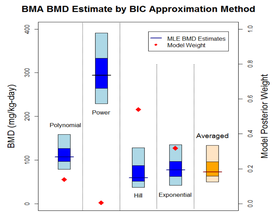


- Benchmark dose (BMD) method proposed by Crump (1984)
- Accepted as default dose-response modeling approach by US EPA (2012)
- Research and development continues to ensure methods used in IRIS reflect state-of-the-science, e.g., BMDS 2.7 adds derivation of BMD upper bound confidence limit (BMDU) to all models (USEPA 2017)

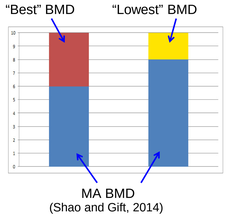
BMDS 3.0 - to be released in FY18

Bayesian Model Averaging

- EPA NCEA and NIOSH are developing Bayesian modeling averaging methods to address and/or account for model uncertainty
- Current methods for single model selection (i.e., AIC-based selection) have been shown to be inadequate (i.e., methods do not achieve nominal coverage rates)
- Current method uses maximum a posteriori estimation and Laplace approximations to generate model weights

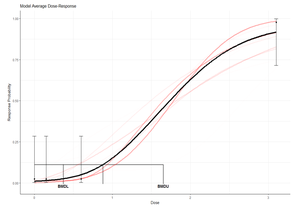


MA may reduce uncertainty in BMD estimates



MA may enhance accuracy of BMD estimates

- Method allows for assignment of model parameters 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 weighting non-linear models more heavily than linear ones



$$\Pr(BMD \mid D) = \sum_{i=1}^{9} \pi_i \Pr(BMD \mid M_i, D)$$

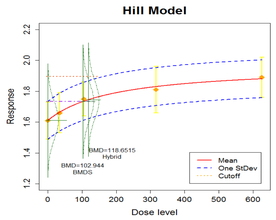
Posterior Distribution of the BMD

$$\alpha = \int_{-\infty}^{BMD_\alpha} \Pr(BMD \mid D) dBMD$$

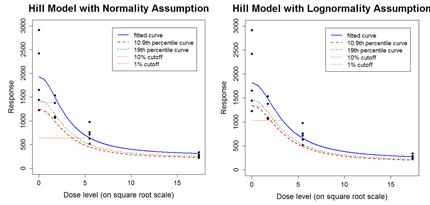
Calculation of the BMDL

BMDS 3.0 - to be released in FY18 (continued)

- **Hybrid Approach** – instead of using change in central tendency, the hybrid approach estimates a BMD using the percentage change of a population in the tail of the distribution
- Use of the hybrid approach for continuous data harmonizes benchmark responses between continuous and dichotomous data



Application of the hybrid approach to estimate BMDs for a continuous endpoint



Comparison of dose-response curves under the normal or log-normal distributional assumptions

- **Log-normality vs. Normality** – Shao and Gift (2013) determined that the distribution assumption has limited impact on the BMD estimates when the within dose-group variance is small
- BMDs defined using the hybrid approach are more sensitive to the distribution assumption

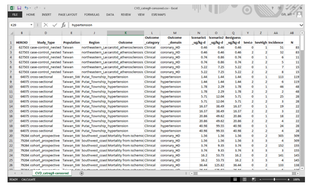
Categorical Regression (CatReg 3.1 released 6/17)

Categorical Regression

- Estimates the probability that a response occurs of a severity level, s, or greater given a concentration, C, and duration of exposure, T, as:

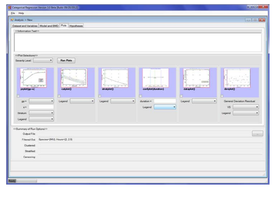
$$P(Y \geq s|C,T) = H[\alpha_s + \beta_{1s} * C + \beta_{2s} * T]$$

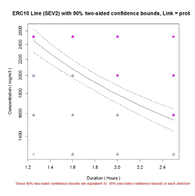
- CatReg allows for meta-analysis of data from multiple studies, endpoints, and test species (USEPA 2017; Milton et al., 2017)
- CatReg accounts for within study correlations (clustering) and allows for the stratification of model parameters to account for response differences across strata of data.

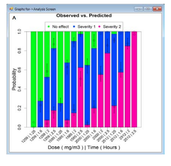


$$\Pr(Y \geq s|C,T,i) = H[\alpha_s + \gamma_i + \beta_1 j \times f_1(C) + \beta_2 k \times f_2(T)],$$
$$s = 1,2,\ldots,S,\quad i = 1,2,\ldots I,\quad j = 1,2,\ldots,J,\quad k = 1,2,\ldots,K$$

- CatReg incorporates hypothesis testing to allow users to determine the most appropriate form of the model (i.e, which variables should be stratified)
- Multiple plotting capabilities are implemented in CatReg





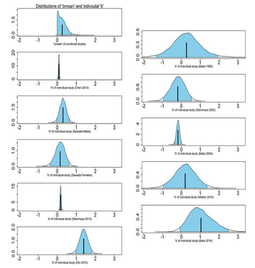


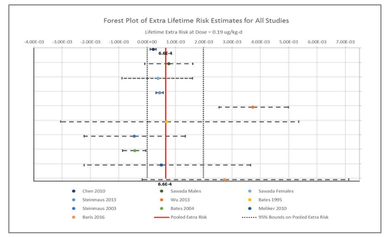
- U-shaped dose-response analysis could be added to future CatReg versions to facilitate assessment of toxicity from excess and deficiency (Milton et al., 2017)

Some Additional Related Developments and Plans

Probabilistic Meta-Analysis Methods for Meta-Analysis of Epidemiological Data

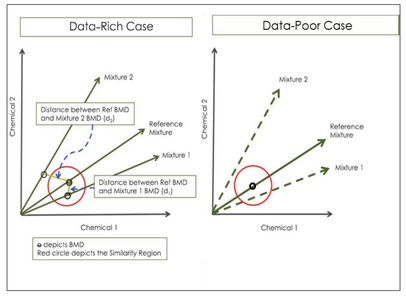
- Probabilistic meta-analysis dose-response methods have been proposed (NRC, 2008, 2013) to better assist risk management decision making
- Meta-analysis tools that allow for the combination of a multiple types of epidemiological studies using Bayesian statistics and hierarchical modeling have been developed to support future Agency health assessments





Mixture Similarity Tool (MiST)

- EPA Excel tool (MiST) based on Marshall et al. (2013)
- Data-Rich Case: Mixtures are similar when distance between reference and candidate mixture BMDs is less than radius of red circle
- Data-Poor Case: Simplifying assumptions to estimate distance via comparison of mixing proportions and weights for components of reference & candidate mixtures.



Addressing NRC Recommendations

New and future developments in dose-response modeling specifically address multiple recommendations provided by NRC (2014)

- "EPA should use formal methods for combining multiple studies and the derivation of IRIS toxicity values"
  - Both CatReg and meta-analysis tools for epidemiological data have been developed to increase IRIS' meta-analytical capabilities
- "Advanced analytic methods, such as Bayesian methods, for integrating data from dose-response assessments and deriving toxicity estimates are underused in the IRS program
  - Bayesian methods have recently been developed for use in IRIS assessments, including Bayesian model averaging and hierarchical Bayesian meta-regression approaches
- "Uncertainty analysis should be conducted systematically and coherently in IRIS assessments
  - Uncertainty analysis is supported by reporting entire confidence interval around BMD (BMDL – BMDU), which is done in the new model averaging method and CatReg

References

Marshall et al. (2013) An empirical approach to sufficient similarity: combining exposure data and mixtures toxicology data. *Risk Analysis*, 33(9), pp. 1582-1595
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US EPA 2017b Categorical Regression (CatReg) v. 3.1, https://www.epa.gov/bmds/catreg