Dichotomous Model Averaging

J. Allen Davis, U.S. EPA
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EPA efsa European Food Safety Authority

DISCLAIMER

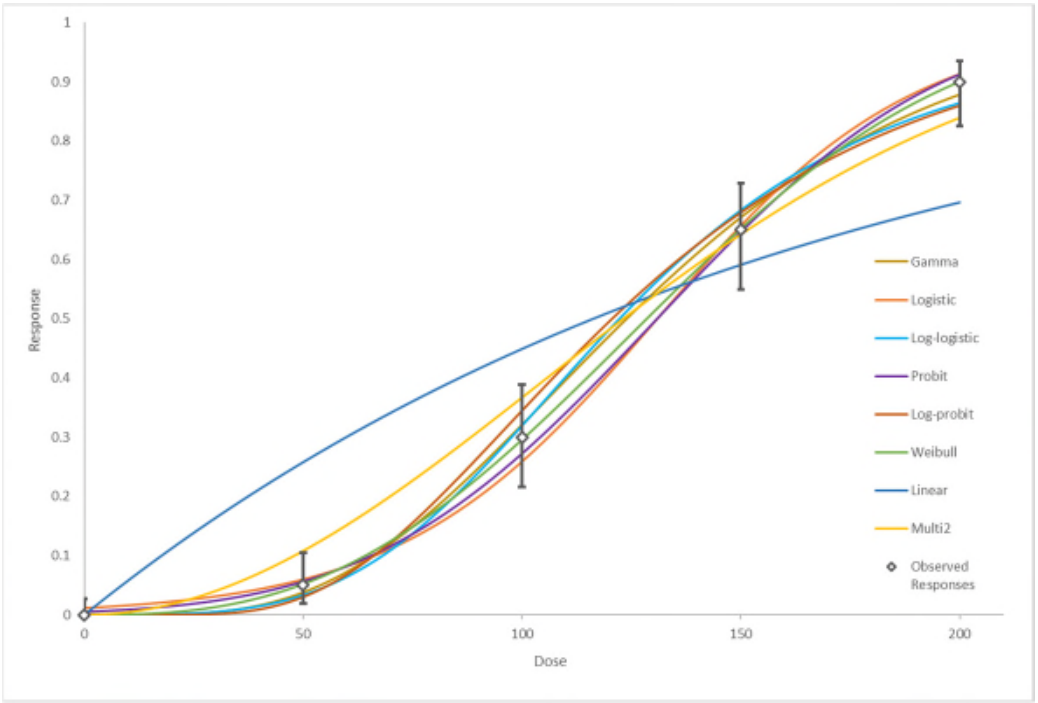
- The views expressed in this presentation are those of the author(s) and do not necessarily reflect the views or policies of the U.S. EPA.

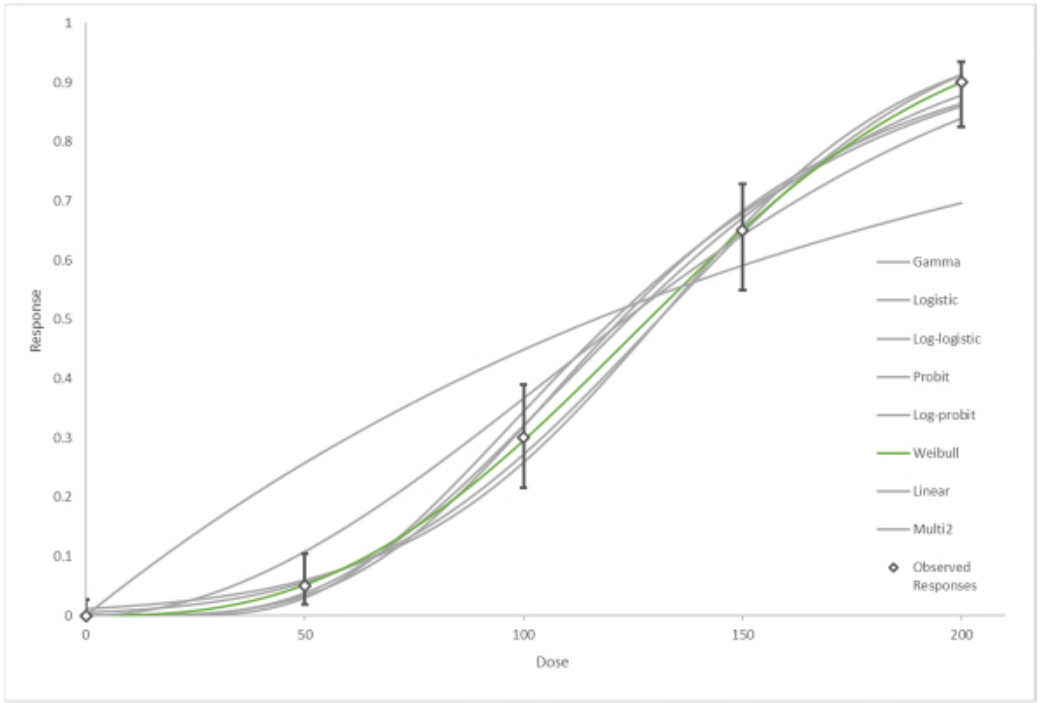
SINGLE MODEL SELECTION

- Ideally, dose-response models would be biologically-based
- These models are rarely available
  - BMD analyses becomes purely statistical effort
  - Multiple models are fit to the observed toxicity data
- Thus, most previous methods of BMD analysis were concerned with picking a *"best"* representative model based on statistical fit or other criteria

SINGLE MODEL SELECTION

- However, when fitting multiple models to a single dataset, many models can statistically fit the data well





SINGLE MODEL SELECTION – QUANTAL DATA

- AIC-based selection criteria did not perform adequately in terms of selecting the "true" model

Table 3. AIC-based model selection percentages over all configurations (A–F) in Table 2 for per-dose sample size of $N=25$

		Selected							
	Model	1	2	3	4	5	6	7	8
Correct	1	16.9	14.5	26.4	35.9	0.1	3.9	1.5	0.9
	2	15.3	14.7	29.1	35	0.1	3.5	1.3	0.8
	3	8.4	9.1	56.5	19.6	0	4.5	1.9	0.1
	4	15.4	13.6	20.8	42.7	0	4.3	2	1.1
	5	12.2	13.5	34.6	33.5	0.1	3.5	1.6	0.9
	6	12.6	11.5	32.1	35.7	0	3.9	3.4	0.8
	7	12.9	11.5	31.8	36.2	0	3.5	3.3	0.7
	8	12.3	13.3	33.8	34.5	0	3.5	1.7	0.9

Source: West et al. (2012). Environmetrics 23: 706-716

Table 4. AIC-based model selection percentages over all configurations (A–F) in Table 2 for per-dose sample size of $N=50$

		Selected							
	Model	1	2	3	4	5	6	7	8
Correct	1	17.6	18.1	21.9	35	0.4	3.4	2.4	1.2
	2	15.8	18.7	25.3	34	0.4	2.8	1.9	1
	3	7.4	8.7	61.9	13.6	0.2	5.1	3	0.1
	4	15.3	14.8	15.4	45.3	0.2	3.7	3.7	1.6
	5	12.5	15.7	33.2	32.3	0.2	3	2.2	0.9
	6	12.4	12	30.6	34.7	0.1	3.5	6	0.9
	7	12.3	12	29.8	35.8	0	3.4	5.9	0.8
	8	12.6	15.2	32.2	33.5	0.2	3	2.4	0.9

Source: West et al. (2012). Environmetrics 23: 706-716

ALTERNATIVES TO SINGLE MODEL SELECTION

- Multiple approaches have been developed or suggested to address and/or characterize model uncertainty
  - Hyper-flexible semi- or non-parametric models
  - Basing BMD confidence interval on lowest BMDL/highest BMDU of adequately fitting models
  - Model averaging methods

DICHOTOMOUS MODEL AVERAGING

- Model averaging ***attempts to*** take into account model uncertainty by incorporating information from all models into the final BMD, BMDL, and BMDU estimation

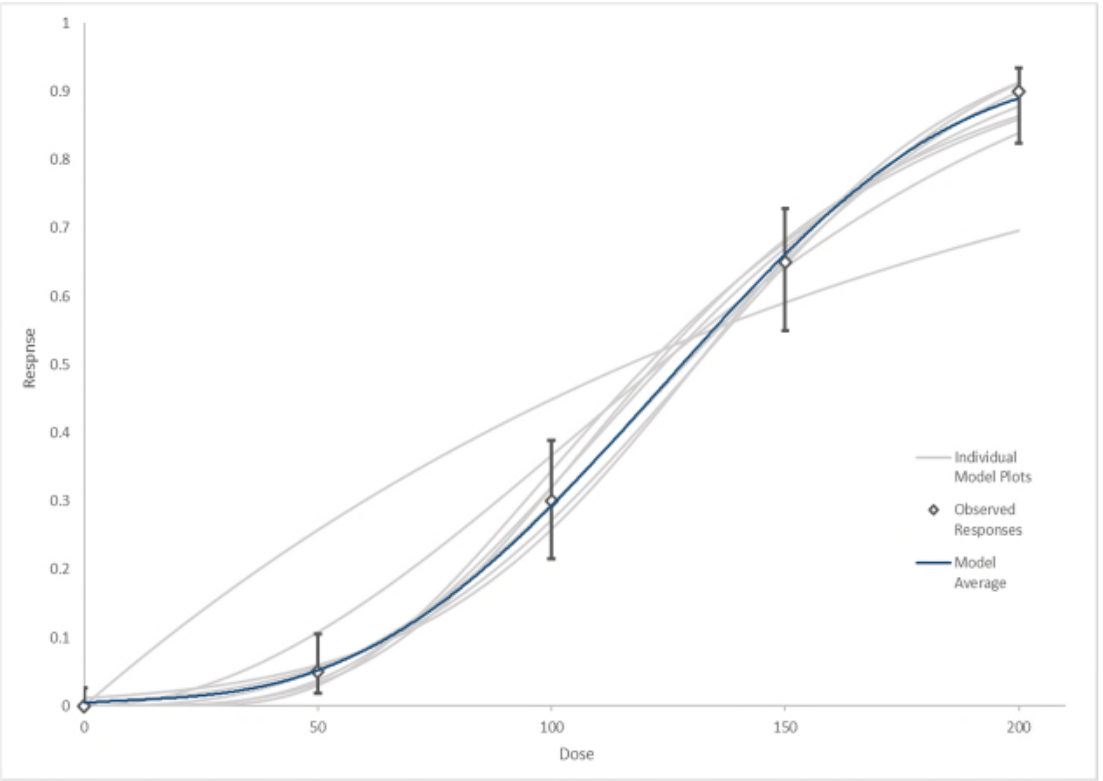
- EFSA's new web-tool and PROAST utilize the Wheeler and Bailer (2007, 2008) *average model* method

DICHOTOMOUS MODEL AVERAGING – MODELS USED

- Logistic: $\pi(\mathrm{d}) = \frac{1}{1+\exp[-(\alpha+\beta d)]}$
- Probit: $\pi(d) = \Phi(\alpha + \beta d)$
- Log-logistic: $\pi(d) = \gamma + \frac{(1-\gamma)}{1+\exp[-(\alpha+\beta \ln(d))]}$
- Log-probit: $\pi(d) = \gamma + (1-\gamma)\Phi[\alpha + \beta \ln(d)]$
- Weibull: $\pi(d) = \gamma + (1-\gamma)[1 - \exp(-\beta d^{\alpha})]$
- Gamma: $\pi(d) = \gamma + (1-\gamma)\frac{1}{\Gamma(\alpha)}\int_0^{\beta d} t^{\alpha-1}e^{-t}dt$
- Multistage: $\pi(d) = \gamma + (1-\gamma)[1 - \exp(-\beta_1 d - \beta_2 d^2 \ldots - \beta_n d^n)$

DICHOTOMOUS MODEL AVERAGING - METHOD

- *Average model* approach:
- $\hat{\pi}_{MA}(d) = \sum_{k=1}^{K} \pi_k\left(\hat{\theta}, d\right) * w_k$
- w_k = model weight based on the AIC

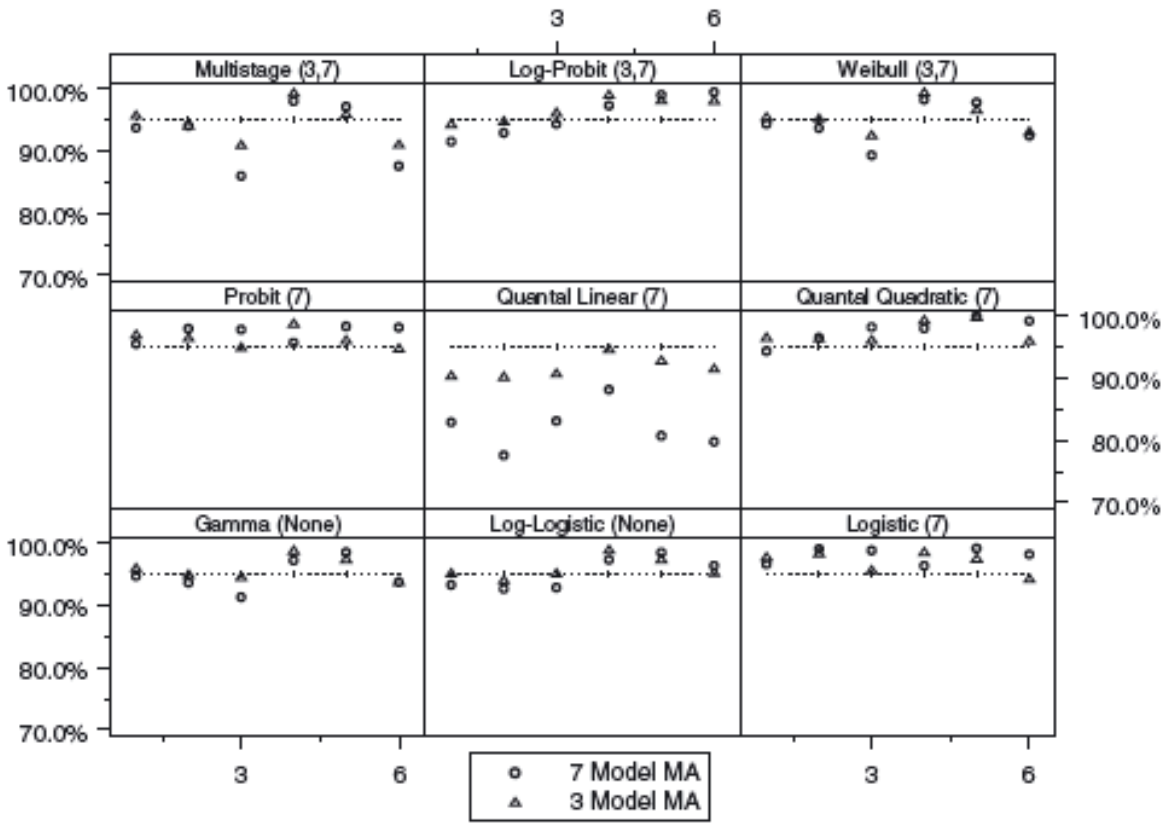


DICHOTOMOUS MODEL AVERAGING – BMD & BMDL

- From the *average model*, the BMD is estimated at the desired risk level (i.e., BMR)
- The BMDL and BMDU are estimated via parametric bootstrapping
  - A user-defined number of parametric bootstrap resamples are generated
  - The models are refit to these resampled data, weights are recalculated and BMDs are estimated
  - The BMDL & BMDU are the desired percentiles (i.e., 5^{th} and 95^{th}) of the generated distribution of BMDs

DICHOTOMOUS MODEL AVERAGING - COVERAGE

- Coverage for MA was generally near or above nominal coverage (95%) at BMR = 10% in simulations (Wheeler and Bailer, 2007)
- Coverage rates for 6 dose designs better than 4 dose designs (shown here)



"AVERAGE MODEL" VS. "AVERAGE DOSE"

- The model averaging method used in Wheeler and Bailer (2007) (and implemented in EFSA's web-tool and PROAST) employs the *average model* method
- Contrast this to the *average dose* method suggested by others
  - $\widehat{BMD}_{MA} = \sum_{k=1}^{K} BMD_K * w_k$, and
  - $\widehat{BMDL}_{MA} = \sum_{k=1}^{K} BMDL_K * w_k$
  - Alternatively, the $\widehat{BMDL}_{MA}$ can be calculated from the distribution of $\widehat{BMD}_{MA}$ if resampling methods are used

"AVERAGE MODEL" VS. "AVERAGE DOSE"

- Wheeler and Bailer (2007) suggested that *average model* methods perform better than *average dose* methods
- At 10% BMR, the percentage of simulations obtaining coverage was:
  - 63% - *average model*
  - 28% - *average dose*
  - 17% - *best single model*

DICHOTOMOUS MODEL AVERAGING - EXAMPLE

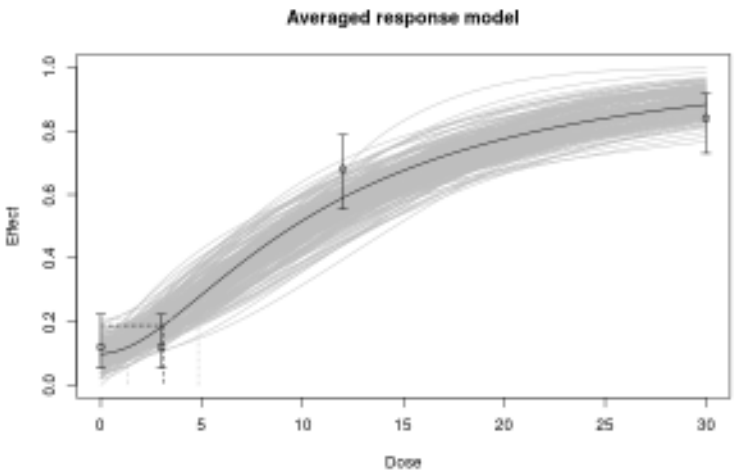
A. The data

Dose (mg/kg day)	No of animals with thyroid epithelial vacuolisation	No of animals in dose group	Sex
0	6	50	F
3	6	50	F
12	34	50	F
30	42	50	F

B. BMR: Default value (extra risk = 10%)

C. Software used: EFSA BMD Platform (under development) + PROAST v. 61.6

Model	Weight	AIC	BMDL	BMDU
Log-probit	0.41	189.72	1.98	5.11
Log-logistic	0.39	189.8	1.84	5.00
Gamma	0.08	192.98	1.21	4.67
Weibull	0.06	193.54	1.10	4.01
Multistage 2°	0.04	194.2	1.35	3.09
Logistic	0.01	198.46	3.31	4.90
Probit	0.00	208.22	n/a	n/a



Method	BMDL	BMDU
Model Averaging	1.37	4.83
Single-model	1.84	5.11

FUTURE DIRECTIONS

- Additional methods for dichotomous and continuous model averaging can be implemented
  - Fully Bayesian methods are being researched by EPA and will be compared to parametric methods
  - These methods are superior to the 2007 method in a number of ways (prior weighting, standardized suites of models, etc.)
- More research comparing *average model* vs. *average dose* methods is needed

CONCLUSIONS

- Model averaging is an improvement over previous single model selection methods
- Model averaging attempts to address model uncertainty by incorporating information from multiple models into the final BMD, BMDL, & BMDU estimation
- The implementation of the *average model* method is ready to use in the latest version of PROAST and is in development as an EFSA web-tool