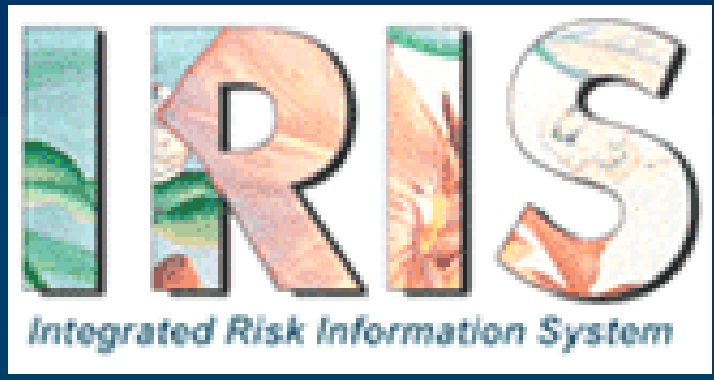
Comments on Mathematical and Statistical Issues in "BMD Uncertainty Analyses"

Allan H. Marcus, Ph.D.



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Overview

- BMD Analyses in Dose-Response Modeling Sometimes Pose Non-Routine Issues
- Typical “Hard” Problems Include
- - Steep changes between adjacent data points (“climbing up” or “falling off a cliff”) with insufficient data between adjacent data values

  - Especially difficult with Weibull quantal endpoint models or power function continuous models and supra-linear dose-response
- Estimates of BMD, BMDL may be highly uncertain
- Uncertainty in supra-linear case shows up as uninformative (?) near-zero BMDLs

Specific Modeling Issues for "Nectorine"

- *The dose-response data for respiratory epithelial adenomas appear to be somewhat supra-linear and may be consistent with several BMDS models*
- *Should we prefer a better-fitting Weibull model to a more plausible biologically based multistage model?*

Do We Need a Much Larger Universe of Models?

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- We need models that connect with biologically-based (or at least biologically-inspired) dose-response models on the one hand (e.g. multi-stage and MVK) and smooth interpolation formulations to simplify BMD/BMDL estimation on the other hand
- We need a large universe of plausible models for sensitivity analyses of methods
- We need a LARGE universe of implausible models as well, because data sometimes are contrary to our expectations, e.g. profoundly non-monotonic models
- Table IV-2 (p. 15) for persimonate shows a common situation where many models have AIC within 1.4 units (most with 0.1) yet BMDL10s differ two-fold, and will differ even more with smaller BMRs.

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The nectorine example is interesting because it raises questions about a common hard problem: supra-linearity. The analogous problem occurs for continuous endpoints analyzed using BMDS power function and Hill function models:

When the power exponent is less than 1, the BMDLs can be forced toward 0 – BUT THEY DON'T HAVE TO BE.

RESPIRATORY EPITHELIAL ADENOMA – WEIBULL MODEL

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- Likelihood Profile Approach (figures later!)

Exponent		AIC	BMD10	BMDL10
0.25		143.7		0.417
0.35		142.8		1.41
0.45		14.2		2.80
0.55		141.9		4.37
0.615		141.9	8.7	5.42
0.65		141.9		5.98
0.75		142.1		7.58
0.85		142.5		9.13
1.0		143.6		11.34
MLE	0.615	143.9	8.7	0.26

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- MATHEMATICAL PROPERTIES OF DOSE-RESPONSE FUNCTIONS TO LOOK AT:
  - Monotonicity vs. non-monotonicity
  - points of inflecton
  - Rates of change of curvature
  - Legitimate, biologically causal multi-modal behavior
  - These are not uncommon in higher-order multi-stage models (equiv. for continuous endpoints, polynomial models)