

# 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?

- ❖ 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.



**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

### ❖ Likelihood Profile Approach (figures later!)

❖ Exponent	AIC	BMD10	BMDL10	
❖ 0.25	143.7		0.417	
❖ 0.35	142.8		1.41	
❖ 0.45	142.2		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

- ❖ **MATHEMATICAL PROPERTIES OF DOSE-RESPONSE FUNCTIONS TO LOOK AT:**
- ❖ Monotonicity vs. non-monotonicity
- ❖ points of inflection
- ❖ 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)