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Lessons Learned: Modeling Cancer Data

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Outline

- Background
  - Data
  - What is dose-response modeling?
    - Benchmark dose
    - Quantifying uncertainty
- Dose-Response methodology:
  - The conventional approach
  - The average model approach
    - What is it?
    - Why use it?
    - Details
- Some General Results
  - Summary
  - Data quality issues
  - Relationship of BMR choice to BMD uncertainty
  - Ranges of BMDs across endpoints

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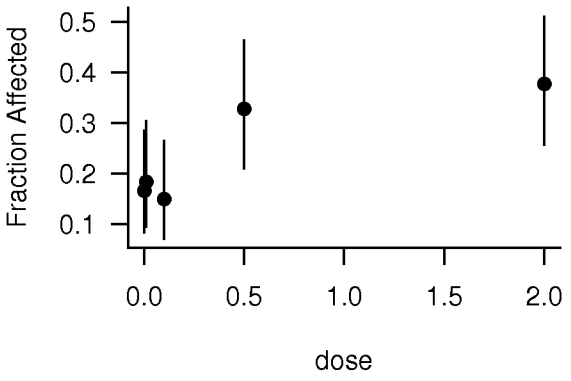
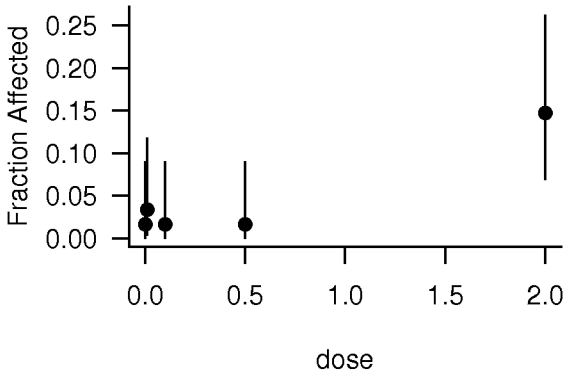
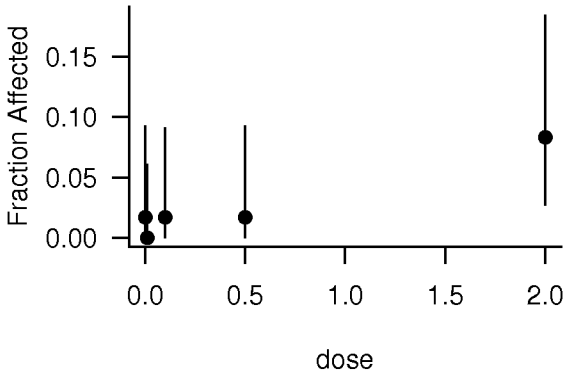
Data

- For each tumour type, #of tumours, # of animals at risk
- Generally multiple studies, both sexes

dose	mammary	mammary_N	CNSglial	CNSglial_N	thyradencarc	thyradencarc_N
0	10	60	1	60	1	58
0.01	11	60	2	59	0	59
0.1	9	60	1	60	1	59
0.5	19	58	1	60	1	58
2	23	61	9	61	5	60







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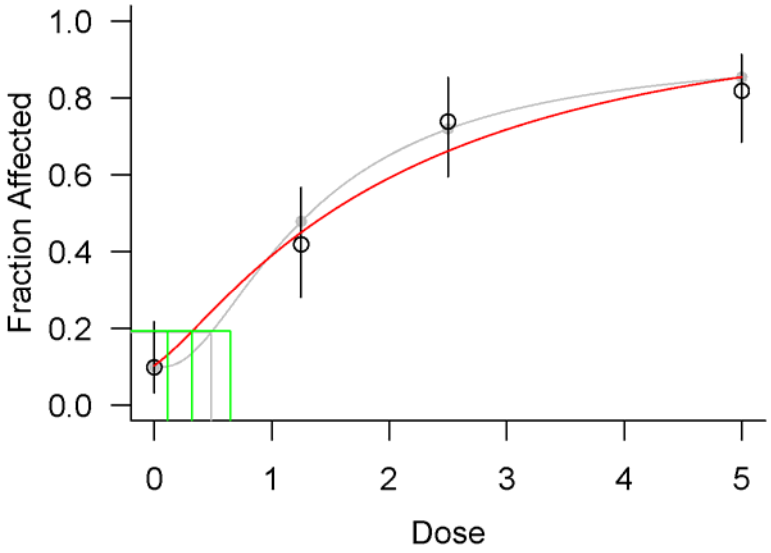
Dose-Response

- Dose-response results from the quantitative interplay at multiple levels among pharmacokinetics, metabolism, cellular and genetic effects, and the competing risk of death due to non-tumour causes.
- These processes determine the expected proportion of animals with tumour in a bioassay.
- When we run the bioassay, random processes operate to give the actual number of animals with tumours.
- Then, we fit simple models to the data, hoping to approximate the true (but unknown) dose-response



- Benchmark dose (BMD) is the dose that gives a standard response level (say, 10% extra risk, for example)

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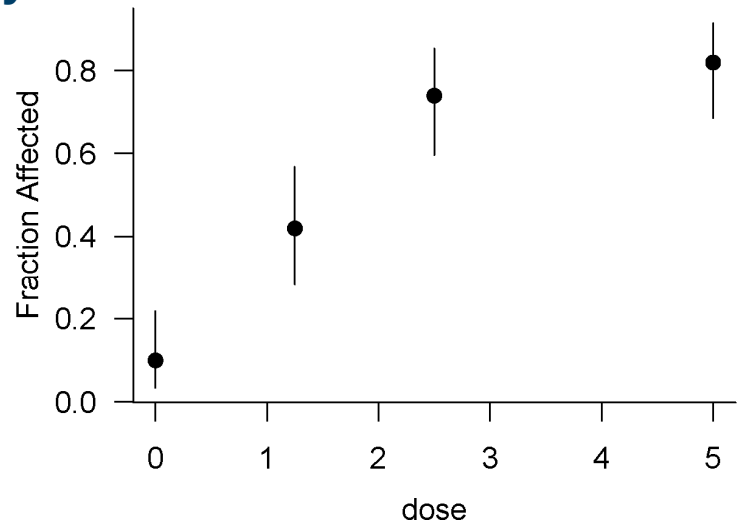
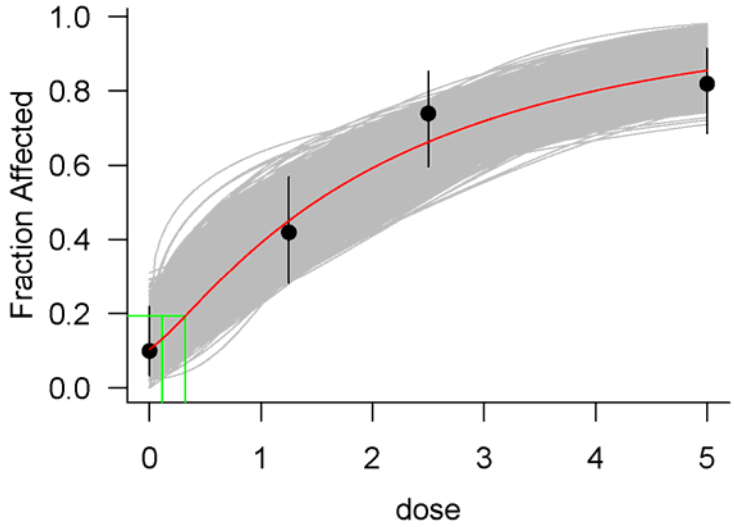
Understanding Dose-Response Uncertainty

- What we DO NOT KNOW:
  - The true dose-response curve
  - The expected fraction of affected animals at doses in our bioassay
  - Experimental errors that affect the dose-response
- We DO KNOW an estimate of the fraction affected based on one experiment.
- Uncertainty in the dose-response function may be characterized by the collection of plausible dose-response curves that are consistent with (or, equivalently, could plausibly have generated) the data





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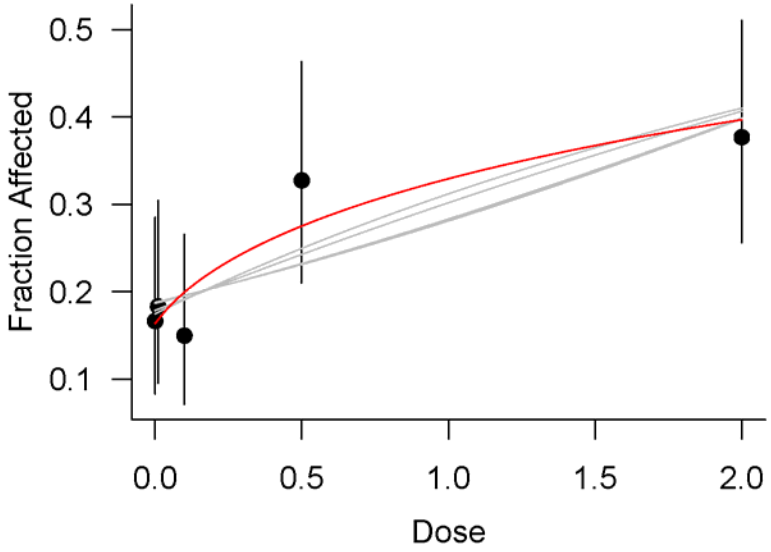
Conventional Dose-Response Modeling

- Fit each of several dose-response models to the data
- BMD CLs depend on the models selected.
- Establish *in advance* a criterion for selecting one of the models, *e.g.*
  - Lowest AIC (criterion based on fit, penalized by number of estimated parameters)
  - Lowest BMDL (ostensibly health protective)
- Neither criterion adequately quantifies the uncertainty
- Selection may be based on trivial differences, as here.



	AIC	BMD	BMDL
logistic	324.1	0.89	0.630
→ loglogistic	323.0	0.56	0.310
probit	324.0	0.86	0.600
→ logprobit	324.1	0.32	0.025
gamma	323.3	0.65	0.400
weibull	323.3	0.65	0.400
multistage	323.3	0.65	0.400

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Model Averaging: Wheeler and Bailer, 2007, Risk Analysis 27: 659—670

- Replace selecting a model with using an average model
  - In a wide range of domains, averaging a predictor can be shown to give results superior to selecting any one of the predictors.
- Use the bootstrap to quantify BMD uncertainty and get a goodness of fit P-value.
- Algorithm:
  1. Fit each of a set of standard DR models to the data set
  2. Compute weights based on the fit of each model:
     a. Weight for model *I* in this analysis is

$$w_i = \frac{\exp\left(-\frac{AIC_i}{2}\right)}{\sum_i \exp\left(-\frac{AIC_i}{2}\right)}$$

     AIC = -2*(loglikelihood of model - #of estimated parameters)
  3. Average Model is weighted average of individual models; BMD computed numerically from average model. x^2 for goodness of fit is calculated as usual.
  4. Bootstrap – using proportions predicted by the above average model, construct 2000 new datasets using binomial sampling, and repeat steps 1 – 3. Use the bootstrap distribution to get CI for BMD, sampling distribution of x^2.

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Models Used in the Average Model Approach

Model	Model equation	Constraints
Logistic	$\pi(d) = \frac{1}{1+\exp\left[-(\alpha+\beta d)\right]}$	$\beta \geq 0$
Log-logistic	$\pi(d) = \gamma \frac{1-\gamma}{1+\exp\left[-(\alpha+\beta \ln(d))\right]}$	$0 \leq \gamma < 1, \quad \beta \geq 1$
Gamma	$\pi(d) = \gamma + \frac{(1-\lambda)}{\Gamma(\alpha)} \int_0^{\beta d} t^{\alpha-1} e^{-t} dt$	$0 \leq \gamma < 1, \quad \alpha \geq 1, \quad \beta \geq 0$
Multistage	$\pi(d) = \gamma + (1-\lambda)\left[1-\exp\left(-\theta_1 d - \theta_2 d^2 - \cdots\right)\right]$	$0 \leq \gamma < 1, \quad \theta_i \geq 0$
Probit	$\pi(d) = \Phi(\alpha+\beta d)$	$\beta \geq 0$
Log-probit	$\pi(d) = \gamma + (1-\gamma)\Phi(\alpha+\beta \ln(d))$	$0 \leq \gamma < 1, \quad \beta \geq 0$
Weibull	$\pi(d) = \gamma + (1-\gamma)\left(1-\exp\left(-\beta d^{\alpha}\right)\right)$	$0 \leq \gamma < 1, \quad \alpha \geq \begin{cases} 0.5 \text{ (MA)} \\ 1 \text{ (BMDS)} \end{cases}$, $\beta \geq 0$

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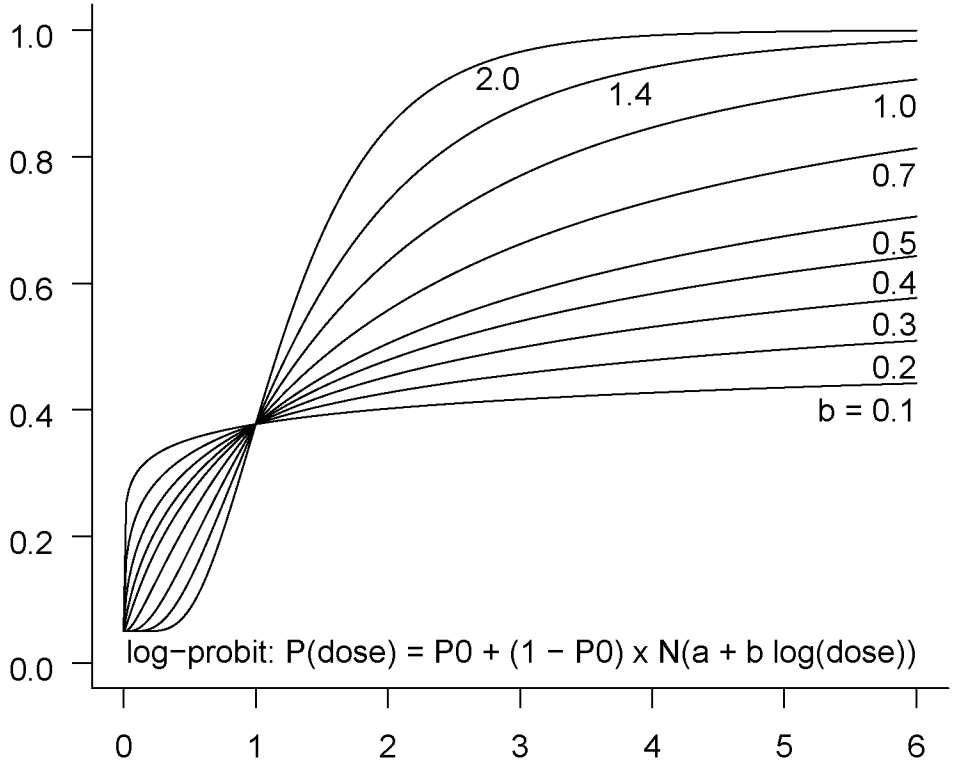
Constraints and Dose-Response Shape

- Several “standard” models (weibull, gamma, log-logistic, log-probit) have a shape parameter.
- When the shape parameter drops below 1, these curves become flatter at higher doses and steeper at lower doses.
- Apparent “plateaus” in a dataset at less than 100% response can force estimates of shape parameters to be < 1, especially if there are no doses with lower responses.



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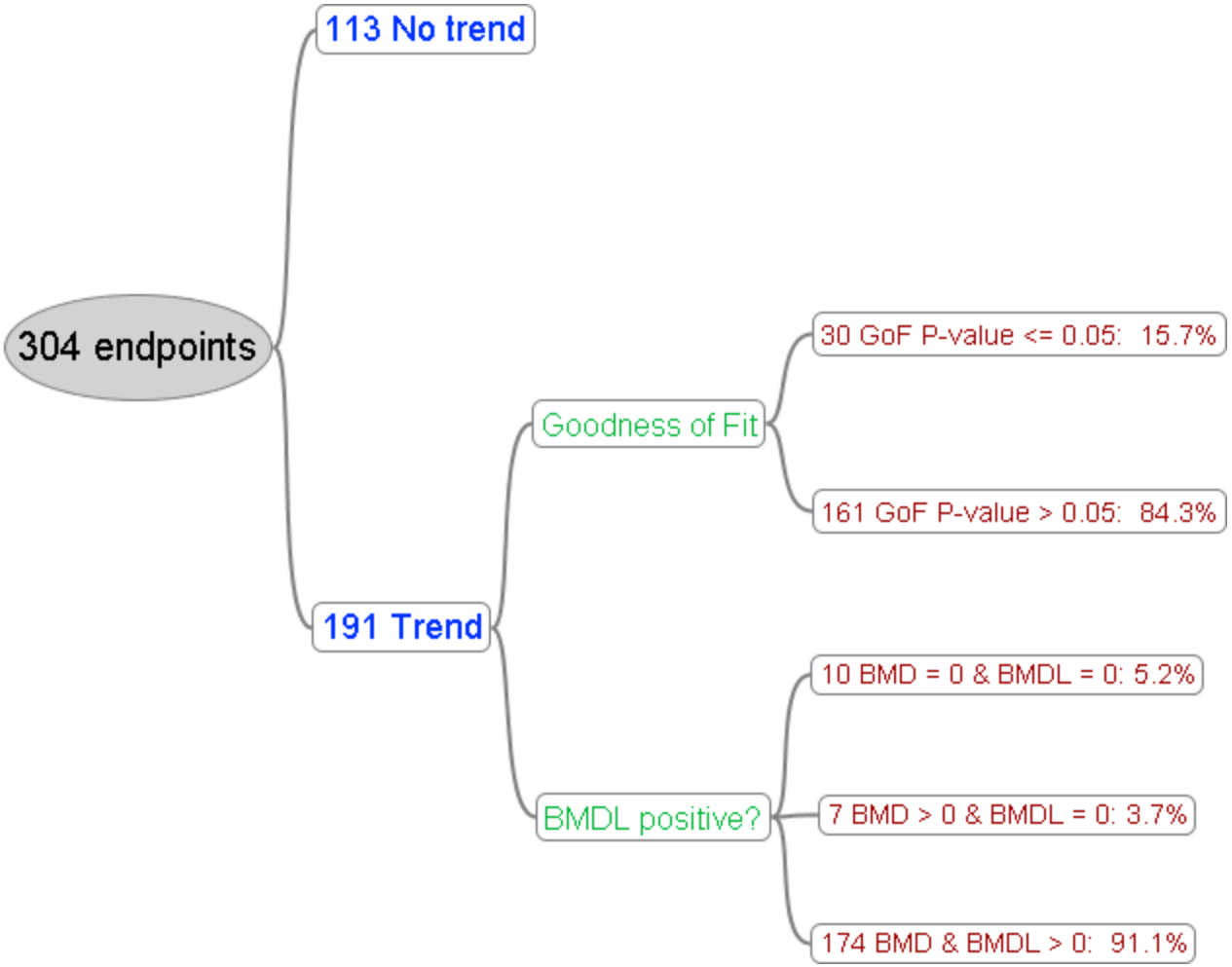
Summary



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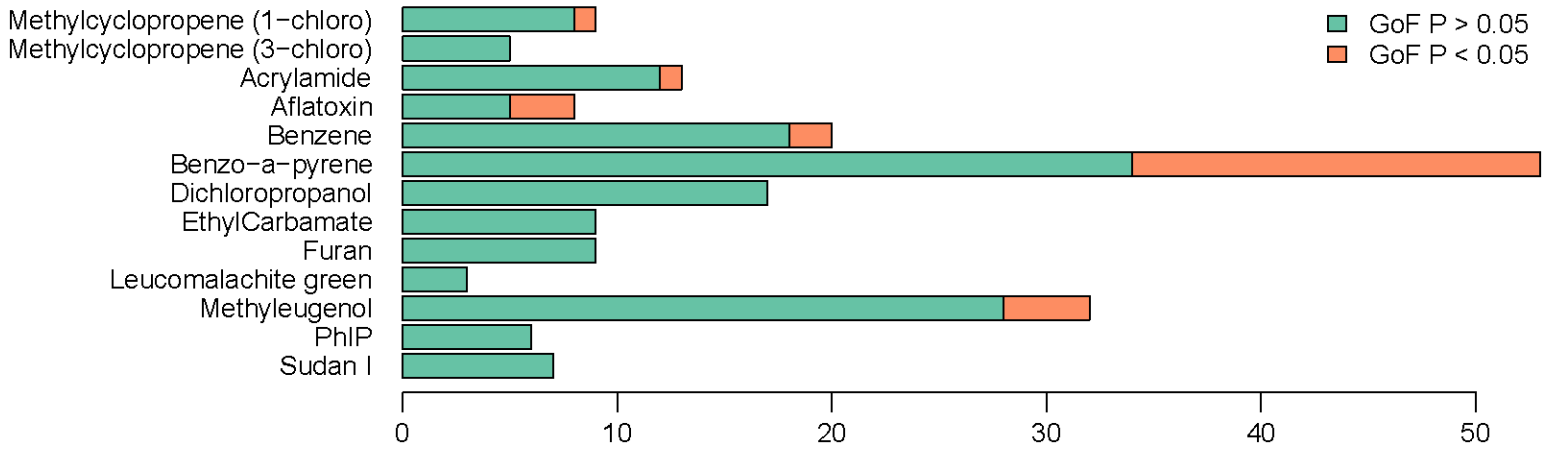
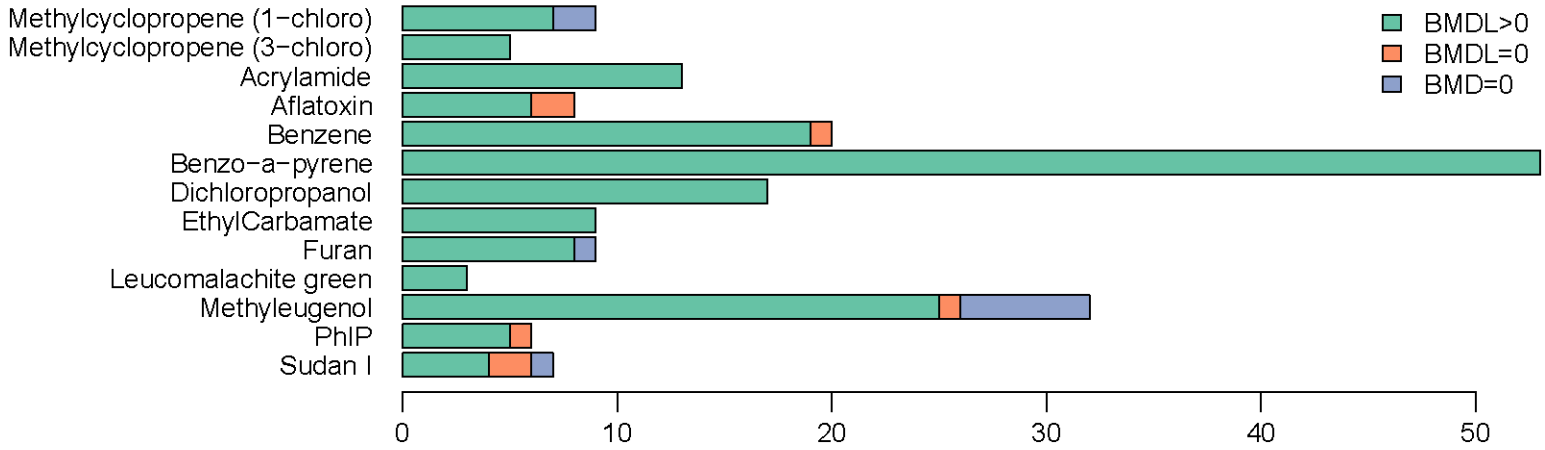
Goodness of Fit and BMD_{10} Status by Chemical





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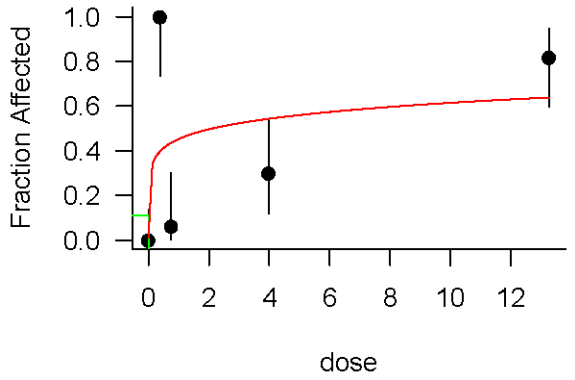
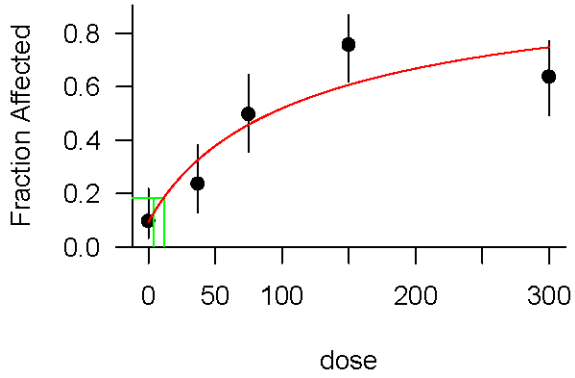
Reasons to Fail Goodness of Fit

- Bad luck (even if we had the right models, we would fail the GoF test about 5% of the time). But, ~ 16% of these datasets fail.
- Experimental error or other problems with the data.
- Inadequate models
  - Saturable metabolism
  - Competing risks





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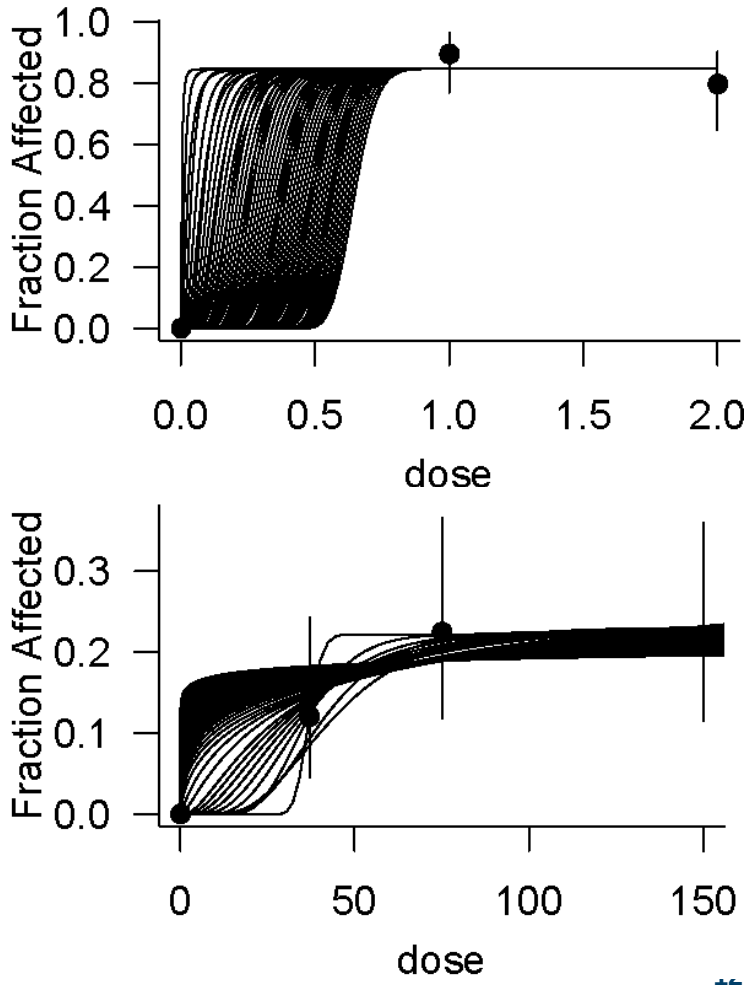
BMD Not Bounded

- In seven of 12 chemicals, at least one $BMDL_{10}$ is essentially 0.
  - In four chemicals, the BMD_{10} estimate is essentiall 0
    - Data are consistent with a range of BMDs
  - In three more chemicals, for at least one endpoint, we can estimate a BMD_{10}, but the $BMDL_{10}$ is essentially 0
    - The data are most consistent with a single value for the BMD, but are adequately consistent with a range of BMDs down to essentially 0.
- These represent failures of the data, not the BMD method; the method is just telling us that the data are inadequate!



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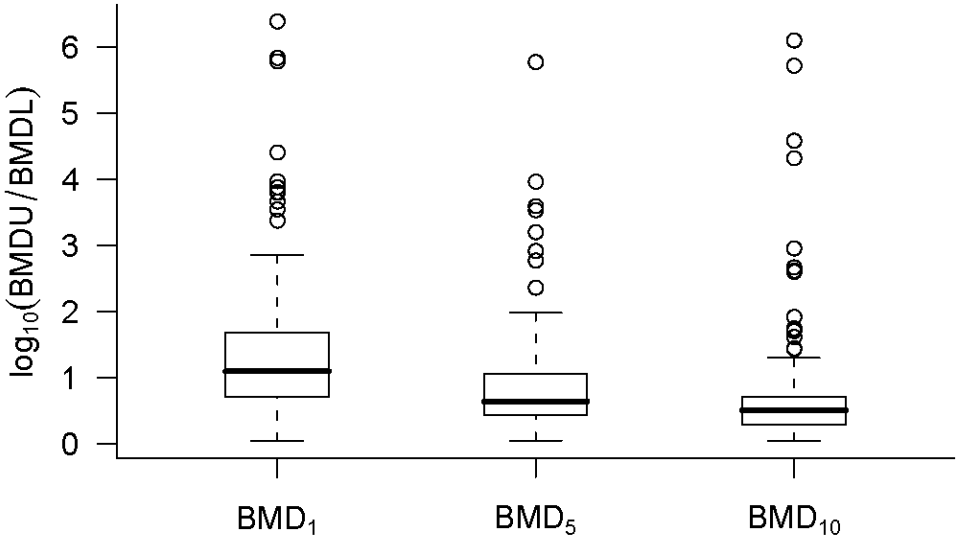
BMR Choice and Uncertainty of the Corresponding BMD

- The average model approach includes model uncertainty and statistical uncertainty in its quantification of BMD uncertainty.
- Use BMDU/BMDL ratios, or $\log_{10}$(BMDU/BMDL) ratios to quantify BMD uncertainty.
- How does this change with BMR among endpoints with positive BMDL and significant trend (that is, BMDL > 0 and BMDU < infinity)?

- Uncertainty increases as BMR decreases; with a large jump between 0.05 and 0.01



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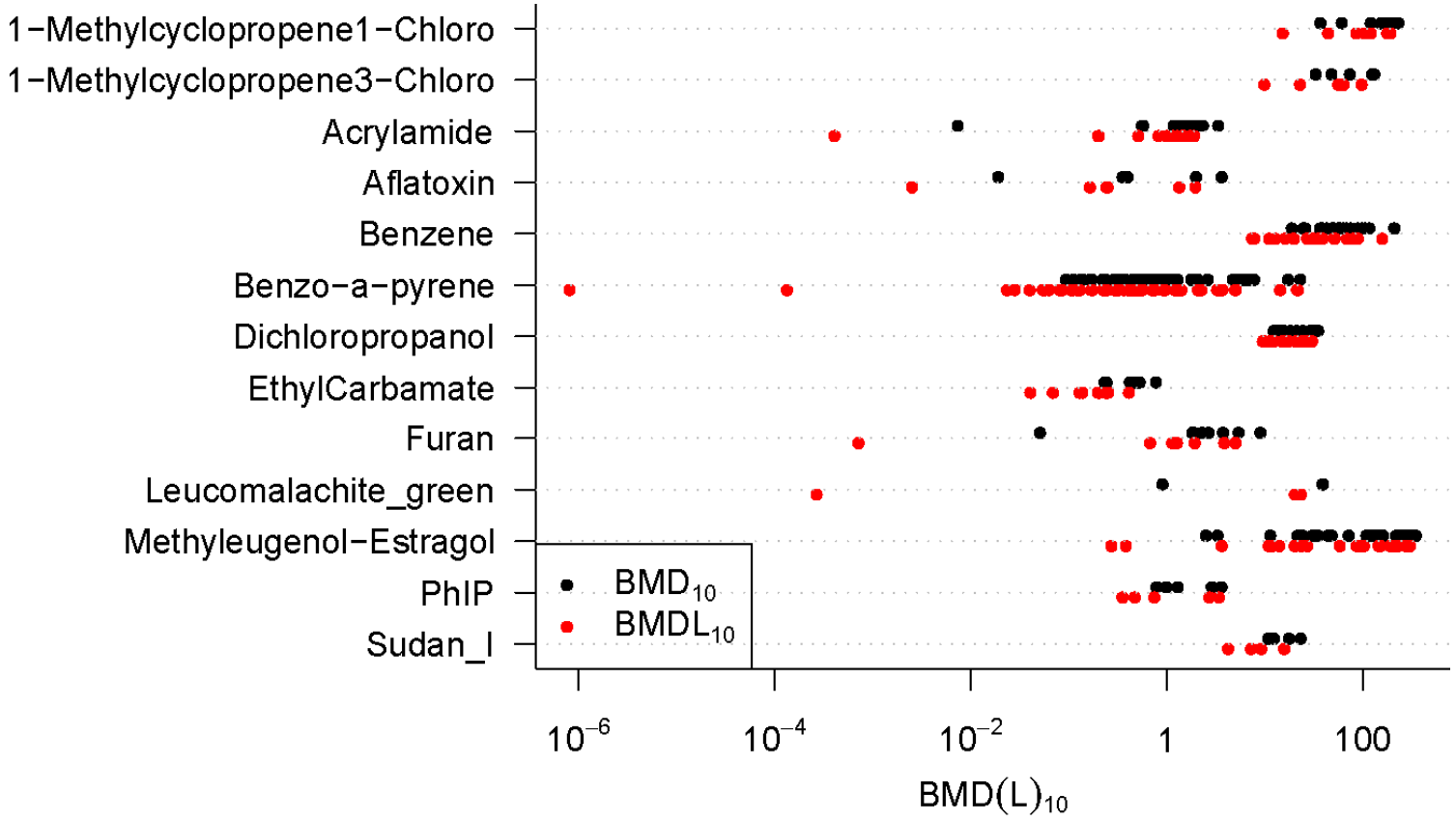
Ranges $BMD(L)_{10}$ Across Endpoints



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Summary

- Modeling is an objective and transparent way to establish points of departure for computing Margins of Exposure.
- The average model approach is practical, and gives results that characterize both statistical uncertainty and uncertainty about the true model (model uncertainty).
- What, at first glance, appears to be a failure of the methodology, that is, extremely low BMDs or BMDLs, actually are useful indicators of poor data quality.
- Standard cancer bioassay design is generally inadequate to reliably compute a PoD.
- A broader class of dose-response models (allowing response to saturate at less than 100%) is needed.
- In these data sets, BMD_{10}'s are least uncertain, followed by BMD_5's, with BMD_1's substantially more uncertain.

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End

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Summary by Chemical

			Goodness of Fit P-value		"Useful" BMD/L?		
	Total	w/Trend	≤ 0.05	> 0.05	BMD = 0	BMDL = 0	BMDL > 0
1-Methylcyclopropene (1-Chloro)	24	9	1	8	2	0	7
1-Methylcyclopropene (3-Chloro)	8	5	0	5	0	0	5
Acrylamide	18	13	1	12	0	0	13
Aflatoxin	8	8	3	5	0	2	6
Benzene	27	20	2	18	0	1	19
Benzo-a-pyrene	66	53	19	34	0	0	53
Dichloropropanol	21	17	0	17	0	0	17
EthylCarbamate	9	9	0	9	0	0	9
Furan	10	9	0	9	1	0	8
Leucomalachite_green	13	3	0	3	0	0	3
Methyleugenol-Estragol	64	32	4	28	6	1	25
PhIP	14	6	0	6	0	1	5
Sudan_I	22	7	0	7	1	2	4
Total	304	191	30	161	10	7	174