Low-dose extrapolation from points of departure (PoD) or from model-averaged estimates

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Outline

- Introduction/Motivation
- Benchmark Dose Estimation
- Low Dose Risk Extrapolation
  - Point of Departure
  - Model Averaging
- Comparison
- Conclusions

Introduction/Motivation

- PROBLEM: estimate a health risk (here, cancer) associated with exposure to a chemical hazard.
- DESIRE: quantitative estimate of risk as exposure levels of interest
- NEED: data set exhibiting a dose-response pattern for QRA
- ISSUE: data may be from expt. with relatively high doses (and may be animal study …)

Low dose risks?

- 1. extrapolate the prediction from a particular DR model to the doses of interest
- 2. fit a model to the data and determine a so-called “Point of departure” (PoD) and then a apply a linear extrapolation (LE).
- 3. something else? (hence the talk …)

1. Apply particular model…

- Select a DR model that fits the observed experimental data and then ask "what is the predicted risk for a dose of interest?"
- Often, the DR curve has little or no biological basis, and other competing models exist (and provide a similar fit to the observed data).
- ISSUE: estimates may differ dramatically between models (related to model behavior at low doses – linear/non-linear) especially in confidence limits are used

2. Point of departure & linear extrapolation …

- EPA (2005) cancer risk guidelines Use linear extrapolation from a PoD for agents - thought to be either **DNA-reactive** with **direct mutagenic activity**; associated with "human exposures or body burdens are high and near doses associated with key precursor events in the carcinogenic process" OR
- AS a **default** if **no plausible mode of action** can be inferred

BMD

- A dose, corresponding to a predefined level of risk (**BMR**), is estimated from a fitted dose-response curve.
- This estimated dose (called the Benchmark Dose **BMD**) is then used for health policy decisions (Crump 1984)
- But many models can be used for BMD estimation…

BMD as PoD

- … and competing models often estimate the dose-response curve very differently for very low risks.

- One solution: Use the **BMD** at the **PoD** for a BMR corresponding to a risk where most models produce similar estimates (e.g. BMR=10%)

- **Linear extrapolation** is used on the BMD (or BMDL) to estimate doses corresponding to the risk at the level of interest.

Linear extrapolation from PoD

- Assumed to be health protective as the linearization often represents an upper bound on the plausible risk.
- Some argue that this method disregards other model information, and leads to dose estimates that are (unnecessarily) too low.
- In this situation, some argue for non-linear models that often lead to BMD(L) estimates that differ by several orders of magnitude at the risk level of interest.

Door #3 … MA-BMD

- Model Averaging (MA) may provide an alternative approach to the PoD method.
- MA synthesizes model information and can extrapolate all model information simultaneously at low doses estimating the BMD directly

Door #4? …

- Could use the MA-BMD as the PoD and follow with a linear extrapolation …

- Now for some additional background before we compare the PoD approach with model averaging for risk analysis.

(actually, lots of options)

- 1. $BMDL_{10}$ (from model with best GOF) with LE (linear extrapolation)
- 2. min $BMDL_{10}$ and LE (PoD=min BMDL10 EFSA and JECFA in Europe – W. Slob)
- 3a. MA-$BMDL_{10}$ and LE (ILSI-Europe has used MA-BMDL10 – W. Slob)
- 3b. MA-BMD_{10} and LE
- 4. MA f(d)
- 5. mBMD=MA-BMD_{05} and then UF (Australia - Fitzgerald & Robinson, 2007)

Common Dichotomous Models:

- logistic model: $$\pi_1(d) = \frac{1}{1+\exp\left[-\left(\alpha+\beta d\right)\right]} \qquad (1)$$
- log-logistic model: $$\pi_2(d) = \gamma + \frac{(1-\gamma)}{1+\exp\left[-\left(\alpha+\beta\ln(d)\right)\right]} \qquad (2)$$
- gamma: $$\pi_3(d) = \gamma + (1-\gamma)\frac{1}{\Gamma(\alpha)}\int_0^{\beta d} t^{\alpha-1}e^{-t}\,dt \qquad (3)$$
- multistage $$\pi_4(d) = \gamma + (1-\gamma)\left[1-\exp(-\theta_1 d - \theta_2 d^2 \ldots)\right] \qquad (4)$$
- probit $$\pi_5(d) = \Phi\left(a + \beta d\right) \qquad (5)$$

Common Dichotomous Models:

- log-probit $$\pi_6(d) = \gamma + (1-\gamma)\Phi\left[a + \beta \ln(d)\right] \quad (6)$$
- quantal-linear $$\pi_7(d) = \gamma + (1-\gamma)\left[1 - \exp(-\beta d)\right] \quad (7)$$
- quantal-quadratic $$\pi_8(d) = \gamma + (1-\gamma)\left[1 - \exp(-\beta d^2)\right] \quad (8)$$
- Weibull $$\pi_9(d) = \gamma + (1-\gamma)\left[1 - \exp(-\beta d^{\alpha})\right] \quad (9)$$

where $\Gamma(\alpha)$= gamma function evaluated at α, for $\Phi(x)$ = CDF N(0,1) and $\pi_i = \gamma$ when d_i=0 for models (2) and (7).

BMD estimation and risk definitions

- Given some dose-response model $\pi(d)$, **excess risk** is often estimated as:

$$r(d) = \frac{\pi(d) - \pi(0)}{1 - \pi(0)}$$

This risk formulation, known **extra risk**, can be thought of as the Pr(adverse outcome | it would have not occurred in absence of exposure). Note: other formulations of excess risk are often used.

BMD Estimation (cont)

- The Benchmark Dose (BMD) is the dose associated with the a specified increase in response relative to the control response (BMR); i.e.:

$$BMR = \frac{\pi(BMD) - \pi(0)}{1 - \pi(0)}$$

- The BMR corresponds to the risk, and for the POD method is usually set at values of 10% (5%, 1%...).

- BMDL = 100×(1-α)% LCL on the BMD.

BMD Estimation (cont)

- Under model averaging the dose-response model is just a weighted average of all models considered.

- The MA-BMD can be defined w.r.t. the MA-$\pi(d)$, or $\pi_{MA}(d)$

Model Averaging - weights

- Given a set of dose-response [e.g, models (1)-(9)] the model average (MA) dose response curve:
  - Estimates the dose-response based upon a weighted average of specific dose-response curves Raftery et al. (1997), Buckland et al. (1997), with the MA dose-response curve estimated as:

$$\pi_{\mathrm{MA}}(d) = \sum_{i=1}^{K} \pi_i(\boldsymbol{\theta}, d) \cdot w_i$$

  - Here weights are formed as:

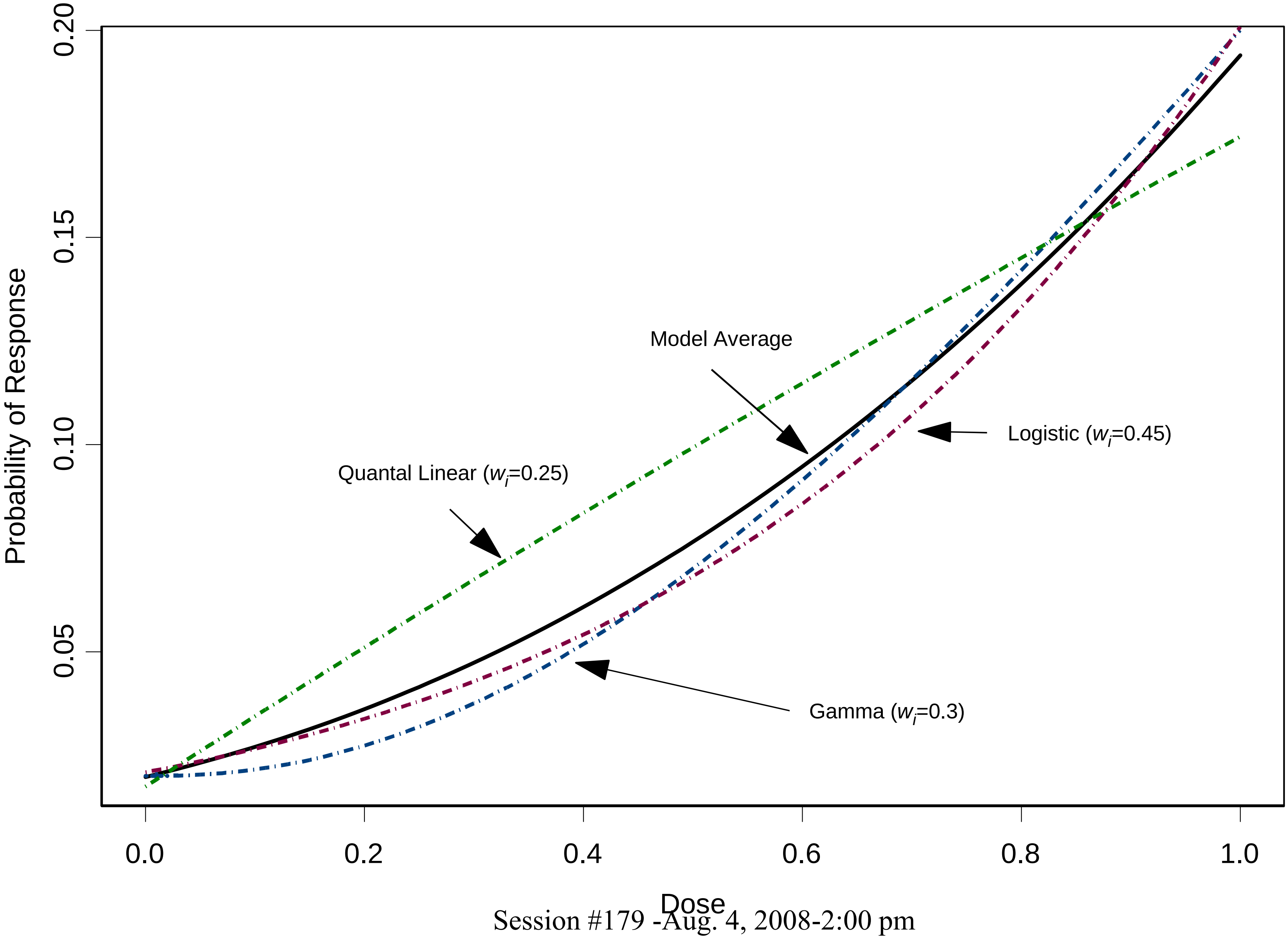
$$w_j = \frac{\exp(-I_j / 2)}{\sum_{i=1}^{K} \exp(-I_i / 2)}$$

  - Where I_i=AIC, I_i=KIC , or I_i=BIC.

Note: Other weight constructions are possible.

Model Averaging - illustrated

- For example consider a hypothetical situation where we fit the Quantal Linear, Gamma and Logistic models.
- Suppose the fit of these models yield model-specific weights w_i of 0.25, 0.30, and 0.45, respectively.


Probability of Response
0.20
0.15
0.10
0.05
0.0
0.2
0.4
0.6
0.8
1.0
Dose
Model Average
Logistic (w_i=0.45)
Quantal Linear (w_i=0.25)
Gamma (w_i=0.3)

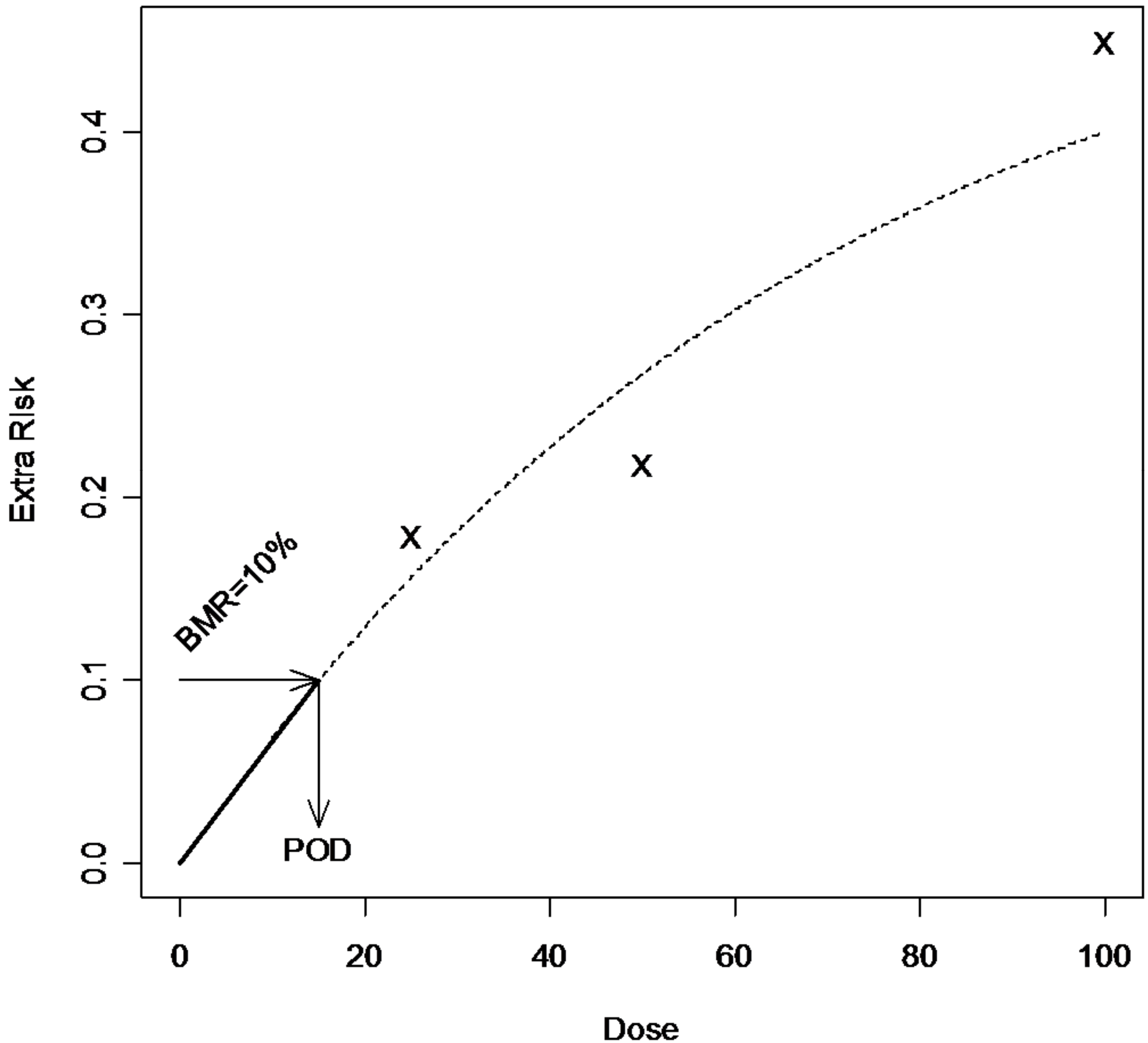
Model Averaging (cont)

- Model averaging has been found to produce estimates that exhibit minimal bias and have good coverage properties. (Wheeler and Bailer, *Risk Analysis* 2007)

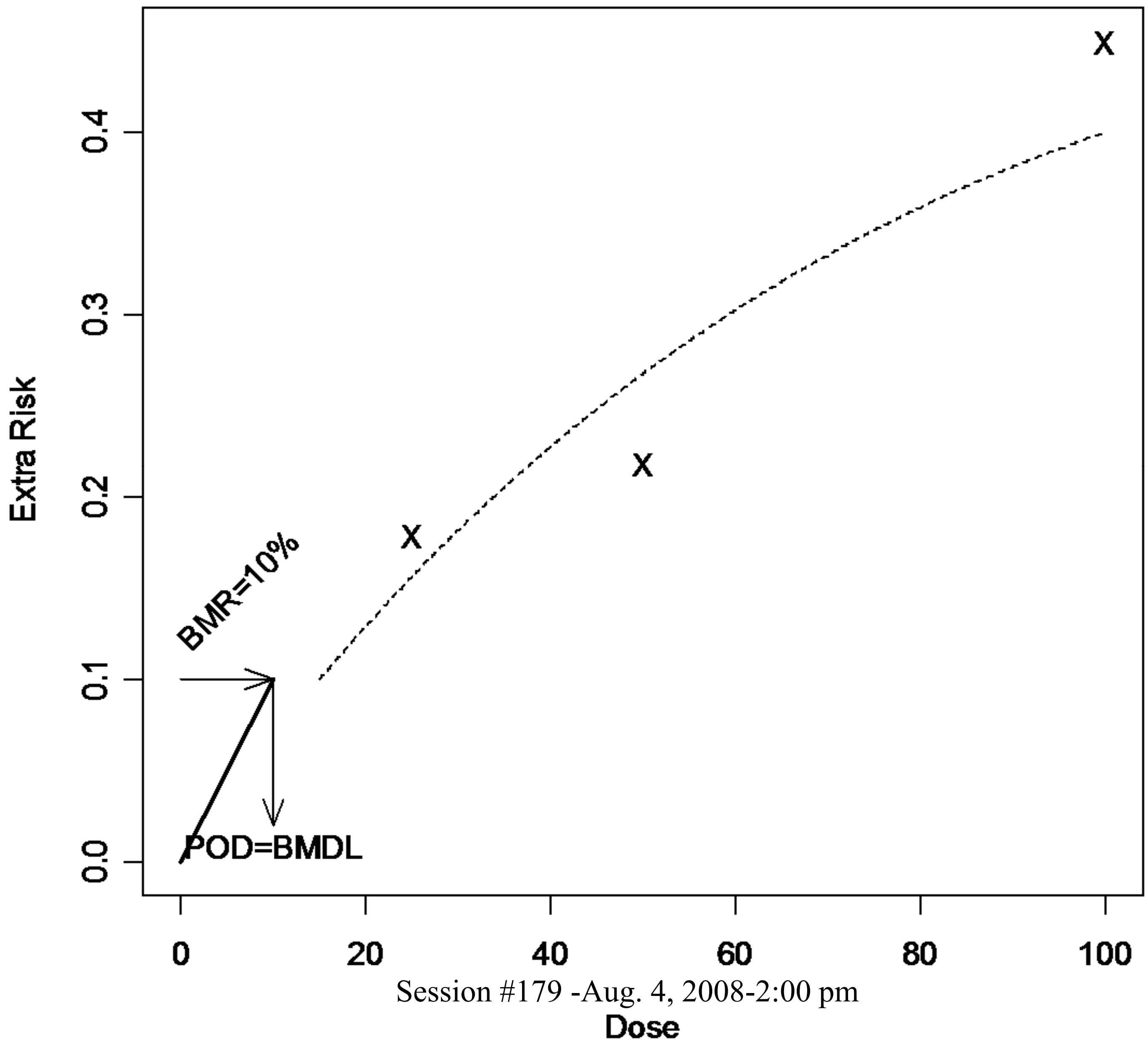
- Which is better: the PoD-LE method with MA defined PoD or MA-f(d) extrapolation estimates?

Linear Extrapolation from a PoD=BMD(L)

- Given a DR model, the PoD estimates doses associated with small risks using a linear linear extrapolation of the BMD.
- EPA cancer guidelines, as well as other authors recommend that the extrapolation be estimated using the $100\times(1-\alpha)\%$ lower bound on the BMD (i.e., the BMDL)



Extra Risk
0.0
0.1
0.2
0.3
0.4
BMR=10%
POD
X
X
X
0
20
40
60
80
100
Dose


X
0.4
0.3
Extra Risk
0.2
X
X
BMR=10%
0.1
POD=BMDL
0.0
0
20
40
60
80
100
Dose

BMD Estimation: Model Averaging

- Model averaging can can estimate the BMD at any level of risk using its own extrapolation, i.e. find BMD s.t. r(BMD)=BMR where $\pi_{MA}(d)$ is used.

- This extrapolation averages over all types of curvature considered and thus may be more robust than using a single model.

- **Question:** how much different is MA from POD Linear extrapolation method?

Comparisons: Low Risk BMD Estimation

- We estimate the Benchmark dose under several conditions and compare the behavior of the PoD-linear extrapolation approach and MA-BMD.

- These examples highlight various forms of curvature as well as sample size considerations.

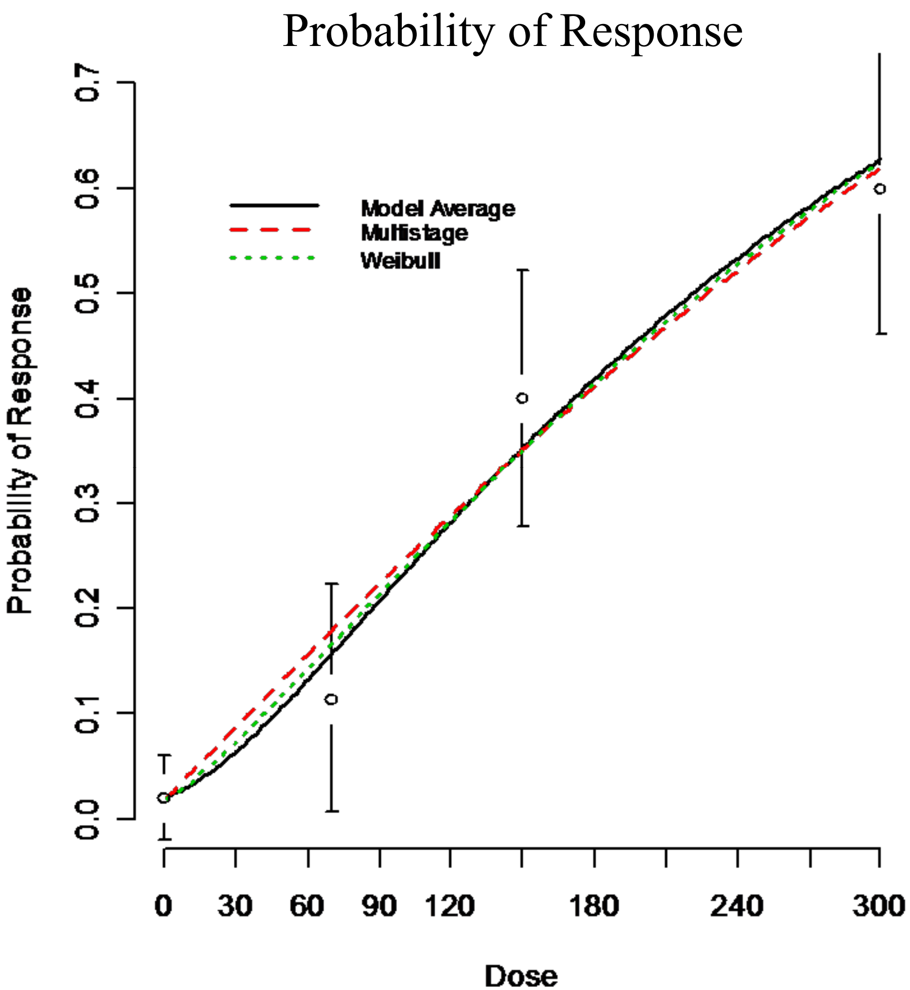
Comparisons

For all comparisons:

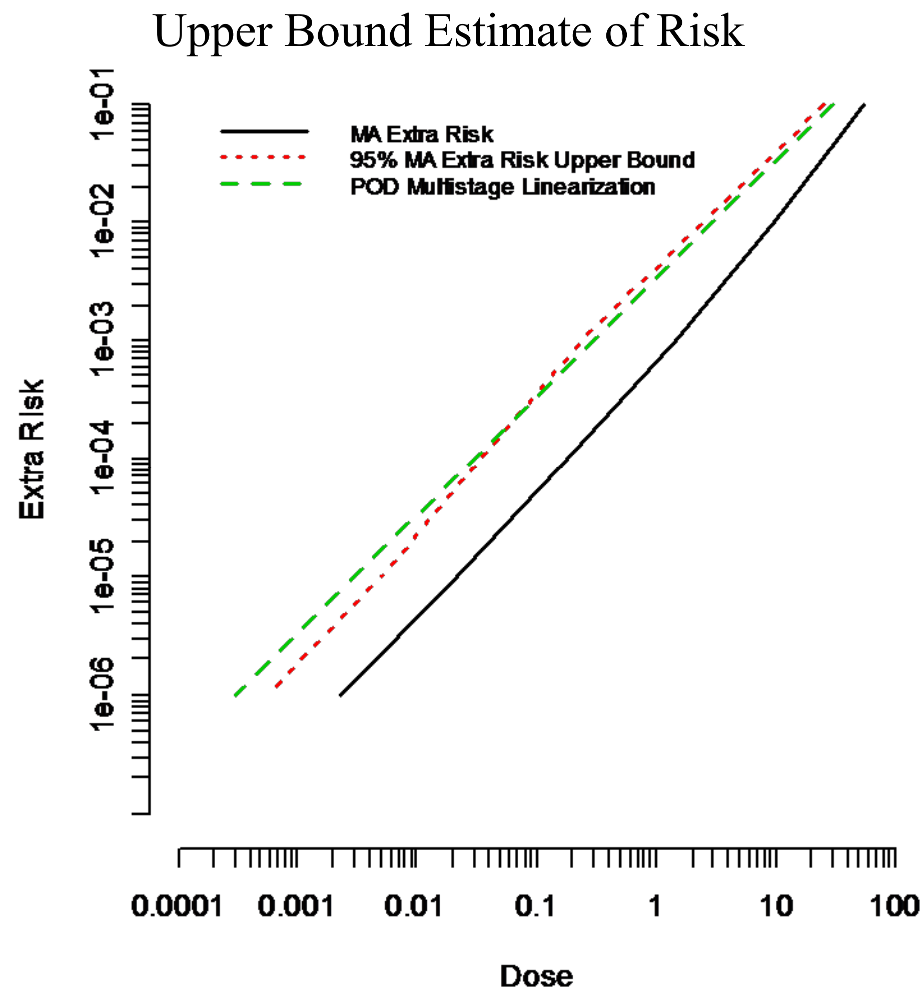
- All model average BMD/BMDL calculations were computed using models (1)-(6) and (9).
- The PoD method was estimated using the linearized multistage model. (i.e., model (4) where the polynomial degree was set to 2) .
- Where noted other non-linear models were also investigated.

Example 1:

- Consider the dose response data from NTP TR-405.
- Here rats were exposed to CI Acid Red 114 in their drinking water at levels of 0,70,150,and 300 ppm.
- Basil Cell Adenoma was the measured response and occurred in 1/50, 4/35, 26/65, and 30/50 rats respective of the above dose groups.



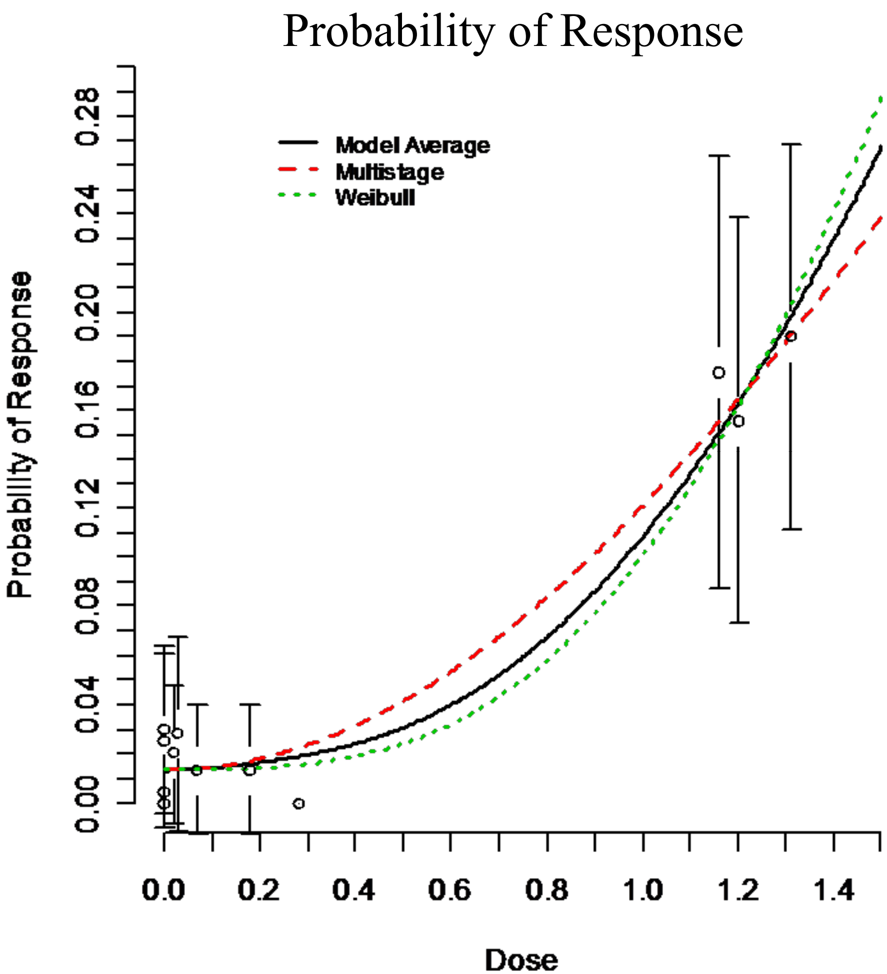
Probability of Response
Probability of Response
Model Average
Multistage
Weibull
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
30
60
90
120
180
240
300
Dose



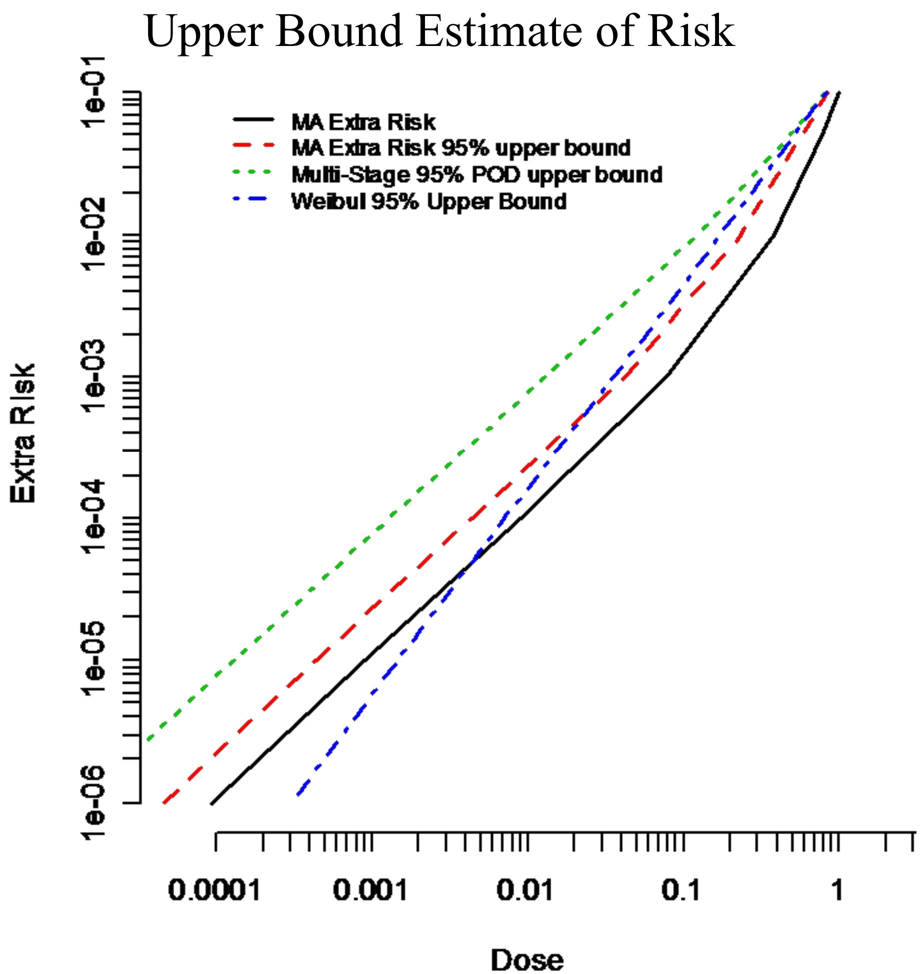
Upper Bound Estimate of Risk
Extra Risk
MA Extra Risk
95% MA Extra Risk Upper Bound
POD Multistage Linearization
1e-06
1e-05
1e-04
1e-03
1e-02
1e-01
0.0001
0.001
0.01
0.1
1
10
100
Dose

Example 2

- Consider TiO_2 lung tumor data which has been combined from the studies of Heinrich et al. (1995) Muhle et al. (1991) and Lee et al. (1985).
- In this combined data set there are 9 total dose groups (including the zero dose)



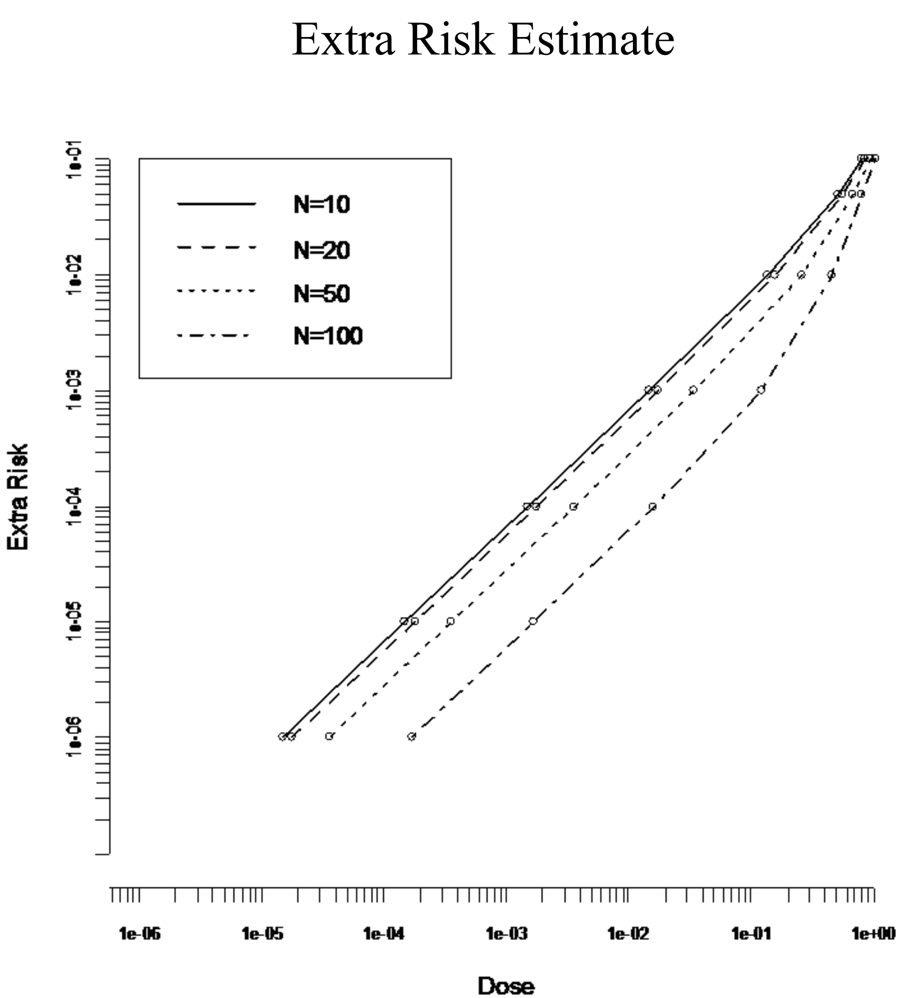
Probability of Response
Model Average
Multistage
Weibull
Probability of Response
0.00
0.04
0.08
0.12
0.16
0.20
0.24
0.28
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
Dose

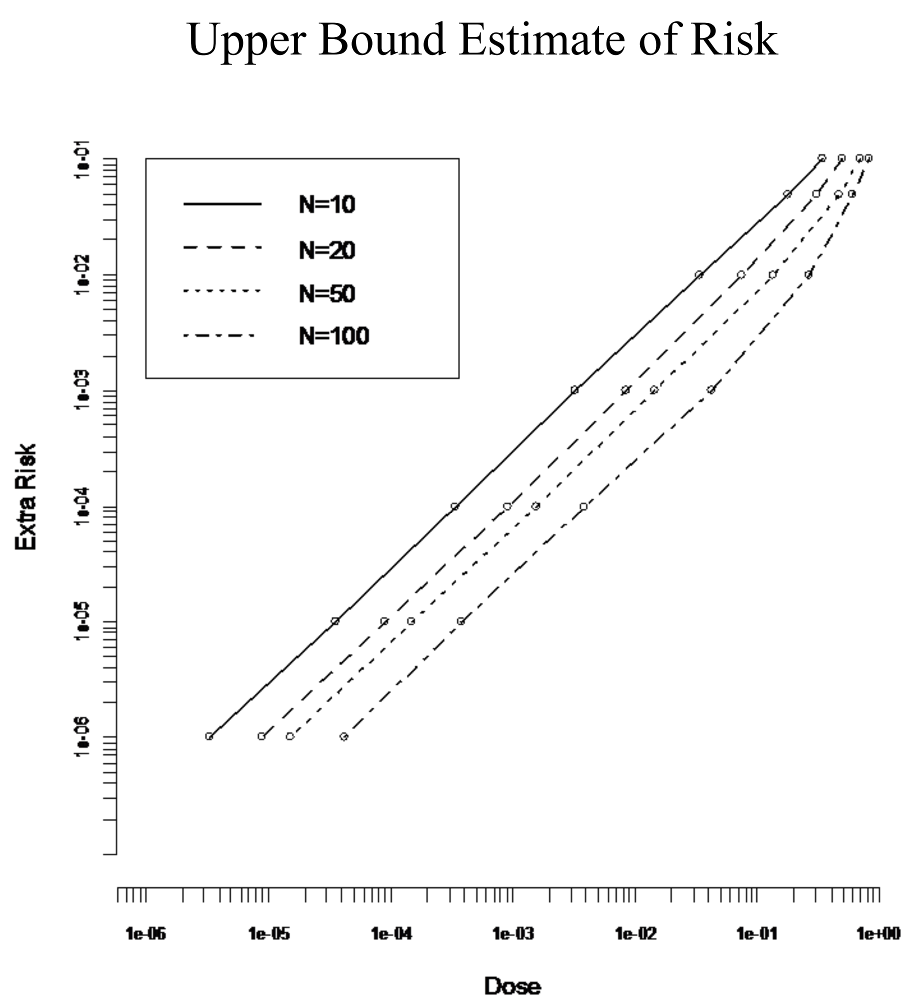


Upper Bound Estimate of Risk
MA Extra Risk
MA Extra Risk 95% upper bound
Multi-Stage 95% POD upper bound
Weibul 95% Upper Bound
Extra Risk
1e-06
1e-05
1e-04
1e-03
1e-02
1e-01
0.0001
0.001
0.01
0.1
1
Dose

(Simulated) Example 3

- Finally consider a fixed true DR: 20%, 20%, 20%, 50%, 90%, at doses of 0, 0.5, 1, 2 and 4.
- Further consider simulated experiments generated with n = 10, 20, 50 and 100, at each dose (given the above response).
- Thus we have the same response, all we do is increase the sample size. We ask the question how does MA-BMD perform?


Extra Risk Estimate
N=10
N=20
N=50
N=100
Extra Risk
Dose
1e-06
1e-05
1e-04
1e-03
1e-02
1e-01
1e+00


Upper Bound Estimate of Risk
N=10
N=20
N=50
N=100
Extra Risk
Dose
1e-06
1e-05
1e-04
1e-03
1e-02
1e-01
1e+00

Comparisons: Trends

- The three examples show some basic trends:
  - In nearly linear dose-response cases, MA produces almost identical results as the PoD method.
  - In non-linear dose-response cases, MA produces different but similar results. Further these results differ by $<10\times$ (e.g. example 2).
  - As the sample size increases the non-linearity of the dose response slowly is included in the MA risk estimates.
  - MA quickly produces an upper bound on risk that is low-dose linear.

Conclusions

- Using model averaging is very similar to the PoD method.
- MA-BMD decreases linearly with risk, which is dependent on the sample size, and curvature assumptions.
- The MA-BMD estimates, especially in the low dose region are nearly identical to a linear extrapolation from the MA chosen point of departure.

More to do …

- All methods may yield est. dose < true dose associated with particular risk level.
- Costs increase as (true dose – est. dose) increases
- Simulation comparison of alternatives is needed

Thanks for your attention!