Bayesian Benchmark Dose Analysis for Probabilistic Risk Assessment – Another Revolution in Dose-Response Assessment

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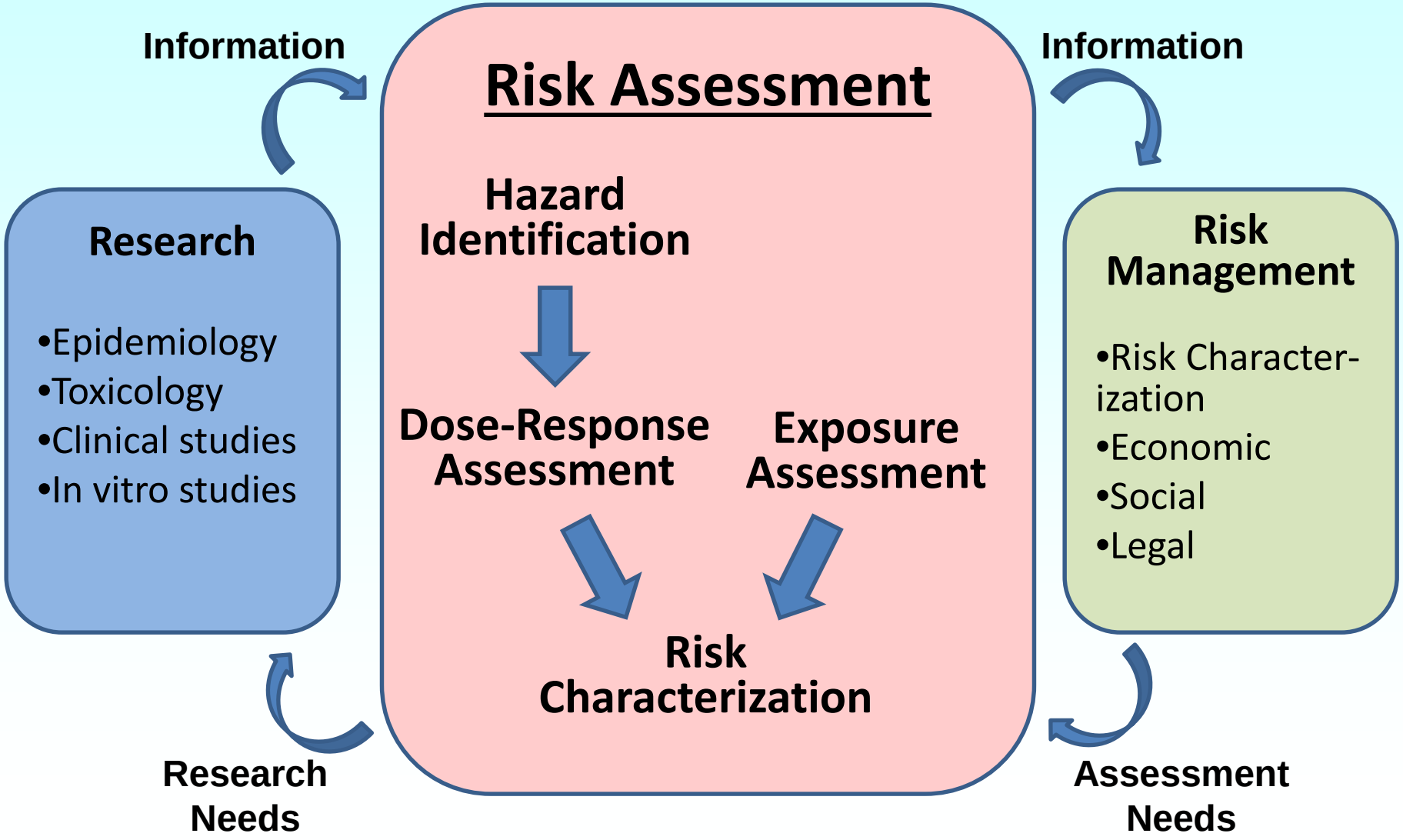
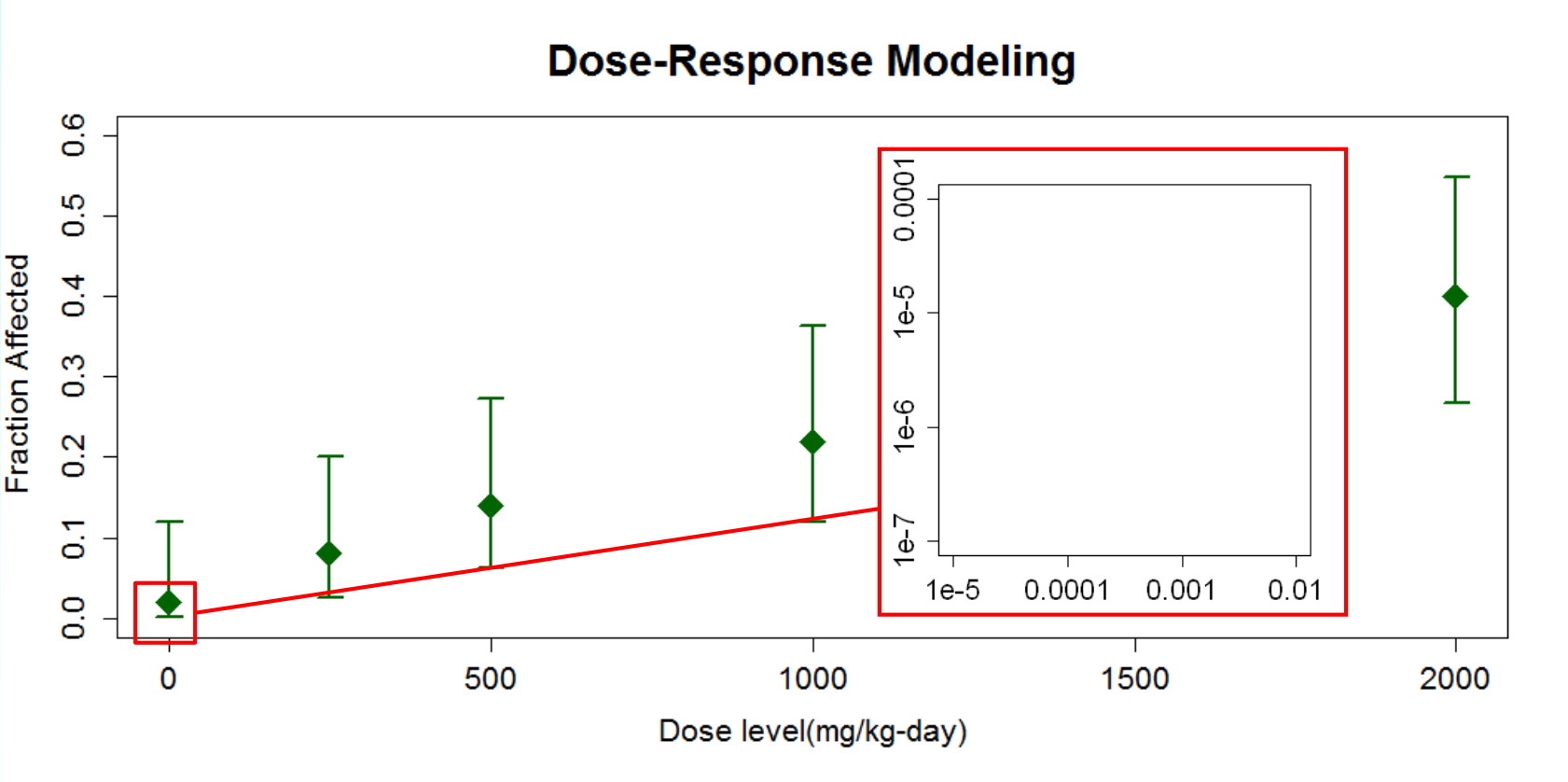
Outline of the Presentation

- Introduction on benchmark dose method
  - In a Bayesian framework
- Introduction on the features of BBMD
  - Cross platform
  - Probabilistic
  - Reliability
  - Advanced BMD estimation (model averaging available)
  - Analyzing epidemiological data
  - Probabilistic low-dose extrapolation
- Plan for future development

NRC Risk Analysis Paradigm



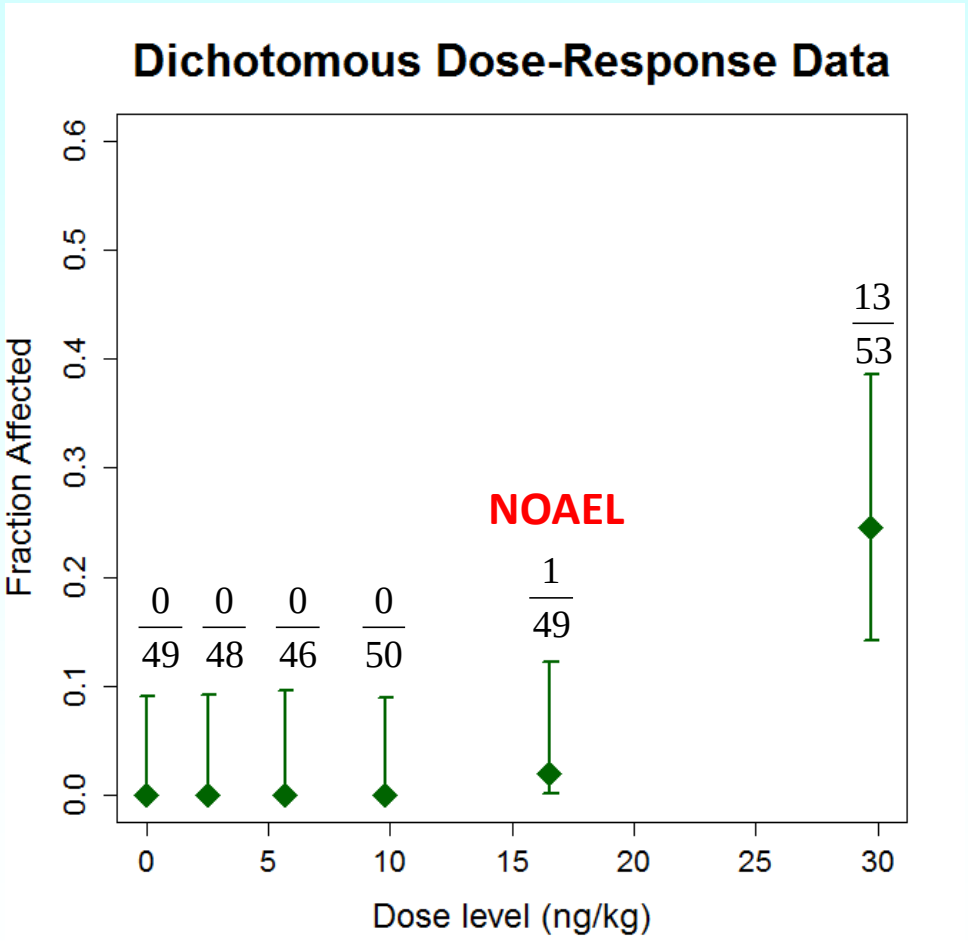
Dose-Response Analysis



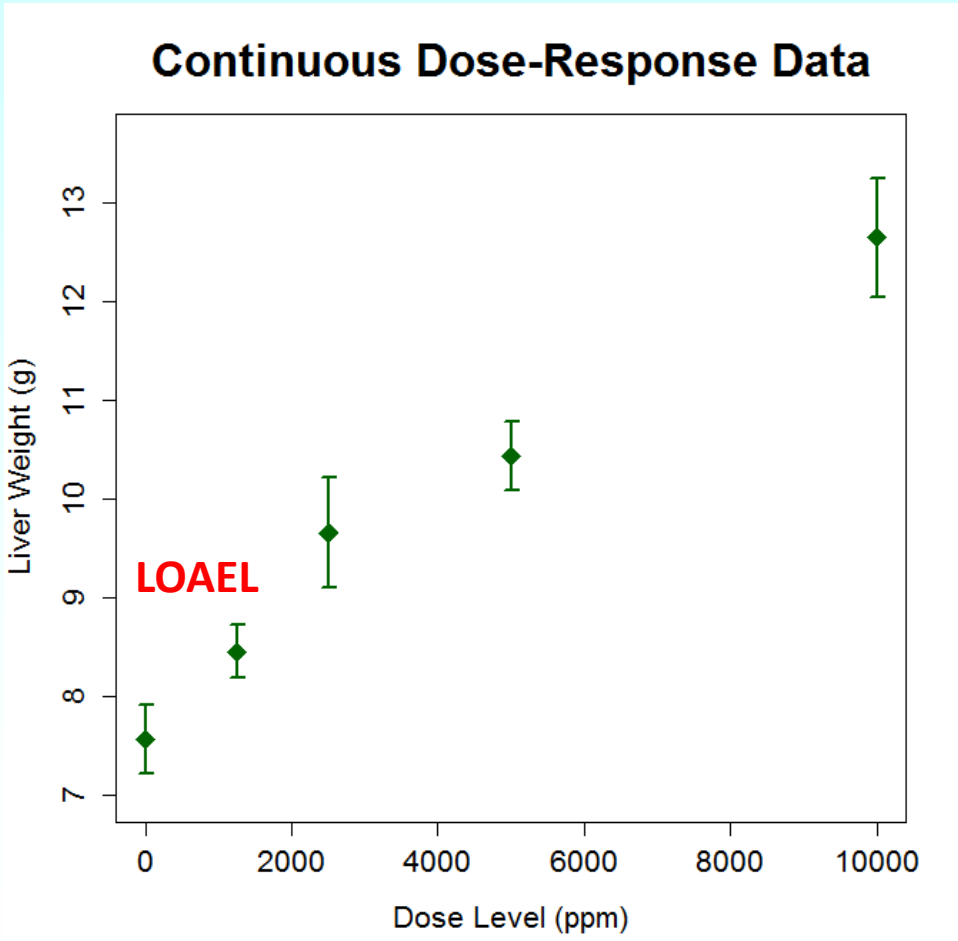
- **Step 1: Deriving Point of Departure (POD)**
- **Step 2: Inference (or “Extrapolation”)**

POD Derivation – Traditional Method

- NOAEL/LOAEL

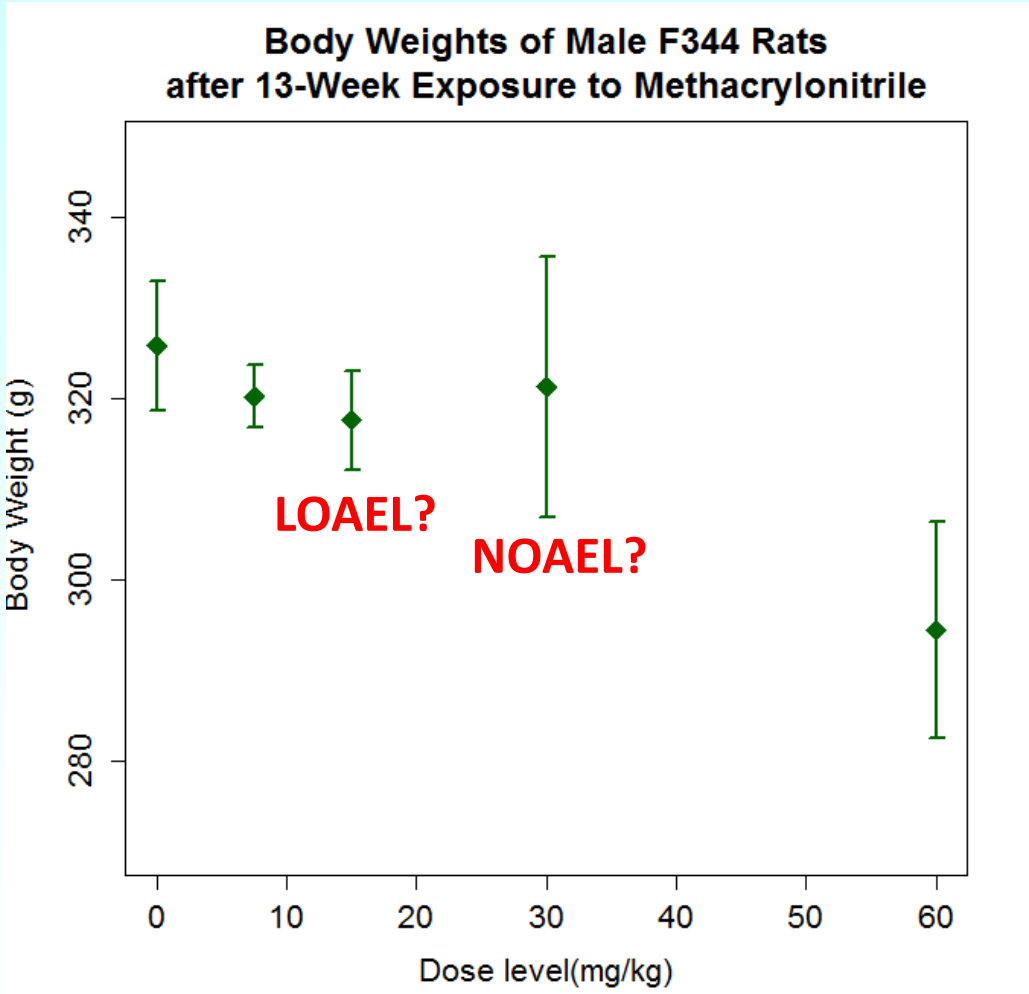


(Data from NTP 2006)



(Data from NTP 2006)

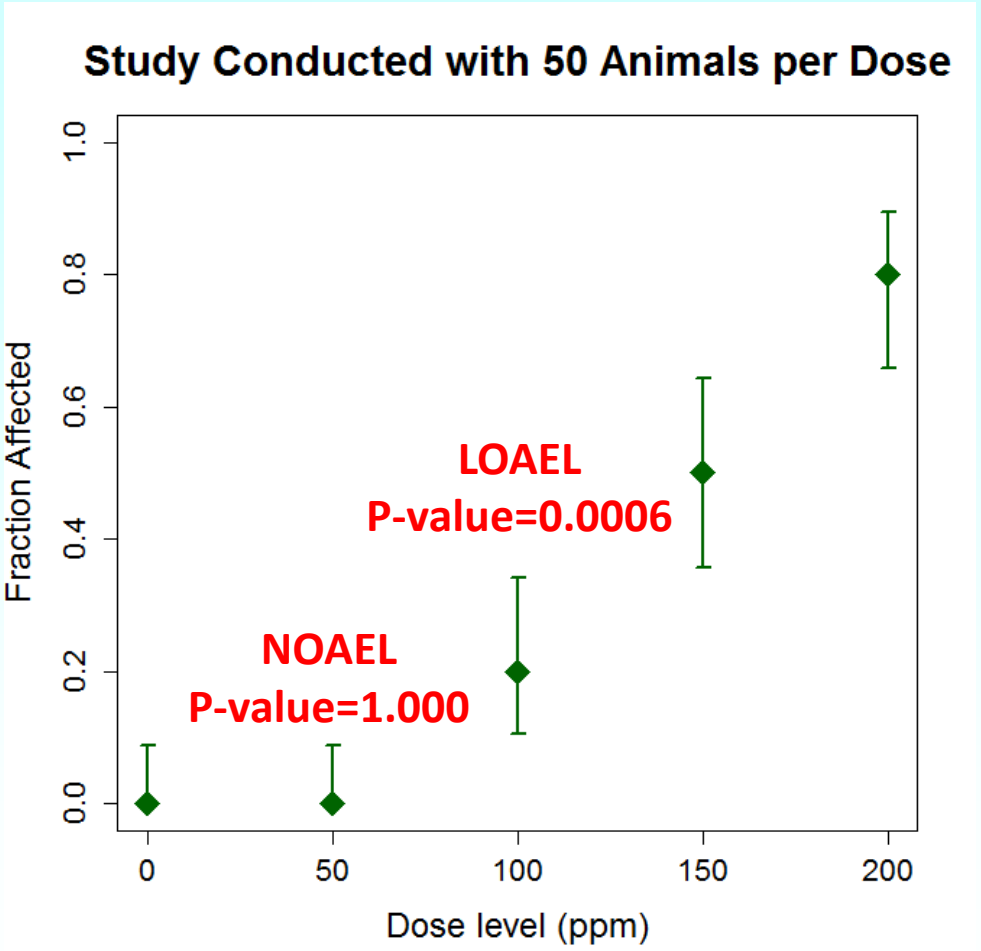
Limitations of NOAEL/LOAEL

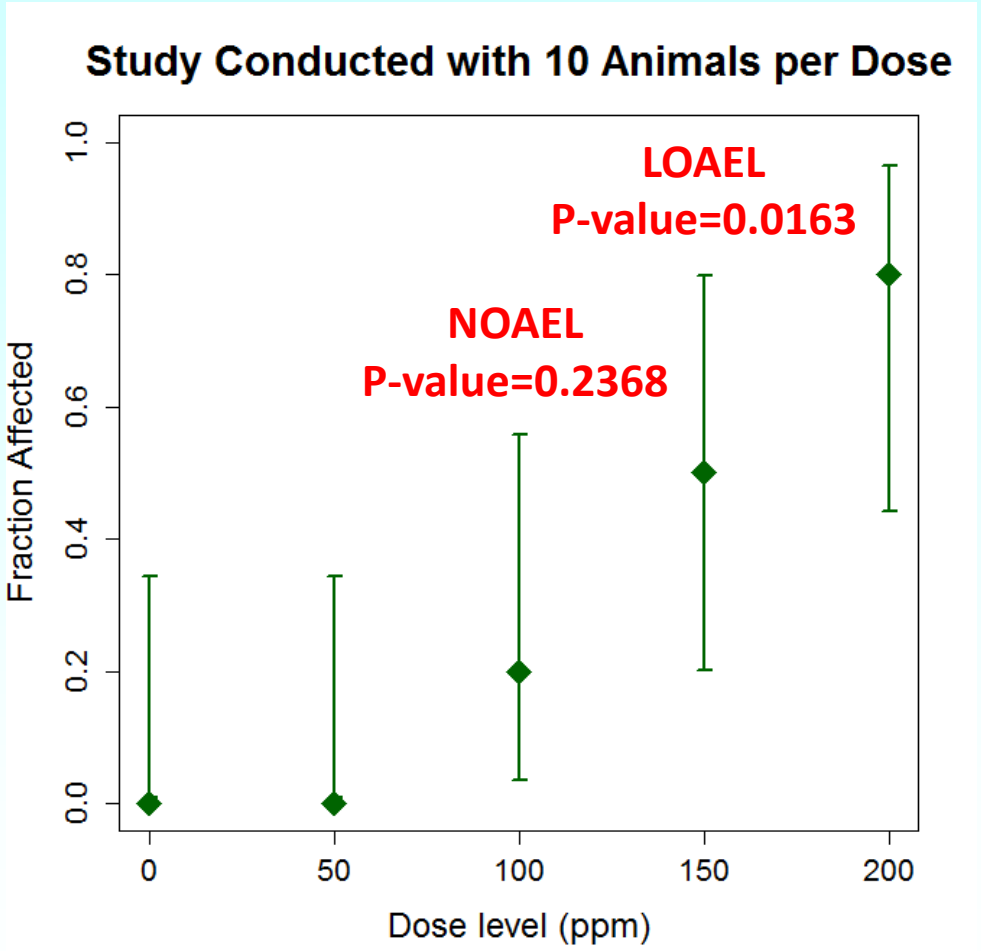


(Data from NTP, 2000)

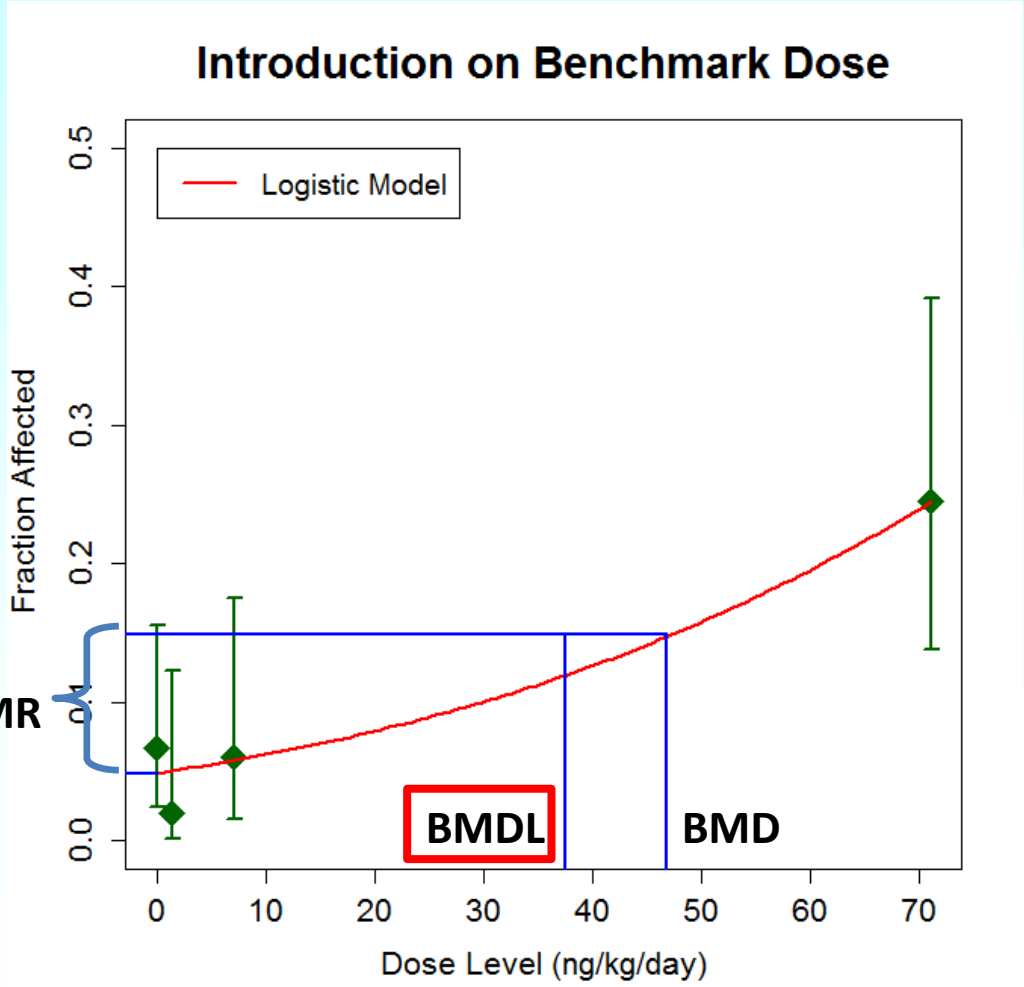
- Highly depends on study design
- Partially uses the information in toxicity study
- Improperly characterizes the uncertainty in responses

NOAEL's Inappropriateness in Quantifying Uncertainty





Benchmark Dose Methodology



- BMD Steps:
  - Fit a DR model
  - Define Benchmark Response (BMR)
  - Calculate BMD/ BMDL
- BMD recognized
  - FAO/WHO (2006)
  - EFSA (2009)
  - US EPA (2012)

Advantages of BMD Approach

Subject	BMD Approach
Dose selection	BMD and BMDL not constrained to be a dose used in study
Sample size	Appropriately considers sample size: as sample size decreases, uncertainty in true response rate increases (i.e., ↓ N = ↓ BMDL)
Cross-study comparison	Observed response levels at a selected BMR are comparable across studies (recommended to use BMD as point of comparison)
Variability and uncertainty in experimental results	Characteristics that influence variability or uncertainty in results (dose selection, dose spacing, sample size) are taken into consideration
Dose-response information	Full shape of the dose-response curve is considered
NOAEL not identified in study	A BMD and BMDL can be calculated even when a NOAEL is missing from the study

Bayesian Benchmark Dose Method

- Most important features of Bayesian BMD
  - Probabilistic estimation
  - Ability to incorporate existing information

- First Revolution in DR assessment
  - NOAEL → BMD
- Second Revolution
  - Point BMD → Probabilistic BMD

- Bayesian BMD (BBMD) estimation system

Frequentist vs. Bayesian

- Frequentist: Parameter (θ) is a fixed but unknown quantity.
  - Using samples to estimate the quantity
  - Different sample may result in different estimates – resulting sampling distribution
- Bayesian: Parameter (θ) is considered as a random variable
  - Using distribution to describe the random variable
  - A state of belief, using data to update the belief

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- Introduction on the features of BBMD
  - Cross platform
  - Probabilistic
  - Reliability
  - Advanced BMD estimation (model averaging available)
  - Analyzing epidemiological data
  - Probabilistic low-dose extrapolation
- Plan for future development

Feature I: Web-based Application

- Available at:
  - https://benchmarkdose.com (or https://benchmarkdose.org)

- Cross-platform accessibility (i.e., not limited by Operation System, Windows, Mac or Linux), anytime and anywhere (with internet access)

- Full Bayesian Analysis featuring the use of Markov Chain Monte Carlo (MCMC)

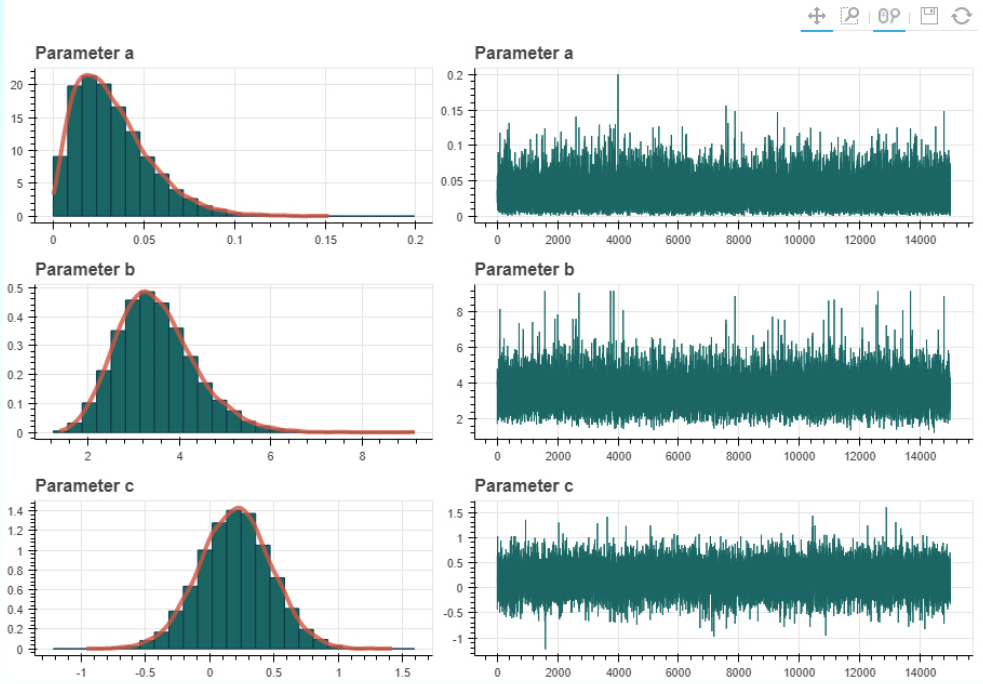
Feature II: Probabilistic Estimates

- Graphical and Textual output of parameter estimation

Correlation matrix:

	a	b	c
a	1	0.284	-0.149
b	0.284	1	0.490
c	-0.149	0.490	1

Parameter charts:



Weibull fit summary

Pystan version: 2.17.0.0

Power parameter lower-bound: 1

```
Inference for Stan model: anon_model_c080672f617d0e7adea9de34dd07fac8.
1 chains, each with iter=30000; warmup=15000; thin=1;
post-warmup draws per chain=15000, total post-warmup draws=15000.

       mean se_mean     sd   2.5%    25%    50%    75%  97.5%  n_eff   Rhat
a      0.03  2.0e-4   0.02 4.4e-3   0.02   0.03   0.04   0.08  10355    1.0
b      2.93  7.8e-3   0.75   1.71   2.42   2.85   3.34   4.63   9176    1.0
c      0.82  1.7e-3   0.16   0.54   0.71   0.81   0.92   1.15   8338    1.0
lp__ -83.84    0.02   1.33 -87.32 -84.44 -83.48 -82.87 -82.34   5413    1.0

Samples were drawn using NUTS at Tue Dec  5 12:34:58 2017.
For each parameter, n_eff is a crude measure of effective sample size,
and Rhat is the potential scale reduction factor on split chains (at
convergence, Rhat=1).
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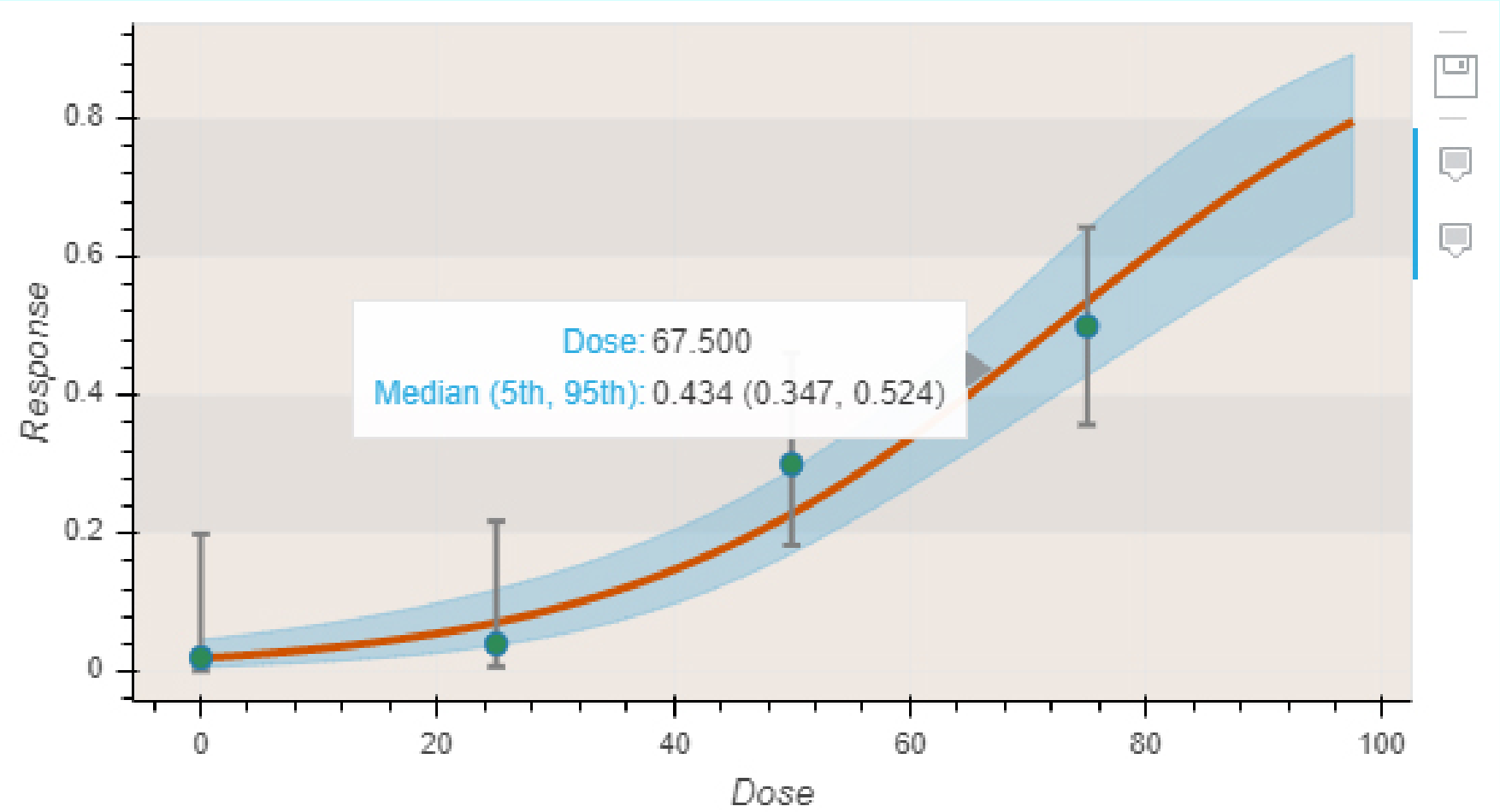
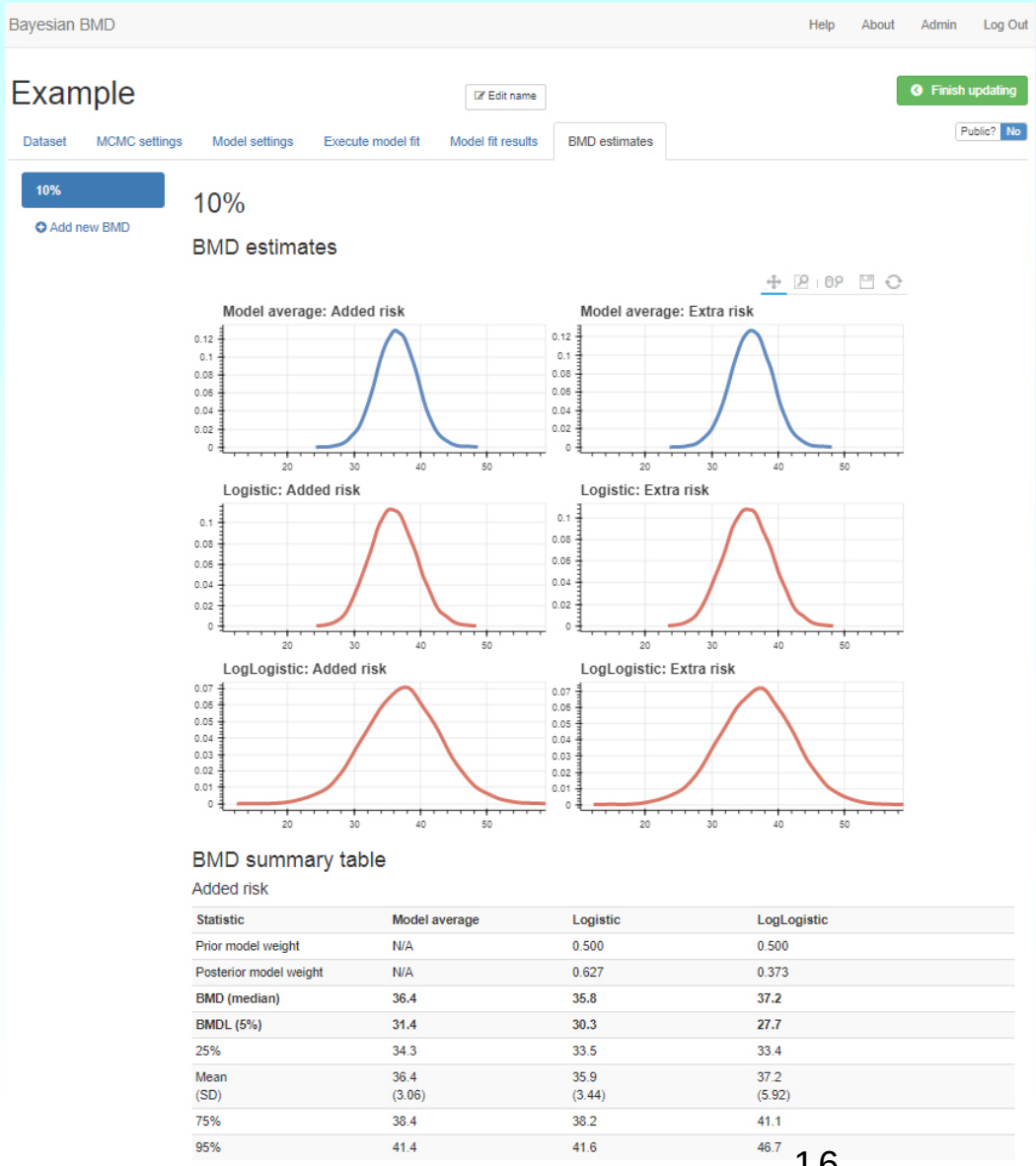
Feature II: Probabilistic Estimates

- Interactive dose-response plot - Visual inspection



Feature II: Probabilistic Estimates

- Probabilistic BMD estimation for individual models and model averaged BMD
  - BMDs estimated from individual continuous model
  - Model averaged BMD estimates



Statistic	Model average	Logistic	LogLogistic
Prior model weight	N/A	0.500	0.500
Posterior model weight	N/A	0.627	0.373
BMD (median)	**36.4**	**35.8**	**37.2**
BMDL (5%)	**31.4**	**30.3**	**27.7**
25%	34.3	33.5	33.4
Mean (SD)	36.4 (3.06)	35.9 (3.44)	37.2 (5.92)
75%	38.4	38.2	41.1
95%	41.4	41.6	46.7

Feature III: Reliability of BBMD

Comparison of BBMD and BMDS for Dichotomous Data

	Quantal-linear	Logistic	Probit	Weibull	Multistage 2	LogLogistic	LogProbit	Dich Hill
BMDS								
No. of Failed BMD	0	0	0	12	0	0	4	773[a]
No. of Failed BMDL	0	8	0	12	1	0	8	833[a]
BMD/BMDL Ratio (at BMR=0.1)	1.51 (1.21 ~ 2.69)	1.30 (1.13 ~ 3.19)	1.31 (1.15 ~ 3.03)	1.70 (1.20 ~ 8.41)	1.62 (1.18 ~ 5.73)	1.89 (1.21 ~ 10.5)	1.49 (1.20 ~ 4.75)	1.69 (1.11 ~ 10.3)
BMD/BMDL Ratio (at BMR=0.01)	1.51 (1.21 ~ 2.67)	1.50 (1.22 ~ 15.5)	1.51 (1.20 ~ 13.9)	2.51 (1.24 ~ 56.2)	2.14 (1.24 ~ 18.6)	3.22 (1.42 ~ 68.0)	1.65 (1.24 ~ 10.2)	4.91 (1.23 ~ 93.6)
No. of Reduced Model	NA	NA	NA	183 to QuantalLinear	184 to QuantalLinear	31 to Logistic	63 to Probit	124 to LogLotistic
BBMD								
No. of Failed BMD	0	0	0	0	0	0	0	0
No. of Failed BMDL	0	0	0	0	0	0	0	0
BMD/BMDL Ratio (at BMR=0.1)	1.53 (1.21 ~ 2.51)	1.29 (1.09 ~ 2.20)	1.29 (1.10 ~ 2.06)	1.69 (1.12 ~ 4.39)	1.60 (1.24 ~ 2.59)	1.77 (1.13 ~ 5.40)	1.47 (1.08 ~ 3.81)	2.31 (1.19 ~ 190.7)[b]
BMD/BMDL Ratio (at BMR=0.01)	1.53 (1.21 ~ 2.50)	1.51 (1.22 ~ 4.30)	1.50 (1.20 ~ 3.92)	3.38 (1.42 ~ 17.5)	2.23 (1.31 ~ 3.49)	3.56 (1.51 ~ 19.36)	2.00 (1.28 ~ 7.01)	4.23 (1.35 ~ 593)[b]
Comparison								
Correlation Coef. For BMD	0.991	0.998	0.997	0.842	0.969	0.830	0.857	0.837
Correlation Coef. For BMDL	1.000	0.985	0.978	0.945	0.988	0.898	0.955	0.855
Ratio of BMDs	1.00 (0.829 ~ 1.18)	1.02 (0.714 ~ 1.25)	1.02 (0.494 ~ 1.32)	1.57 (0.481 ~ 24.7)	0.929 (0.205 ~ 1.67)	1.54 (0.737 ~ 29.8)	1.58 (0.865 ~ 8.98)	1.26 (0.530 ~ 29.8)
Ratio of BMDLs	1.00 (0.888 ~ 1.89)	1.03 (0.973 ~ 2.44)	1.02 (0.942 ~ 2.71)	1.68 (1.02 ~ 9.63)	1.06 (0.530 ~ 1.29)	1.93 (1.05 ~ 18.0)	1.66 (1.06 ~ 6.10)	1.59 (0.079 ~ 21.5)

[a] The BMDS directly reports "error" for BMD and BMDL when the number of dose groups is fewer than the number of model parameters in the Dichotomous Hill model. 186 out of the 518 datasets have only 3 dose groups, therefore, 744 (=186×4) in these failed BMDs or BMDLs are due to insufficient dose groups.
[b] For the BMD/BMDL ratios calculated using the Dichotomous Hill model in the BBMD system, all results from the 518 datasets (including those having only three dose groups) are included. (From Shao and Shapiro, 2017, in press)

Feature III: Reliability of BBMD

Comparison of BBMD and BMDS for Continuous Data

	Linear	Power	Hill	Exponential 2	Exponential 3	Exponential 4	Exponential 5
BMDS							
No. of Failed BMD	2	0	34[a]	0	0	2	36[a]
No. of Failed BMDL	2	2	38[a]	1	1	3	37[a]
BMD/BMDL Ratio (at rel change=0.1)	1.28 (1.07 ~ 2.85)	1.39 (1.05 ~ 12.9)	2.16 (1.08 ~ 1.72e7)	1.28 (1.07 ~ 2.14)	1.34 (1.07 ~ 6.97)	1.54 (1.09 ~ 207)	2.16 (1.13 ~ 441)
BMD/BMDL Ratio (at rel change=0.01)	1.28 (1.07 ~ 2.85)	1.85 (1.07 ~ 33.4)	4.49 (1.20 ~ 1.32e6)	1.27 (1.07 ~ 2.14)	1.63 (1.07 ~ 46.96)	1.65 (1.11 ~ 211)	4.64 (1.32 ~ 985)
No. of Reduced Model	NA	52 to Linear	NA	NA	57 to Exponential 2	24 to Exponential 2	22 to Exponential 3/4
BBMD							
No. of Failed BMD	0	0	1	0	0	0	0
No. of Failed BMDL	0	0	1	0	0	0	0
BMD/BMDL Ratio (at rel change=0.1)	1.27 (1.07 ~ 2.28)	1.33 (1.06 ~ 4.50)	2.05 (1.12 ~ 11.3)[b]	1.25 (1.07 ~ 2.16)	1.30 (1.06 ~ 5.66)	1.59 (1.17 ~ 22.5)	1.98 (1.06 ~ 32.5)[b]
BMD/BMDL Ratio (at rel change=0.01)	1.27 (1.07 ~ 2.28)	3.07 (1.13 ~ 23.0)	3.91 (1.44 ~ 36.1)[b]	1.25 (1.07 ~ 2.16)	3.29 (1.12 ~ 25.1)	1.69 (1.22 ~ 19.6)	3.95 (1.44 ~ 25.8)[b]
Comparison							
Correlation Coef. For BMD	0.999	0.946	0.822	0.989	0.919	0.960	0.805
Correlation Coef. For BMDL	0.994	0.960	0.927	0.992	0.950	0.861	0.847
Ratio of BMDs	0.988 (0.685 ~ 1.29)	1.22 (0.797 ~ 34.0)	1.13 (0.036 ~ 1537)	0.988 (0.823 ~ 1.27)	1.34 (0.848 ~ 32.8)	0.874 (0.113 ~ 1.32)	1.05 (0.093 ~ 7.57)
Ratio of BMDLs	0.994 (0.719 ~ 2.09)	1.43 (0.916 ~ 10.0)	1.68 (0.639 ~ 4.5e6)	0.986 (0.802 ~ 1.37)	1.41 (0.954 ~ 11.7)	0.871 (0.039 ~ 94.3)	1.30 (0.080 ~ 181)

[a] The BMDS directly reports "error" for BMD and BMDL when the number of dose groups is fewer than the number of model parameters in the Hill model and Exponential 5 model. 16 out of the 108 datasets have only 3 dose groups, therefore, 32 (=16×2) in these failed BMDs or BMDLs are due to insufficient dose groups.

[b] For the BMD/BMDL ratios calculated using the Hill model and Exponential 5 model in the BBMD system, all results from the 108 datasets (including those having only three dose groups) are included. (Cited from Shao and Shapiro, 2017 in press)

Feature IV: Advanced BMD Calculation

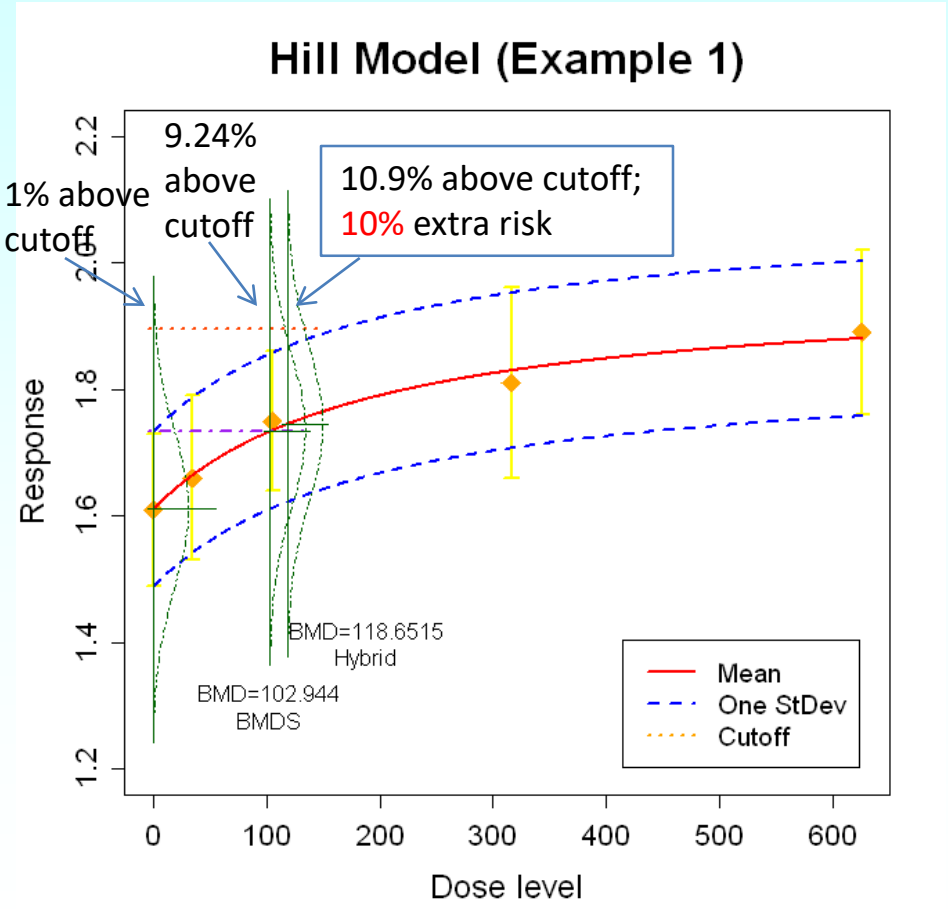
- BBMD: posterior predictive p-value (PPP):
  - Use likelihood as the key statistic
  - Likelihood value of predicted responses and original data are calculated and compared
  - 0.05 <= PPP <= 0.95
- BBMD: model weight
  - Compute model weight was introduced in Wasserman (2000) using two equations below:
  - $$\Pr(\mathcal{M}_j|Data) = \frac{\hat{m}_j}{\sum_{k=1}^{K}\hat{m}_k} \qquad \log(\hat{m}_j) = \hat{\ell}_j - \frac{q_j}{2}\log(n)$$

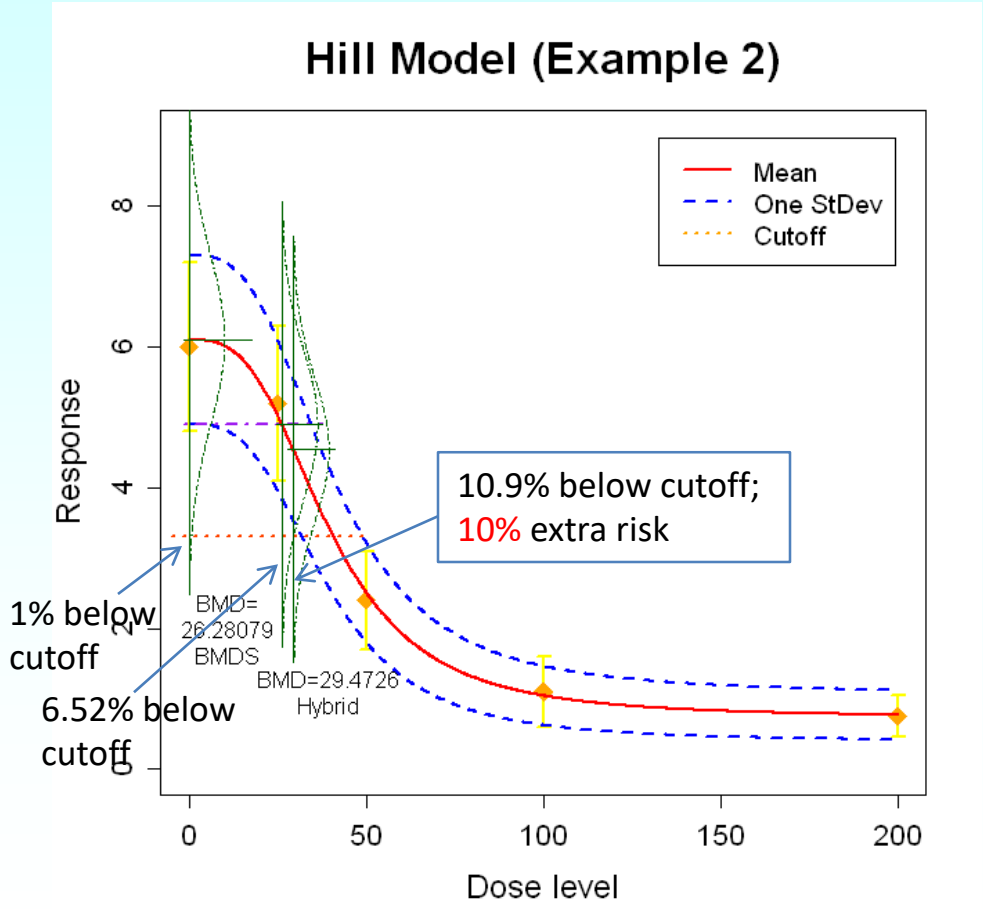
Feature IV: Advanced BMD Calculation

- Model averaged BMD for dichotomous and continuous data (Shao et al 2018)
  - The model averaged BMD can be expressed as:
    - $\Pr(BMD_{ma}|Data) = \sum_{k=1}^{K} \Pr(BMD_k|\mathcal{M}_k, Data)\Pr(\mathcal{M}_k|Data)$
    - $\Pr(\mathcal{M}_j|Data) = \frac{\hat{m}_j \Pr(\mathcal{M}_j)}{\sum_{k=1}^{K} \hat{m}_k \Pr(\mathcal{M}_k)}$
- Define BMD based on central tendency or tails for continuous data
  - Traditional approach and hybrid approach

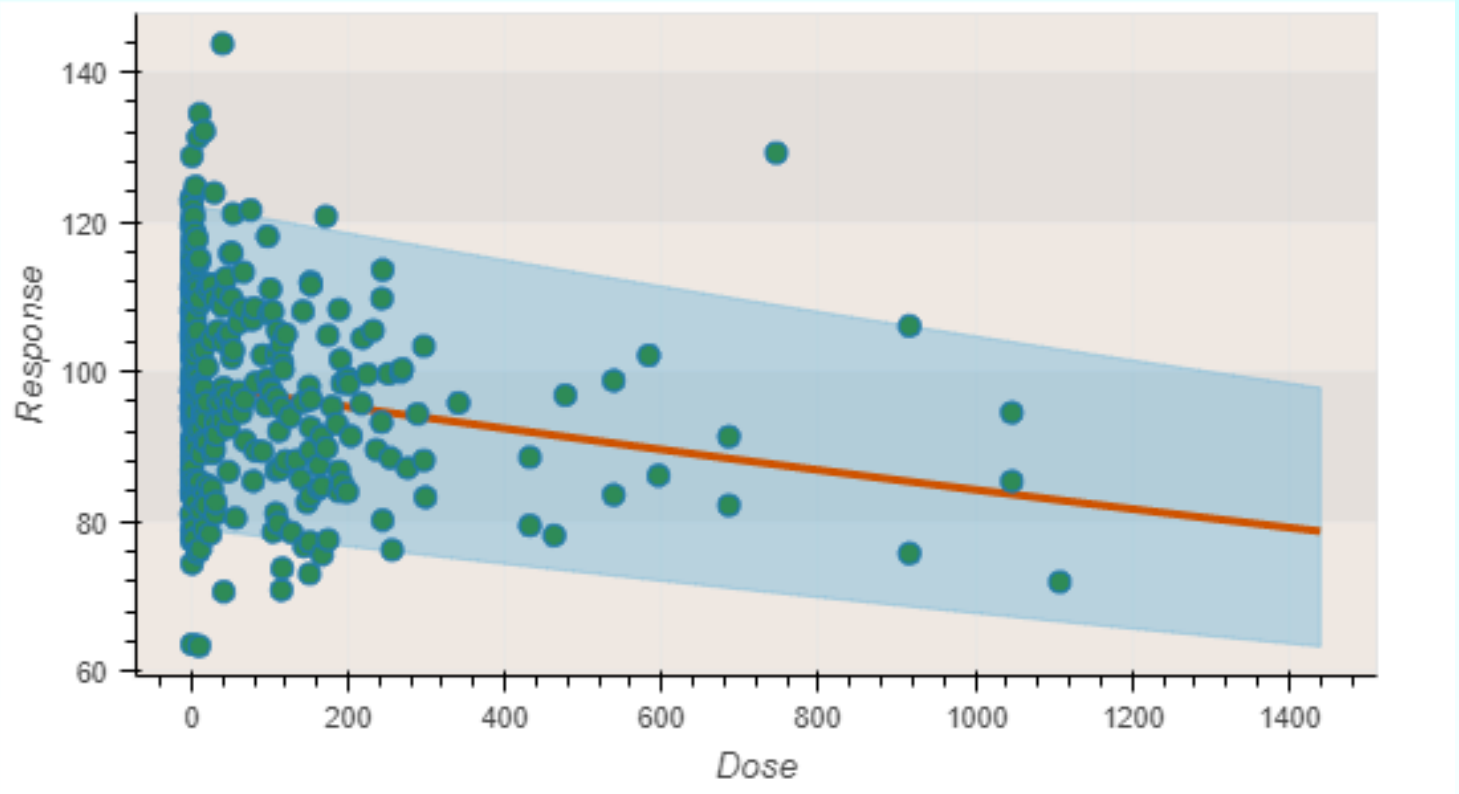
Feature IV: Advanced BMD Calculation

- Based on tails (i.e., hybrid approach Crump 1995)





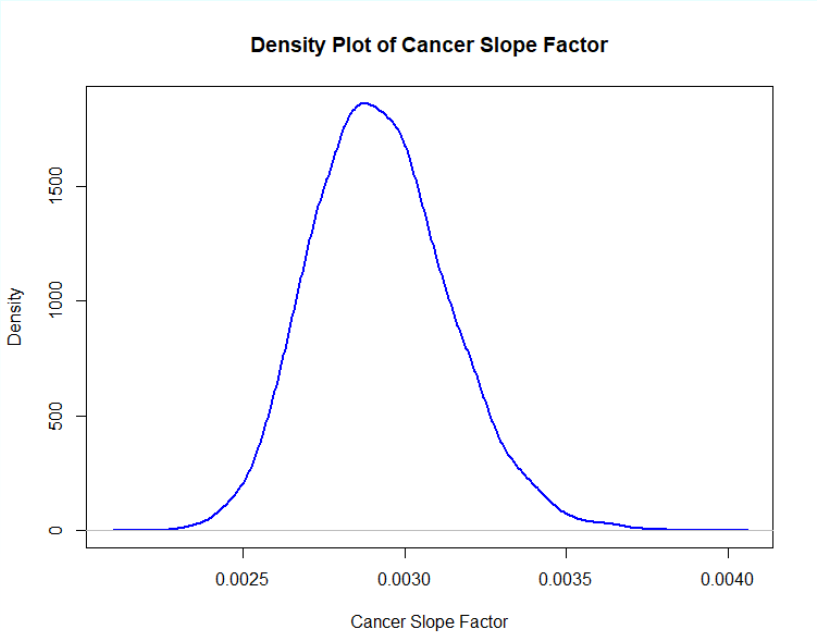
Feature V: Analyzing Epidemiological Data

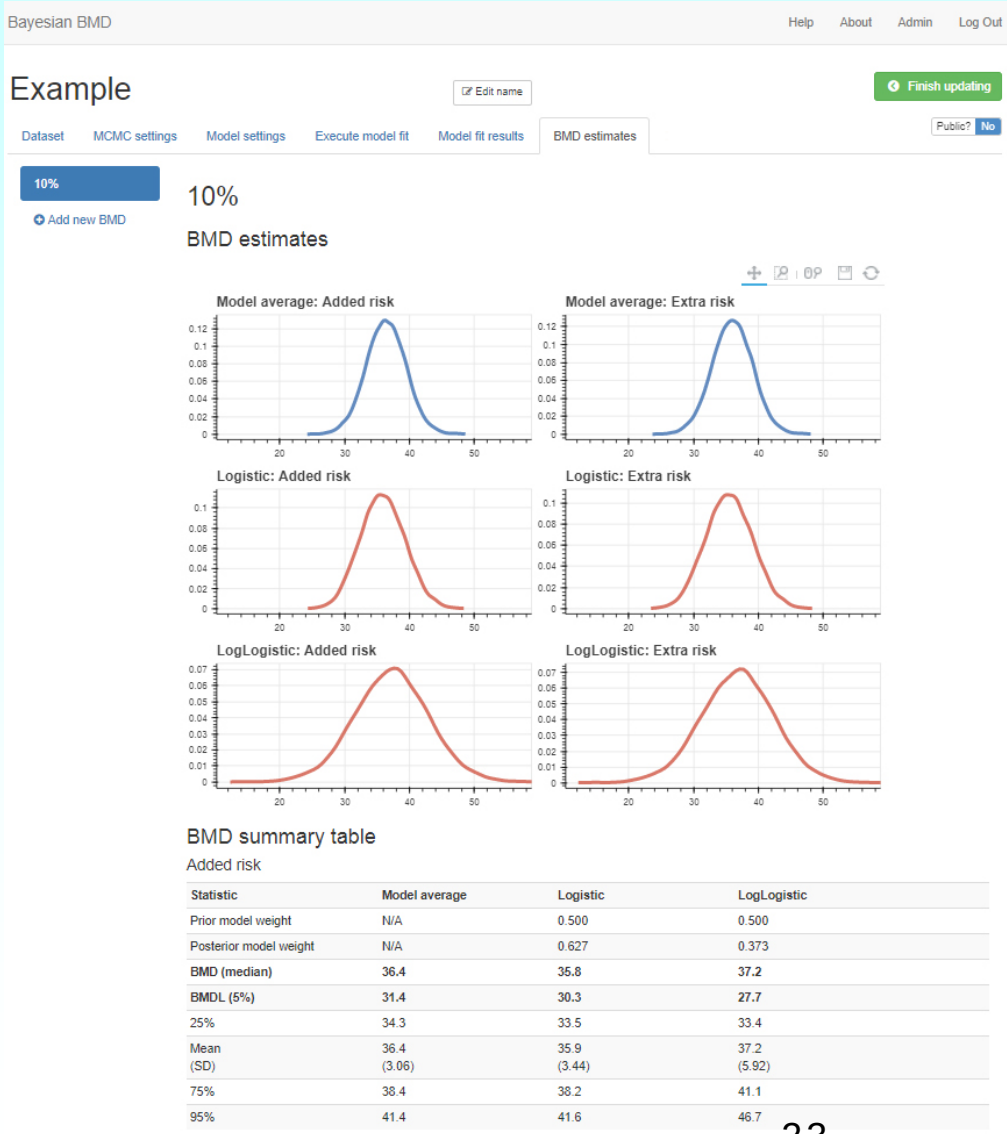


- Subjects have a unique exposure and response level

Feature VI: Probabilistic Low-dose Extrapolation

- For cancer risk assessment
  - Distributional estimates of cancer slope factor (CSF)
    - Currently: $CSF = \frac{BMR}{BMDL}$
    - New: $CSF = \frac{BMR}{BMD(distribution)}$





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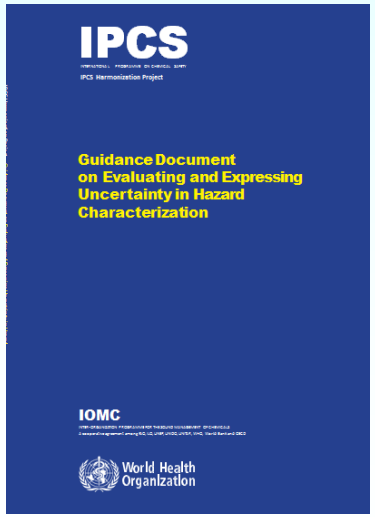
Feature VI: Probabilistic Low-dose Extrapolation

- Available in the BBMD system
- UFs are expressed as lognormal distributions [traditional UF separated to difference (μ) and uncertainty (σ)]
- Monte Carlo simulations are implemented to derive the final human dose distribution



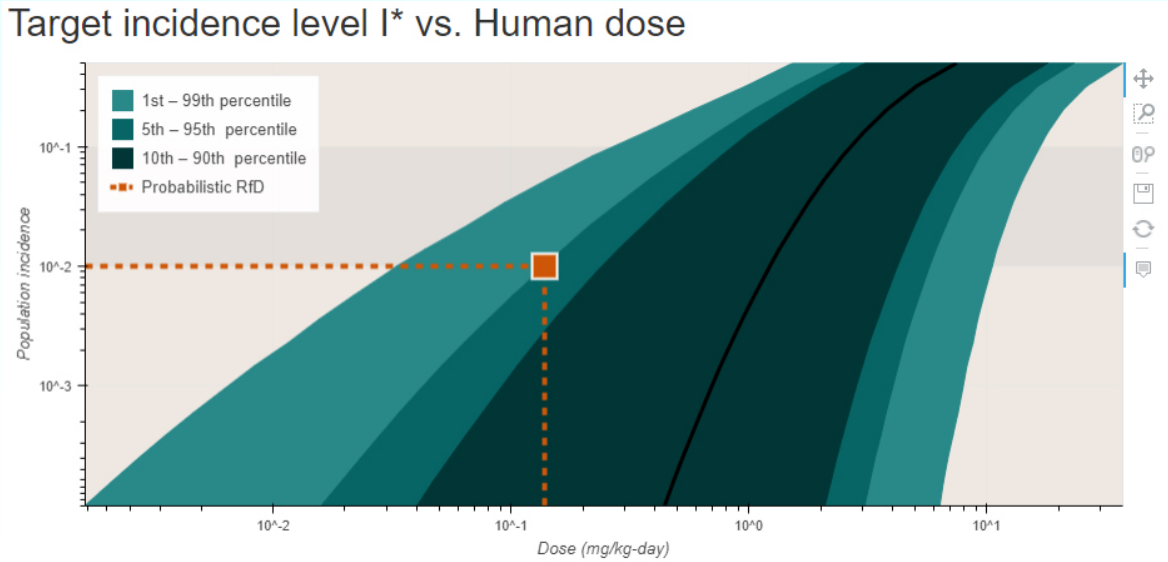
$$RfD = \frac{NOAEL(BMDL)}{UF_A \times UF_H}$$

$$HD_M^I = \frac{BMD_M \times DAF}{UF_A \times UF_{H,I}}$$

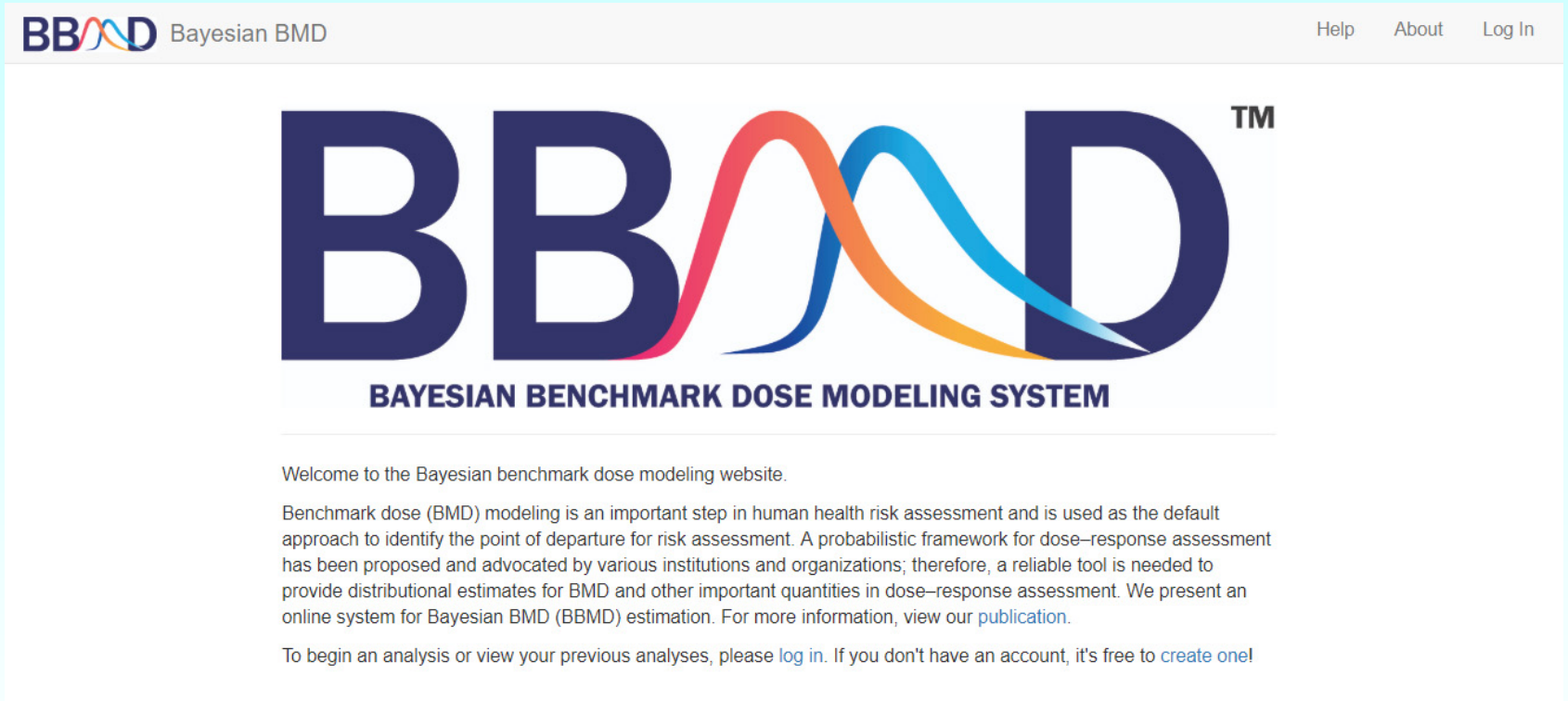
Dosimetric Adjustment Factor for Body Size differences

Interspecies Factor for remaining TK and TD differences

Human Variability Factor for Incidence I



Bayesian Benchmark Dose Modeling System

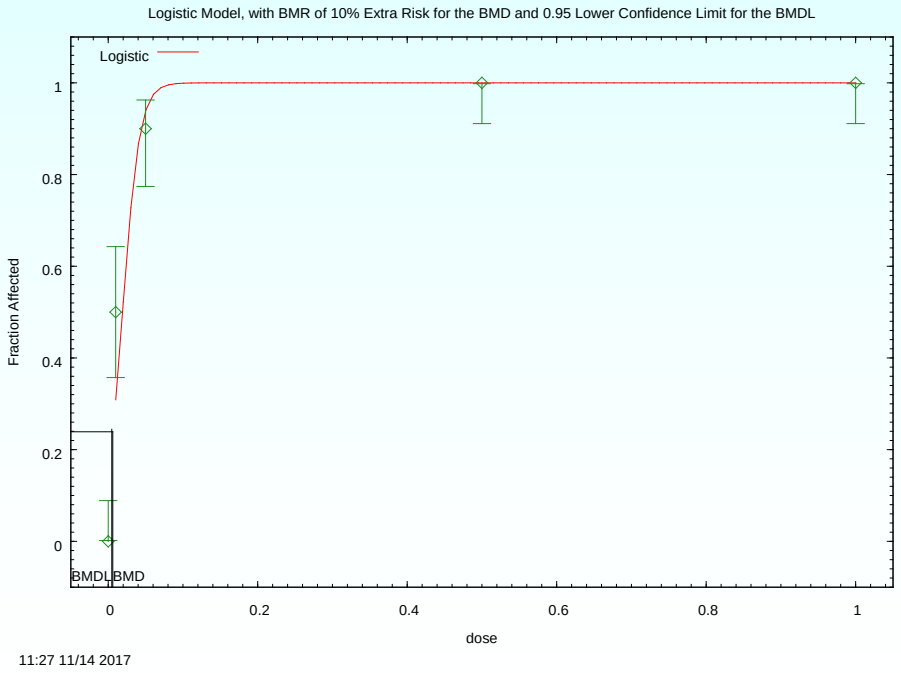


Available at:

https://benchmarkdose.com (or https://benchmarkdose.org)

Additional Discussion: Prior of Model Parameters

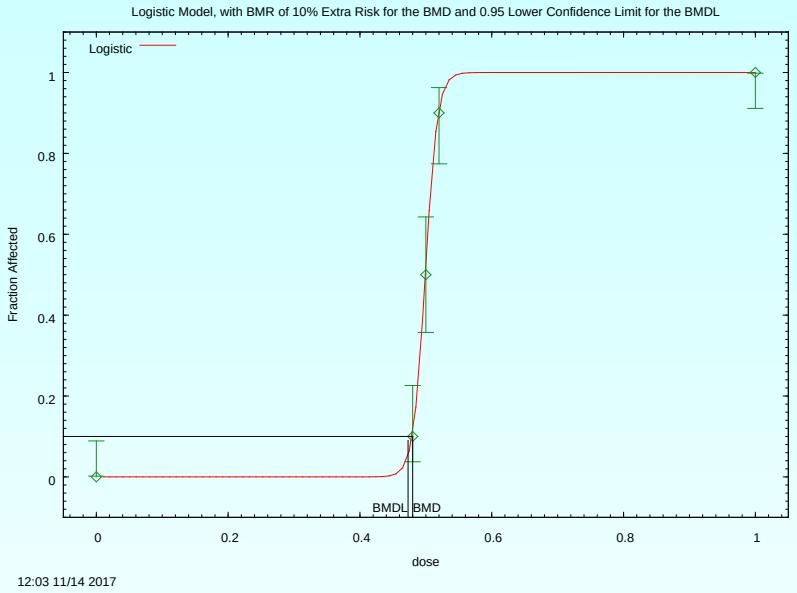
- Significant impact on model shape
- Significant impact on model weight
- Goal: **Flexible and Objective!**

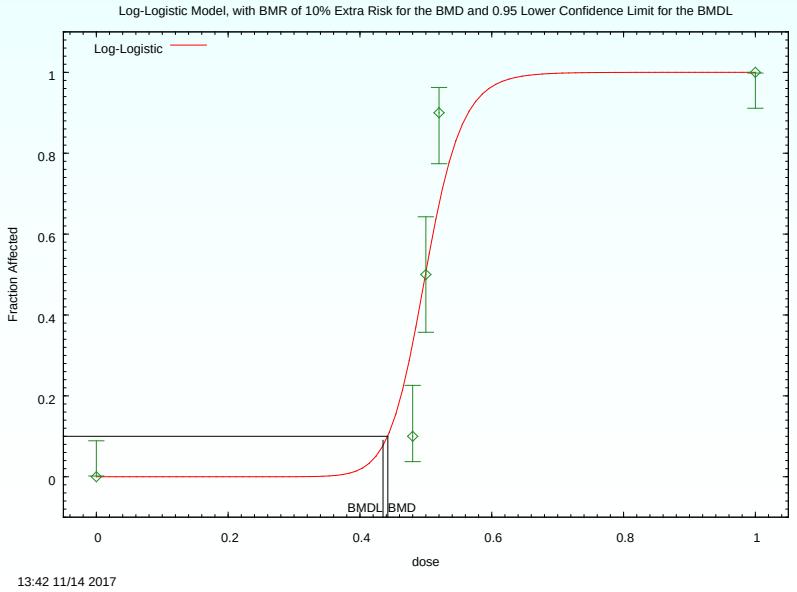


Dose	N	Incidence
0	50	0
0.01	50	25
0.05	50	45
0.5	50	50
1	50	50

Logistic: β1 = -1.7; β2=88.5
Log-logistic: β1 = 0; β2=6.7; β3=1.47
…
…

Prior of Model Parameters





Dose	N	Incidence
0	50	0
0.48	50	5
0.5	50	25
0.52	50	45
1	50	50

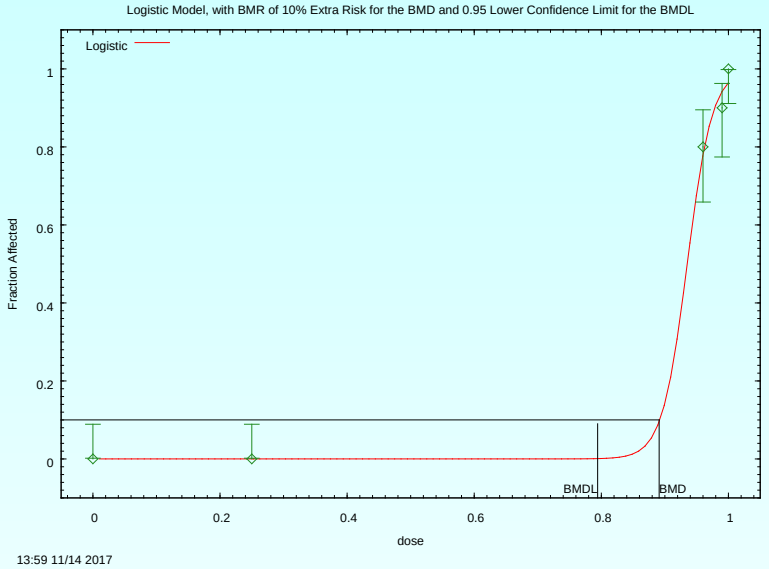
Logistic: β1 = -54.9; β2 = 109.8

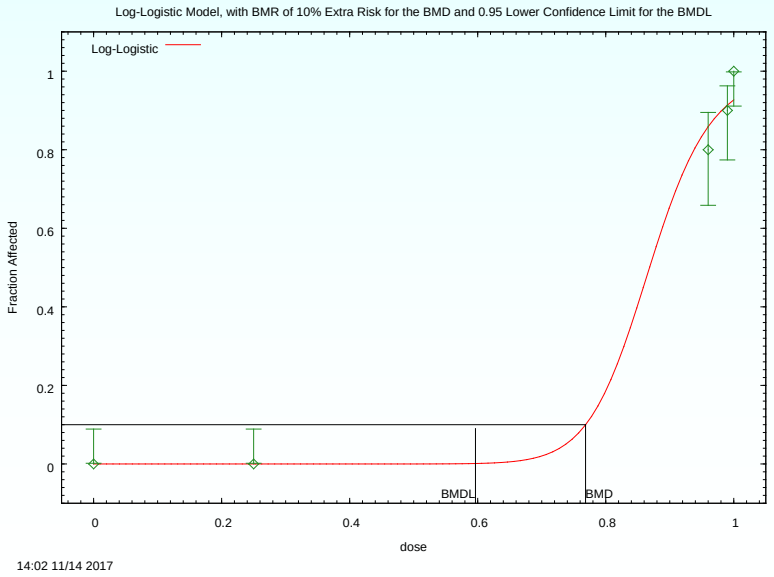
…

Log-logistic: β1 = 0; β2=12.49; β3=**18**

…

Prior of Model Parameters





Dose	N	Incidence
0	50	0
0.25	50	0
0.96	50	40
0.99	50	45
1	50	50

Logistic: $\beta_1 = -47.6$; $\beta_2 = 50.9$

…

Log-logistic: $\beta_1 = 0$; $\beta_2 = 2.54$; $\beta_3 = \mathbf{18}$

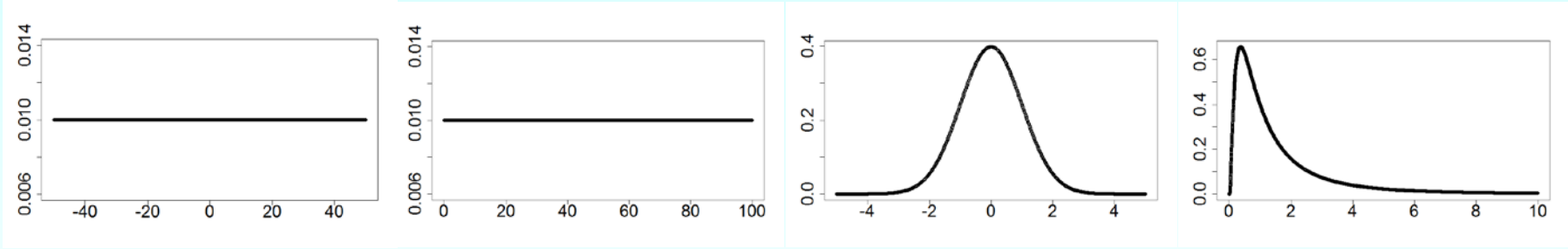
…

Impact of Parameter Priors

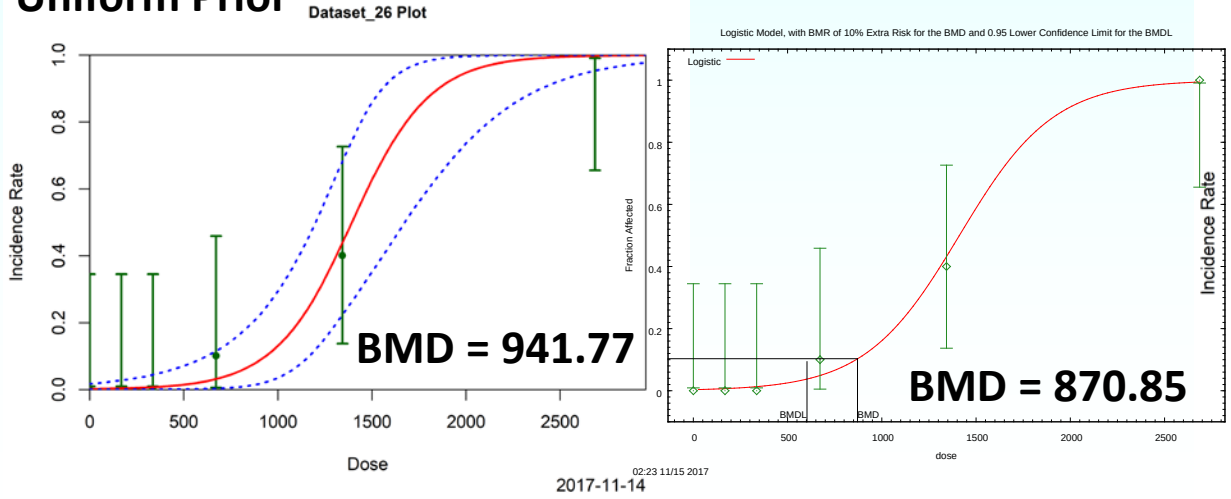
Logistic model: $f(d) = \frac{1}{1+\exp(-a-b\times d)}$

0	10	0
168	10	0
336	10	0
672	10	1
1343	10	4
2686	10	10

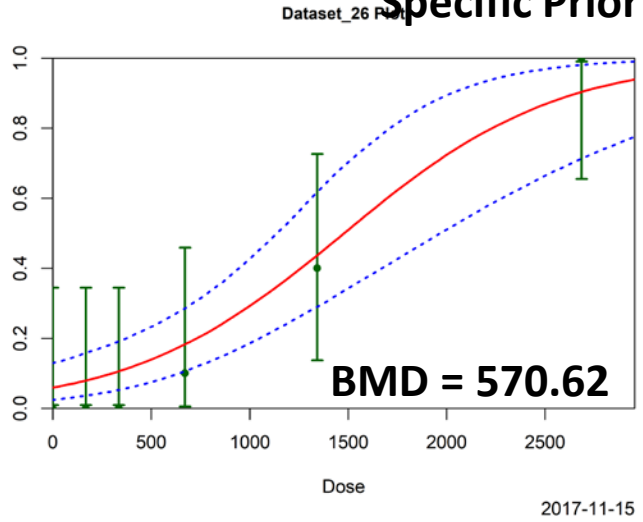
Prior in BBMD		A Very Specific Prior	
a ~ Unif (-50, 50)	b ~ Unif (0, 100)	a ~ N (0, 1)	Log(b) ~ N(0, 1)



Uniform Prior



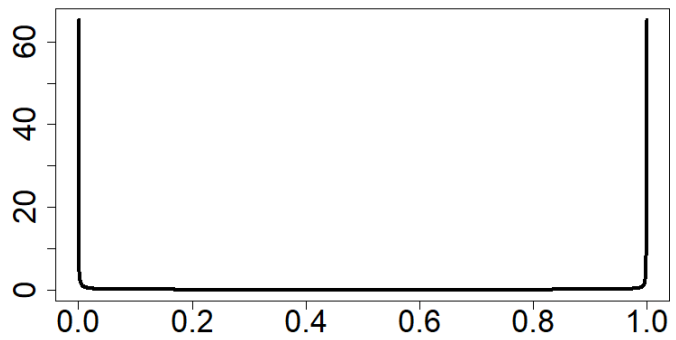
Specific Prior

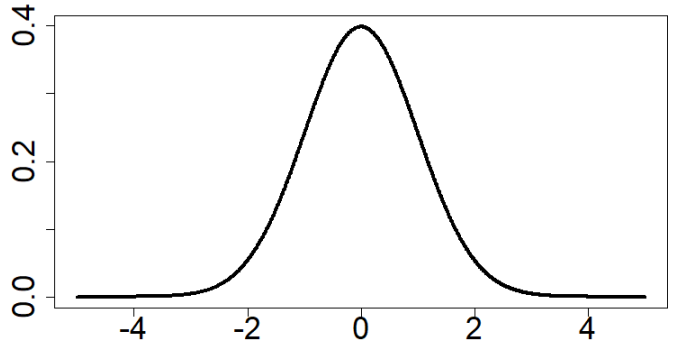


Impact of Parameter Priors

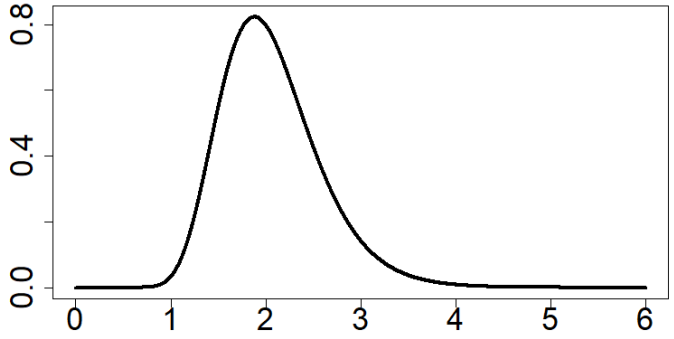
LogLogistic model: $f(d) = a + \frac{1-a}{1+\exp[-b-g\times\log(d)]}$

Prior in BBMD			A Very Specific Prior		
a ~ U(0,1)	b ~ U(-5,15)	g ~ U(r,15)	$a = \frac{1}{\pi}\arctan(\Psi) + \frac{1}{2}$ Ψ~N(0,100)	b ~ Normal (0, 1)	Log(g) ~ N (log(2),0.25)





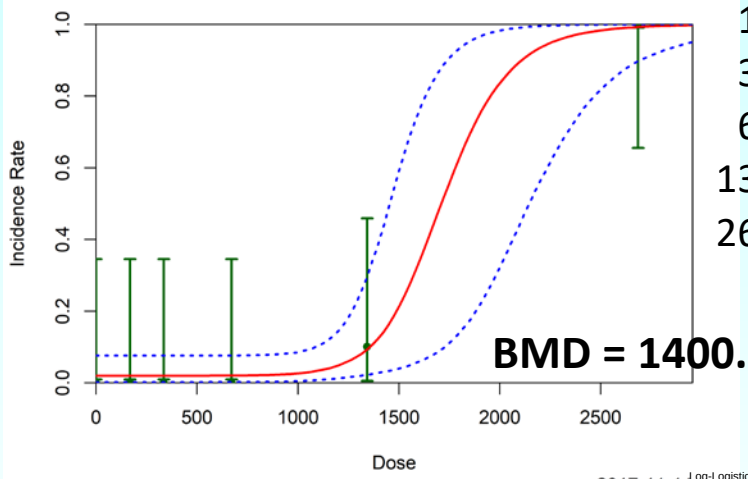
Show the BBMD system



Impact of Parameter Priors

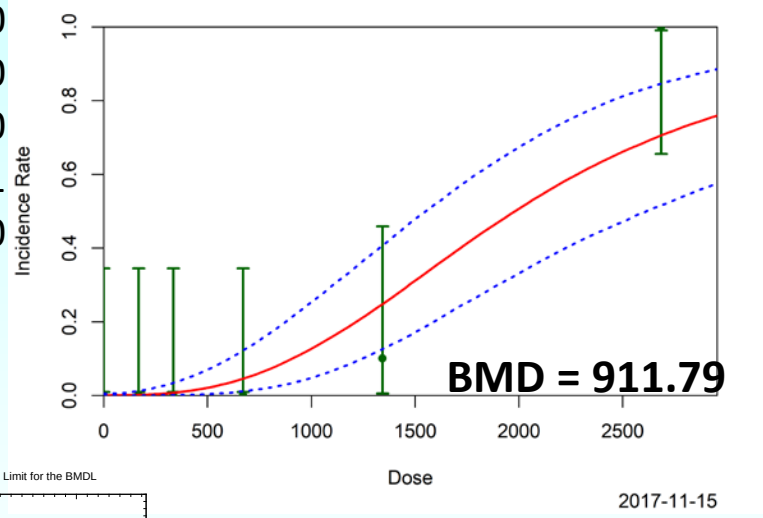
LogLogistic model: $f(d) = a + \frac{1-a}{1+\exp[-b-g\times\log(d)]}$

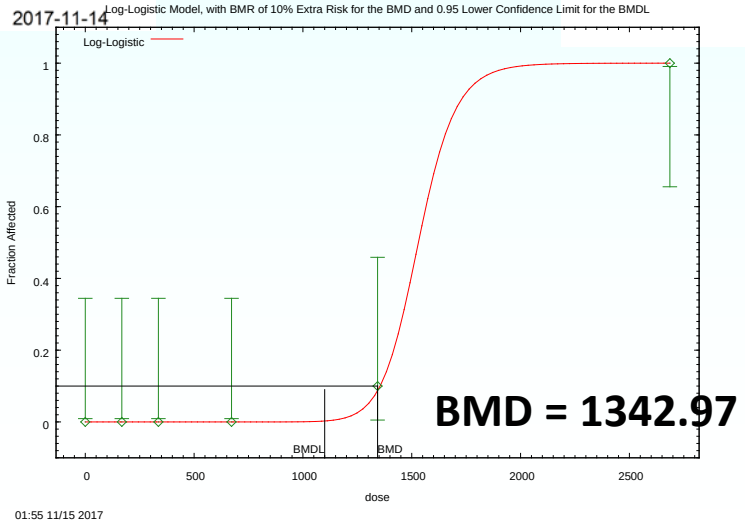
Uniform Prior



0	10	0
168	10	0
336	10	0
672	10	0
1343	10	1
2686	10	10

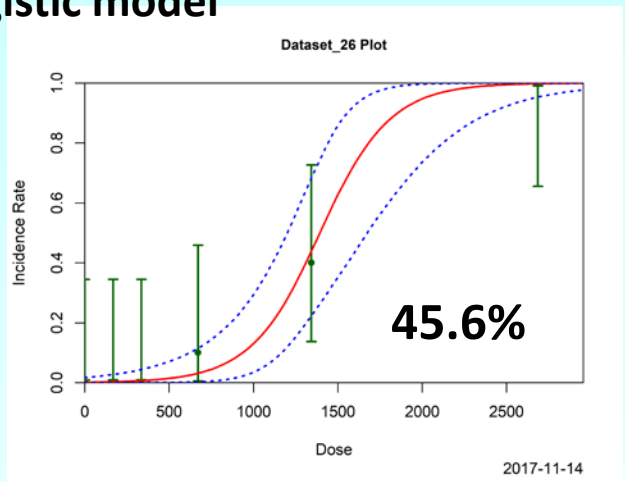
Specific Prior



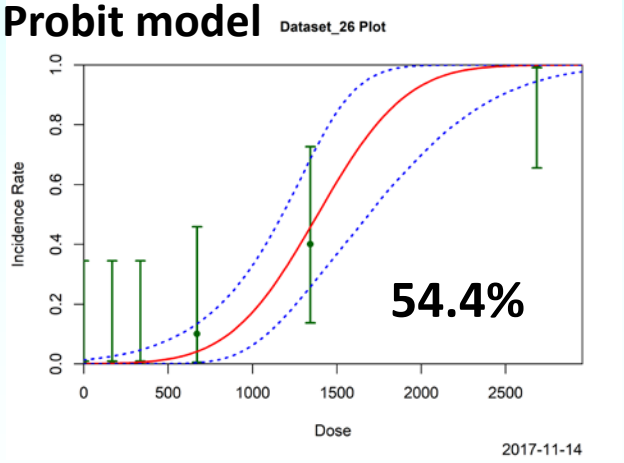


Impact on Model Weight

Logistic model

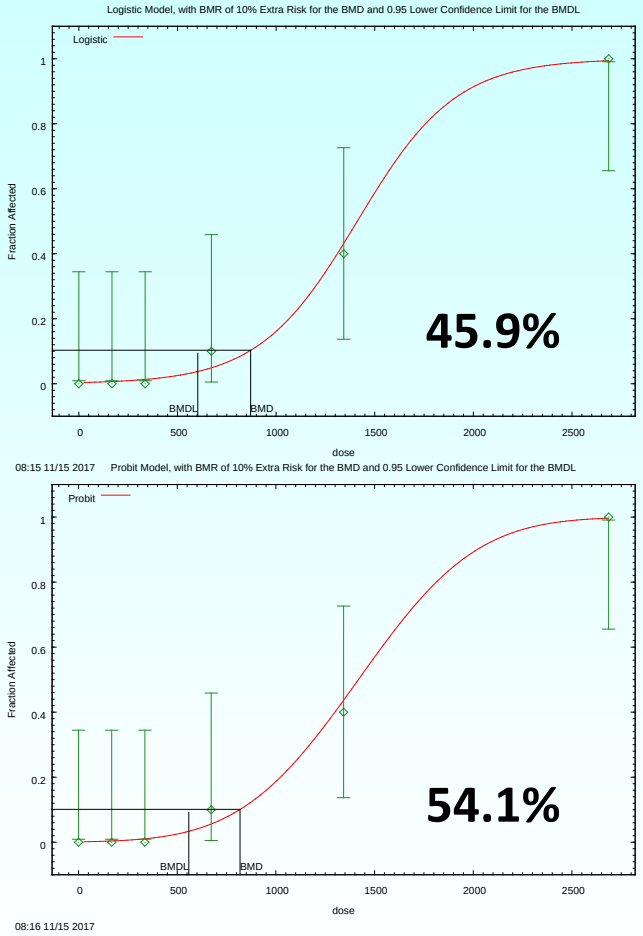


Probit model



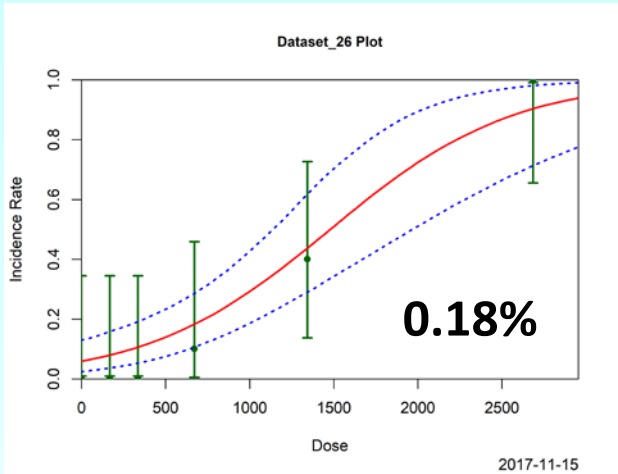
Without impact of parameter prior

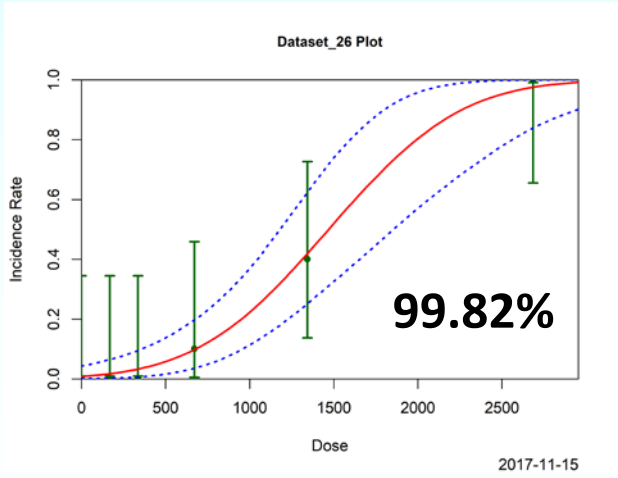
$$\log \hat{m}_j = \hat{\ell}_j - \frac{d_j}{2} \log n$$



BIC Weighting

$$\Pr(M_k \mid D) = \frac{\exp(-0.5BIC_k)}{\sum_{t=1}^{K} \exp(-0.5BIC_t)}$$





With impact of parameter prior

$$m_j = \frac{\mathscr{L}_j(\theta_j)\, p_j(\theta_j)}{p_j(\theta_j \mid y^n)}$$

Plan for Future BBMD Development

- Key features of BBMD: probabilistic estimation and ability to incorporate information
- Ongoing developments
  - Batch processing for dichotomous and continuous data
  - Bayesian categorical data analysis for BMD estimation
- Short-term: incorporating informative prior probability distributions for dose-response models (supported by NIH/NCATS)
  - Empirical prior distributions for different endpoints
  - User can specify the prior distributions
- Long-term: a smart quantitative chemical risk assessment system
- Monthly webinar on BBMD system introduction and software updates
  - Please subscribe to BBMD list by sending an email to: BBMD-L-SUBSCRIBE@INDIANA.EDU

Thank You!
Questions?

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