



Case Study: Application of Dose-Response Model Averaging to Chloroform

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Workshop: Advancing Quantitative Analysis in Human Health Assessments through Probabilistic Methods

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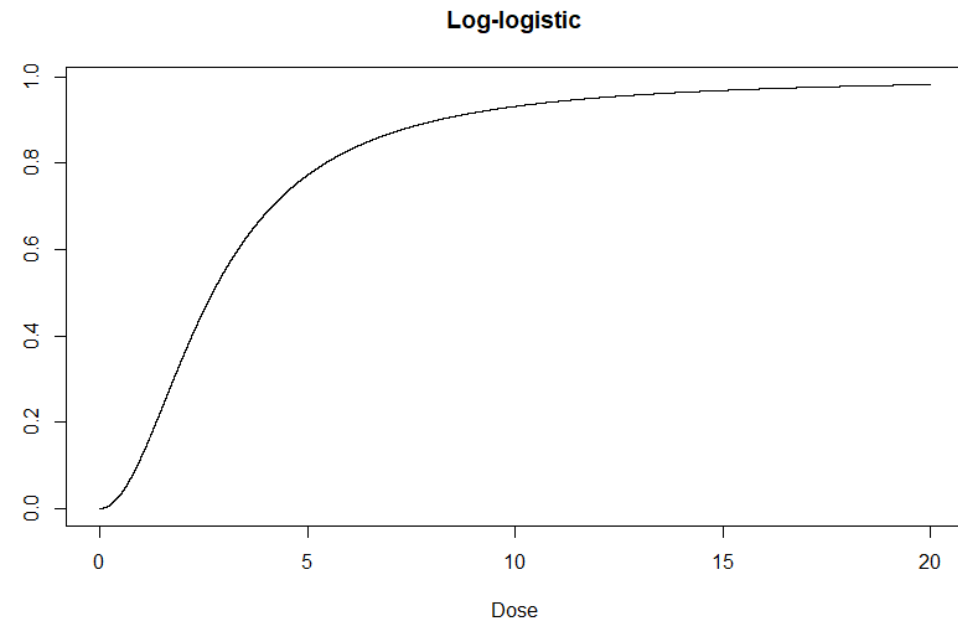
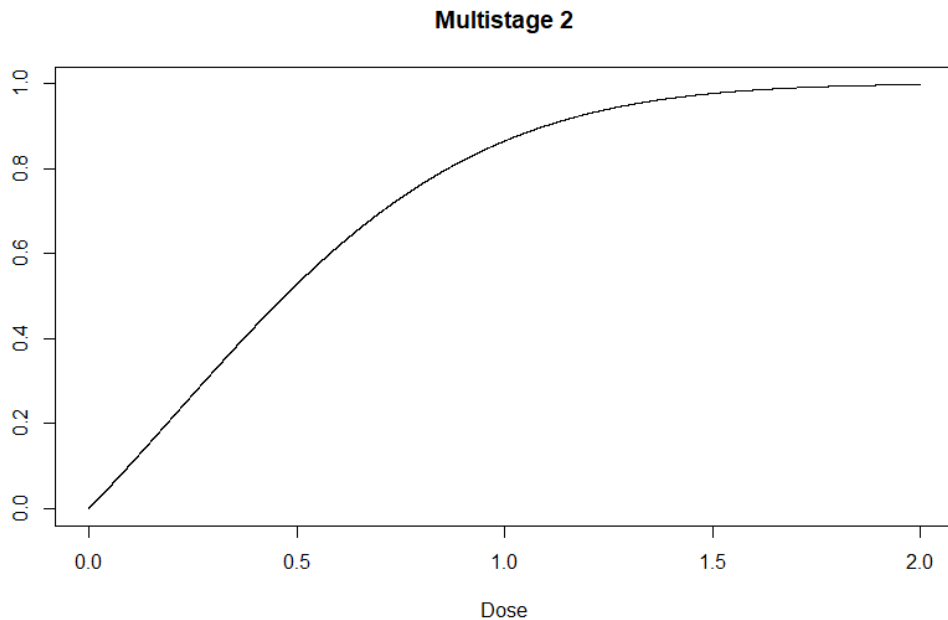
- Case study summary
- Prior distributions
- Examples of model averaging applied to selected chloroform endpoints
- Sensitivity analysis

- To ground the evaluation of model averaging in current efforts, this case study uses datasets being considered in an in-development draft IRIS¹ toxicological review of chloroform-inhalation.
- Bayesian model averaging was applied to a collection of dichotomous endpoints from chloroform animal studies.
- Constructing model weights was done using a Laplace approximation, as included in BMDS² (Wheeler et al., 2020).
- Analysis done in the R package ToxicR.
- Both the BMDS priors (v 3.3) and ToxicR priors were applied.
- Sensitivity analysis conducted by varying the priors with higher and lower variance.

¹ Integrated Risk Information System

² Benchmark Dose Software

- Models included for model averaging:
 - Quantal-linear, multistage (degree 2), Weibull, gamma, dichotomous Hill, logistic, log-logistic, probit, log-probit



- All parameter prior distributions had the form normal or lognormal.
- Example: Priors for log-logistic model in BMDS and ToxicR

$$p(x) = g + \frac{1 - g}{1 + \exp[-\alpha - \beta \log x]}$$

Distribution	Parameter	Mean ^a	SD ^a
Normal	g^b	0	2
Normal	α	0	1
Lognormal	β	0.69315	0.5

^aFor the lognormal prior, values are the log-mean and log-SD.

^blogit(g) has normal prior.

- Example: Priors for Weibull model in BMDS and ToxicR

$$p(x) = g + (1 - g)[1 - \exp(-\beta x^\alpha)]$$

Distribution	Parameter	BMDS Mean ^a	BMDS SD ^a	ToxicR Mean ^a	ToxicR SD ^a
Normal	g^b	0	2	0	2
Lognormal	β	0.69315	0.42426	0.42426	0.5
Lognormal	α	0	1	0	1.5

^aFor the lognormal priors, values are the log-mean and log-SD.

^blogit(g) has normal prior.

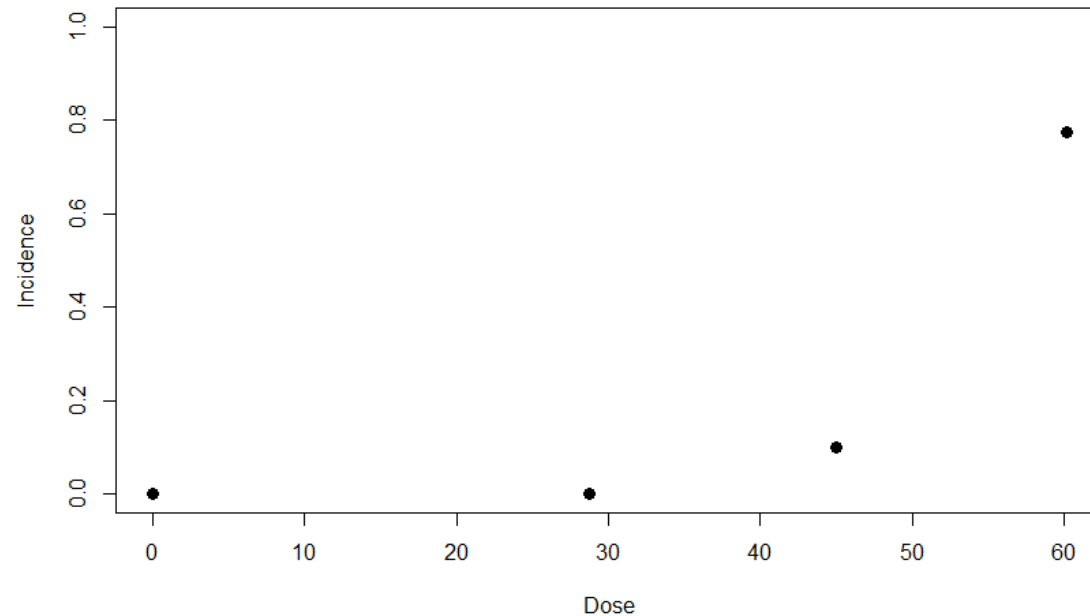
- BMDS and ToxicR mostly yielded similar results.



Example: Kidney tubule dilation in female rats (Yamamoto, 2002)

- Dose-response data:

Internal dose (mg/L-d)	0	28.7	45.0	60.2
Response	0 / 50	0 / 50	5 / 50	38 / 49





Example: Kidney tubule dilation in female rats (Yamamoto, 2002)

Model average results from ToxicR (BMDS priors)

Model	BMD (BMDL, BMDU)	Pr(M Data)
Probit	41.95 (38.00 ,45.01)	0.488
Log-Probit	44.00 (40.40 ,46.91)	0.428
Weibull	42.29 (37.93 ,46.02)	0.037
Log-Logistic	43.15 (39.16 ,46.41)	0.033
Hill	43.16 (39.27 ,46.30)	0.013
Logistic	38.48 (33.97 ,42.10)	0.001
Quantal-Linear	13.22 (10.32 ,17.37)	0.000
Multistage	17.70 (13.66 ,21.69)	0.000
Gamma	33.11 (27.15 ,37.92)	0.000

Model Average BMD: 42.90 (38.60, 46.23) 90.0% CI



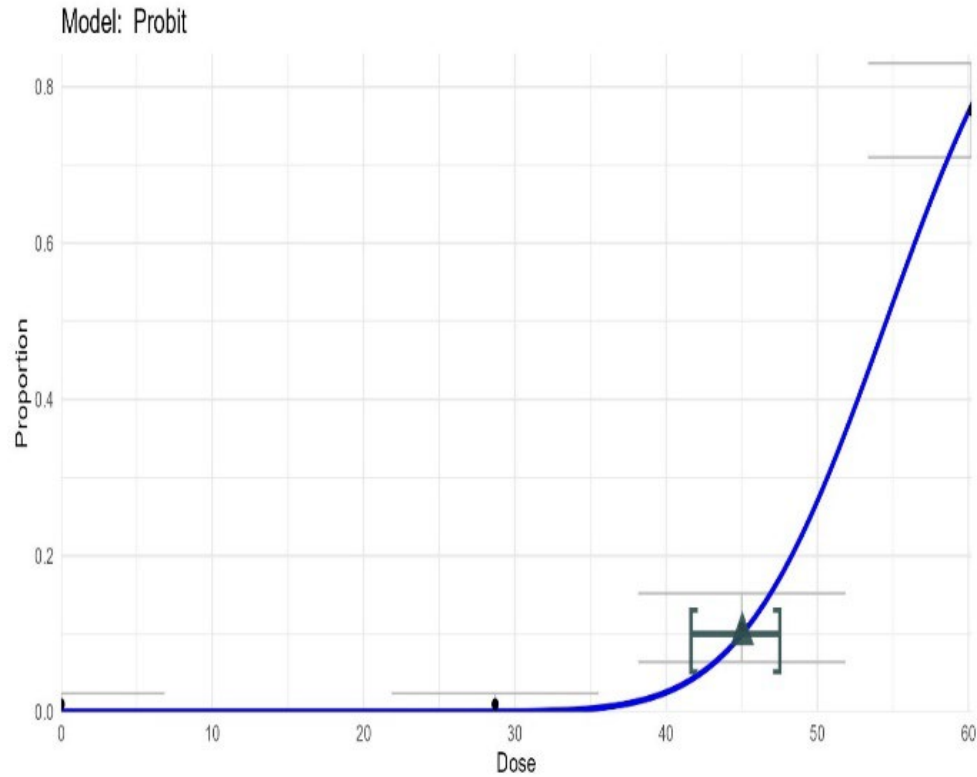
Example: Kidney tubule dilation in female rats (Yamamoto, 2002)

- BMD results:

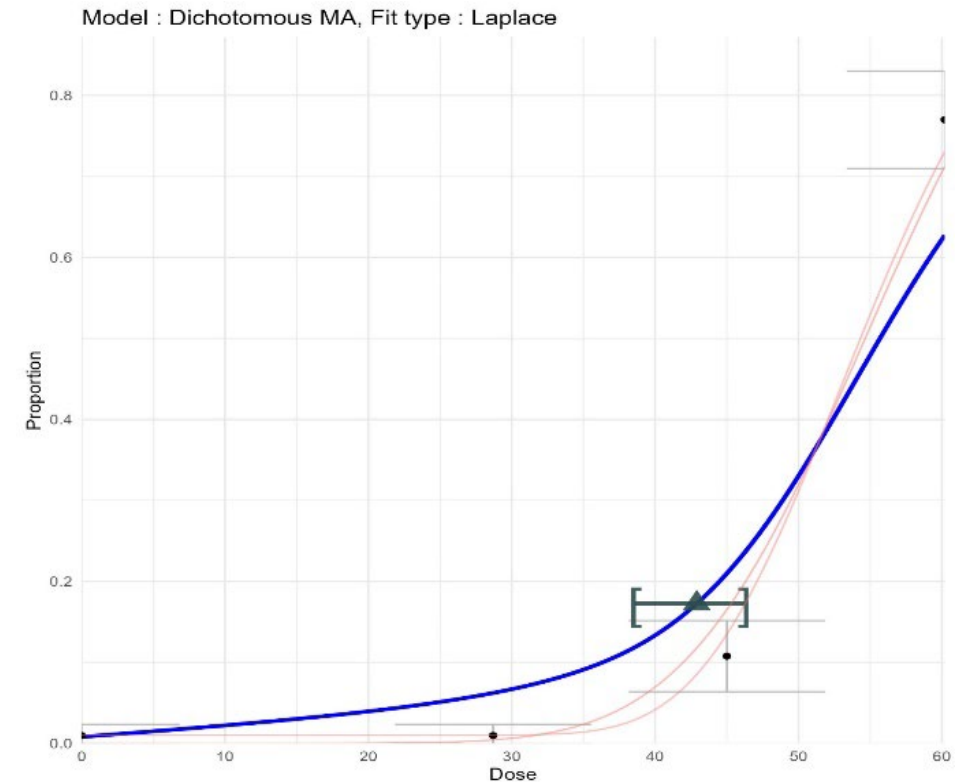
Method	BMD (mg/L-d)	BMDL (mg/L-d)
Maximum likelihood (probit)	45.0	41.8
Model average (BMDS priors)	42.9	38.6 ^a

^aModel average BMDL is 8% lower than maximum likelihood BMDL.

Example: Kidney tubule dilation in female rats (Yamamoto, 2002)



Single model (maximum likelihood)



Model average (Bayesian)



Example: Hepatic lesions in female mice (Larson, 1996)

- Dose-response data:

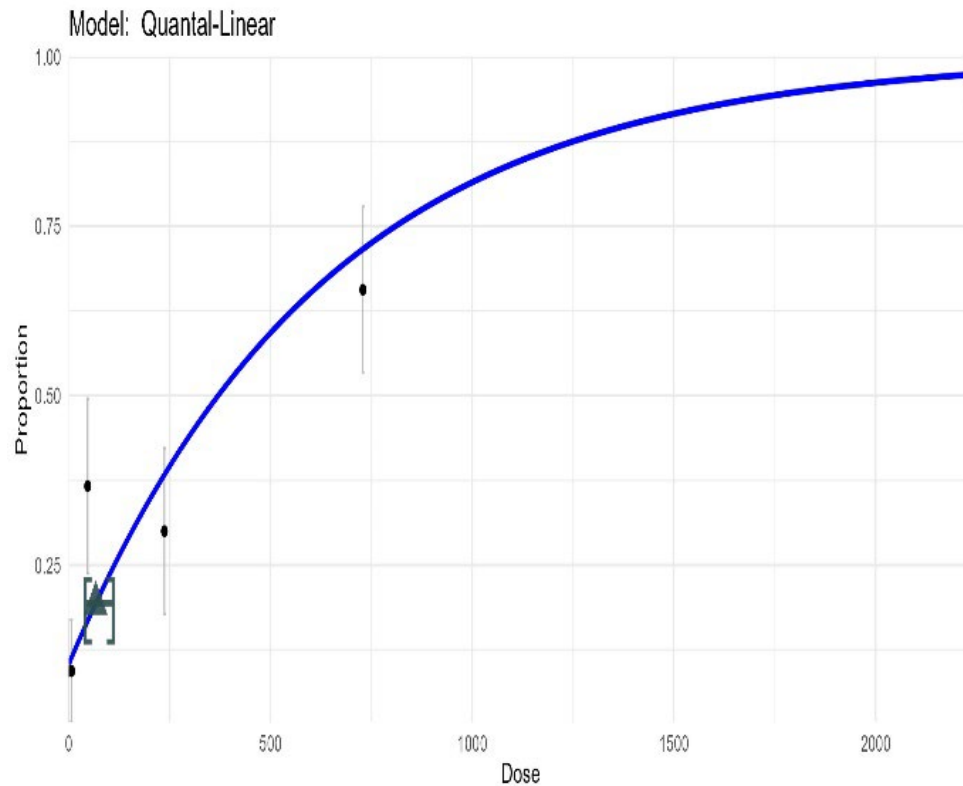
Internal dose (mg/L-d)	0	7	46.8	237	729	2240
Response	1 / 15	1 / 15	5 / 14	4 / 14	10 / 15	15 / 15

- BMD results:

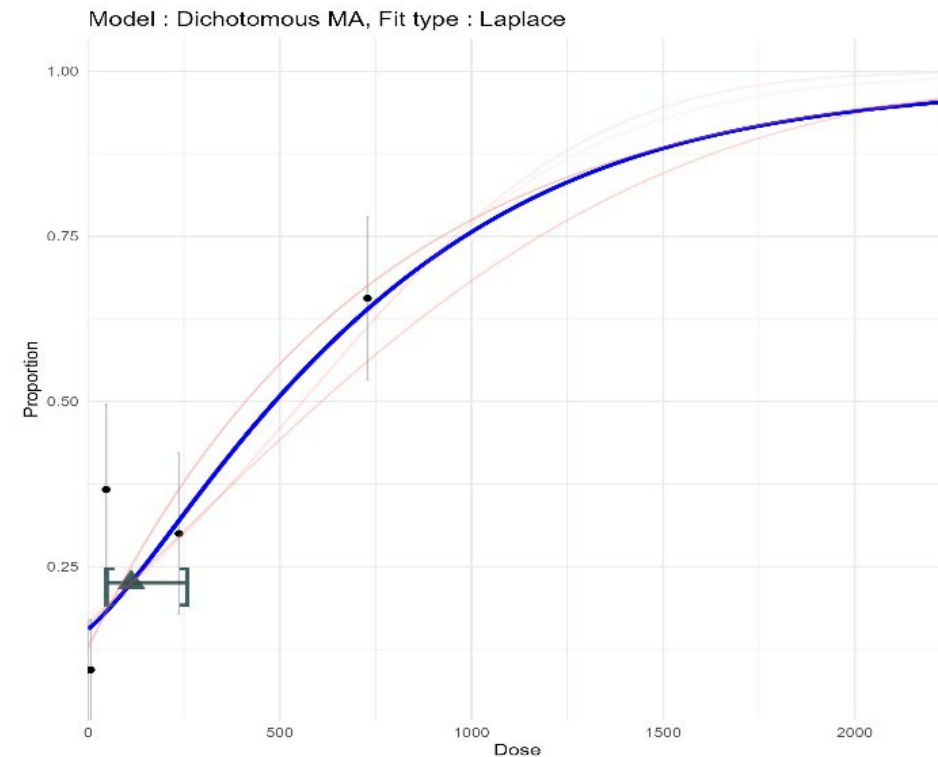
Method	BMD (mg/L-d)	BMDL (mg/L-d)
Maximum likelihood (quantal-linear)	66.8	43.8
Model average (BMDS priors)	112.5	52.0 ^a

^aModel average BMDL is 19% higher than maximum likelihood BMDL.

Example: Hepatic lesions in female mice (Larson, 1996)



Single model (maximum likelihood)



Model average (Bayesian)



Example: Kidney lesions in male mice (Larson, 1996)

- Dose-response data:

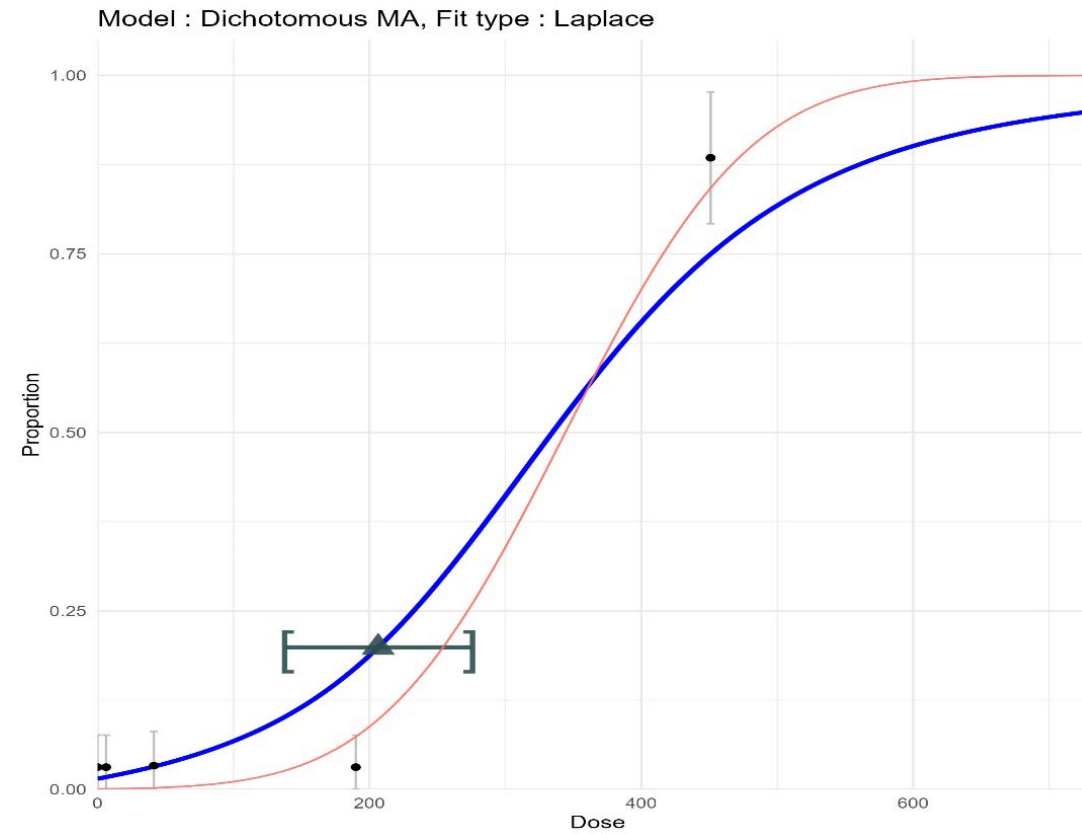
Internal dose (mg/L-d)	0	6.3	41.4	190	451	736
Response	0 / 15	0 / 15	0 / 14	0 / 15	11 / 12	14 / 14

- BMD results:

POD	Value (mg/L-d)	Value (mg/L-d)
Traditional	LOAEL = 451	NOAEL = 190
Model average (BMDS priors)	BMD = 206	BMDL = 139 ^a

^aModel average BMDL is 27% lower than NOAEL.

Example: Kidney lesions in male mice (Larson, 1996)



Model average (Bayesian)



Example: Respiratory metaplasia in female rats (Yamamoto, 2002)

- Dose-response data:

Internal dose (mg/L-d)	0	1.79	5.36	16.1
Response	0 / 50	43 / 50	48 / 50	45 / 49



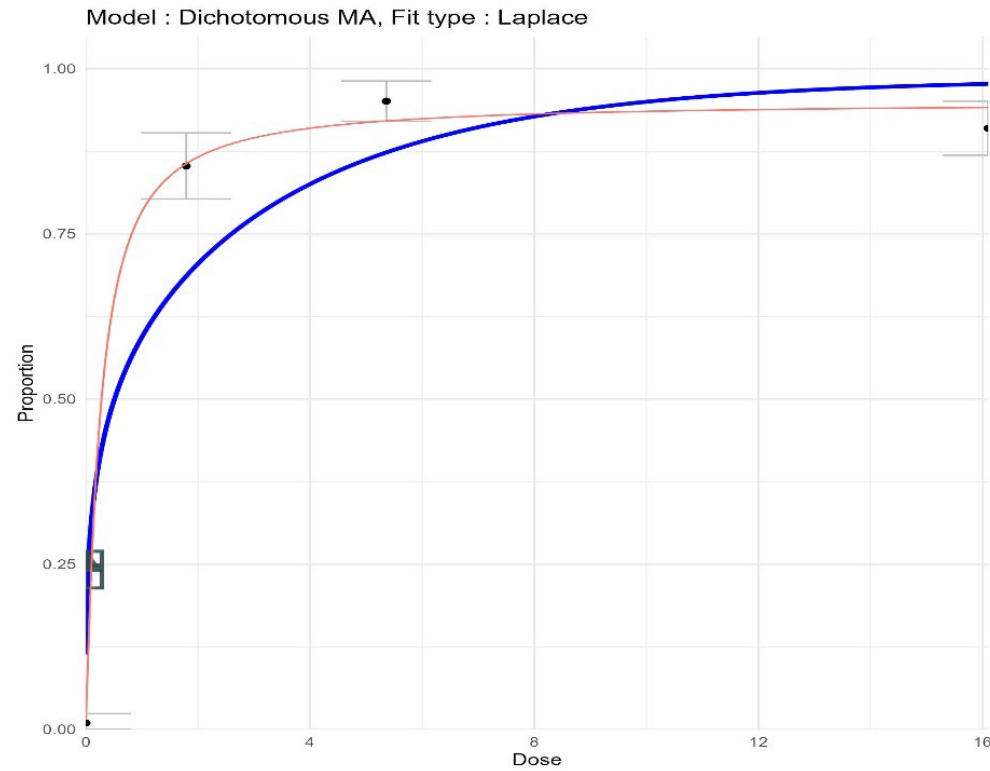
Example: Respiratory metaplasia in female rats (Yamamoto, 2002)

Model average results from ToxicR (BMDS priors)

Model	BMD (BMDL, BMDU)	Pr(M Data)
Hill	0.04 (0.00 ,0.26)	0.975
Log-Logistic	0.00 (0.00 ,0.04)	0.017
Log-Probit	0.01 (0.00 ,0.07)	0.007
Quantal-Linear	0.25 (0.20 ,0.31)	0.000
Multistage	0.28 (0.23 ,0.35)	0.000
Weibull	0.00 (0.00 ,0.01)	0.000
Gamma	0.00 (0.00 ,0.02)	0.000
Logistic	0.70 (0.55 ,0.93)	0.000
Probit	0.98 (0.79 ,1.24)	0.000

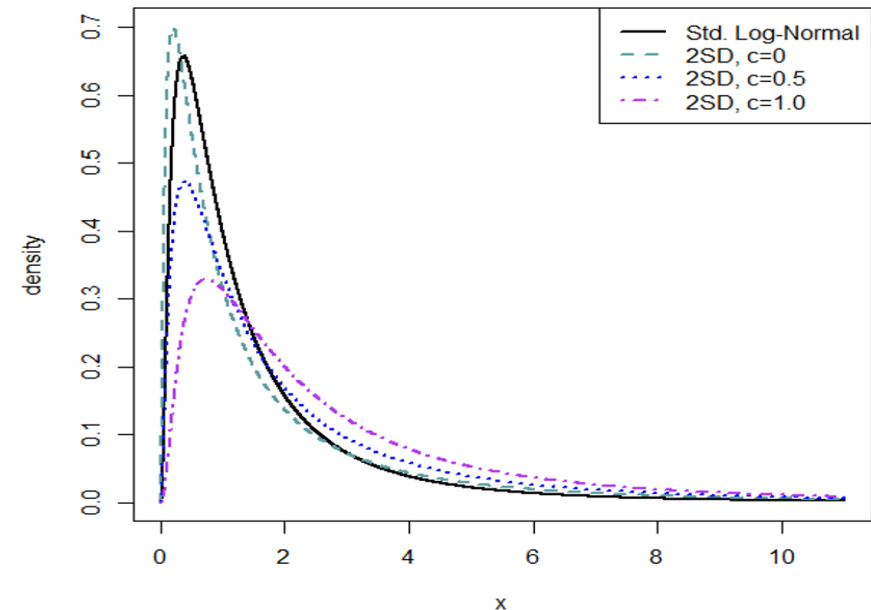
Model Average BMD: 0.04 (0.00, 0.26) 90.0% CI

Example: Respiratory metaplasia in female rats (Yamamoto, 2002)



Model average (Bayesian)

- Standard deviation (SD) of every parameter prior for every model multiplied by 2, 5, 10, and 0.5.
- For lognormal priors, additional variation incorporated three ways:
 - Through geometric variance (GV)
 - Through median
 - Half through GV, half through median



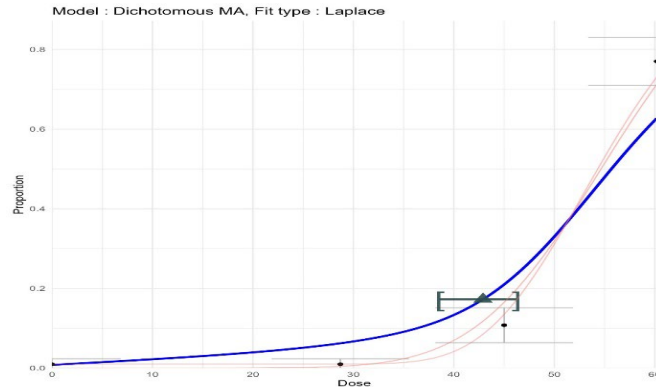


Example: Kidney tubule dilation in female rats (Yamamoto, 2002)

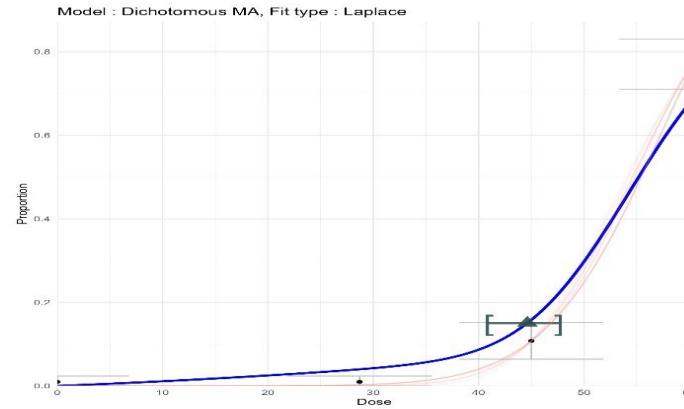
Model average priors (BMDS)	BMD (mg/L-d)	BMDL (mg/L-d)
Default	42.9	38.6
10 SD (for lognormal, all additional variation incorporated through GV)	44.6 (+4%)	40.9 (+6%)
10 SD (for lognormal, half additional variation incorporated through GV, half through median)	44.7 (+4%)	41.1 (+6%)
10 SD (for lognormal, all additional variation incorporated through median)	44.9 (+5%)	41.2 (+7%)



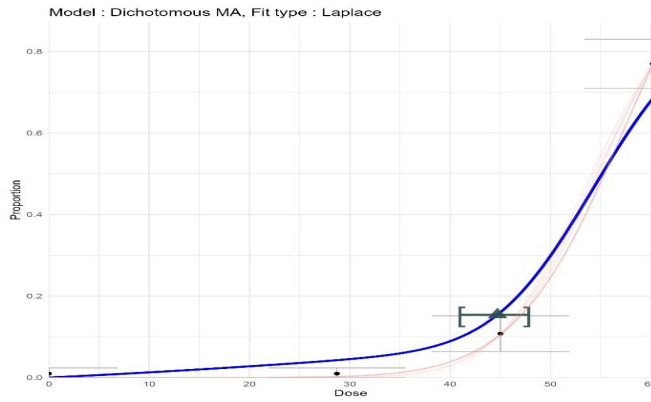
Example: Kidney tubule dilation in female rats (Yamamoto, 2002)



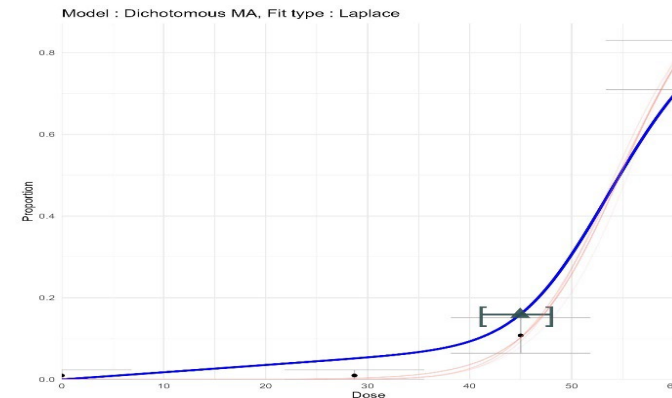
Default priors



10 SD; all additional variation in GV



10 SD; half additional variation in GV, half in median



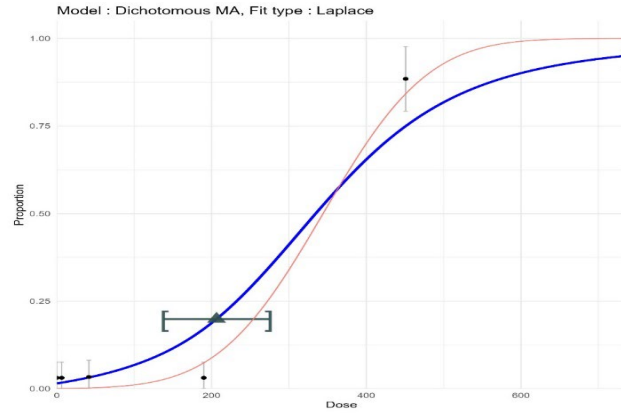
10 SD; all additional variation in median



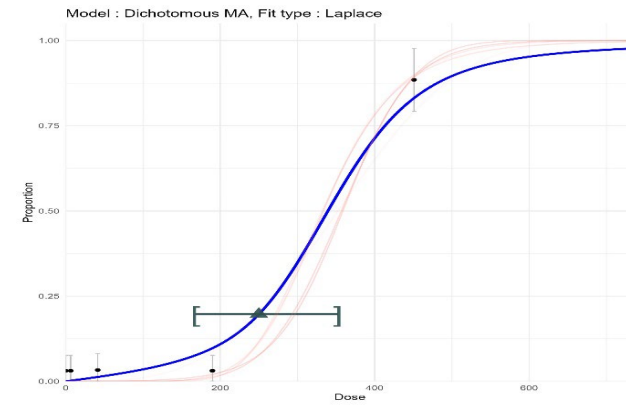
Example: Kidney lesions in male mice (Larson, 1996)

Model average priors	BMD (mg/L-d)	BMDL (mg/L-d)
Default	206	139
10 SD (for lognormal, all additional variation incorporated through GV)	250 (+21%)	168 (+21%)
10 SD (for lognormal, half additional variation incorporated through GV, half through median)	253 (+22%)	171 (+23%)
10 SD (for lognormal, all additional variation incorporated through median)	290 (+41%)	192 (+38%)

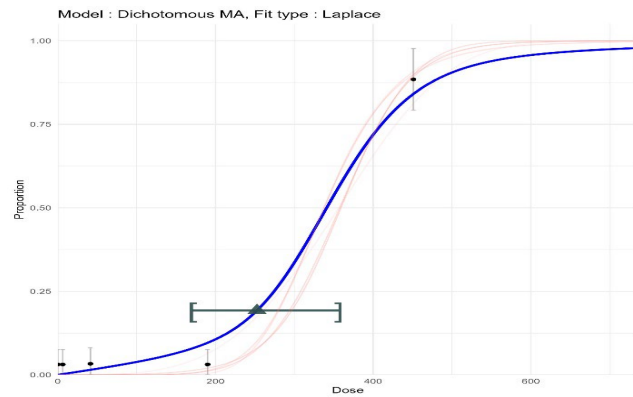
Example: Kidney lesions in male mice (Larson, 1996)



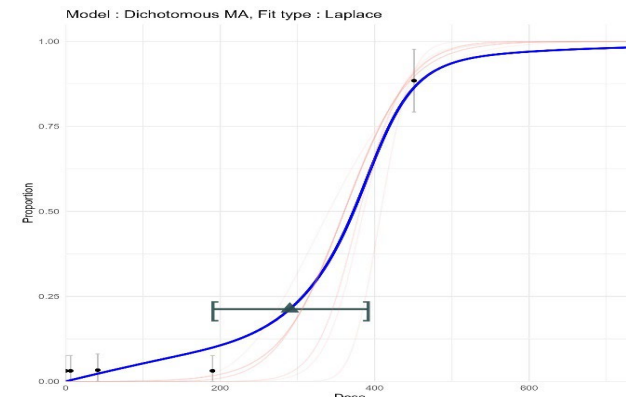
Default priors



10 SD; all additional variation in GV



10 SD; half additional variation in GV, half in median



10 SD; all additional variation in median

- In many cases (esp. for “well-behaved” datasets), Bayesian model averaging yields results that are not very different from single model selection using maximum likelihood.
- Bayesian model averaging sometimes yields reasonable results for datasets that are not otherwise amenable to modeling.
- For some datasets, modeling is not advised, even with model averaging.
 - Explore assessment of model fit and adequacy of data for modeling.



Acknowledgements and References

- Collaborators: Christine Cai, Colin Peterson, Hyunsu Ju
- Chloroform co-assessment managers: Margaret Pratt, Andre Weaver
- Wheeler, M.W., et al., 2020. Quantitative risk assessment: developing a Bayesian approach to dichotomous dose–response uncertainty. *Risk Anal.* 40, 1706–1722.
- BMDS: <https://www.epa.gov/bmnds>
- ToxicR: <https://github.com/NIEHS/ToxicR>