Annex to: Update of the risk assessment of inorganic arsenic in food.
doi:10.2903/j.efsa.2024.8488

Annex E5 Benchmark concentration modelling reports

Relative increase of the background incidence after adjustment for confounders by 5%

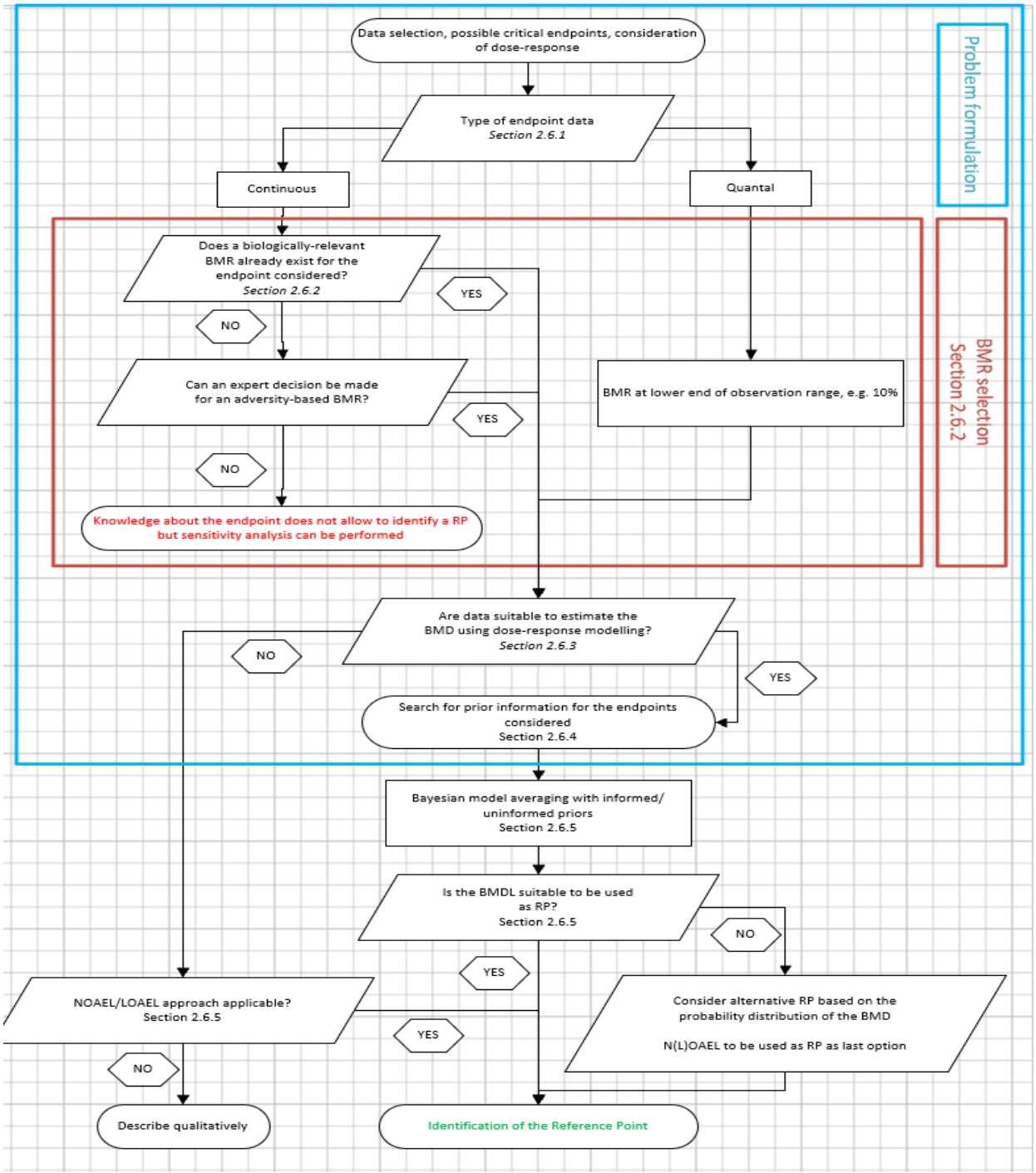
Annex E5 provides a comprehensive overview of the benchmark concentration (BMC) analyses carried out for the studies used in the uncertainty analysis, employing the model averaging technique. In contrast to the used benchmark dose (BMD) modelling approach, which utilised total iAs exposure as the exposure metric for BMD analyses, the BMC analyses in this Annex are based on water iAs concentrations (µg/L) or water iAs daily intakes (µg) in the case of Steinmaus et al. (2014a). Using water iAs concentrations (rather than total exposures) as a basis for modelling creates a dose-response shape that differs somewhat due to differences in relative dose spacing. This is illustrated in the Appendix of this Annex. The BMC analyses were conducted in accordance with the EFSA BMD guidance (EFSA Scientific Committee, 2022).

E5.1 Selection of the BMR

As BMR the CONTAM Panel decided to use a relative increase of the background incidence after adjustment for confounders by 5%.

E5.2 Software Used

Results are obtained using the EFSA web-tool for Bayesian BMD analysis, which uses the R-package [BMABMDR] version 0.0.0.9060 for the underlying calculations.



Flowchart to derive a Reference Point (RP) from a dose-response dataset of a specified endpoint, using BMD analysis. Figure from EFSA BMD guidance (EFSA Scientific Committee, 2022).

Table 1: Comparison of the BMD results using different exposure metrics for modelling (total iAs exposure vs. water iAs concentrations/daily iAs intake in water).

Study	Exposure metric for modelling					
	Total iAs exposure (µg/kg b.w. per day)			Water iAs concentrations (µg/L) or daily iAs intake in water (µg)		
	$BMDL_{05}$ (µg/kg b.w. per day)	BMD_{05} (µg/kg b.w. per day)	$BMDU_{05}$ (µg/kg b.w. per day)	$BMDL_{05}$ (µg/kg b.w. per day)	BMD_{05} (µg/kg b.w. per day)	$BMDU_{05}$ (µg/kg b.w. per day)
Chen et al. (2010a) lung cancer	1.21	4.97	10.80	1.74	5.30	10.98
Chen et al. (2010b) bladder cancer	0.15	1.33	5.46	0.77	1.78	5.76
Leonardi et al. (2012) skin cancer	0.011	0.047	0.079	0.11	0.12	0.17
Pierce et al. (2011) skin lesions	0.80	1.61	2.86	1.56	2.02	3.07
Steinmaus et al. (2014a) lung cancer (the highest 5-year average, daily intakes)	0.17	0.76	1.71	0.36	0.59	0.96

E5.3 BMC modelling reports

Chen et al. (2010a) lung cancer, relative BMR 5%

Data Description

The endpoint to be analyzed is: Adj.cases for lung cancer

Data used for analysis:

Water.conc	Adj..cases	N
5.00	48	2288
29.95	48	2093
74.95	19	907
199.95	29	909
300.00	33	691

The 'Value for CES' is set to 0.00107143.

Extended dose range is not applied.

Informative background prior: min: 0.020769231; the most likely: 0.020979021; max: 0.021188811. Shape parameter is applied.

The 'Sampling Method' is set to Bridge Sampling.

Results

Information pertaining to this endpoint.

Goodness of Fit

Best fitting model fits sufficiently well (Bayes factor is 1.96e-04).

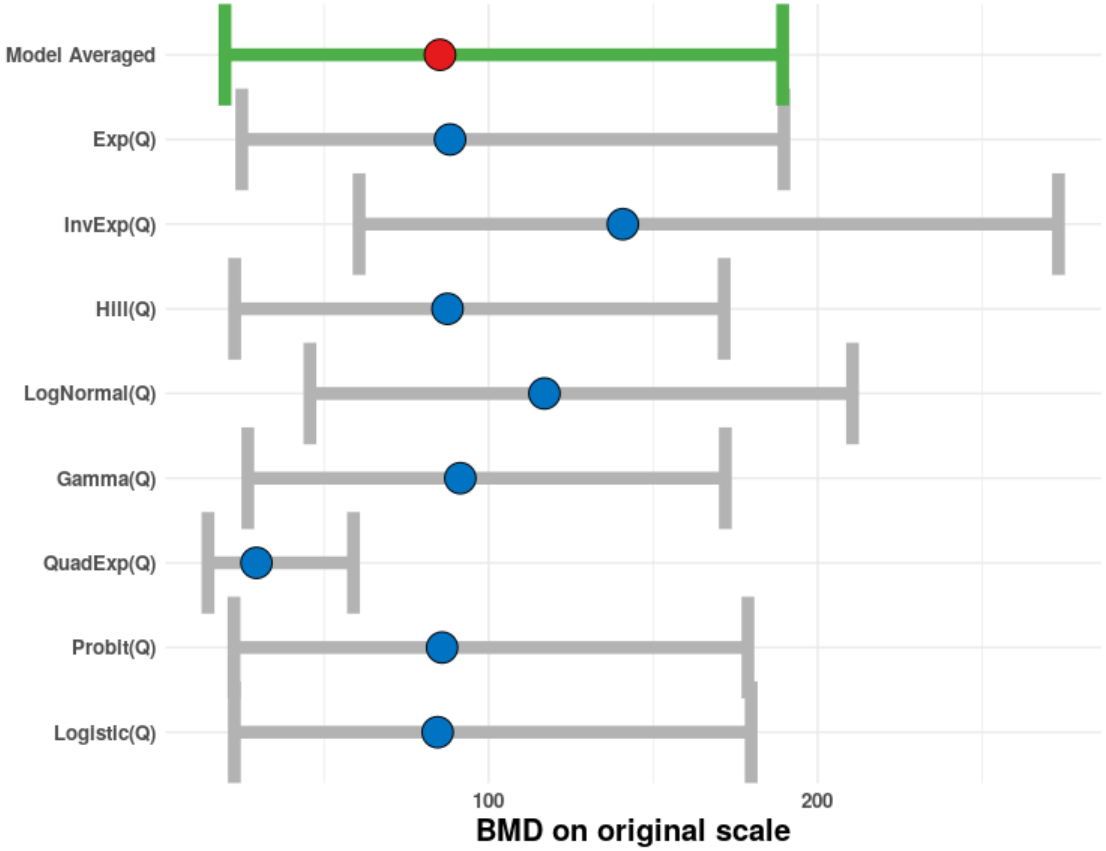
Model Averaged BMC

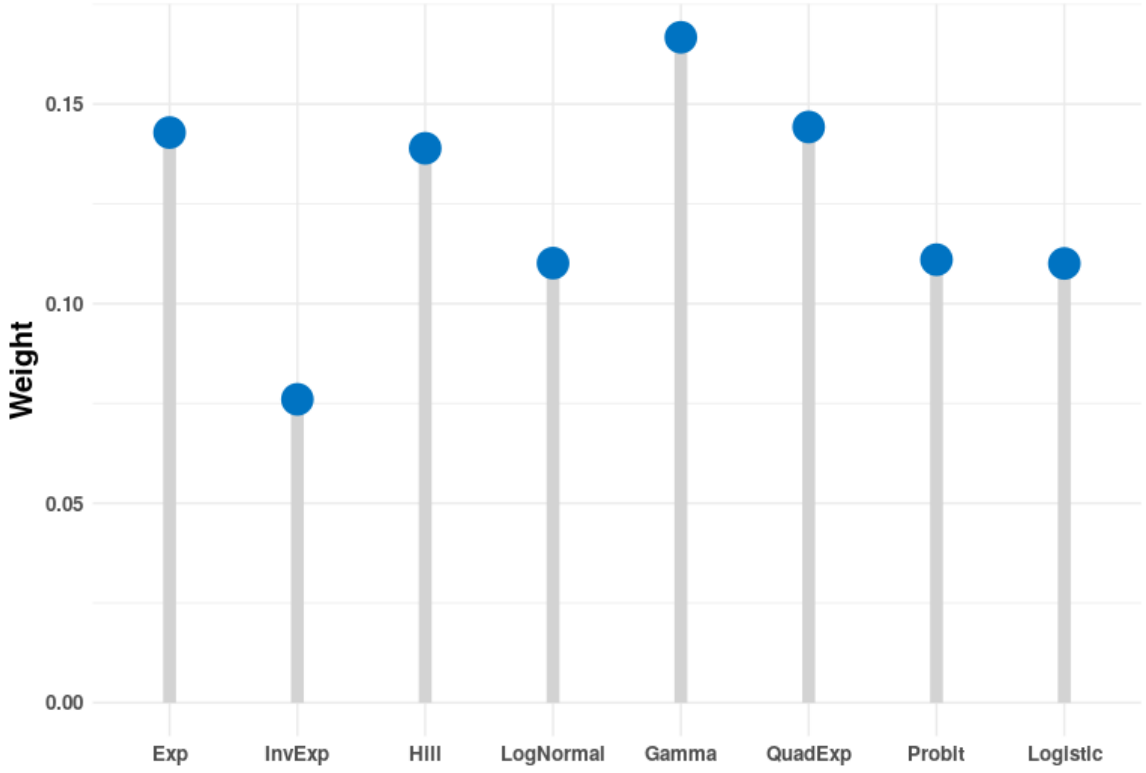
Model	Type	BMCL	BMC	BMCU
Model Averaged	BS	19.883	85.237	189.357

Estimated BMCs per model

Model	BMCL	BMC	BMCU	Model Weights	Converged
E4_Q	25.001	88.284	189.749	0.143	1
IE4_Q	60.651	140.797	273.169	0.076	0
H4_Q	22.833	87.509	171.571	0.139	1
LN4_Q	45.710	116.966	210.578	0.110	1
G4_Q	26.825	91.403	171.944	0.167	1
QE4_Q	14.730	29.464	58.942	0.144	1
P4_Q	22.633	85.873	178.801	0.111	1
L4_Q	22.743	84.503	179.796	0.110	1

Plots of Fitted Models

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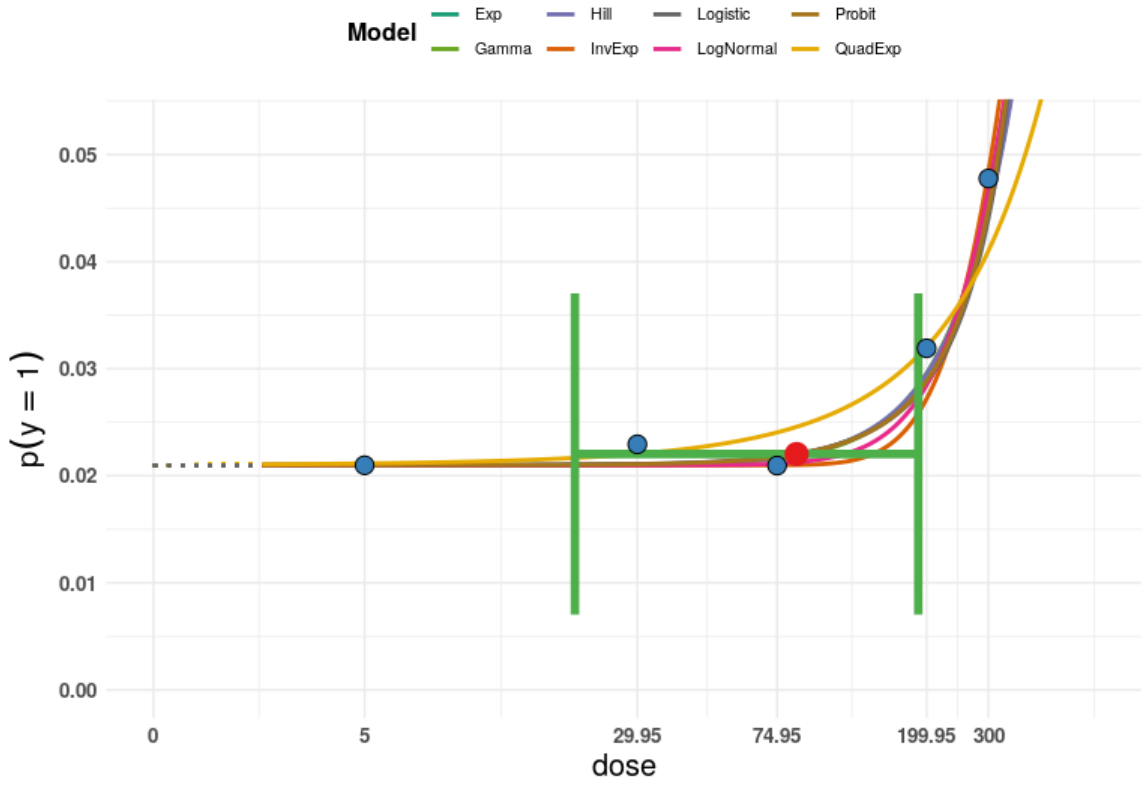
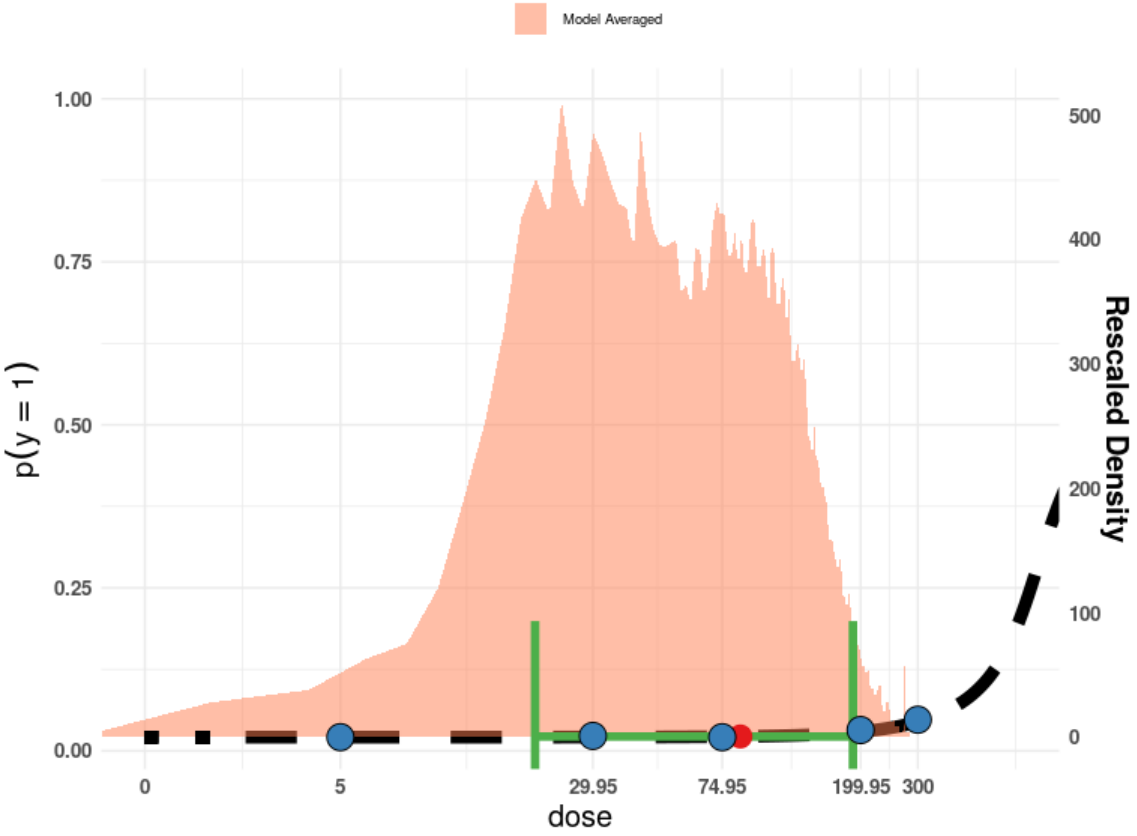
0.05
0.00
Exp
InvExp
Hill
LogNormal
Gamma
QuadExp
Probit
Logistic


Model
Exp
Hill
Logistic
Probit
Gamma
InvExp
LogNormal
QuadExp
p(y = 1)
0.05
0.04
0.03
0.02
0.01
0.00
0
5
29.95
74.95
199.95
300
dose


Model Averaged
1.00
0.75
0.50
0.25
0.00
p(y = 1)
500
400
300
200
100
0
Rescaled Density
0
5
29.95
74.95
199.95
300
dose

Chen et al. (2010b) bladder cancer, relative BMR 5%

Data Description

The endpoint to be analyzed is: Adj.cases for bladder cancer

Data used for analysis:

Water.conc.µg/L	Adj..cases	N
5.00	3	2288
29.95	5	2093
74.95	3	907
199.95	7	909
300.00	11	691

The 'Value for CES' is set to 6.565e-05.

Extended dose range is not applied.

Informative background prior: min: 0.00111451; the most likely: 0.001311189; max: 0.001507867. Shape parameter is applied.

The 'Sampling Method' is set to Bridge Sampling.

Results

Information pertaining to this endpoint.

Goodness of Fit

Best fitting model fits sufficiently well (Bayes factor is 3.06e-04).

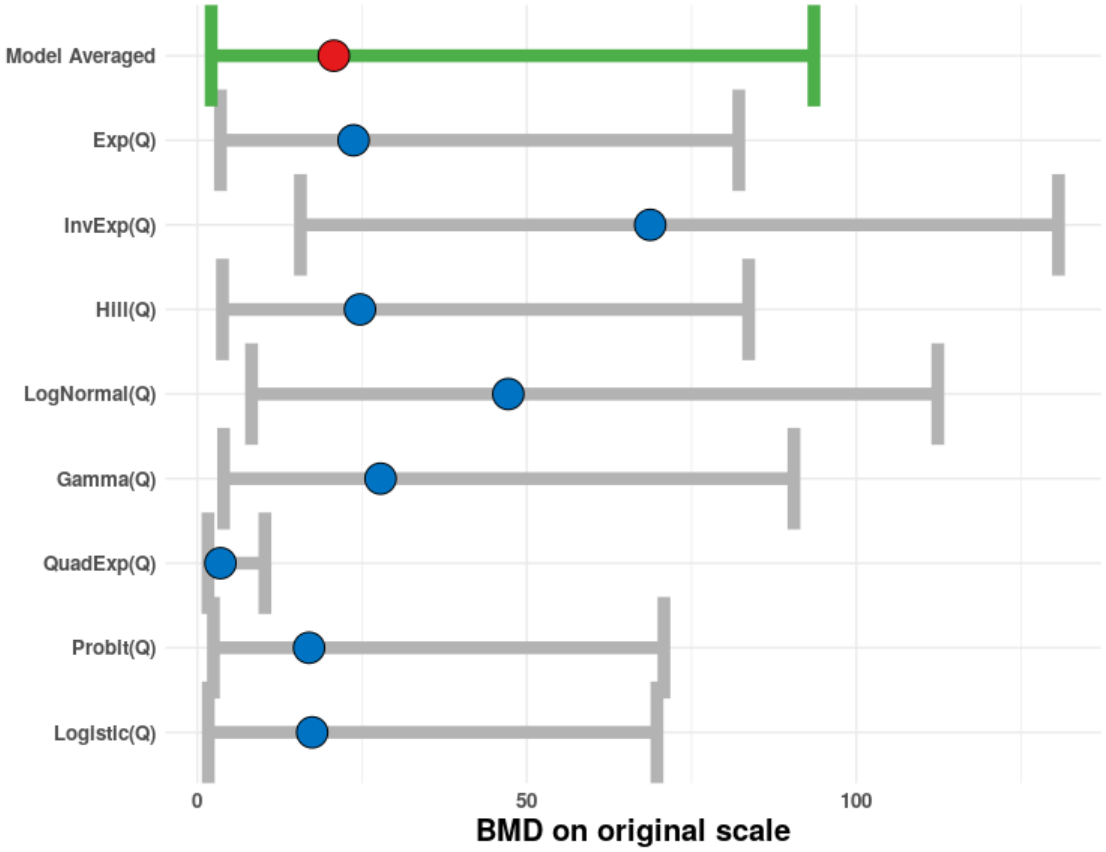
Model Averaged BMC

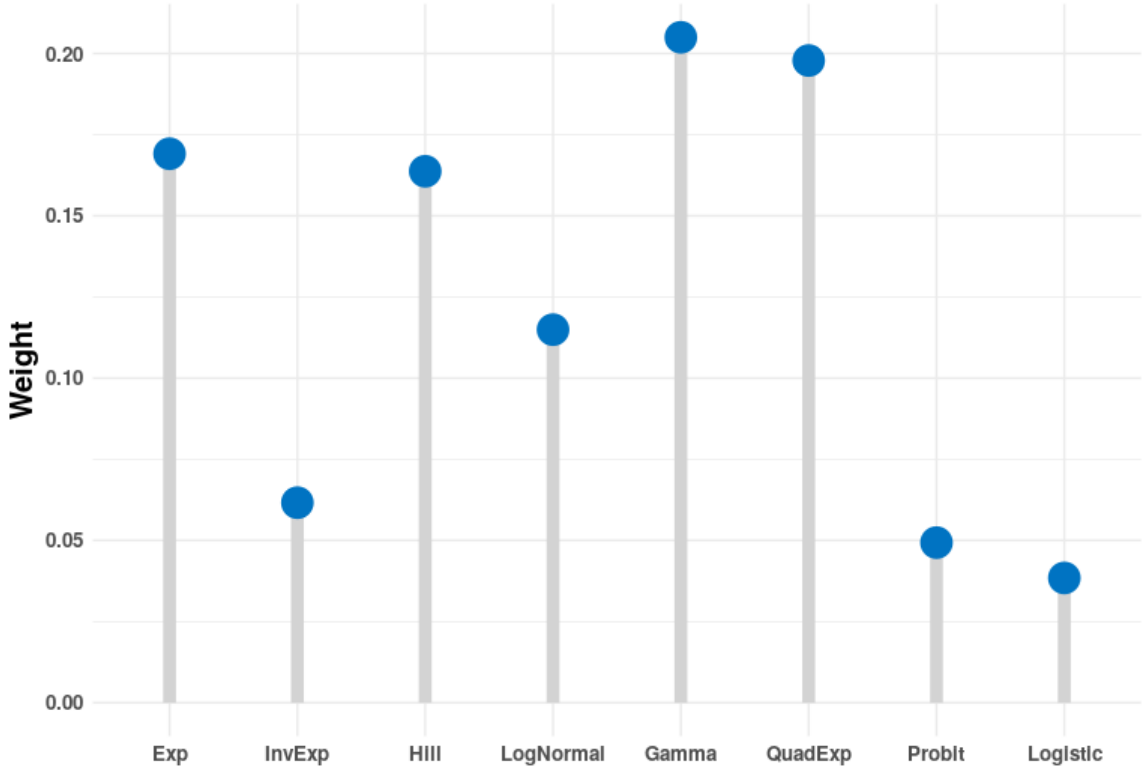
Model	Type	BMCL	BMC	BMCU
Model Averaged	BS	2.105	20.724	93.584

Estimated BMCs per model

Model	BMCL	BMC	BMCU	Model Weights	Converged
E4_Q	3.510	23.710	82.183	0.169	1
IE4_Q	15.651	68.728	130.696	0.062	1
H4_Q	3.814	24.688	83.679	0.164	1
LN4_Q	8.238	47.193	112.387	0.115	1
G4_Q	3.984	27.806	90.542	0.205	1
QE4_Q	1.620	3.510	10.255	0.198	1
P4_Q	2.446	16.957	70.815	0.049	1
L4_Q	1.662	17.433	69.759	0.038	1

Plots of Fitted Models

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0.05
0.00
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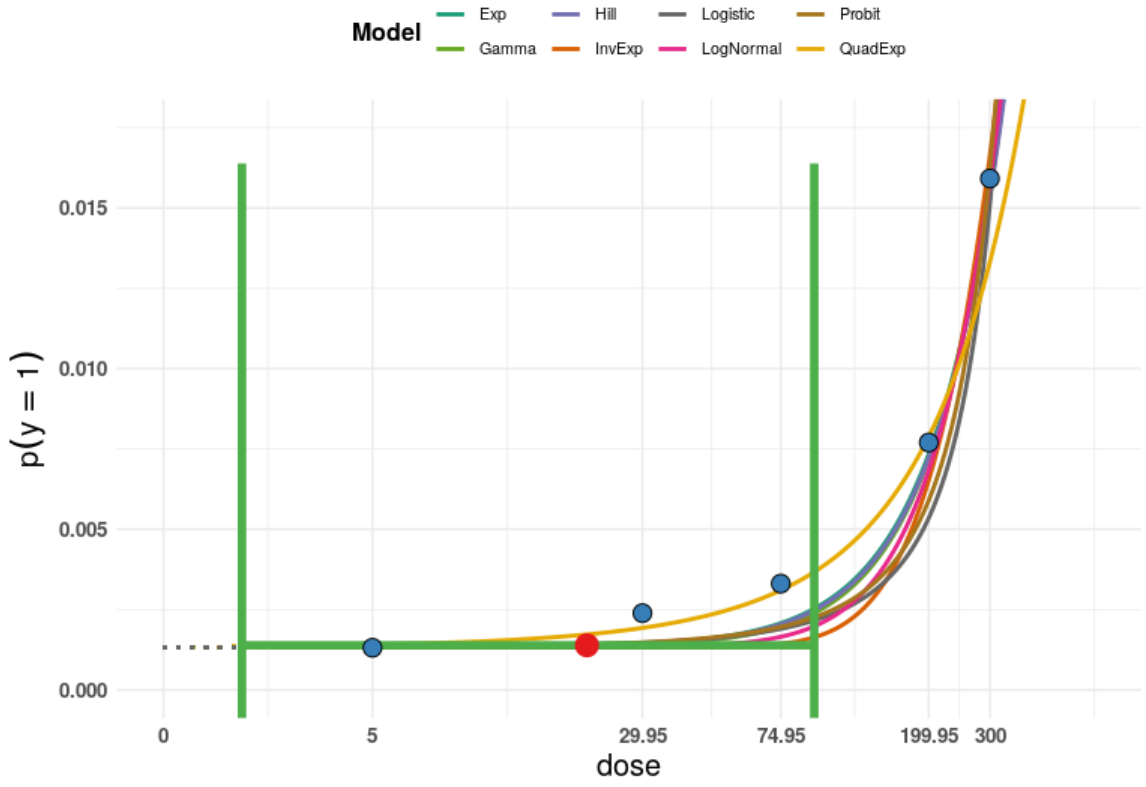
Hill
LogNormal
Gamma
QuadExp
Probit
Logistic


Model
Exp
Hill
Logistic
Probit
Gamma
InvExp
LogNormal
QuadExp
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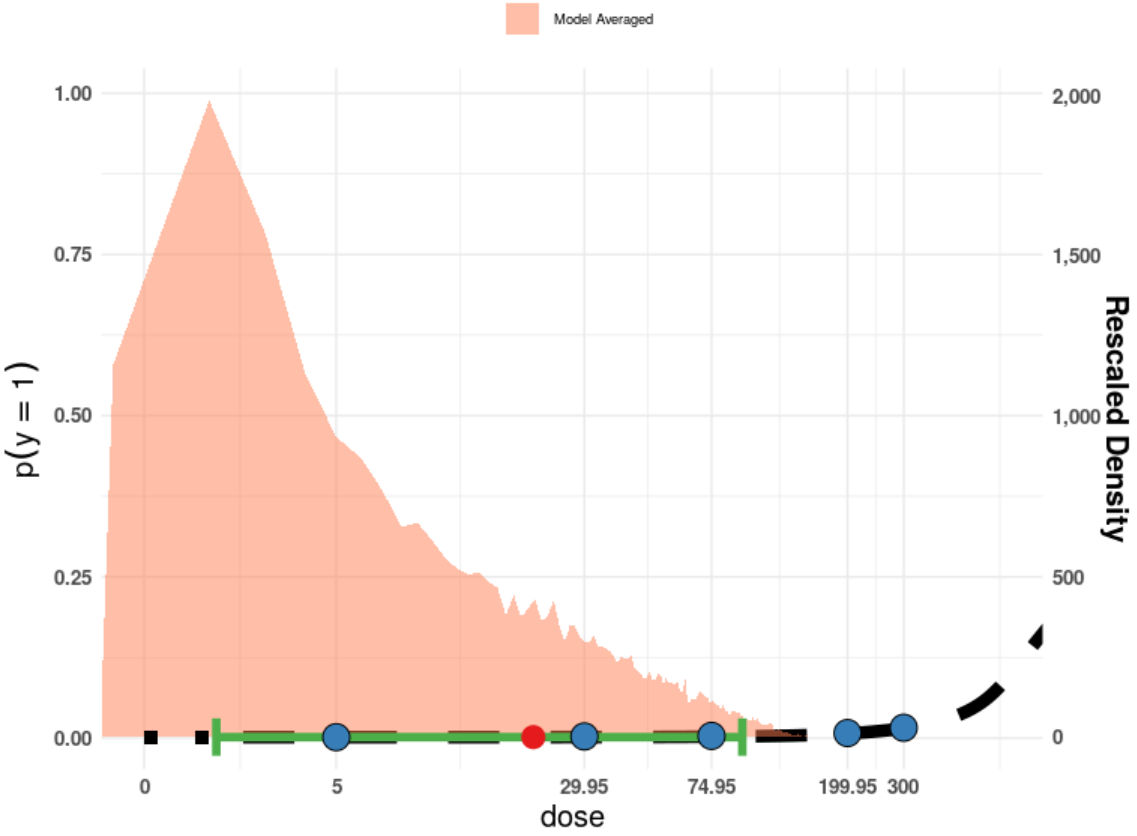
0.010
0.005
0.000
0
5
29.95
74.95
199.95
300
dose


Model Averaged
1.00
0.75
0.50
0.25
0.00
p(y = 1)
2,000
1,500
1,000
500
0
Rescaled Density
0
5
29.95
74.95
199.95
300
dose

Leonardi et al. (2012) skin cancer, relative BMR 5%

Data Description

The endpoint to be analyzed is: Adj.cases for skin cancer

Data used for analysis:

Water.conc.µg/L	Adj..cases	N
0.340	59	4e+05
0.830	82	4e+05
3.990	70	4e+05
13.265	101	4e+05
93.415	179	4e+05

The 'Value for CES' is set to 7.38e-06.

Extended dose range is not applied.

Informative background prior: min: 0.000146025; the most likely: 0.0001475; max: 0.000148975. Shape parameter is applied.

The 'Sampling Method' is set to Bridge Sampling.

Results

Information pertaining to this endpoint.

Goodness of Fit

Best fitting model fits sufficiently well (Bayes factor is 2.74e-06).

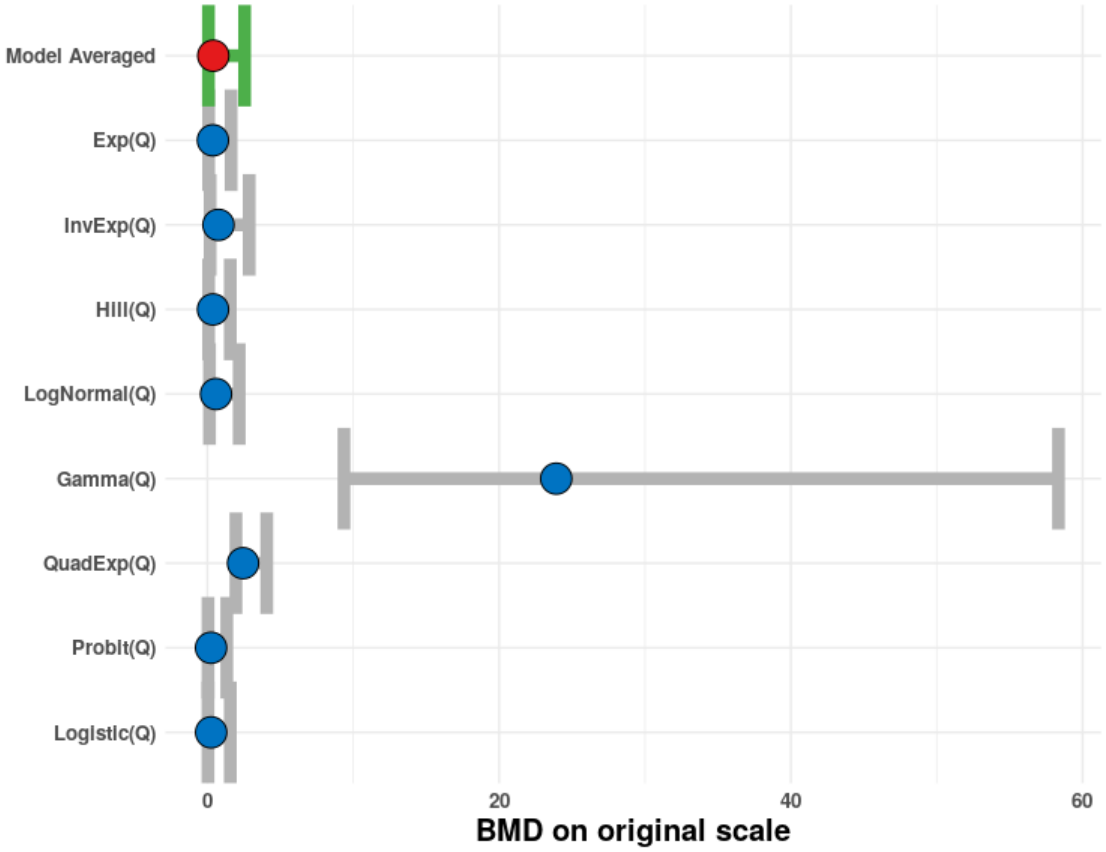
Model Averaged BMC

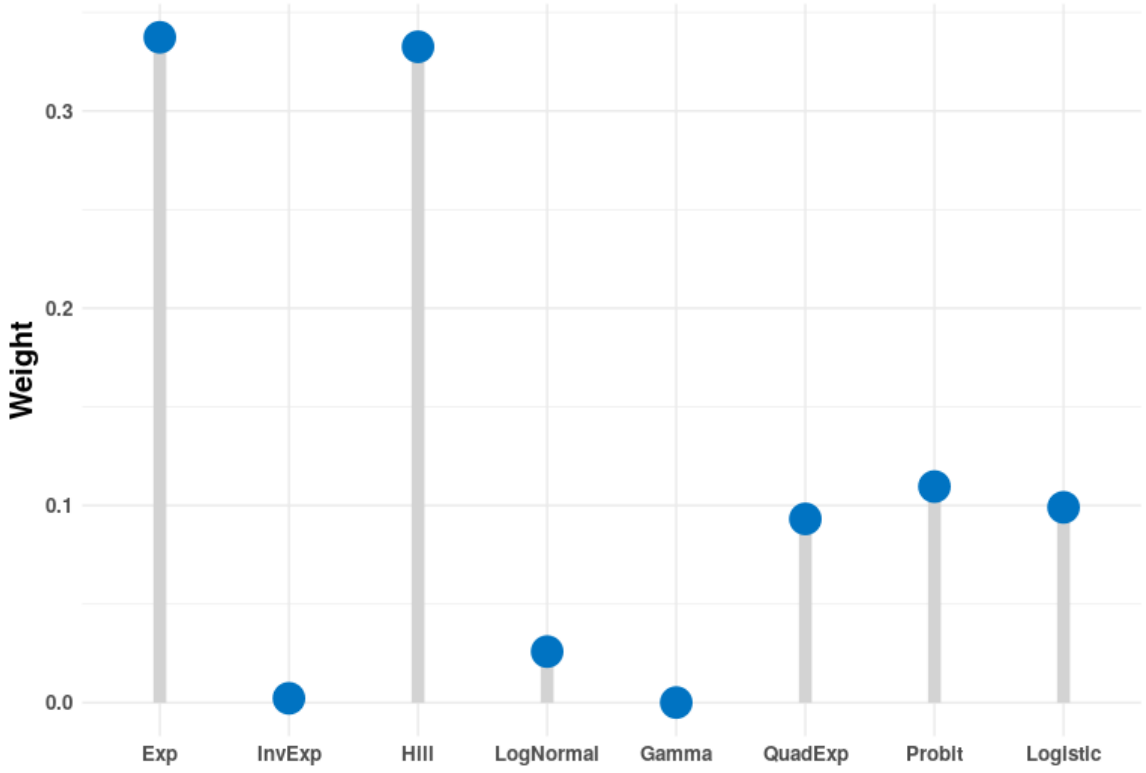
Model	Type	BMCL	BMC	BMCU
Model Averaged	BS	0.07	0.401	2.548

Estimated BMCs per model

Model	BMCL	BMC	BMCU	Model Weights	Converged
E4_Q	0.082	0.376	1.622	0.337	1
IE4_Q	0.182	0.754	2.862	0.002	1
H4_Q	0.081	0.383	1.567	0.333	1
LN4_Q	0.140	0.589	2.178	0.026	1
G4_Q	9.361	23.916	58.347	0.000	0
QE4_Q	1.955	2.442	4.068	0.093	1
P4_Q	0.040	0.249	1.327	0.110	1
L4_Q	0.038	0.254	1.569	0.099	1

Plots of Fitted Models

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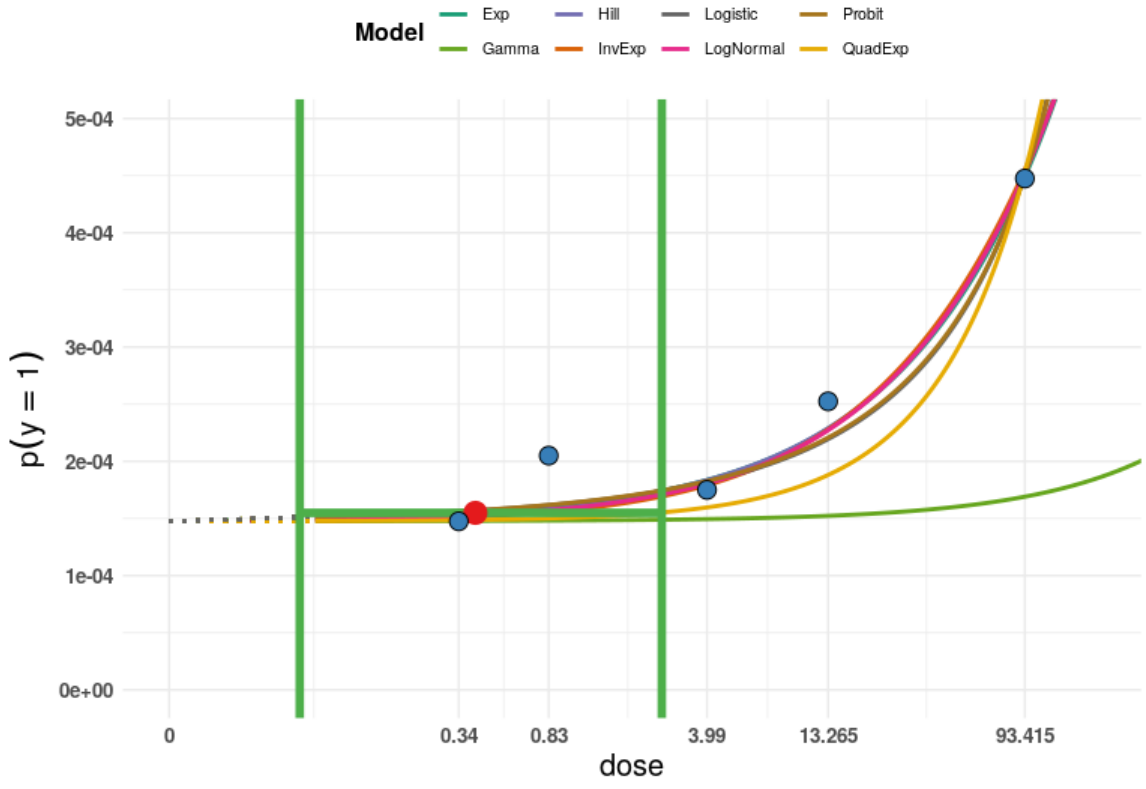
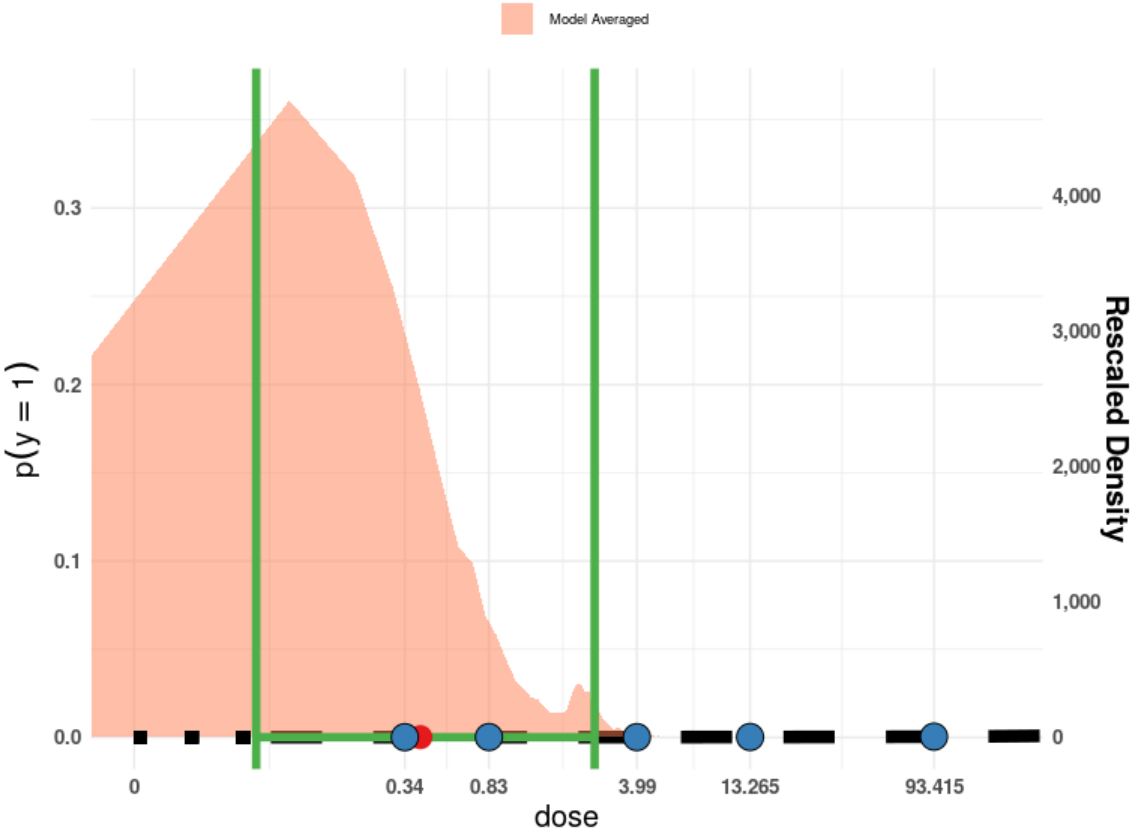
0.1
0.0
Exp
InvExp
Hill
LogNormal
Gamma
QuadExp
Probit
Logistic


Model
Exp
Hill
Logistic
Probit
Gamma
InvExp
LogNormal
QuadExp
p(y = 1)
5e-04
4e-04
3e-04
2e-04
1e-04
0e+00
0
0.34
0.83
3.99
13.265
93.415
dose


Model Averaged
p(y = 1)
0.3
0.2
0.1
0.0
4,000
3,000
2,000
1,000
0
Rescaled Density
0
0.34
0.83
3.99
13.265
93.415
dose

Pierce et al. (2011) skin lesions, relative BMR 5%

Data Description

The endpoint to be analyzed is: Adj.cases for skin lesions

Data used for analysis:

Water.conc.µg/L	Adj..cases	N
5.05	117	2358
30.05	123	2118
75.05	145	1726
150.05	314	2855
200.10	115	617

The 'Value for CES' is set to 0.00261044.

Extended dose range is not applied.

Informative background prior: min: 0.049122137; the most likely: 0.049618321; max: 0.050114504. Shape parameter is applied.

The 'Sampling Method' is set to Bridge Sampling.

Results

Information pertaining to this endpoint.

Goodness of Fit

Best fitting model fits sufficiently well (Bayes factor is 5.60e-03).

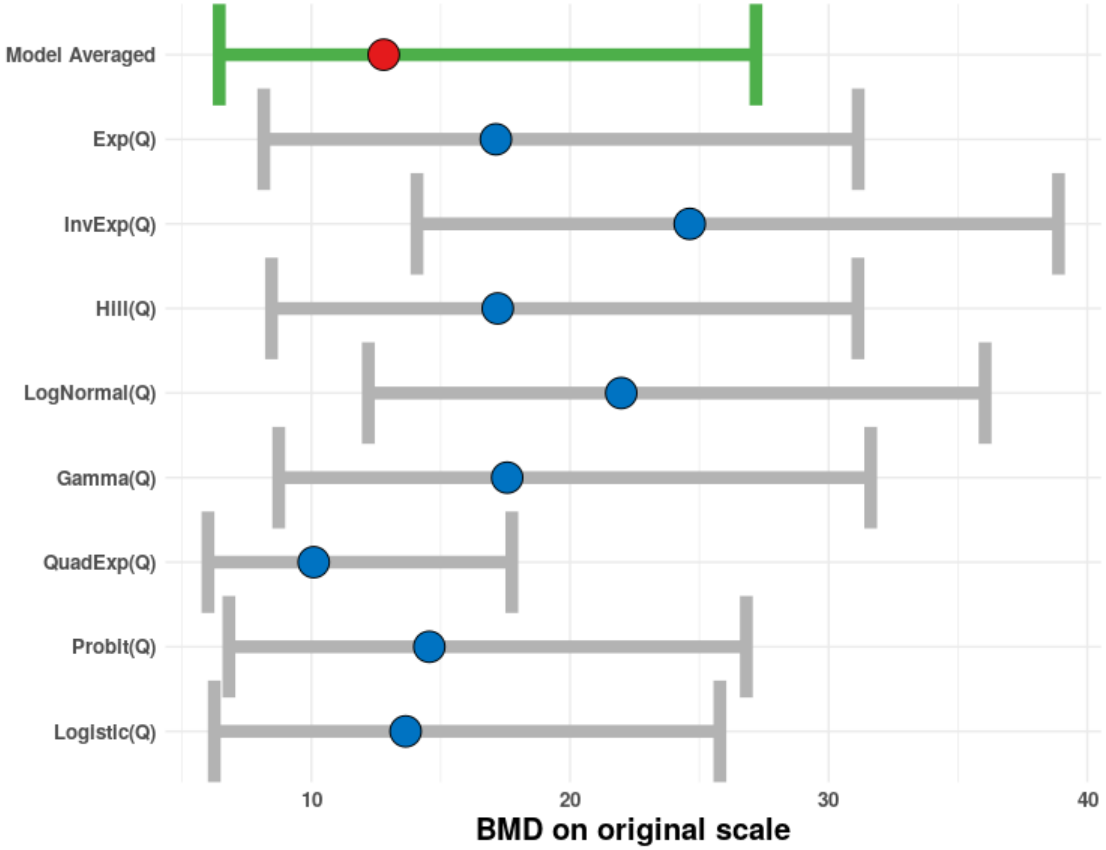
Model Averaged BMC

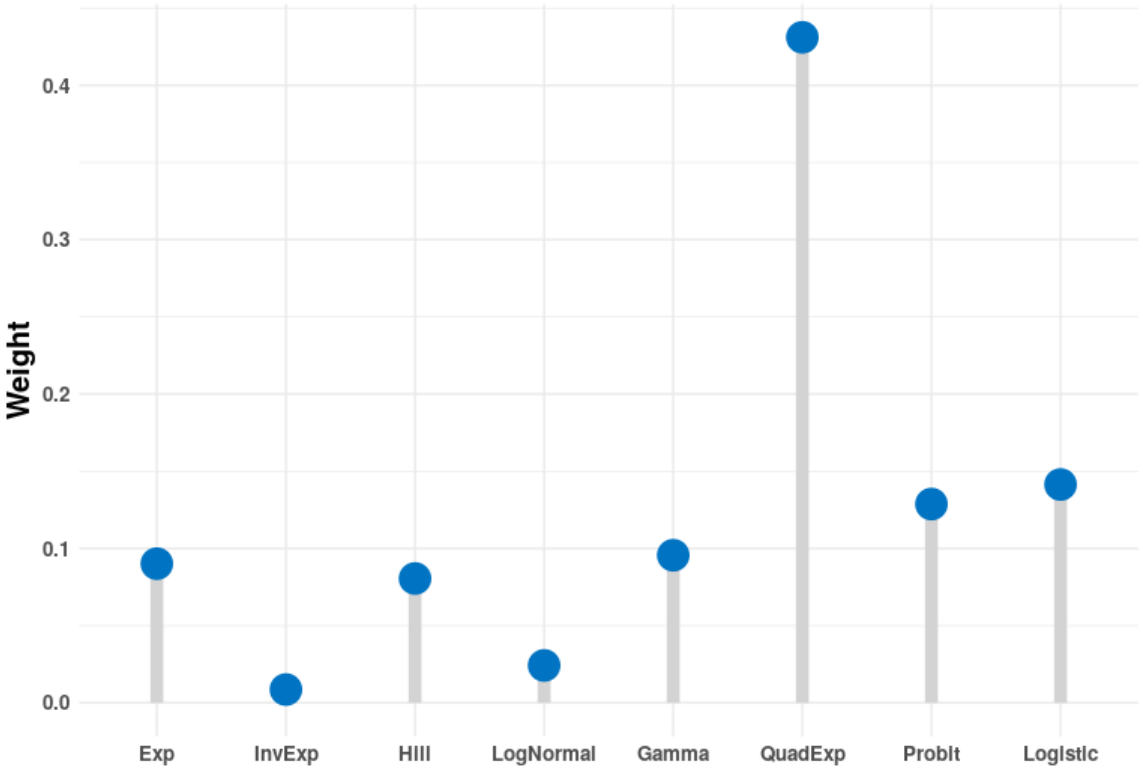
Model	Type	BMCL	BMC	BMCU
Model Averaged	BS	6.437	12.798	27.189

Estimated BMCs per model

Model	BMCL	BMC	BMCU	Model Weights	Converged
E4_Q	8.161	17.135	31.143	0.090	1
IE4_Q	14.083	24.627	38.887	0.009	1
H4_Q	8.458	17.205	31.132	0.080	1
LN4_Q	12.203	21.980	36.050	0.024	1
G4_Q	8.738	17.570	31.624	0.096	1
QE4_Q	6.002	10.091	17.750	0.431	1
P4_Q	6.811	14.560	26.818	0.129	1
L4_Q	6.245	13.644	25.794	0.141	1

Plots of Fitted Models

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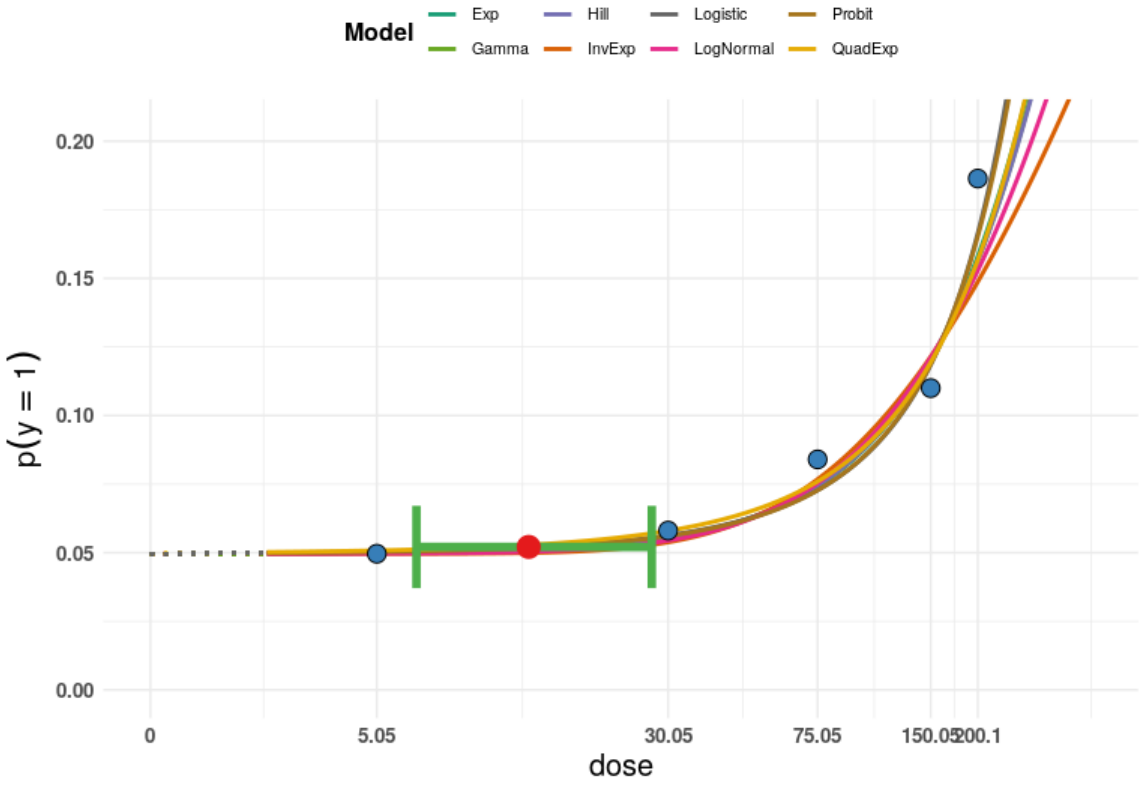
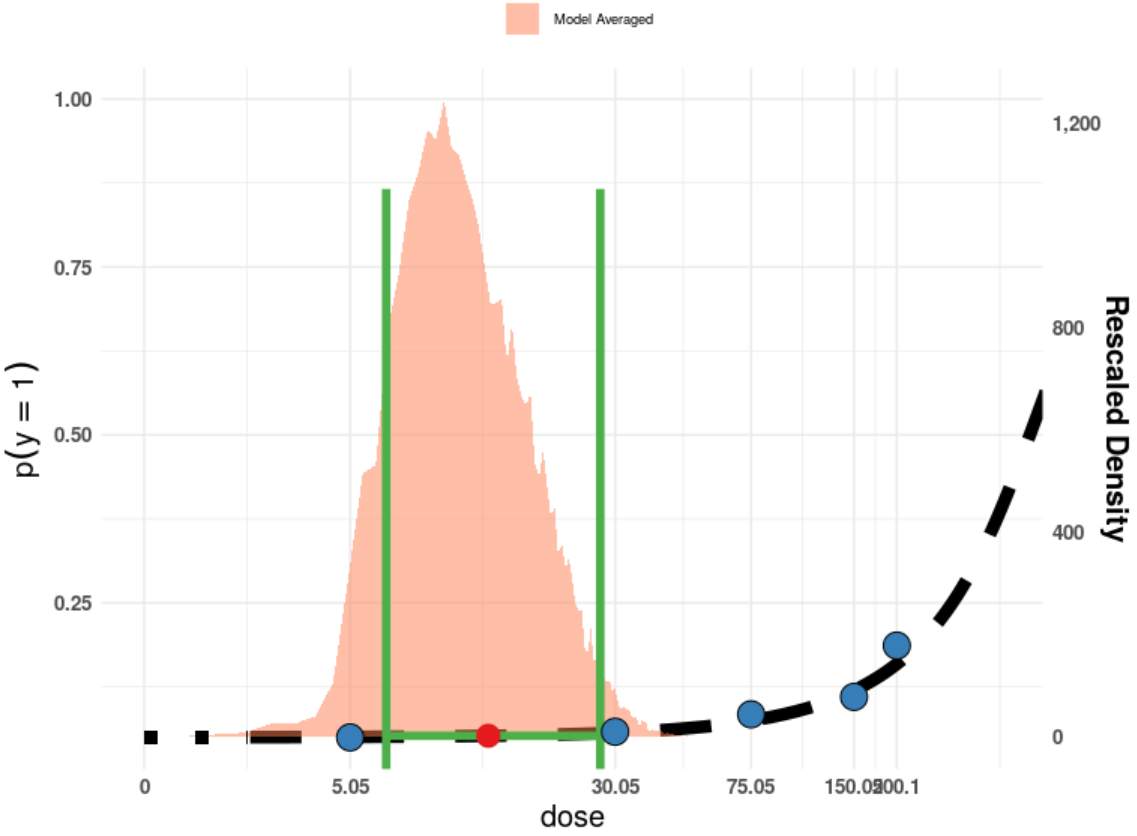
0.2
0.1
0.0
Exp
InvExp
Hill
LogNormal
Gamma
QuadExp
Probit
Logistic


Model
Exp
Hill
Logistic
Probit
Gamma
InvExp
LogNormal
QuadExp
p(y = 1)
0.20
0.15
0.10
0.05
0.00
0
5.05
30.05
75.05
150.05
200.1
dose


Model Averaged
1.00
0.75
0.50
0.25
p(y = 1)
1,200
800
400
0
Rescaled Density
0
5.05
30.05
75.05
150.05
200.1
dose

Steinmaus et al. (2014a) lung cancer, relative BMR 5%

Exposure: the highest 5-year average, based on arsenic daily intakes (the preferred exposure estimate for the study)

Data Description

The endpoint to be analyzed is: Adj.cases for lung cancer

Data used for analysis:

Water.daily.intake.µg	Adj..cases	N
6.6	25	79688
34.5	30	77344
55.8	37	67969

The 'Value for CES' is set to 1.569e-05.

Extended dose range is not applied.

Informative background prior: min: 0.000310586; the most likely: 0.000313724; max: 0.000316861. Shape parameter is applied.

The 'Sampling Method' is set to Bridge Sampling.

Results

Information pertaining to this endpoint.

Goodness of Fit

Best fitting model fits sufficiently well (Bayes factor is 1.72e+00).

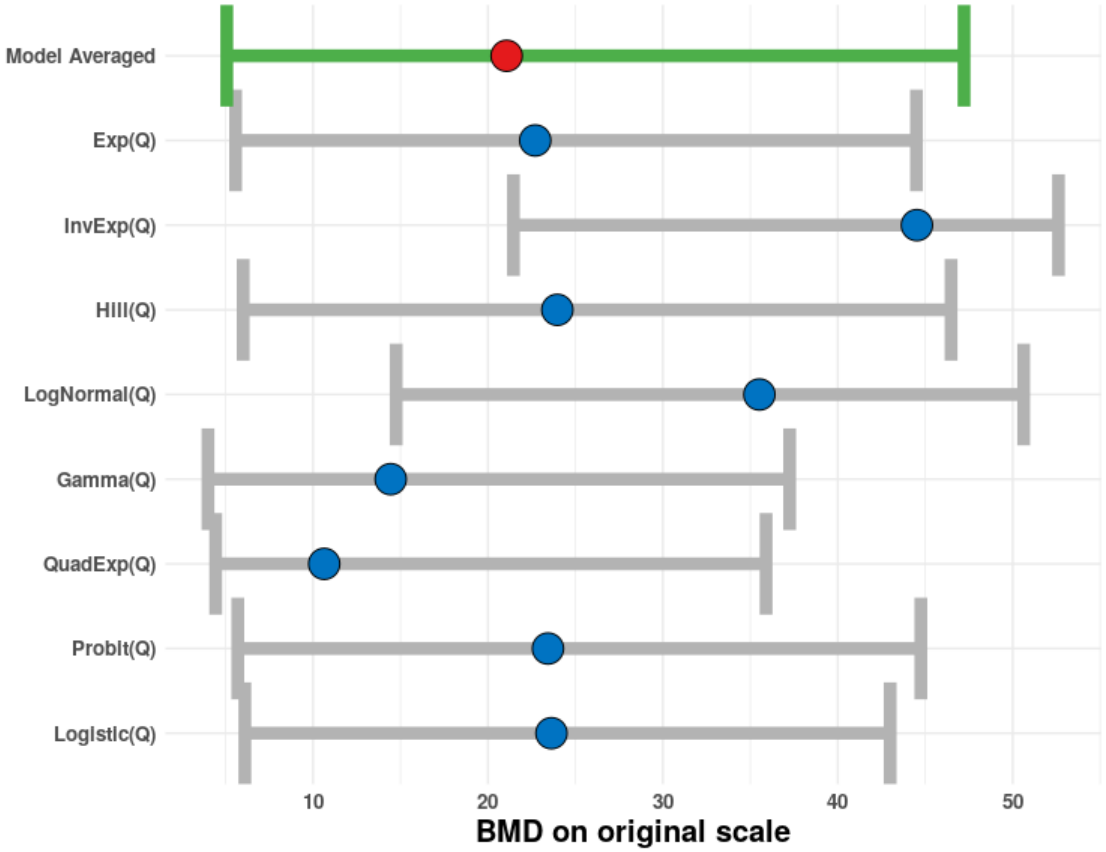
Model Averaged BMC

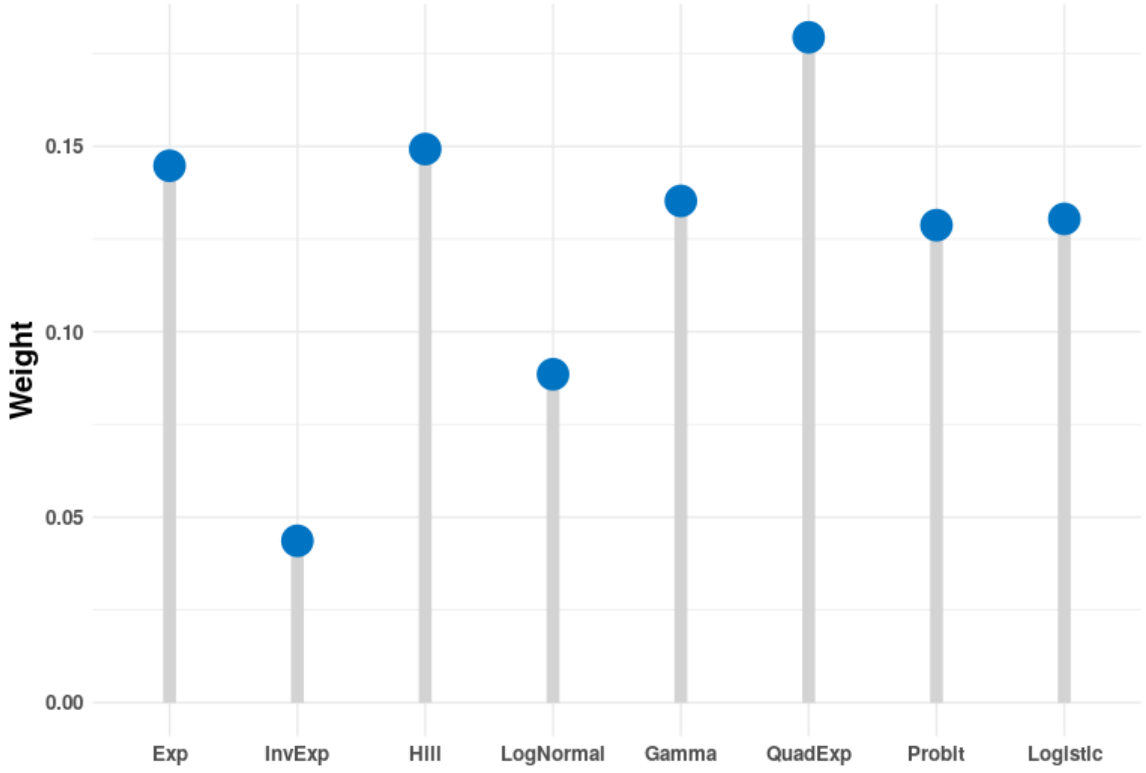
Model	Type	BMCL	BMC	BMCU
Model Averaged	BS	5.067	21.068	47.218

Estimated BMCs per model

Model	BMCL	BMC	BMCU	Model Weights	Converged
E4_Q	5.571	22.702	44.498	0.145	1
IE4_Q	21.457	44.523	52.618	0.044	1
H4_Q	6.005	23.966	46.477	0.149	1
LN4_Q	14.752	35.518	50.627	0.089	1
G4_Q	3.993	14.438	37.248	0.135	0
QE4_Q	4.434	10.637	35.900	0.179	1
P4_Q	5.696	23.431	44.750	0.129	1
L4_Q	6.101	23.629	42.994	0.130	1

Plots of Fitted Models

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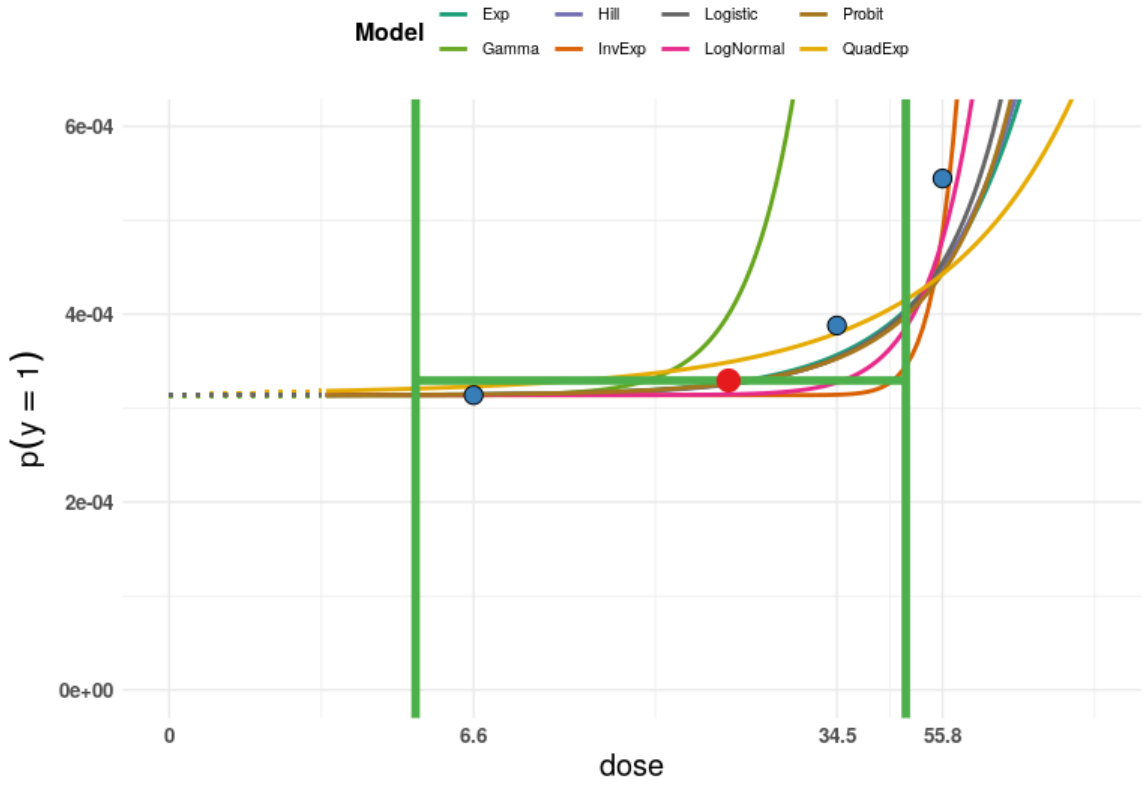
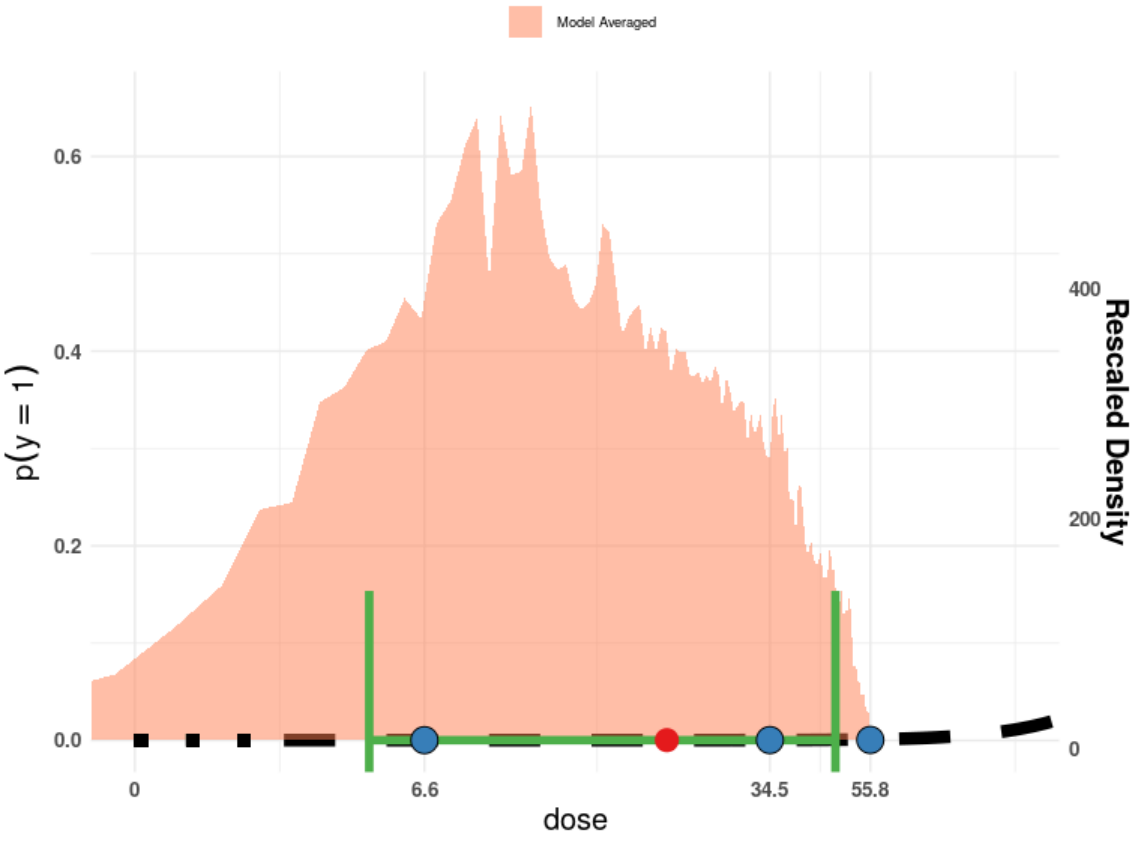
0.10
0.05
0.00
Exp
InvExp
Hill
LogNormal
Gamma
QuadExp
Probit
Logistic


Model
Exp
Hill
Logistic
Probit
Gamma
InvExp
LogNormal
QuadExp
p(y = 1)
6e-04
4e-04
2e-04
0e+00
0
6.6
34.5
55.8
dose


Model Averaged
0.6
0.4
0.2
0.0
p(y = 1)
400
200
0
Rescaled Density
0
6.6
34.5
55.8
dose

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Appendix

Using water iAs concentrations (rather than total exposures) as a basis for modelling creates a dose-response shape that differs somewhat due to differences in relative dose spacing as illustrated for Pierce et al. (2011).