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

Annex E4 Benchmark dose modelling reports

Relative increase of the background incidence after adjustment for confounders by 50%

Annex E4 provides a comprehensive overview of the benchmark dose (BMD) analyses carried out for the studies used in the uncertainty analysis, employing the model averaging technique. The BMD analyses were conducted in accordance with the EFSA BMD guidance (EFSA Scientific Committee, 2022).

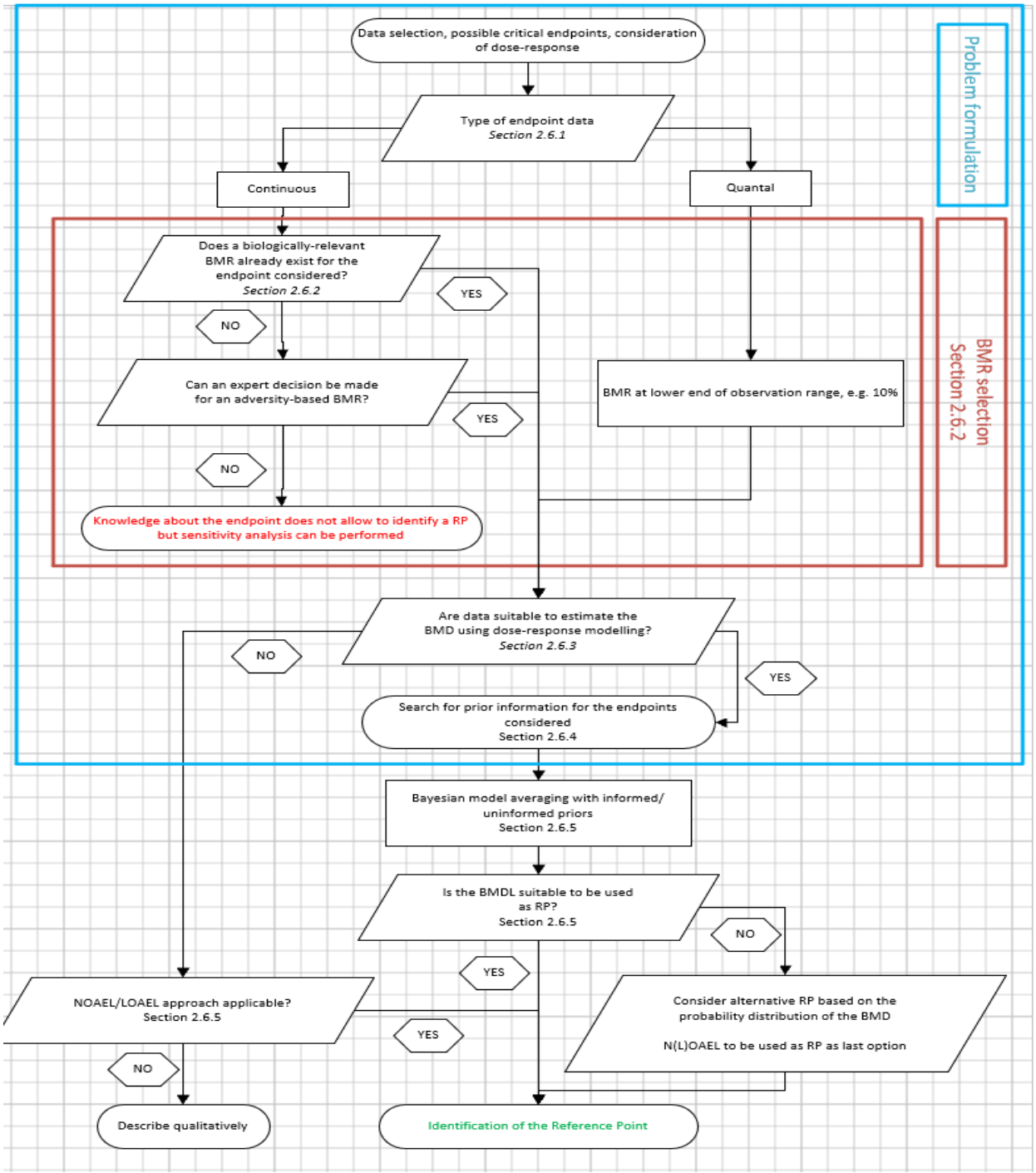
E4.1 Selection of the BMR

The BMD is identified as the specific dose that corresponds to the desired BMR level. To assess the uncertainty associated with the BMD, a 90% confidence interval is estimated, with the lower bound denoted as BMDL and the upper bound as BMDU. The BMDL and BMDU values help to quantify the range within which the true BMD value is expected to lie.

As BMR the CONTAM Panel decided to use a relative increase of the background incidence after adjustment for confounders by 50%.

E4.2 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).

E4.3 BMD modelling reports

Chen et al. (2010b) bladder cancer, relative BMR 50%

Data Description

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

Data used for analysis:

Exposure.µg.kg.bw.per.day	Adj.cases	N
0.927	3	2288
2.288	5	2093
4.743	3	907
11.561	7	909
17.018	11	691

The 'Value for CES' is set to 0.00065646.

Extended dose range is not applied.

Informative background prior: min: 0.00129808; the most likely: 0.00131119; max: 0.00132430. 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 1.73e-04).

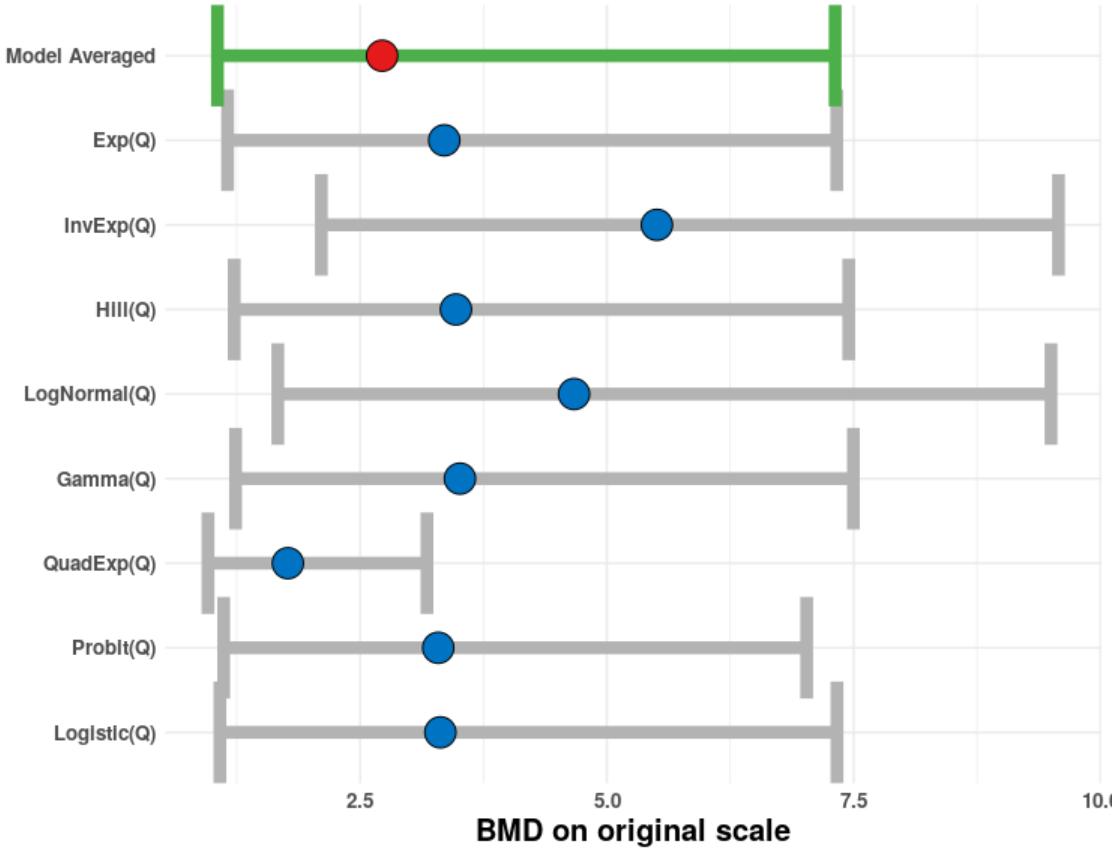
Model Averaged BMD

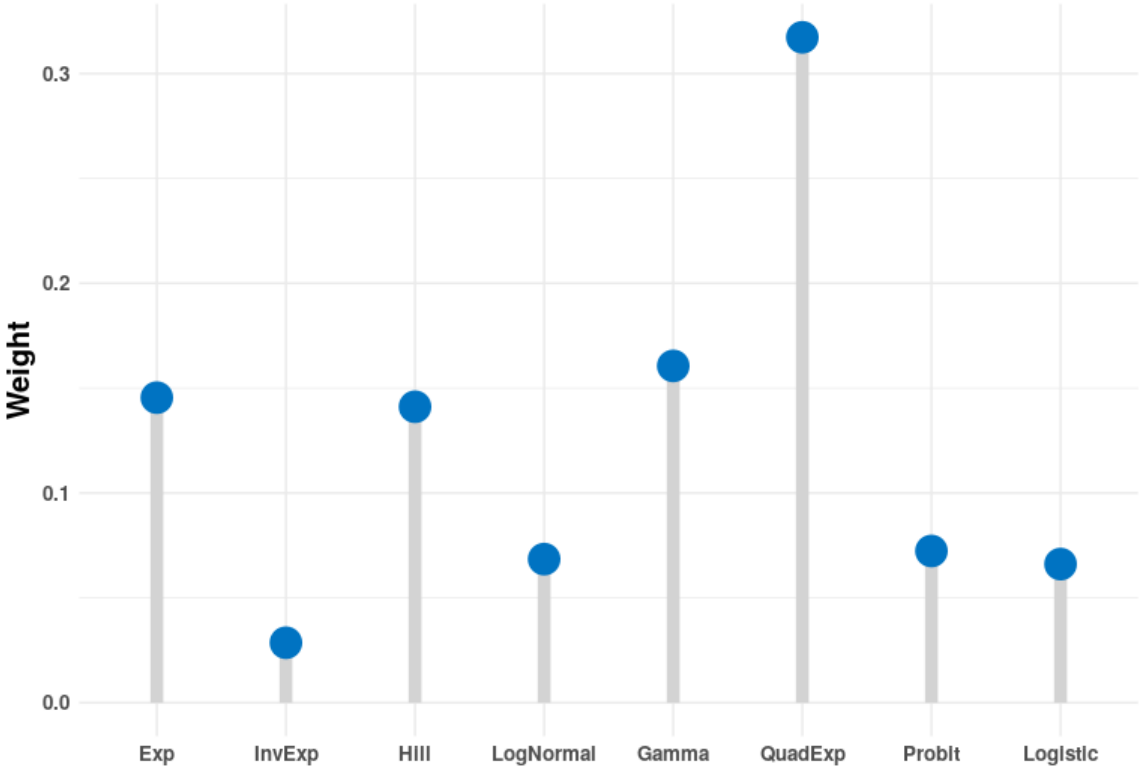
Model	Type	BMDL	BMD	BMDU
Model Averaged	BS	1.055	2.724	7.313

Estimated BMDs per model

Model	BMDL	BMD	BMDU	Model Weights	Converged
E4_Q	1.159	3.353	7.329	0.145	1
IE4_Q	2.108	5.507	9.576	0.029	1
H4_Q	1.225	3.472	7.451	0.141	1
LN4_Q	1.667	4.668	9.500	0.068	1
G4_Q	1.239	3.512	7.498	0.161	1
QE4_Q	0.960	1.769	3.178	0.317	1
P4_Q	1.119	3.292	7.024	0.072	1
L4_Q	1.081	3.314	7.332	0.066	1

Plots of Fitted Models

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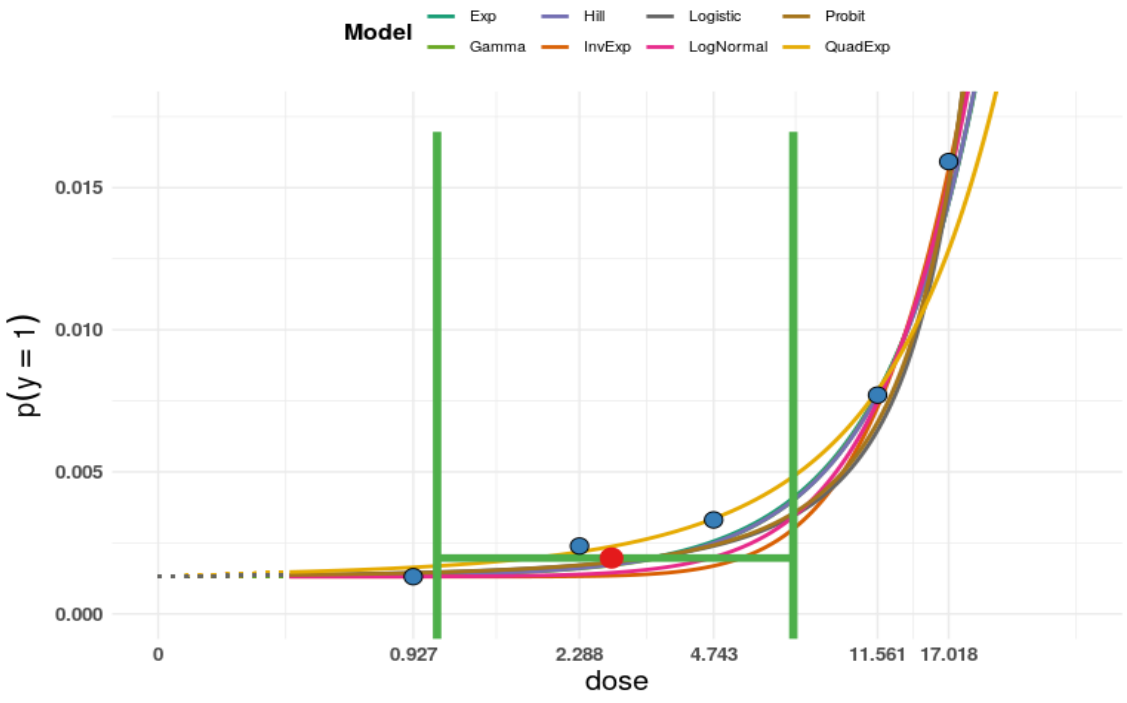
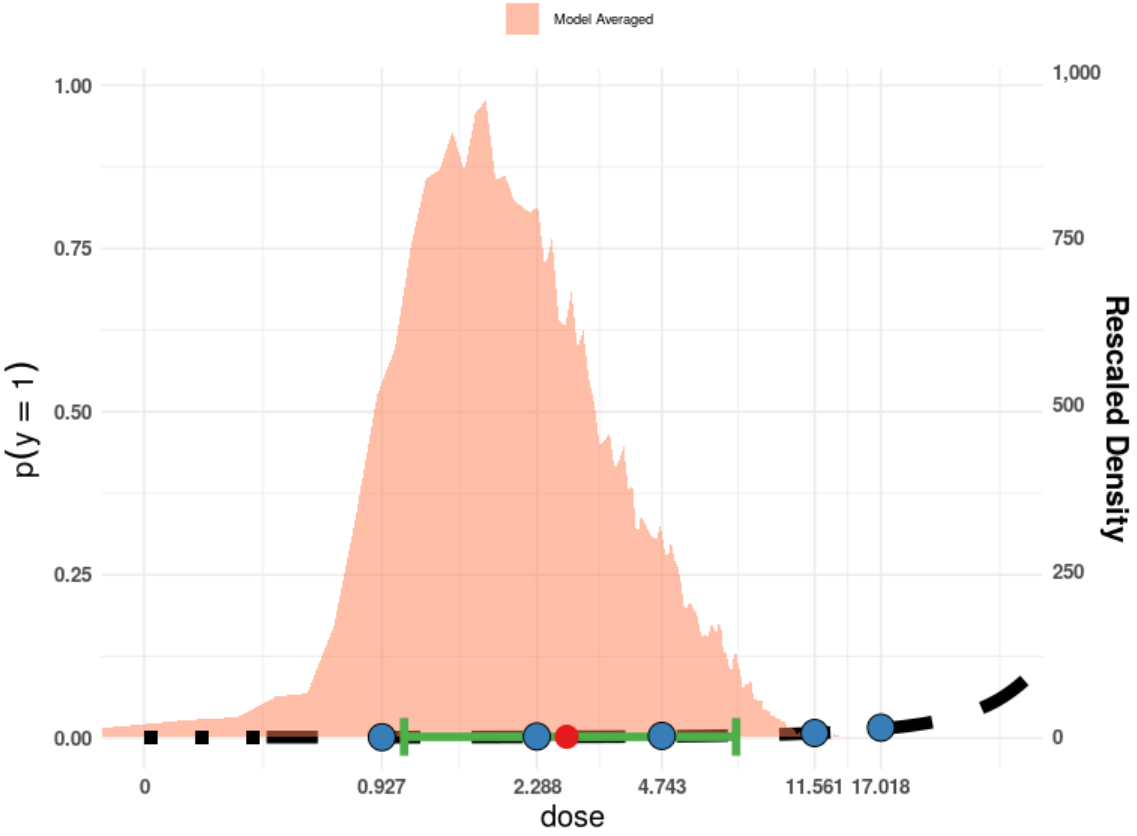
0.2
0.1
0.0
Exp
InvExp
Hill
LogNormal
Gamma
QuadExp
Probit
Logistic


Model
Exp
Hill
Logistic
Probit
Gamma
InvExp
LogNormal
QuadExp
p(y = 1)
0.015
0.010
0.005
0.000
0
0.927
2.288
4.743
11.561
17.018
dose


Model Averaged
1.00
0.75
0.50
0.25
0.00
p(y = 1)
1,000
750
500
250
0
Rescaled Density
0
0.927
2.288
4.743
11.561
17.018
dose

Steinmaus et al. (2013) bladder cancer, relative BMR 50%

Exposure: lifetime average before 1971, based on arsenic daily intakes

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

Data used for analysis:

Exposure.µg.kg.bw.per.day	Adj.cases	N
0.44	30	140802
1.57	36	136557
5.18	74	108962
7.79	92	63679

The 'Value for CES' is set to 0.00010656.

Extended dose range is applied.

Informative background prior: min: 0.00021093; the most likely: 0.00021307; max: 0.00021520. 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 1.44e-03).

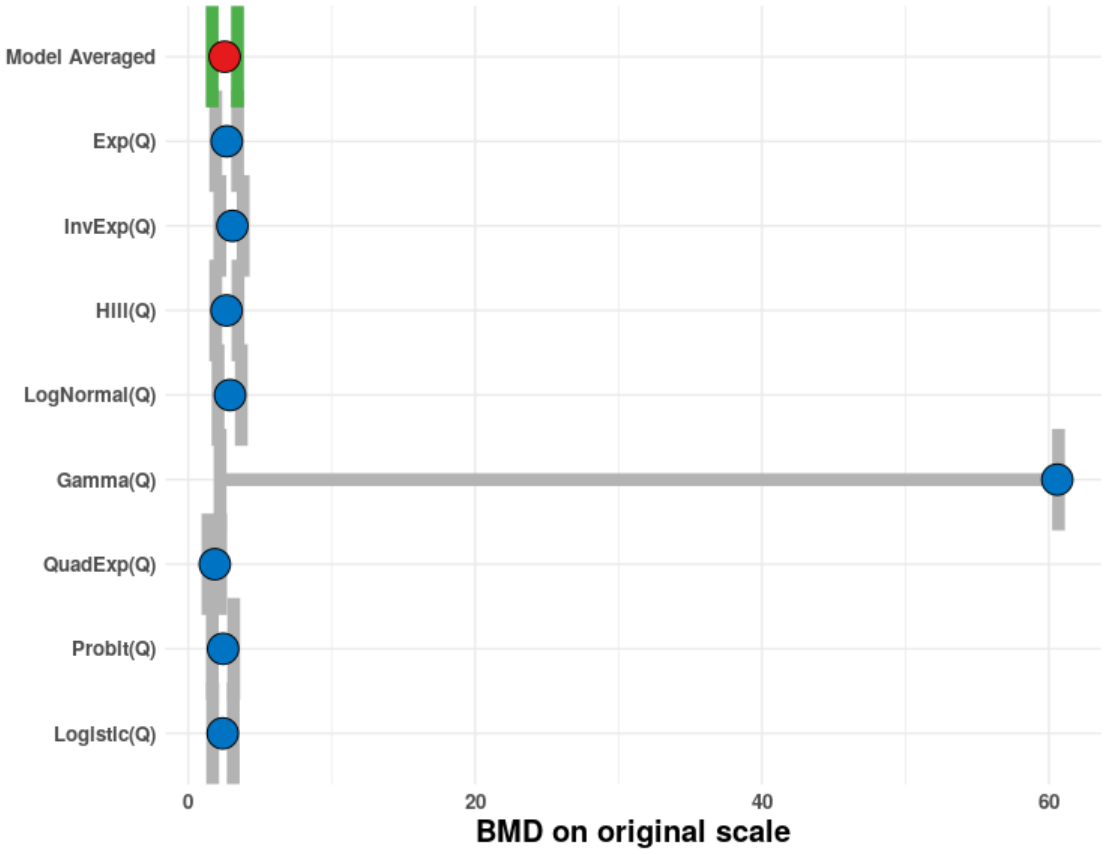
Model Averaged BMD

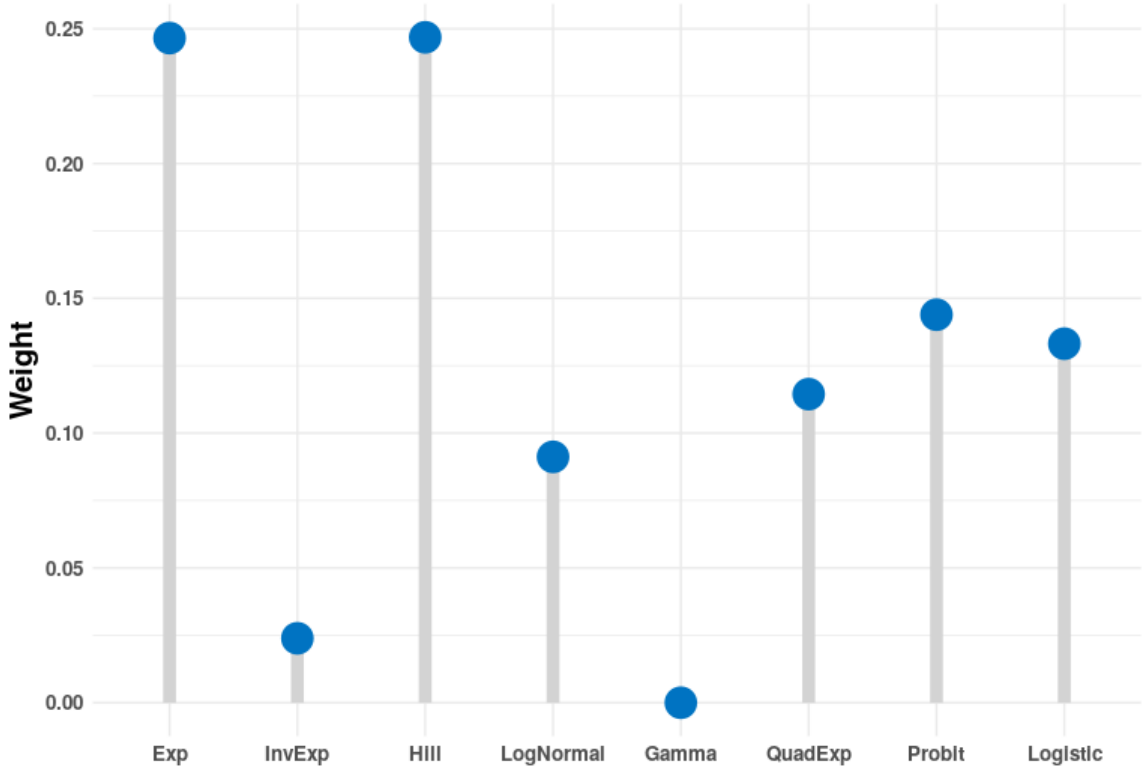
Model	Type	BMDL	BMD	BMDU
Model Averaged	BS	1.671	2.542	3.438

Estimated BMDs per model

Model	BMDL	BMD	BMDU	Model Weights	Converged
E4_Q	1.920	2.688	3.447	0.247	1
IE4_Q	2.208	3.080	3.831	0.024	1
H4_Q	1.919	2.673	3.470	0.247	1
LN4_Q	2.080	2.914	3.702	0.091	1
G4_Q	2.222	60.588	60.674	0.000	0
QE4_Q	1.379	1.856	2.259	0.114	1
P4_Q	1.682	2.434	3.172	0.144	1
L4_Q	1.704	2.406	3.139	0.133	1

Plots of Fitted Models




Weight
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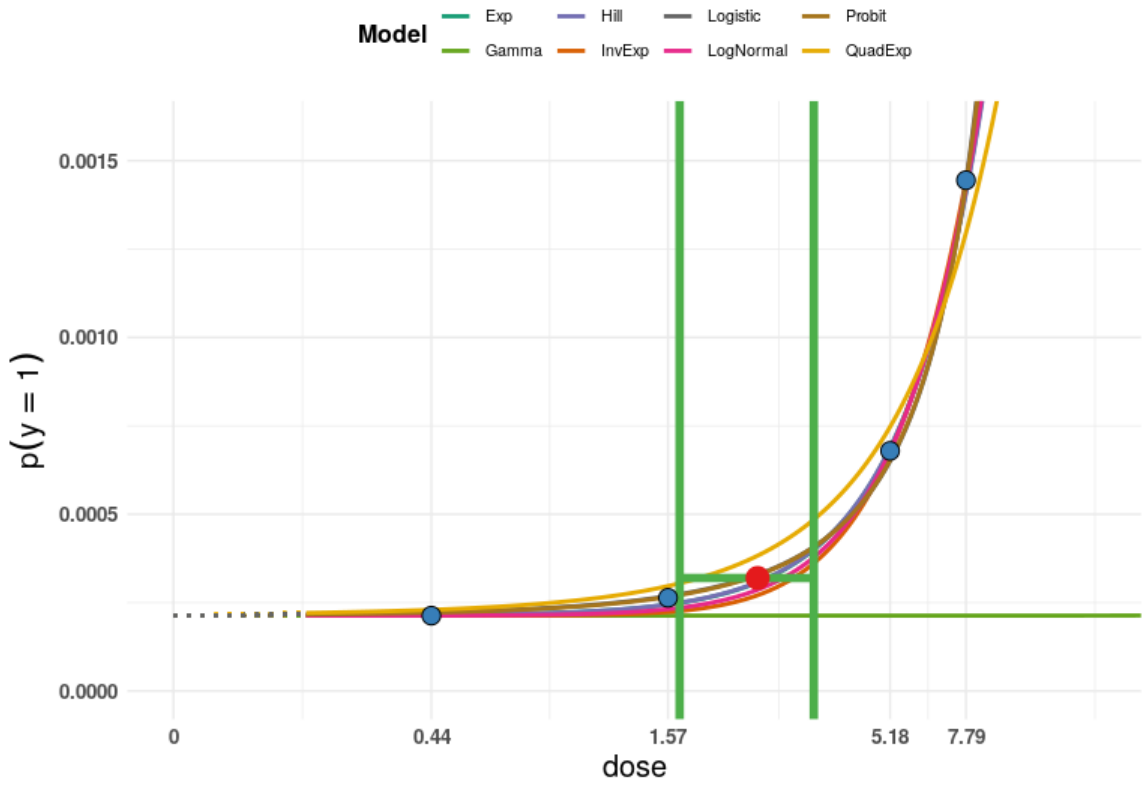
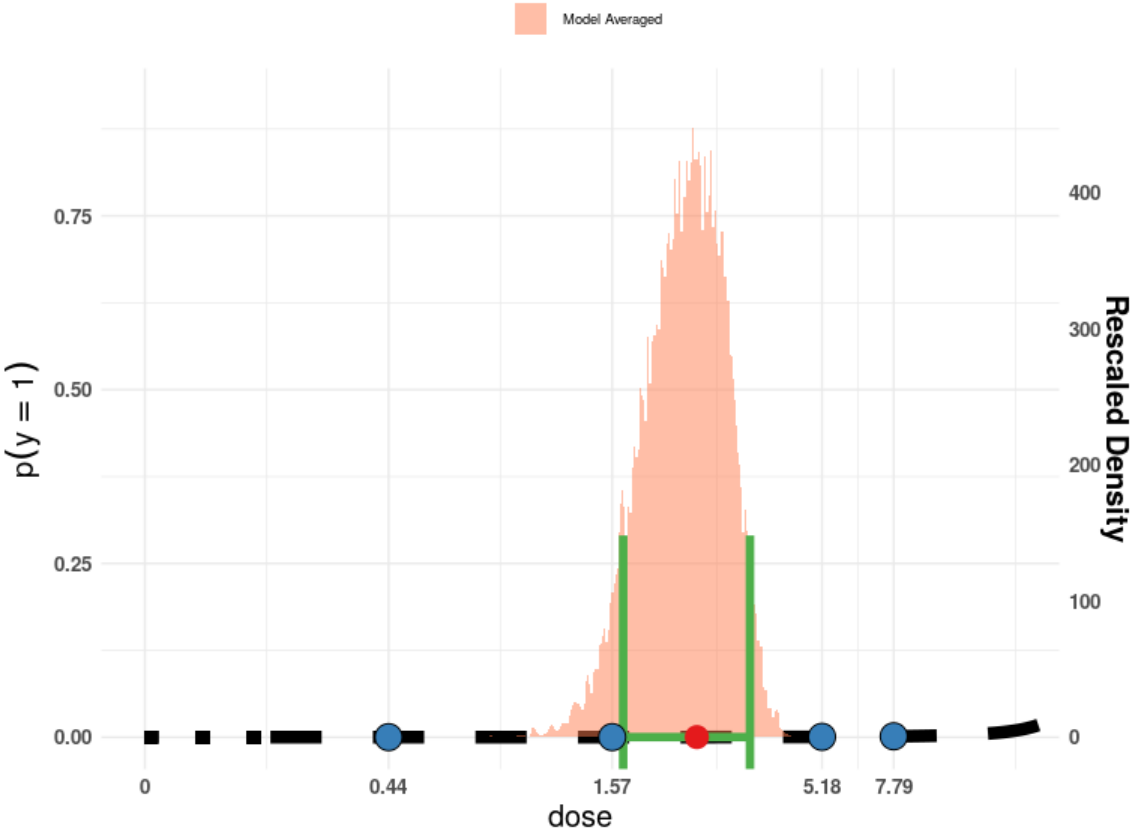
0.20
0.15
0.10
0.05
0.00
Exp
InvExp
Hill
LogNormal
Gamma
QuadExp
Probit
Logistic


Model
Exp
Hill
Logistic
Probit
Gamma
InvExp
LogNormal
QuadExp
p(y = 1)
0.0015
0.0010
0.0005
0.0000
0
0.44
1.57
5.18
7.79
dose


Model Averaged
0.75
0.50
0.25
0.00
p(y = 1)
400
300
200
100
0
Rescaled Density
0
0.44
1.57
5.18
7.79
dose

Steinmaus et al. (2014a) lung cancer, relative BMR 50%

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:

Exposure.µg.kg.bw.per.day	Adj.cases	N
0.36	25	79688
0.70	30	77344
2.00	37	67969

The 'Value for CES' is set to 0.00015691.

Extended dose range is not applied.

Informative background prior: min: 0.00031059; the most likely: 0.00031372; max: 0.00031686. 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 1.08e+00).

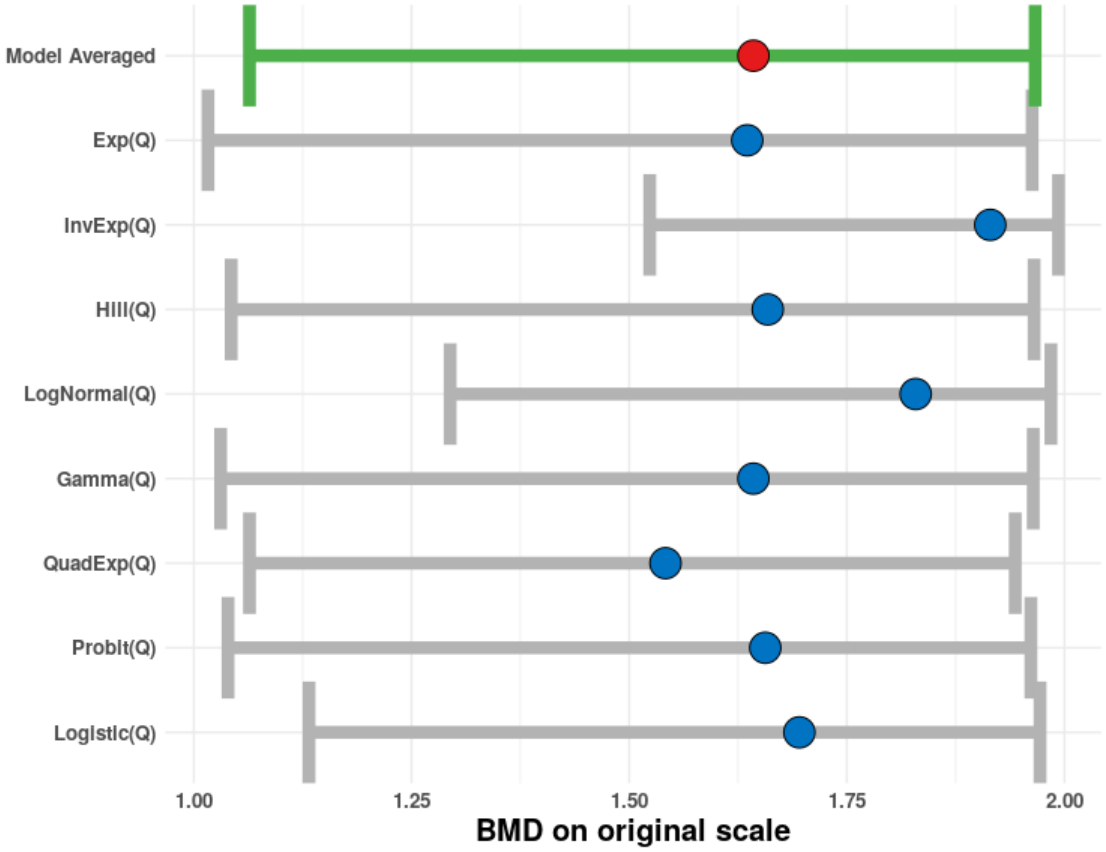
Model Averaged BMD

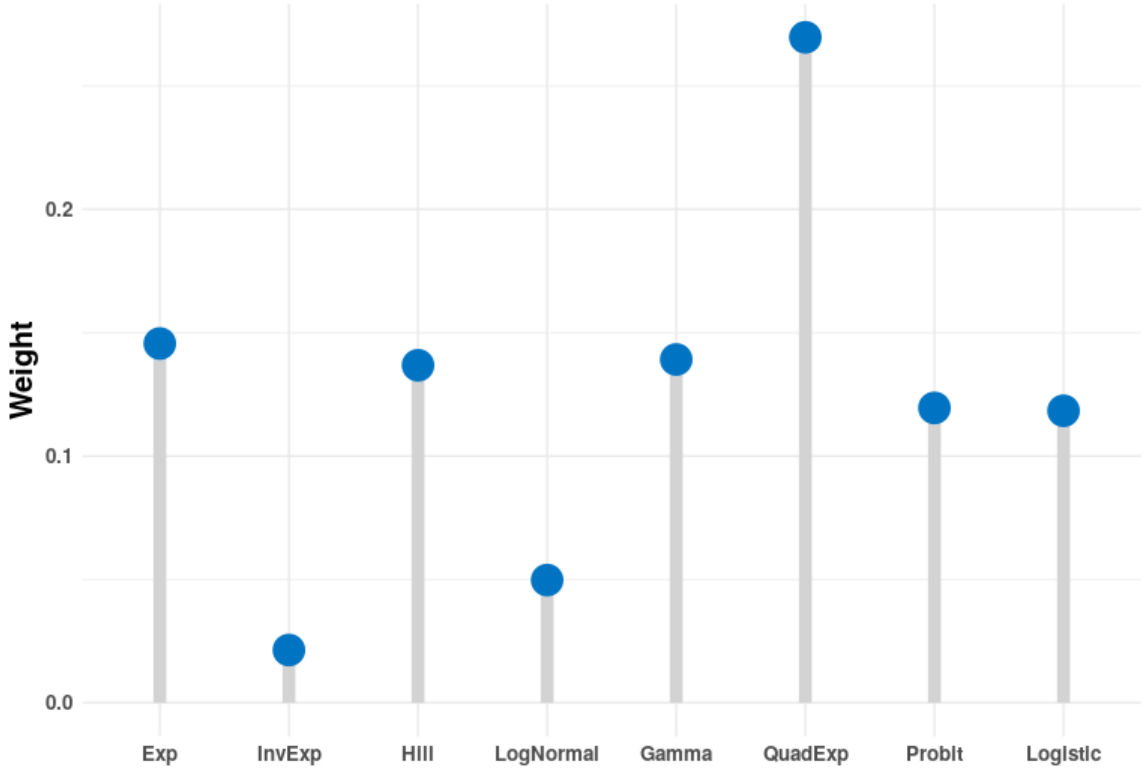
Model	Type	BMDL	BMD	BMDU
Model Averaged	BS	1.064	1.643	1.966

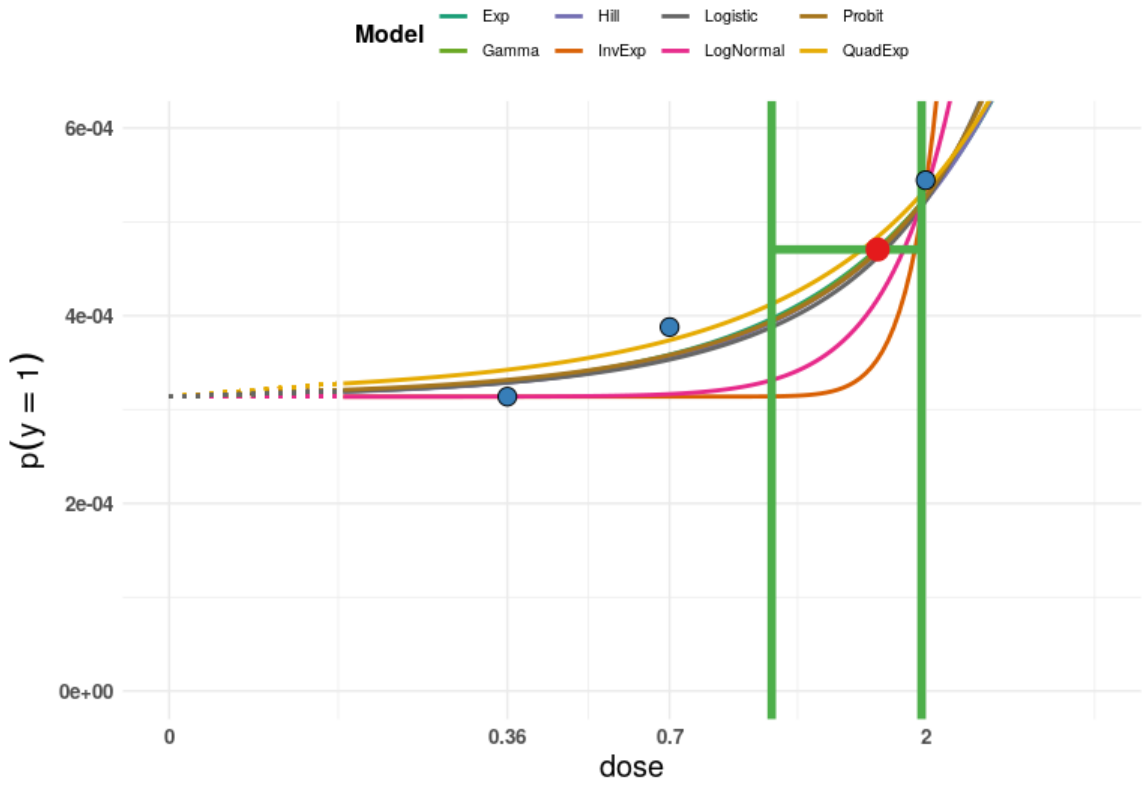
Estimated BMDs per model

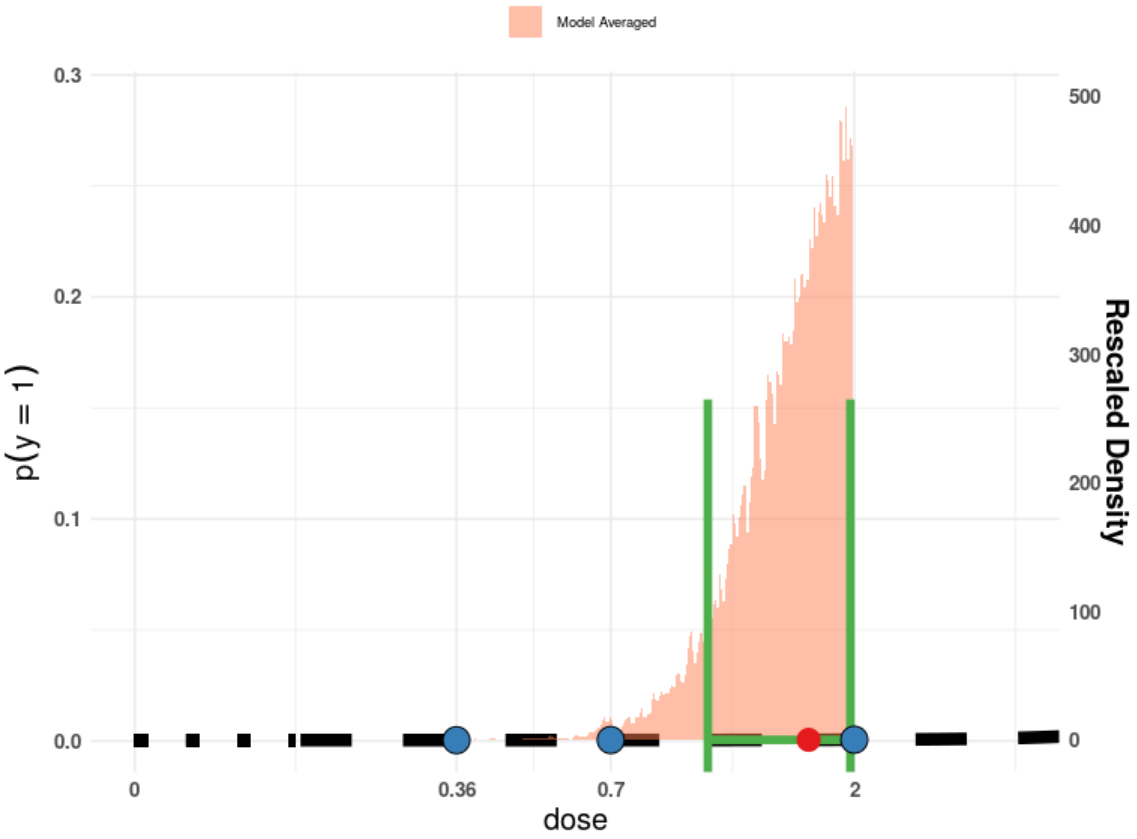
Model	BMDL	BMD	BMDU	Model Weights	Converged
E4_Q	1.016	1.636	1.963	0.146	1
IE4_Q	1.524	1.915	1.993	0.021	1
H4_Q	1.043	1.659	1.965	0.137	1
LN4_Q	1.294	1.829	1.984	0.050	1
G4_Q	1.031	1.643	1.964	0.139	1
QE4_Q	1.064	1.542	1.943	0.270	1
P4_Q	1.039	1.656	1.961	0.119	1
L4_Q	1.132	1.695	1.972	0.118	1

Plots of Fitted Models




Weight
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)
6e-04
4e-04
2e-04
0e+00
0
0.36
0.7
2
dose


Model Averaged
0.3
0.2
0.1
0.0
p(y = 1)
500
400
300
200
100
0
Rescaled Density
0
0.36
0.7
2
dose

References

Chen CL, Chiou HY, Hsu LI, Hsueh YM, Wu MM, Wang YH and Chen CJ, 2010b. Arsenic in drinking water and risk of urinary tract cancer: a follow-up study from northeastern Taiwan. Cancer Epidemiol Biomarkers Prev, 19:101-110. doi: 10.1158/1055-9965.Epi-09-0333

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