Annex to: Update of the risk assessment on tetrabromobisphenol A (TBBPA) and its derivatives in food. doi:10.2903/j.efsa.2024.8859

ANNEX C - Benchmark dose modelling

This Annex contains the details of the benchmark dose (BMD) modelling performed on experimental animal data. It consists of an introductory subsection describing the approach followed in the modelling (Section A.1.) and the individual BMD reports per study (Section A.2.).

1. Introduction

In this section, a general description of the approach followed in the modelling is given.

1.1. Selection of the benchmark response

The BMD is defined as the estimated dose that corresponds with a predefined change in response compared with the background response. The benchmark response (BMR) is the response corresponding with the estimated BMD of interest.

The Panel on Contaminants in the Food Chain (CONTAM Panel) selected a BMR of 10% for the neurodevelopmental effects. This percentage of variation is commonly used to reflect the natural variability of neurobehaviour end points in the absence of any biological consideration of severity to justify a different BMR. This is also in line with the approach taken for the update of the risk assessment on polybrominated diphenyl ethers (PBDEs) (EFSA CONTAM Panel, 2024). For the carcinogenicity, the Panel selected the default BMR of 10% for quantal data.

A 90% confidence interval around the BMD was estimated; the lower bound is reported by the benchmark dose lower confidence limit (BMDL) and the upper bound by the benchmark dose upper confidence limit (BMDU).

1.2. Software used

Results are obtained using the European Food Safety Authority (EFSA) web-based tool for Bayesian BMD analysis, which uses the R package (BMABMDR; version 0.0.0.9073) for the underlying calculations.

1.3. Specification of deviations from default assumptions

All the results were calculated using the bridge sampling as numerical method, which is more accurate and computationally demanding than the Laplace approximation set as a default (EFSA Scientific Committee, 2022).

The Panel selected the following default models:

A default set of fitted models for continuous end points

Family	Model	$y \mid x \sim N(\mu(x), \sigma^2)$ Dose–response function $(\mu(x))$	$y \mid x \sim LOGN(\mu(x), \sigma^2)$ Dose–response function $(e^{\mu(x)})$
1a	Exponential[(i)]	$a \cdot \left(1 + (c-1) \cdot \left(1 - e^{-b \cdot x^d}\right)\right)$	$e^{a \cdot \left(1 + (c-1) \cdot \left(1 - e^{-b \cdot x^d}\right)\right)}$
	Inverse Exponential	$a \cdot \left(1 + (c-1) \cdot e^{-b \cdot x^{-d}}\right)$	$e^{a \cdot \left(1 + (c-1) \cdot e^{-b \cdot x^{-d}}\right)}$
	Hill[(ii)]	$a \cdot \left(1 + (c-1) \cdot \left(1 - \frac{b}{b + x^d}\right)\right)$	$e^{a \cdot \left(1 + (c-1) \cdot \left(1 - \frac{b}{b + x^d}\right)\right)}$
	Log-Normal	$a \cdot (1 + (c-1) \cdot \Phi(\log(b) + d \cdot \log(x)))$	$e^{a \cdot (1 + (c-1) \cdot \Phi(\log(b) + d \cdot \log(x)))}$
1b	Gamma[(iii)]	$a \cdot \left(1 + (c-1) \cdot \frac{\gamma(d, b \cdot x)}{\Gamma(d)}\right)$	$e^{a \cdot \left(1 + (c-1) \cdot \frac{\gamma(d, b \cdot x)}{\Gamma(d)}\right)}$
	LMS-two stage	$a \cdot \left(1 + (c-1) \cdot \left(1 - e^{-b \cdot x - d \cdot x^2}\right)\right)$	$e^{a \cdot \left(1 + (c-1) \cdot \left(1 - e^{-b \cdot x - d \cdot x^2}\right)\right)}$
2	Probit increasing	$a \cdot \Phi(c + b \cdot x^d)$	$e^{a \cdot \Phi(c + b \cdot x^d)}$
	Probit decreasing	$a \cdot (1 + \Phi(c)) - a \cdot \Phi(c + b \cdot x^d)$	$e^{a \cdot (1 + \Phi(c)) - a \cdot \Phi(c + b \cdot x^d)}$
	Logistic increasing	$a \cdot \frac{e^{c + b \cdot x^d}}{1 + e^{c + b \cdot x^d}}$	$e^{a \cdot \frac{e^{c + b \cdot x^d}}{1 + e^{c + b \cdot x^d}}}$
	Logistic decreasing	$a \cdot \left(1 + \frac{e^c}{1 + e^c}\right) - a \cdot \frac{e^{c + b \cdot x^d}}{1 + e^{c + b \cdot x^d}}$	$e^{a \cdot \left(1 + \frac{e^c}{1 + e^c}\right) - a \cdot \frac{e^{c + b \cdot x^d}}{1 + e^{c + b \cdot x^d}}}$

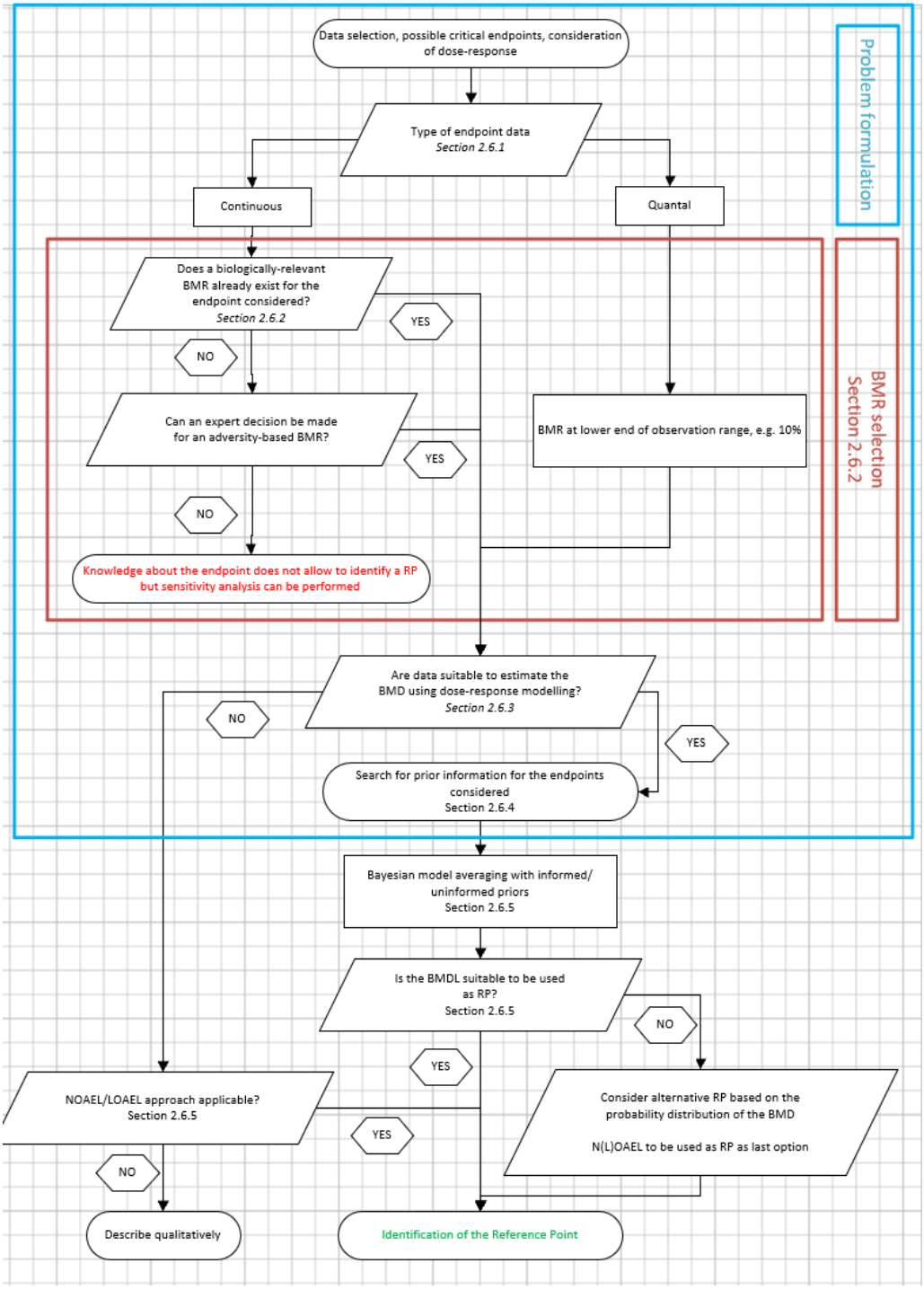
Default set of fitted models for quantal end points

Family	Model	$y \mid x \sim Bernoulli(\pi(x))$ Dose–response function $(\mu(x))$
1a	Exponential	$a + (1 - a) \cdot \left(1 - e^{-b \cdot x^d}\right)$
	Inverse Exponential	$a + (1 - a) \cdot e^{-b \cdot x^{-d}}$
	Hill	$a + (1 - a) \cdot \left(1 - \frac{b}{b + x^d}\right)$
	Log-Normal	$a + (1 - a) \cdot \Phi(\log(b) + d \cdot \log(x))$
1b	Gamma	$a + (1 - a) \cdot \frac{\gamma(d, b \cdot x)}{\Gamma(d)}$
	LMS-two stage	$a + (1 - a) \cdot \left(1 - e^{-b \cdot x - d \cdot x^2}\right)$
2	Probit increasing	$\Phi\left(a + b \cdot x^d\right)$
	Logistic increasing	$\frac{e^{a + b \cdot x^d}}{1 + e^{a + b \cdot x^d}}$

1.4. Procedure for selection of the BMDL

Flow chart to derive a Reference Point from a dose–response data set of a specified end point using a benchmark dose (BMD) analysis.

BMDL: benchmark dose lower confidence limit; BMR: benchmark response; LOAEL: lowest-observed-adverse-effect level; NOAEL: no-observed-adverse-effect level.


Data selection, possible critical endpoints, consideration of dose-response
Type of endpoint data
Section 2.6.1
Continuous
Quantal
Problem formulation
Does a biologically-relevant BMR already exist for the endpoint considered?
Section 2.6.2
YES
NO
Can an expert decision be made for an adversity-based BMR?
YES
NO
BMR at lower end of observation range, e.g. 10%
BMR selection
Section 2.6.2
Knowledge about the endpoint does not allow to identify a RP but sensitivity analysis can be performed
Are data suitable to estimate the BMD using dose-response modelling?
Section 2.6.3
NO
YES
Search for prior information for the endpoints considered
Section 2.6.4
Bayesian model averaging with informed/ uninformed priors
Section 2.6.5
Is the BMDL suitable to be used as RP?
Section 2.6.5
NO
YES
NOAEL/LOAEL approach applicable?
Section 2.6.5
YES
Consider alternative RP based on the probability distribution of the BMD
N(L)OAEL to be used as RP as last option
NO
Describe qualitatively
Identification of the Reference Point

2. TBBPA–selected studies

2.1. Rock et al. (2019)–latency (seconds) to enter light box in male Wistar Han rats exposed by gavage to TBBPA from GD6 to PND90–model averaging

2.1.1. Data description

The end point to be analysed is latency (s) to enter light box.

Data used for analysis

TBBPA (mg/kg bw per day)	Latency (s)	SD	N
0.0	18.04	15.15	10
0.1	28.57	24.00	15
25.0	42.34	34.18	9
250.0	54.45	74.17	13

SD: standard deviation; TBBPA: tetrabromobisphenol A.

2.1.2. Selection of the BMR

The BMR used is a 10% change in mean response compared to the controls. The BMD is the dose corresponding with the BMR of interest.

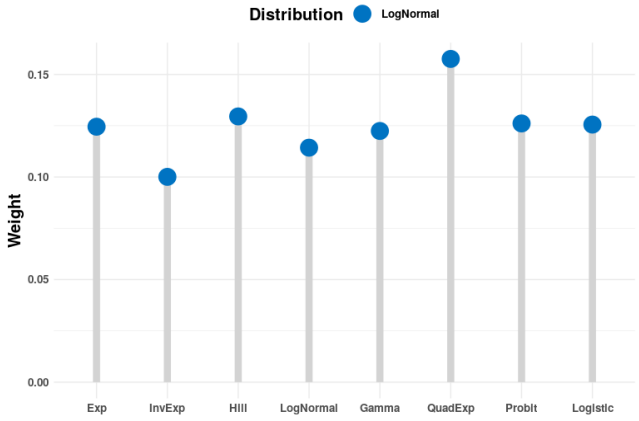
A 90% confidence interval around the BMD will be estimated; the lower bound is reported by the BMDL and the upper bound, by the BMDU.

2.1.3. Results

Response variable: **latency (s) to enter light box**

Estimated BMDs per model

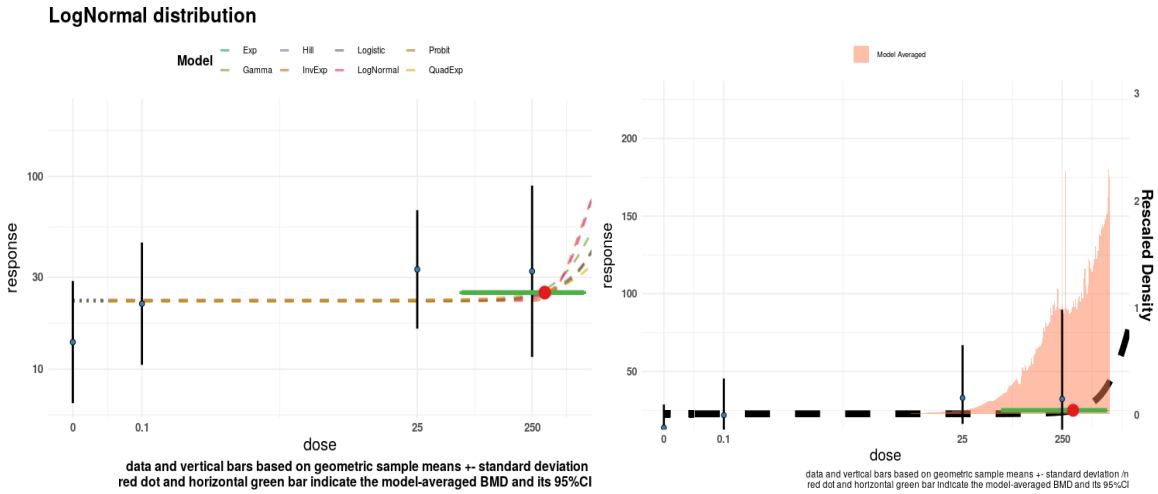
Model	BMDL	BMD	BMDU	Model weights	Converged
E4_LN	59.013	333.550	701.515	0.125	1
IE4_LN	103.973	375.729	718.837	0.100	1
H4_LN	60.078	316.492	697.766	0.130	1
LN4_LN	82.949	353.364	715.061	0.114	1
G4_LN	56.686	269.998	694.723	0.122	0
QE4_LN	52.720	292.926	697.324	0.158	1
P4_LN	62.354	336.052	708.772	0.126	1
L4_LN	57.000	337.637	705.168	0.126	1



Final BMD values

Sensitivity.Analysis	Model	Type	BMDL	BMD	BMDU
default	Model averaged	BS	61.484	329.471	707.425

Visualization



2.2. Rock et al. (2019)–light box entries (bouts) in male Wistar Han rats exposed by gavage to tetrabromobisphenol A from GD6 to PND90–model averaging

2.2.1. Data description

A. The end point to be analysed is light box entries.

Data used for analysis

TBBPA (mg/kg bw per day)	Light box entries (bouts)	SD	Animals (n)
0.0	5.545	1.368	11
0.1	5.400	2.063	15
25.0	4.600	2.413	10
250.0	4.308	2.463	13

SD: standard deviation; TBBPA: tetrabromobisphenol

2.2.2. Selection of the BMR

The BMR used is a 10% change in mean response compared to the controls. The BMD is the dose corresponding with the BMR of interest.

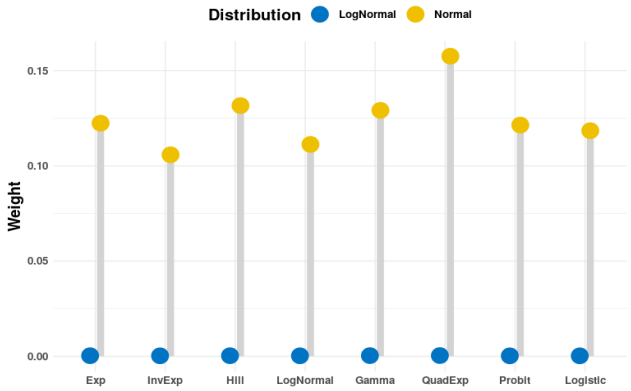
A 90% confidence interval around the BMD will be estimated; the lower bound is reported by the BMDL and the upper bound, by the BMDU.

2.2.3. Results

Response variable: **light box entries**

Estimated BMDs per model

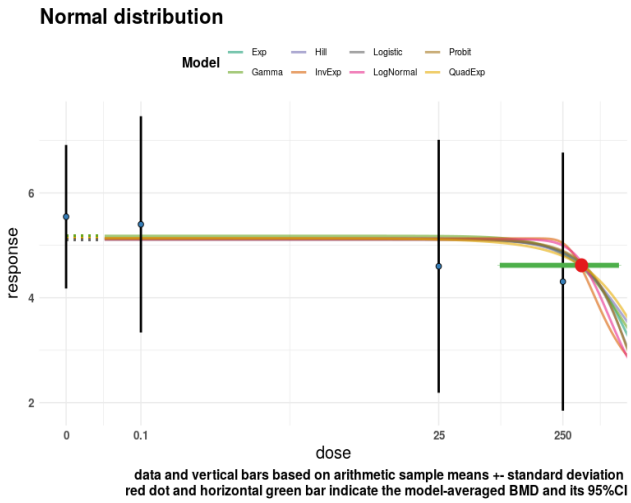
Model	BMDL	BMD	BMDU	Model weights	Converged
E4_N	69.387	356.868	709.136	0.122	1
IE4_N	72.473	343.951	701.363	0.106	1
H4_N	70.319	342.623	703.276	0.132	1
LN4_N	86.119	371.808	713.613	0.111	1
G4_N	70.198	320.425	702.967	0.129	1
QE4_N	81.648	345.811	700.744	0.158	1
P4_N	77.408	375.481	716.956	0.121	1
L4_N	84.323	371.456	706.077	0.118	1
E4_LN	38.374	257.677	708.893	0.000	1
IE4_LN	30.523	238.558	691.332	0.000	1
H4_LN	26.672	237.167	687.318	0.000	1
LN4_LN	30.068	247.618	688.115	0.000	1
G4_LN	35.155	260.021	719.013	0.000	1
QE4_LN	46.813	208.225	669.437	0.000	1
P4_LN	36.869	264.529	690.416	0.000	1
L4_LN	21.689	266.195	681.358	0.000	1

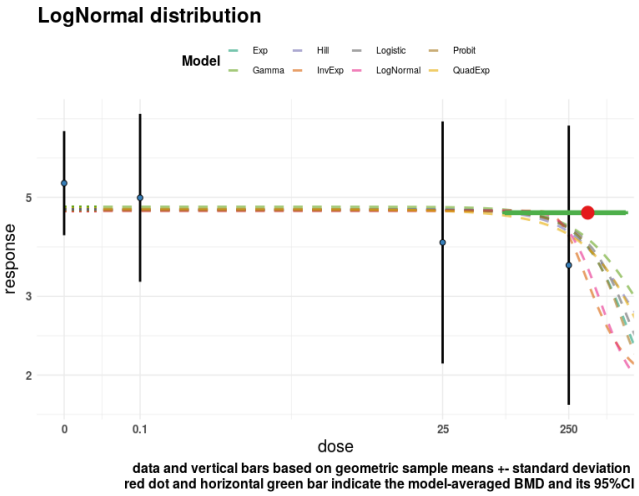


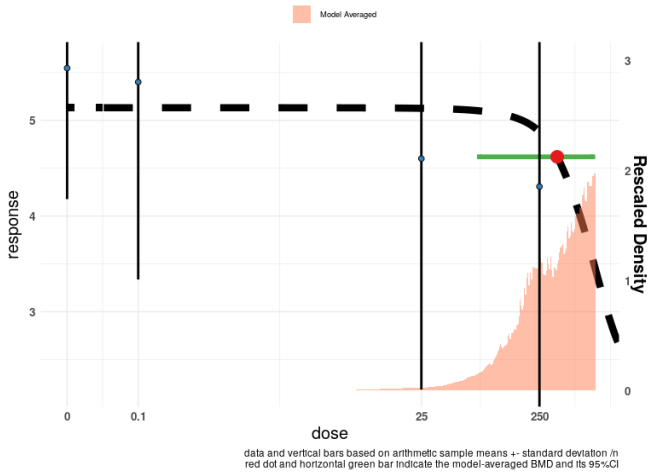
Final BMD values

Sensitivity.Analysis	Model	Type	BMDL	BMD	BMDU
default	Model averaged	BS	77.572	353.357	706.588

Visualization







2.3. Rock et al. (2019)–open arms entries (n) in Male Wistar Han rats exposed by gavage to TBBPA from GD6 to PND90–model averaging

2.3.1. Data description

The end point to be analysed is open arms entries (n).

Data used for analysis

TBBPA (mg/kg bw per day)	Open arms entries (n)	SD	Animals (n)
0.0	5.364	1.963	11
0.1	4.200	2.396	15
25.0	3.500	2.415	10
250.0	3.077	1.382	13

SD: standard deviation; TBBPA: tetrabromobisphenol A.

2.3.2. Selection of the BMR

The BMR used is a 10% change in mean response compared to the controls. The BMD is the dose corresponding with the BMR of interest.

A 90% confidence interval around the BMD will be estimated; the lower bound is reported by the BMDL, and the upper bound, by the BMDU.

2.3.4. Results

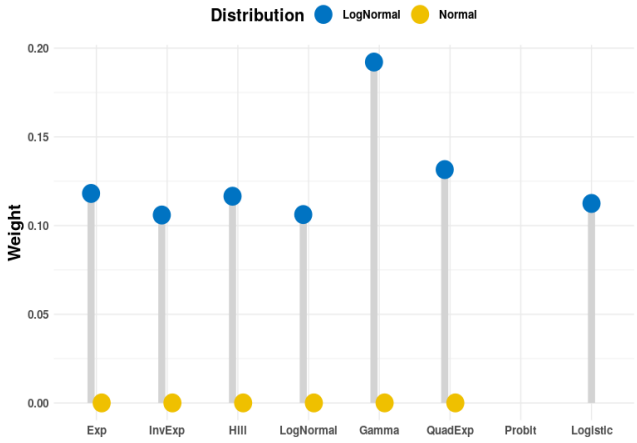
Response variable: **open arms entries**

Estimated BMDs per model

Model	BMDL	BMD	BMDU	Model weights	Converged
E4_N	8.364	155.595	649.496	0.000	1
IE4_N	8.058	162.963	653.709	0.000	1

H4_N	8.783	158.845	658.200	0.000	1
LN4_N	7.722	155.101	648.051	0.000	1
G4_N	10.462	239.801	709.703	0.000	1
QE4_N	7.404	149.842	639.636	0.000	1
E4_LN	3.218	132.714	648.672	0.118	1
IE4_LN	3.664	137.101	659.787	0.106	1
H4_LN	4.294	143.255	649.381	0.117	1
LN4_LN	3.331	140.315	653.928	0.106	1
G4_LN	8.398	285.722	704.766	0.192	0
QE4_LN	3.369	134.033	657.210	0.132	1
L4_LN	3.267	144.947	646.443	0.112	1

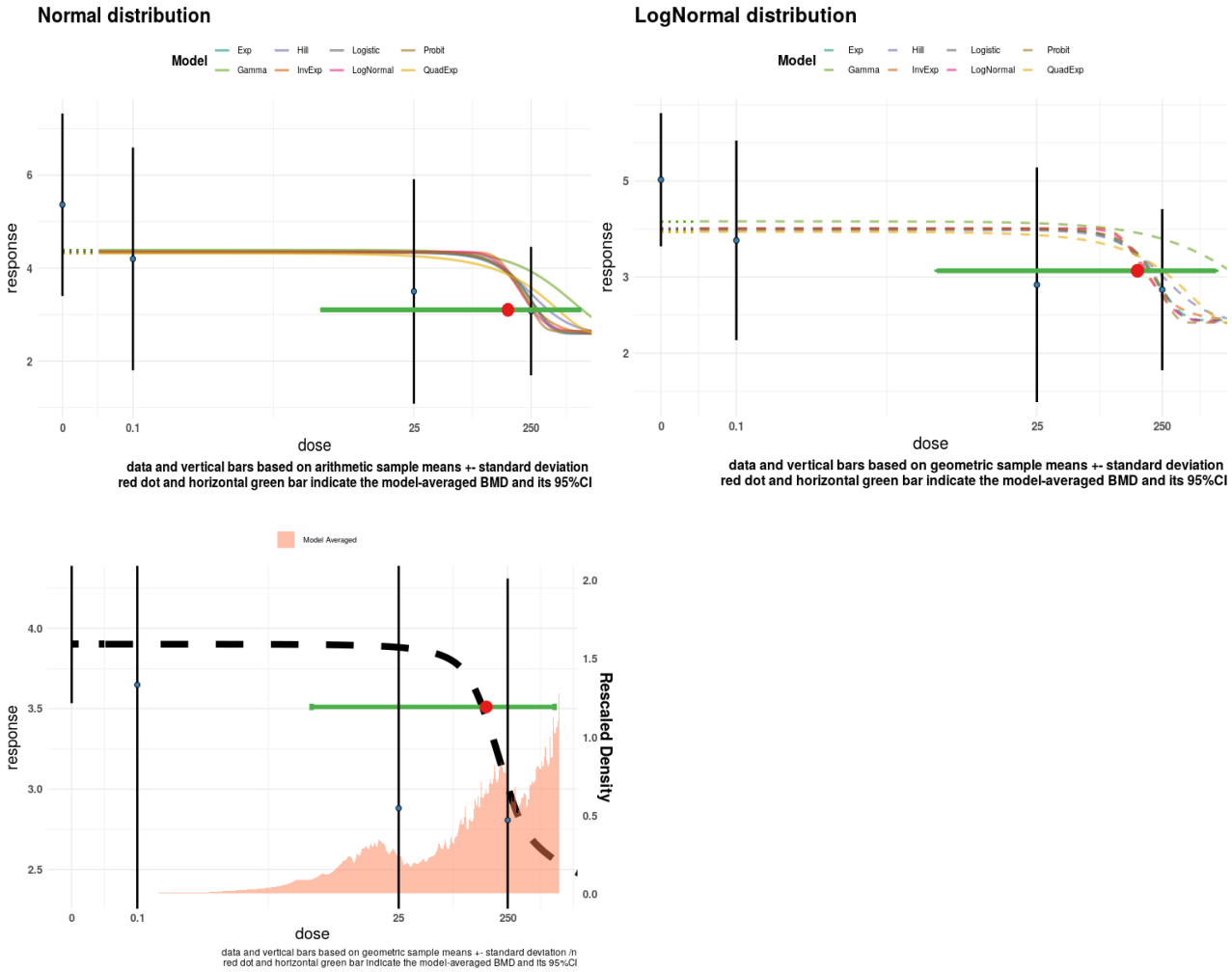
Weights for model averaging



Final BMD values

Model	Type	BMDL	BMD	BMDU
Model Averaged	BS	3.451	141.018	655.466

Visualization



2.4. Kim et al. (2017)–learning and memory in a passive avoidance test (day 2) in adult male C57Bl6/J mice exposed by gavage to TBBPA for 2 weeks–model averaging

2.4.1. Data description

The end point to be analysed is latency (s).

Data used for analysis

TBBPA (mg/kg bw per day)	Latency (s)	SE	Animals (n)
0	241	20.9	7
20	194	23.2	7
100	152	27.2	7
500	134	34.5	7

SE: standard error; TBBPA: tetrabromobisphenol A.

2.4.2. Selection of the BMR

The BMR used is a 10% change in mean response compared to the controls. The BMD is the dose corresponding with the BMR of interest.

A 90% confidence interval around the BMD will be estimated; the lower bound is reported by BMDL and the upper bound by BMDU.

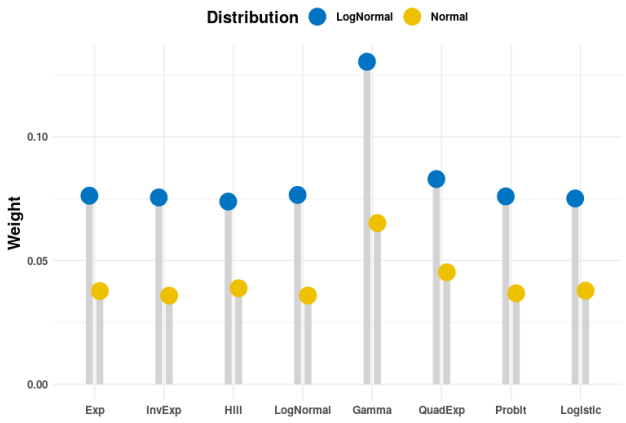
2.4.3. Results

Response variable: **latency**

Estimated BMDs per model

Model	BMDL	BMD	BMDU	Model weights	Converged
E4_N	11.652	140.935	1241.909	0.038	1
IE4_N	10.051	99.472	1170.258	0.036	1
H4_N	10.562	112.904	1209.304	0.039	1
LN4_N	11.336	120.672	1206.492	0.036	1
G4_N	14.785	611.643	1422.195	0.065	0
QE4_N	8.893	111.750	1190.753	0.045	1
P4_N	12.290	150.653	1219.777	0.037	1
L4_N	12.139	148.133	1227.110	0.038	1
E4_LN	10.367	75.783	850.056	0.076	1
IE4_LN	11.722	71.719	567.648	0.076	1
H4_LN	9.460	66.562	611.113	0.074	1
LN4_LN	11.102	71.536	600.092	0.077	1
G4_LN	16.135	91.568	1371.061	0.130	0
QE4_LN	6.916	53.121	808.783	0.083	1
P4_LN	11.204	73.409	825.331	0.076	1
L4_LN	11.037	71.618	783.344	0.075	1

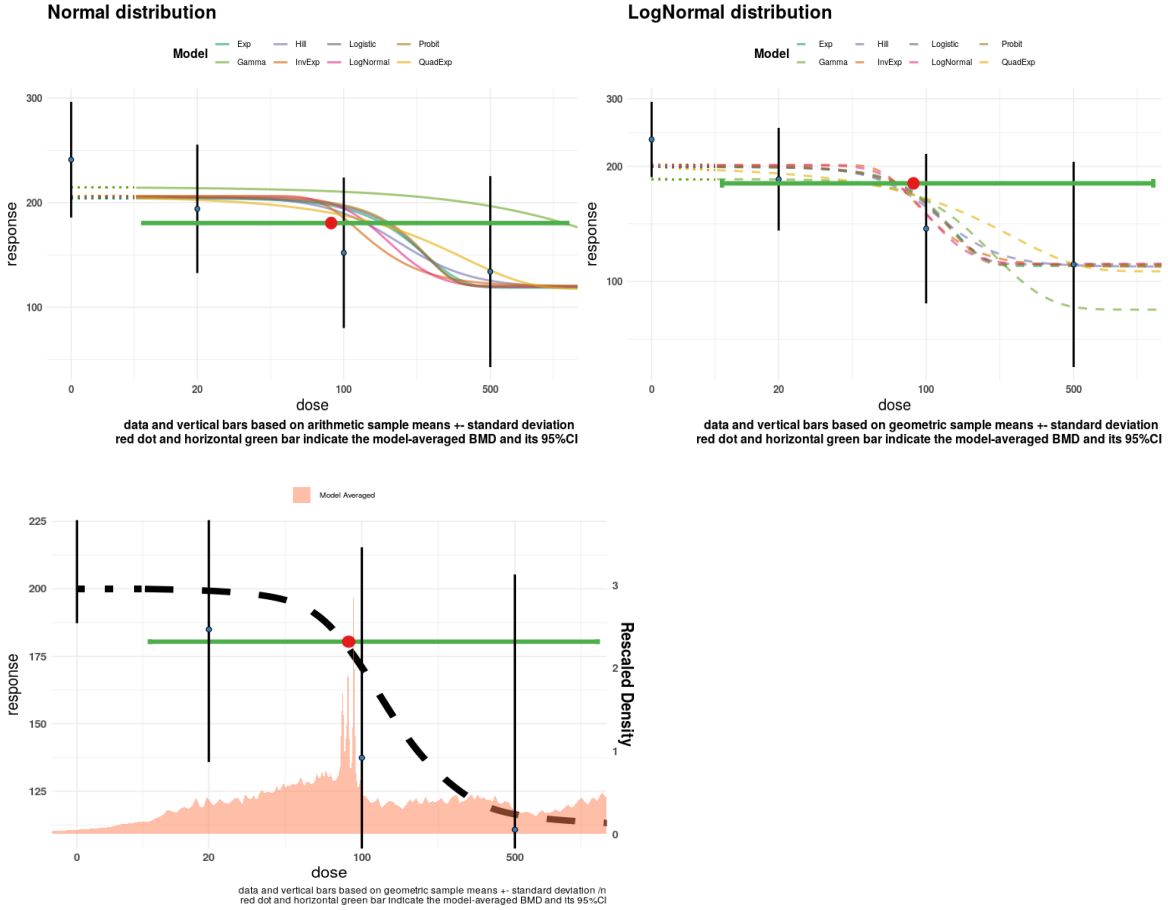
Weights for model averaging



Final BMD values

Model	Type	BMDL	BMD	BMDU
Model averaged	BS	10.283	79.292	1,007.641

Visualization



2.5. Cope et al. (2015)–brain parietal thickness in Sprague-Dawley Rats male/female pups exposed by gavage to TBBPA for 10 weeks prior to mating plus 3 weeks of gestation/lactation–model averaging

2.5.1. Data description

The end point to be analysed is brain parietal thickness.

Data used for analysis

TBBPA (mg/kg bw per day)	Brain parietal thickness (mm)	SD	Animals (n)
0	1.61	0.188	10
10	1.56	0.104	10
100	1.49	0.100	10
1000	1.23	0.113	10

SD: standard deviation; TBBPA: tetrabromobisphenol A.

2.5.2. Selection of the BMR

The BMR used is a 10% change in mean response compared to the controls. The BMD is the dose corresponding with the BMR of interest.

A 90% confidence interval around the BMD will be estimated; the lower bound is reported by the BMDL, and the upper bound, by the BMDU.

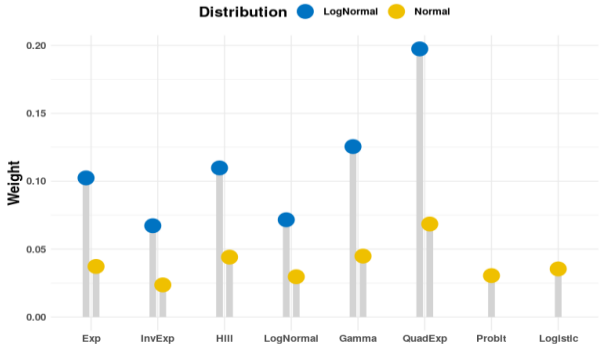
2.5.3. Results

Response variable: **brain parietal thickness**

Estimated BMDs per model

Model	BMDL	BMD	BMDU	Model weights	Converged
E4_N	122.828	429.899	835.615	0.037	1
IE4_N	140.130	560.385	891.177	0.024	1
H4_N	123.595	391.320	834.786	0.044	1
LN4_N	140.158	561.231	919.387	0.030	0
G4_N	136.145	430.944	802.824	0.045	1
QE4_N	273.634	483.693	686.980	0.068	1
P4_N	117.099	435.589	851.530	0.030	1
L4_N	128.023	460.799	881.007	0.035	1
E4_LN	127.011	445.978	834.464	0.102	1
IE4_LN	154.450	642.231	922.314	0.067	1
H4_LN	134.350	478.162	917.427	0.110	0
LN4_LN	152.130	595.964	897.839	0.072	1
G4_LN	145.624	458.981	796.514	0.125	1
QE4_LN	288.079	470.643	660.396	0.197	1

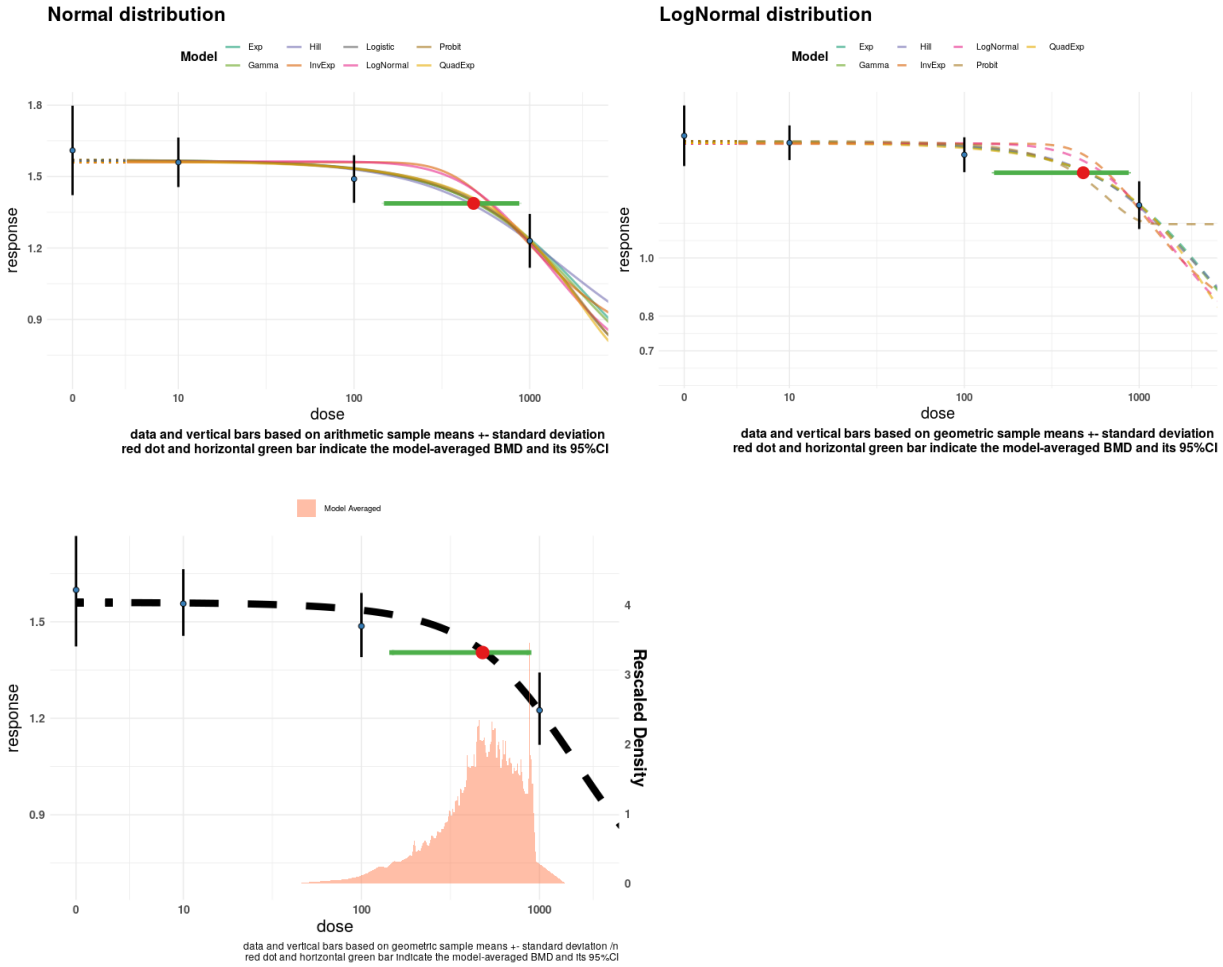
Weights for model averaging



Final BMD values

Model	Type	BMDL	BMD	BMDU
Model averaged	BS	154.401	475.501	845.274

Visualization



2.6. NTP (2014)–uterus adenocarcinoma (n) in female Wistar Han rats exposed by gavage for 2 years to TBBPA–model averaging

2.6.1. Data description

The end point to be analysed is uterus adenocarcinoma.

Data used for analysis

TBBPA (mg/kg bw per day)	Uterus adenocarcinoma (n)	Animals (n)
0.0	4	50
178.6	10	50
357.0	15	50
714.0	16	50

TBBPA: tetrabromobisphenol A.

2.6.2. Selection of the BMR

The BMR used is 10%, set as the default value for quantal data. The BMD is the dose corresponding with the BMR of interest.

A 90% confidence interval around the BMD will be estimated; the lower bound is reported by the BMDL, and the upper bound, by the BMDU.

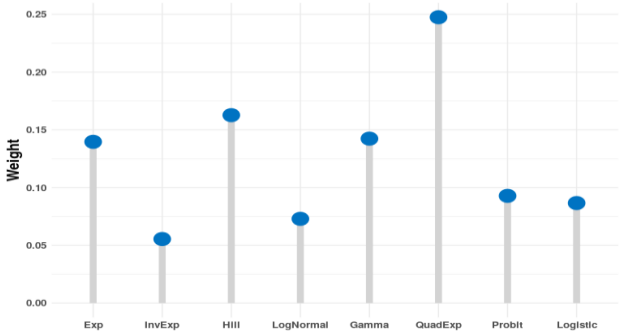
2.6.3. Results

Response variable: **uterus adenocarcinoma**

Estimated BMDs per model

Model	BMDL	BMD	BMDU	Model weights	Converged
E4_Q	74.192	275.125	1346.092	0.140	1
IE4_Q	83.918	253.777	1132.251	0.055	1
H4_Q	67.476	260.823	1240.842	0.163	1
LN4_Q	83.247	283.291	1338.865	0.073	1
G4_Q	79.374	283.940	903.016	0.142	1
QE4_Q	177.883	319.193	968.123	0.248	1
P4_Q	81.945	331.960	1434.465	0.093	1
L4_Q	90.544	357.605	1545.080	0.087	1

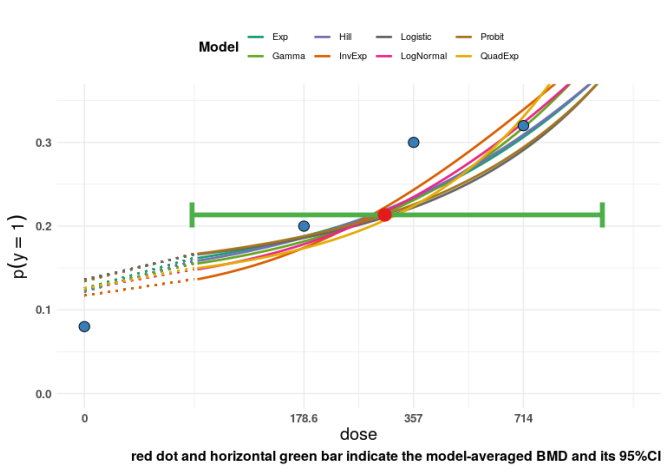
Weights for model averaging

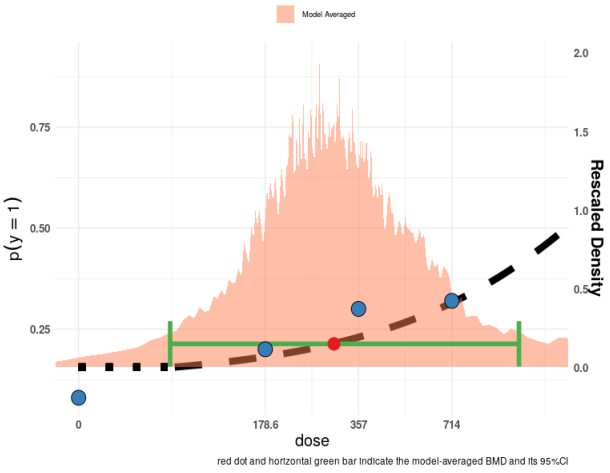


Final BMD values

Model	Type	BMDL	BMD	BMDU
Model averaged	BS	88.11	297.462	1,175.243

Visualization





2.7. NTP (2014)–uterus adenoma, adenocarcinoma, and MMMT combined (n) in female Wistar Han rats exposed by gavage for 2 years to TBBPA–model averaging

2.7.1. Data description

The end point to be analysed is uterus adenoma, adenocarcinoma, and malignant mixed Mullerian tumour (MMMT) combined.

Data used for analysis

TBBPA (mg/kg bw per day)	Uterus adenoma, adenocarcinoma, and MMMT combined (n)	Animals (n)
0.0	6	50
178.6	11	50
357.0	16	50
714.0	19	50

MMMT: malignant mixed Mullerian tumour; TBBPA: tetrabromobisphenol A.

2.7.2. Selection of the BMR

The BMR used is 10%, set as the default value for quantal data. The BMD is the dose corresponding with the BMR of interest.

A 90% confidence interval around the BMD will be estimated; the lower bound is reported by the BMDL, and the upper bound, by the BMDU.

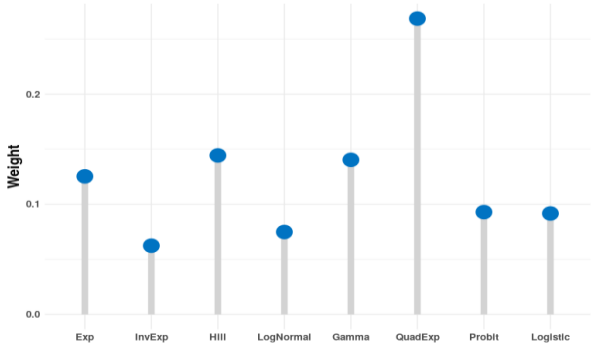
2.7.3. Results

Response variable: **uterus adenoma, adenocarcinoma, and MMMT combined**

Estimated BMDs per model

Model	BMDL	BMD	BMDU	Model weights	Converged
E4_Q	87.011	318.840	1348.799	0.125	1
IE4_Q	112.610	332.835	1303.863	0.062	1
H4_Q	88.325	307.106	1393.270	0.144	1
LN4_Q	112.661	346.417	1408.934	0.075	1
G4_Q	105.572	325.639	979.846	0.140	1
QE4_Q	173.189	311.137	956.186	0.268	1
P4_Q	113.525	385.722	1416.492	0.093	1
L4_Q	107.085	382.125	1547.763	0.092	1

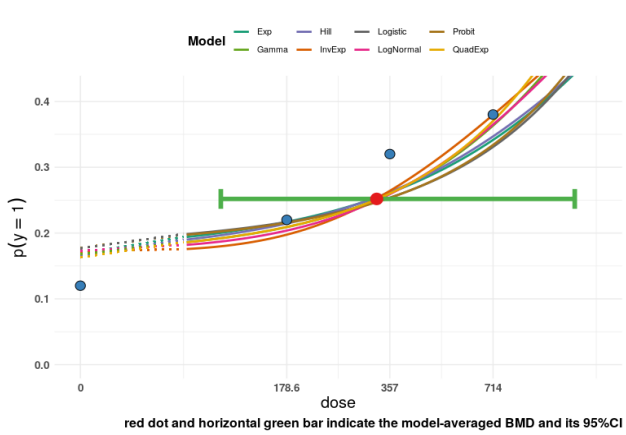
Weights for model averaging

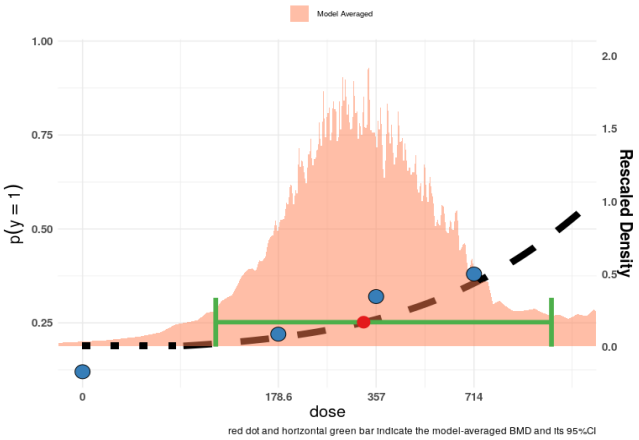


Final BMD values

Model	Type	BMDL	BMD	BMDU
Model averaged	BS	114.68	326.786	1,235.811

Visualization





2.8. NTP (2014)–testis interstitial cell adenoma (n) in Male Wistar Han rats exposed by gavage for 2 years to TBBPA–model averaging

2.8.1. Data description

The end point to be analysed is testis interstitial cell adenoma.

Data used for analysis

TBBPA (mg/kg bw per day)	Testis interstitial cell adenoma (n)	Animals (n)
0.0	0	50
178.6	0	50
357.0	1	50
714.0	3	50

TBBPA: tetrabromobisphenol A.

2.8.2. Selection of the BMR

The BMR used is 10%, set as the default value for quantal data. The BMD is the dose corresponding with the BMR of interest.

A 90% confidence interval around the BMD will be estimated; the lower bound is reported by the BMDL, and the upper bound, by the BMDU.

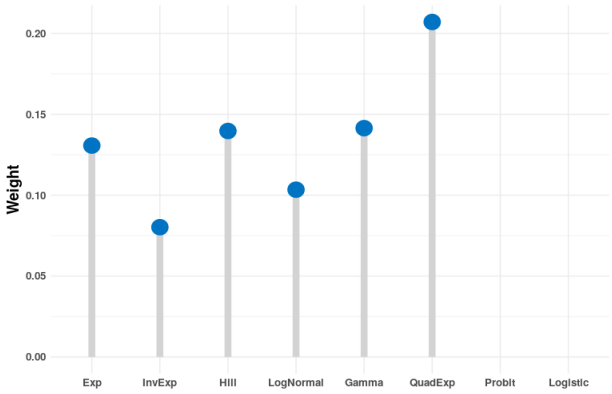
2.8.3. Results

Response variable: **testis interstitial cell adenoma**

Estimated BMDs per model

Model	BMDL	BMD	BMDU	Model weights	Converged
E4_Q	743.380	1226.147	2006.979	0.131	1
IE4_Q	710.255	1064.905	2000.224	0.080	1
H4_Q	740.764	1216.843	2020.729	0.140	1
LN4_Q	718.137	1111.605	2025.088	0.103	1
G4_Q	679.819	1147.503	1941.979	0.141	0
QE4_Q	829.340	1431.232	2066.804	0.207	1

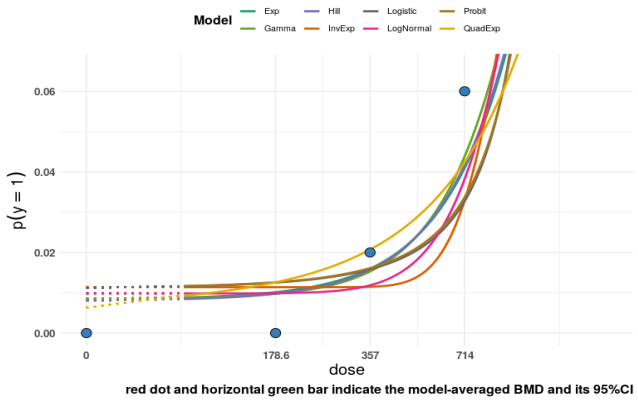
Weights for model averaging

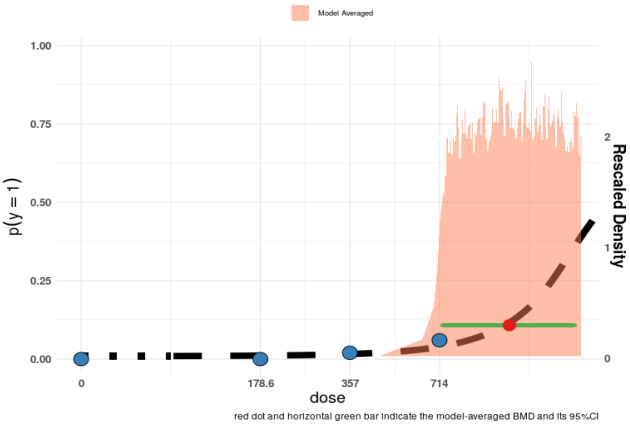


Final BMD values

Model	Type	BMDL	BMD	BMDU
Model averaged	BS	733.778	1,226.079	2,025.379

Visualization





2.9. NTP (2014)–uterus atypical endometrial hyperplasia (n) in female Wistar Han rats exposed by gavage for 2 years to TBBPA–model averaging

2.9.1. Data description

The end point to be analysed is uterus atypical endometrial hyperplasia.

Data used for analysis

TBBPA (mg/kg bw per day)	Uterus atypical endometrial hyperplasia (n)	Animals (n)
0.0	2	50
178.6	13	50
357.0	11	50
714.0	13	50

TBBPA: tetrabromobisphenol A.

2.9.2. Selection of the BMR

The BMR used is 10% set as default value for quantal data. The BMD is the dose corresponding with the BMR of interest.

A 90% confidence interval around the BMD will be estimated; the lower bound is reported by the BMDL, and the upper bound, by the BMDU.

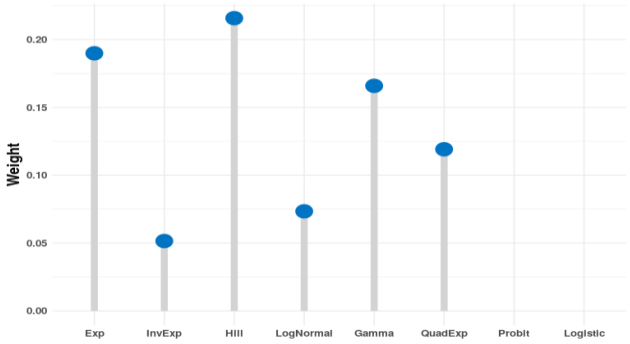
2.9.3. Results

Response variable: **uterus atypical endometrial hyperplasia**

Estimated BMDs per model

Model	BMDL	BMD	BMDU	Model weights	Converged
E4_Q	38.459	197.615	1291.504	0.190	1
IE4_Q	39.599	178.186	1479.692	0.052	0
H4_Q	34.468	176.327	935.755	0.216	1
LN4_Q	36.859	180.248	891.431	0.073	1
G4_Q	33.244	191.512	692.348	0.166	1
QE4_Q	191.767	352.012	1019.558	0.119	1

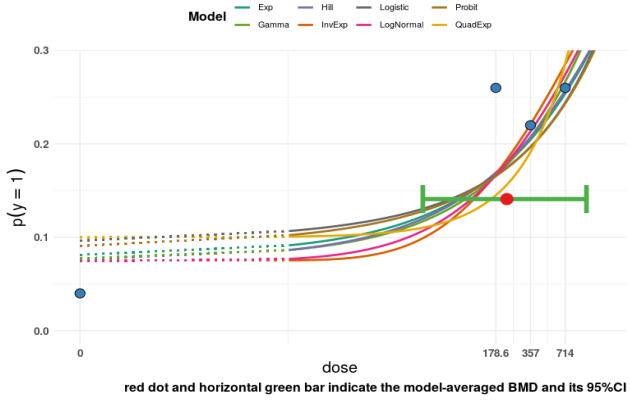
Weights for model averaging

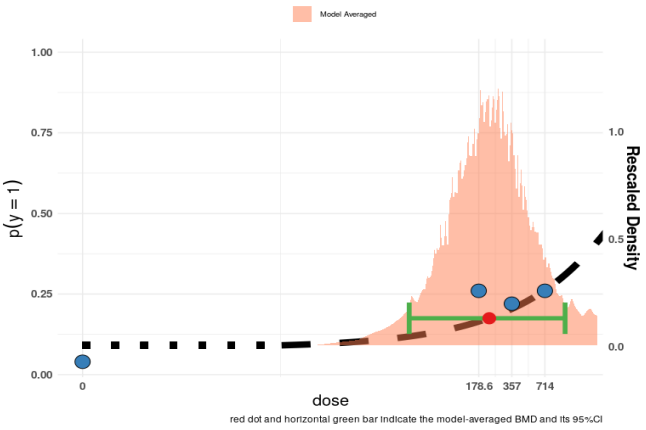


Final BMD values

Model	Type	BMDL	BMD	BMDU
Model averaged	BS	41.631	222.61	1,090.156

Visualization





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Abbreviations

BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDU	benchmark dose upper confidence limit
BMR	benchmark response
CONTAM Panel	EFSA Panel on Contaminants in the Food Chain
EFSA	European Food Safety Authority
LOAEL	lowest-observed adverse effect level
MMMT	malignant mixed Mullerian tumour
NOAEL	no-observed-adverse-effects level