

- 1 Annex to:
- 2 EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), xxxxxxxxxx, 20xx. Scientific
- 3 Opinion - Update of the risk assessment of hexabromocyclododecanes (HBCDDs) in food. EFSA Journal
- 4 20xx;xx(xx):xxxx.
- 5 © 20xx European Food Safety Authority. EFSA Journal published by John Wiley and Sons Ltd on
- 6 behalf of European Food Safety Authority.

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ANNEX C - Benchmark Dose (BMD) modelling

C.1. Introduction

This Appendix contains the details of the BMD modelling performed on experimental animal data. In this introduction a general description of the approach followed in the modelling is given.

Selection of the BMR

The benchmark dose (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 CONTAM Panel considered the default BMRs of 5% and 10% for continuous and quantal data, respectively, as indicated in the EFSA guidance on BMD in risk assessment (EFSA SC, 2017). Deviations from the default BMR were selected on a case by case basis and are justified in the specific modelling reports in this Appendix.

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

Software used

Results were obtained using the EFSA web-tool for BMD analysis, which used the R-package PROAST, version 66.40, for the underlying calculations.

Averaging results from multiple fitted benchmark dose models (used only for modelling of quantal data) is based on the methodology in Wheeler and Bailer (2008).

Specification of deviations from default assumptions

No deviations from general assumptions were introduced.

The CONTAM Panel selected the following default models:

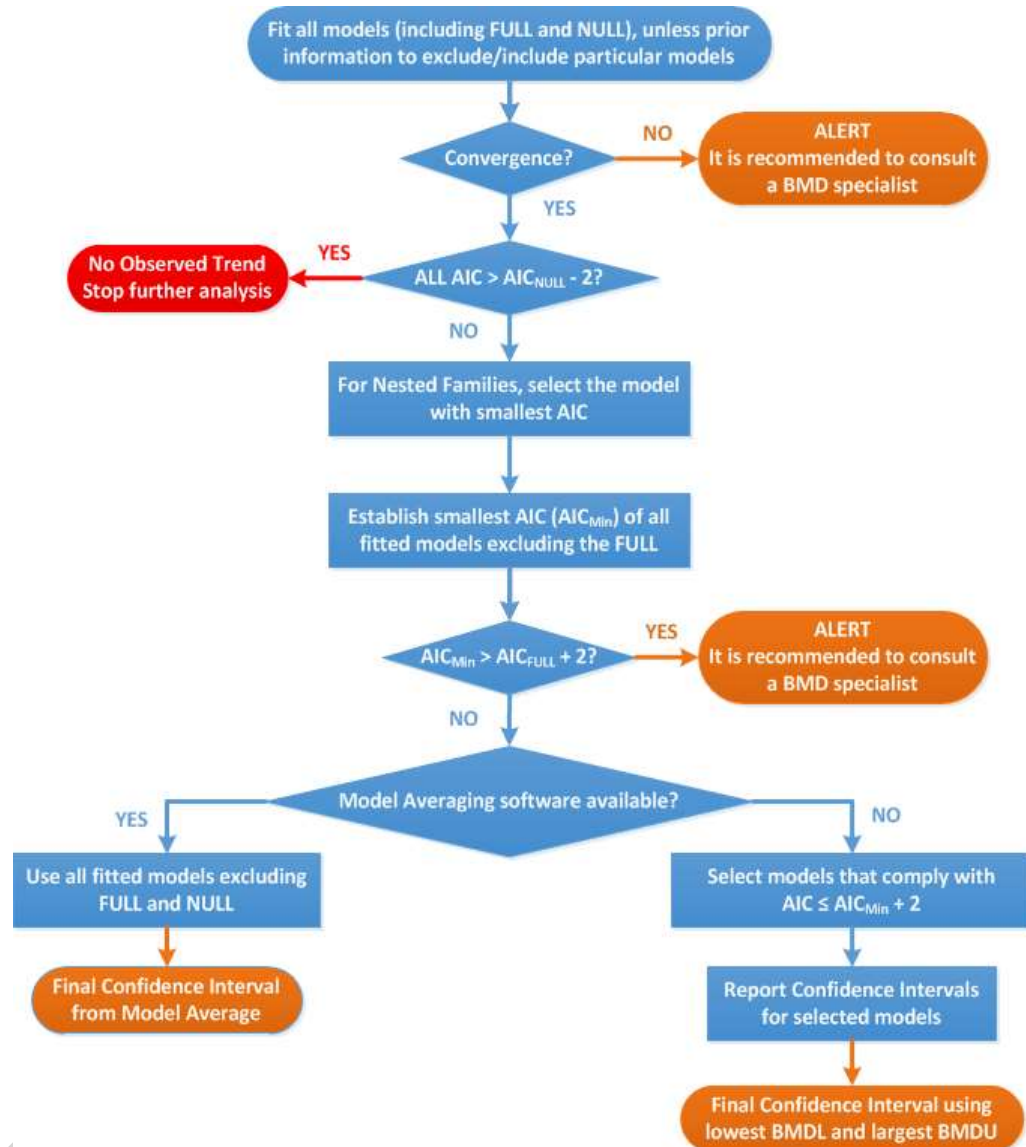
Default set of fitted models:

Model	Number of parameters	Formula
Null	1	$y = a$
Full	no. of groups	$y = \text{group mean}$
Exp model 3	3	$y = a \cdot \exp(bx^d)$
Exp model 4	4	$y = a \cdot (c - (c - 1)\exp(-bx^d))$
Hill model 3	3	$y = a \cdot \left(1 - \frac{x^d}{b^d + x^d}\right)$
Hill model 4	4	$y = a \cdot \left(1 - \frac{(c - 1) \cdot x^d}{b^d + x^d}\right)$
Inverse Exponential	4	$y = a \cdot (1 + (c - 1)\exp(-bx^{-d}))$
Log-Normal Family	4	$y = a \cdot (1 + (c - 1)\Phi(\ln b + d \ln x))$

Procedure for selection of BMDL

BMDL was selected applying the following flowchart given in the EFSA SC (2017) guidance:

Flowchart for selection of BMDL



C.2. Locomotion in mice exposed by gavage to HBCDDs at PND10 (Eriksson et al., 2006) – Model averaging

35 Data description

36 The endpoint to be analyzed is: Locomotion.

37 Data used for analysis:

D	Locomotion	SD	N
0.0	500	83	10
0.9	415	53	10
13.5	215	59	10

38 Selection of the BMR

39 The BMR (benchmark response) used is a 10% change in mean response compared to the controls.

40 The BMD (benchmark dose) is the dose corresponding with the BMR of interest.

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

43 Results

44 **Response variable:** locomotion

45 Fitted Models

model	converged	loglik	npar	AIC
full model	yes	7.81	4	-7.62
null model	yes	-16.35	2	36.70
Expon. m3-	yes	7.81	4	-7.62
Expon. m5-	yes	7.81	5	-5.62
Hill m3-	yes	7.81	4	-7.62
Hill m5-	yes	7.81	5	-5.62
Inv.Expon. m3-	yes	7.81	4	-7.62
Inv.Expon. m5-	yes	7.81	5	-5.62
LN m3-	yes	7.81	4	-7.62
LN m5-	yes	7.81	5	-5.62

46 Estimated Model Parameters

47 EXP

48 estimate for var- : 0.03479

49 estimate for a- : 493.3

50 estimate for CED- : 0.3551

51 estimate for d- : 0.5818

52 HILL

53 estimate for var- : 0.03479

54 estimate for a- : 493.3

55 estimate for CED- : 0.3563

56 estimate for d- : 0.5849

57 INVEXP

58 estimate for var- : 0.03479
59 estimate for a- : 493.3
60 estimate for CED- : 0.4233
61 estimate for d- : 0.1256

62 **LOGN**

63 estimate for var- : 0.03479
64 estimate for a- : 493.3
65 estimate for CED- : 0.3942
66 estimate for d- : 0.2169

67 **Weights for Model Averaging**

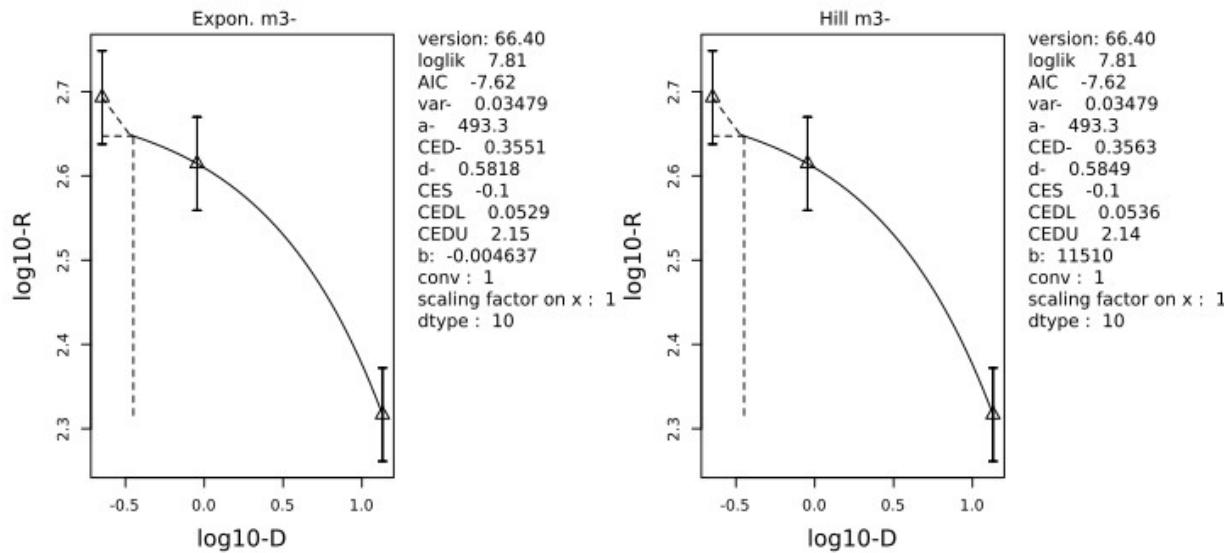
EXP	HILL	INVEXP	LOGN
0.25	0.25	0.25	0.25

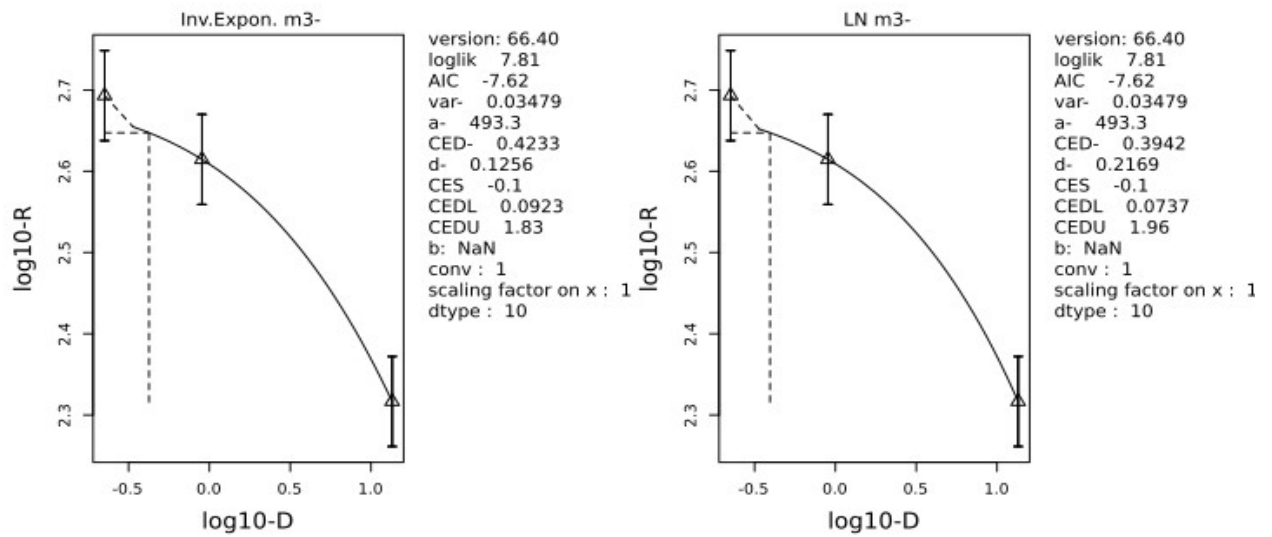
68 **Final BMD Values**

endpoint	subgroup	BMDL	BMDU
Locomotion		0.08	2.09

69 Confidence intervals for the BMD are based on 200 bootstrap data sets.

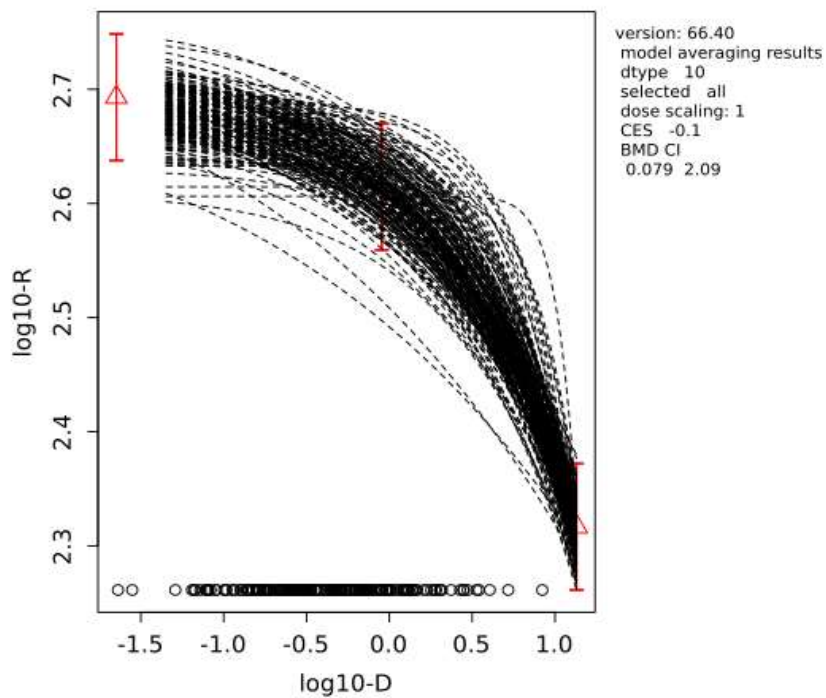
70 **Visualization**





78

bootstrap curves based on model averaging



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C.3. Locomotion in mice exposed by gavage to HBCDDs at PND10 (Eriksson et al., 2006) – Lowest model

80 Data Description

81 The endpoint to be analyzed is: Locomotion.

82 Data used for analysis:

D	Locomotion	SD	N
0.0	500	83	10
0.9	415	53	10
13.5	215	59	10

83 Selection of the BMR

84 The BMR (benchmark response) used is a 10% change in mean response compared to the controls.

85 The BMD (benchmark dose) is the dose corresponding with the BMR of interest.

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

88 Results

89 Response variable: Locomotion

90 Fitted Models

model	converged	loglik	npar	AIC
full model	yes	7.81	4	-7.62
null model	yes	-16.35	2	36.70
Expon. m3-	yes	7.81	4	-7.62
Expon. m5-	yes	7.81	5	-5.62
Hill m3-	yes	7.81	4	-7.62
Hill m5-	yes	7.81	5	-5.62
Inv.Expon. m3-	yes	7.81	4	-7.62
Inv.Expon. m5-	yes	7.81	5	-5.62
LN m3-	yes	7.81	4	-7.62
LN m5-	yes	7.81	5	-5.62

91 Estimated Model Parameters

92 EXP

93 estimate for var- : 0.03479

94 estimate for a- : 493.3

95 estimate for CED- : 0.3551

96 estimate for d- : 0.5818

97 HILL

98 estimate for var- : 0.03479

99 estimate for a- : 493.3

100 estimate for CED- : 0.3563

101 estimate for d- : 0.5849

102 INVEXP

103 estimate for var- : 0.03479
104 estimate for a- : 493.3
105 estimate for CED- : 0.4233
106 estimate for d- : 0.1256

107 **LOGN**

108 estimate for var- : 0.03479
109 estimate for a- : 493.3
110 estimate for CED- : 0.3942
111 estimate for d- : 0.2169

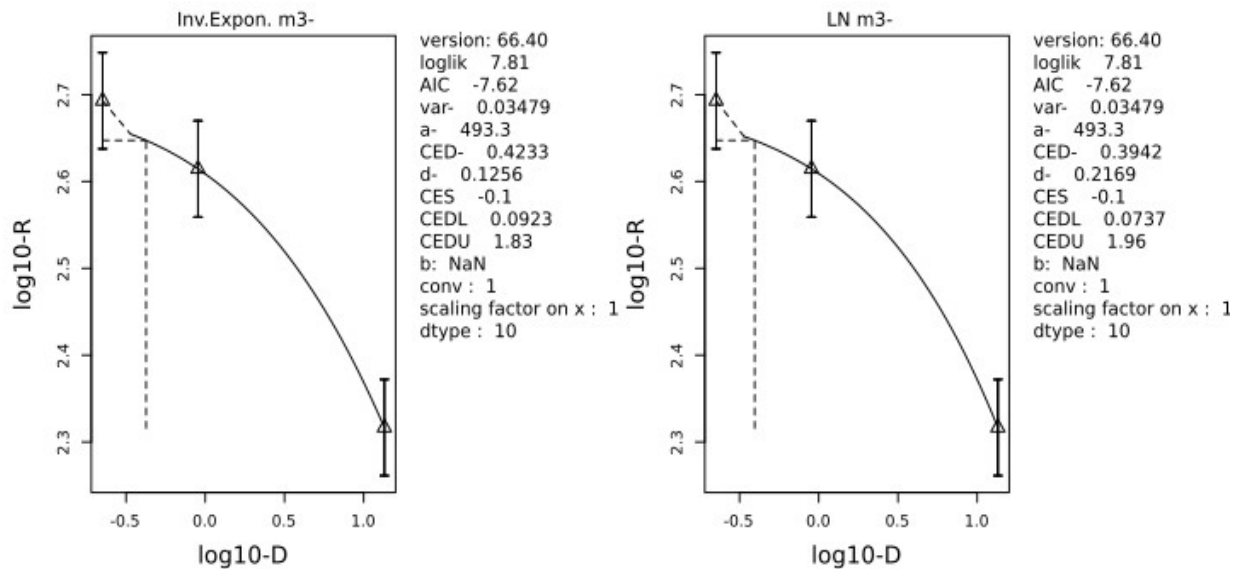
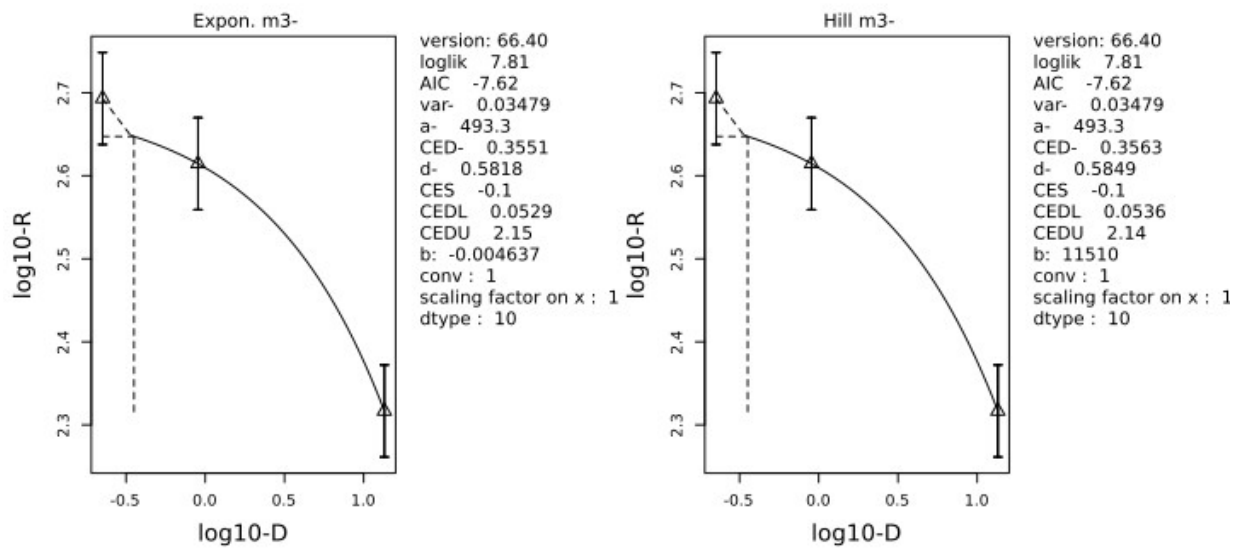
112 **Final BMD Values**

model	BMDL	BMDU	BMD
Expon. m3-	0.05	2.15	0.36
Hill m3-	0.05	2.14	0.36
LN m3-	0.07	1.96	0.39
Inv.Expon. m3-	0.09	1.83	0.42

113 **Lowest BMDL and highest BMDU Values**

subgroup	bmdl.lowest	bmdu.highest
all	0.0529	2.15

114 **Visualization**



C.4. Rearing in mice exposed by gavage to HBCDDs at PND10 (Eriksson et al., 2006) – Model averaging

Data Description

The endpoint to be analyzed is: Rearing.

Data used for analysis:

D	R	SD	N
0.0	1580	280	10
0.9	1190	250	10
13.5	282	77	10

Selection of the BMR

The BMR (benchmark response) used is a 10% change in mean response compared to the controls.

The BMD (benchmark dose) 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.

Results

Response variable: Rearing

Fitted Models

model	converged	loglik	npar	AIC
full model	yes	4.35	4	-0.70
null model	yes	-35.54	2	75.08
Expon. m3-	yes	4.35	4	-0.70
Expon. m5-	yes	4.35	5	1.30
Hill m3-	yes	4.35	4	-0.70
Hill m5-	yes	4.35	5	1.30
Inv.Expon. m3-	yes	4.35	4	-0.70
Inv.Expon. m5-	yes	4.35	5	1.30
LN m3-	yes	4.35	4	-0.70
LN m5-	yes	4.35	5	1.30

Estimated Model Parameters

EXP

estimate for var- : 0.04381

estimate for a- : 1556

estimate for CED- : 0.1981

estimate for d- : 0.6696

HILL

estimate for var- : 0.04381

estimate for a- : 1556

estimate for CED- : 0.2004

estimate for d- : 0.6762

139 **INVEXP**

140 estimate for var- : 0.04381
141 estimate for a- : 1556
142 estimate for CED- : 0.2941
143 estimate for d- : 0.1658

144 **LOGN**

145 estimate for var- : 0.04381
146 estimate for a- : 1556
147 estimate for CED- : 0.2518
148 estimate for d- : 0.2699

149 **Weights for Model Averaging**

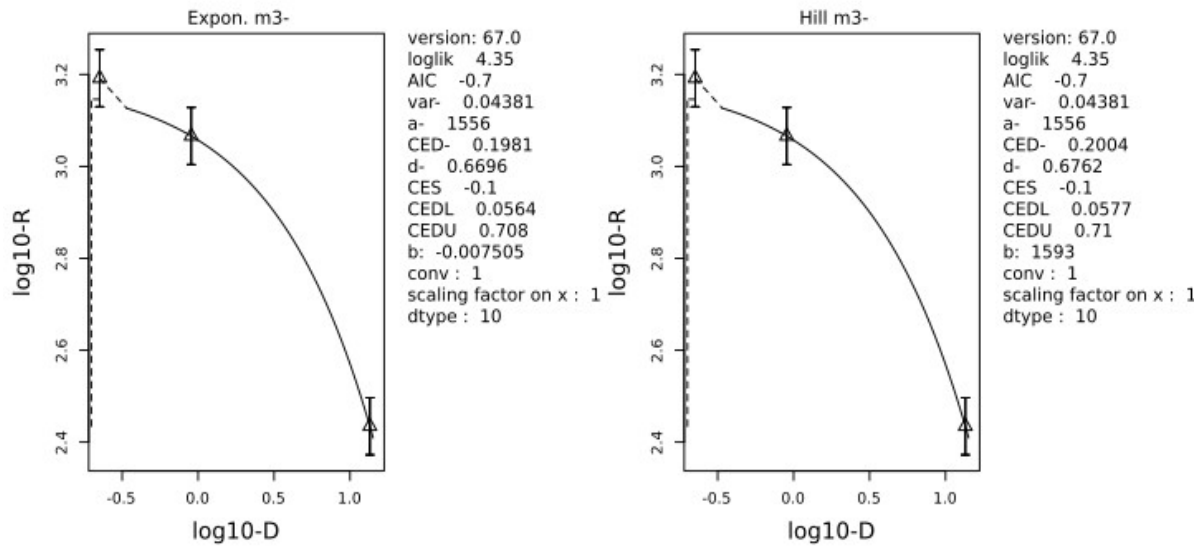
EXP	HILL	INVEXP	LOGN
0.25	0.25	0.25	0.25

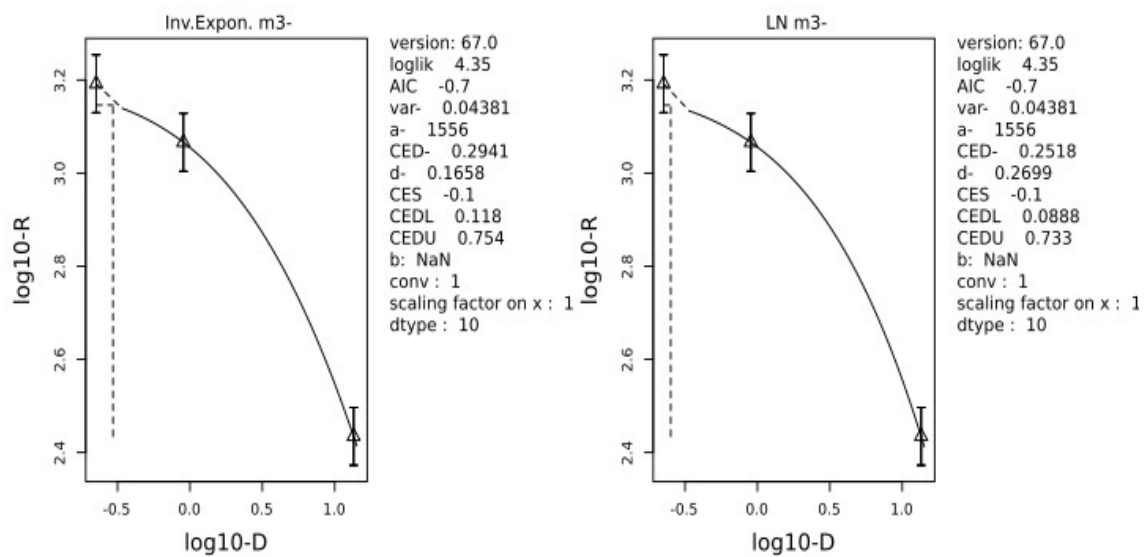
150 **Final BMD Values**

endpoint	subgroup	BMDL	BMDU
R		0.09	0.76

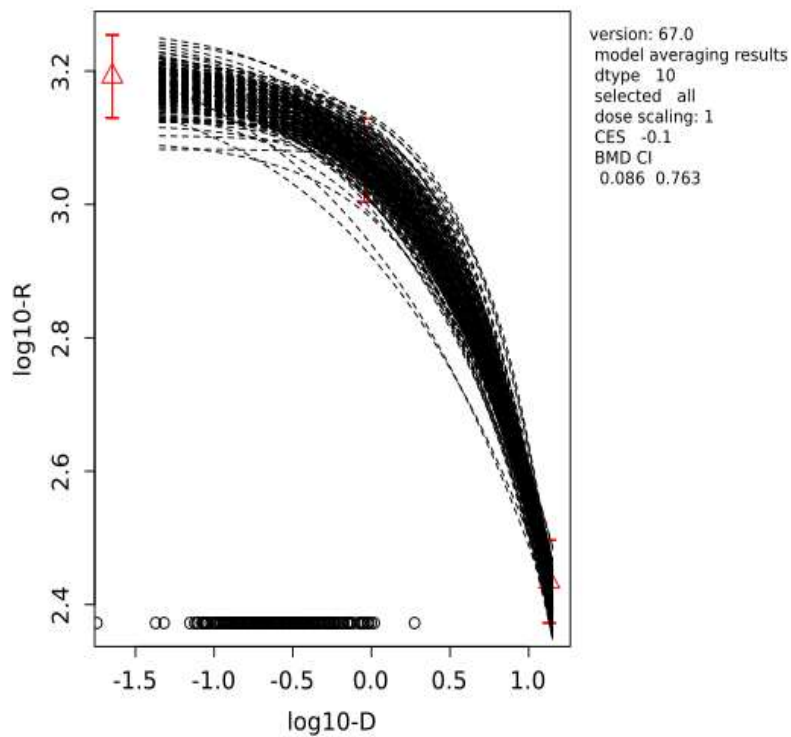
151 Confidence intervals for the BMD are based on 200 bootstrap data sets.

152 **Visualization**





**bootstrap curves
based on model averaging**



C.5. Rearing in mice exposed by gavage to HBCDDs at PND10 (Eriksson et al., 2006) – Lowest model

154 Data Description

155 The endpoint to be analysed is: Rearing.

156 Data used for analysis:

D	Rearing	SD	N
0.0	1580	280	10
0.9	1190	250	10
13.5	282	77	10

157 Selection of the BMR

158 The BMR (benchmark response) used is a 10% change in mean response compared to the controls.

159 The BMD (benchmark dose) is the dose corresponding with the BMR of interest.

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

162 Results

163 Response variable: Rearing

164 Fitted Models

model	converged	loglik	npar	AIC
full model	yes	4.35	4	-0.70
null model	yes	-35.54	2	75.08
Expon. m3-	yes	4.35	4	-0.70
Expon. m5-	yes	4.35	5	1.30
Hill m3-	yes	4.35	4	-0.70
Hill m5-	yes	4.35	5	1.30
Inv.Expon. m3-	yes	4.35	4	-0.70
Inv.Expon. m5-	yes	4.35	5	1.30
LN m3-	yes	4.35	4	-0.70
LN m5-	yes	4.35	5	1.30

165 Estimated Model Parameters

166 EXP

167 estimate for var- : 0.04381

168 estimate for a- : 1556

169 estimate for CED- : 0.1981

170 estimate for d- : 0.6696

171 HILL

172 estimate for var- : 0.04381

173 estimate for a- : 1556

174 estimate for CED- : 0.2004

175 estimate for d- : 0.6762

176 **INVEXP**

177 estimate for var- : 0.04381

178 estimate for a- : 1556

179 estimate for CED- : 0.2941

180 estimate for d- : 0.1658

181 **LOGN**

182 estimate for var- : 0.04381

183 estimate for a- : 1556

184 estimate for CED- : 0.2518

185 estimate for d- : 0.2699

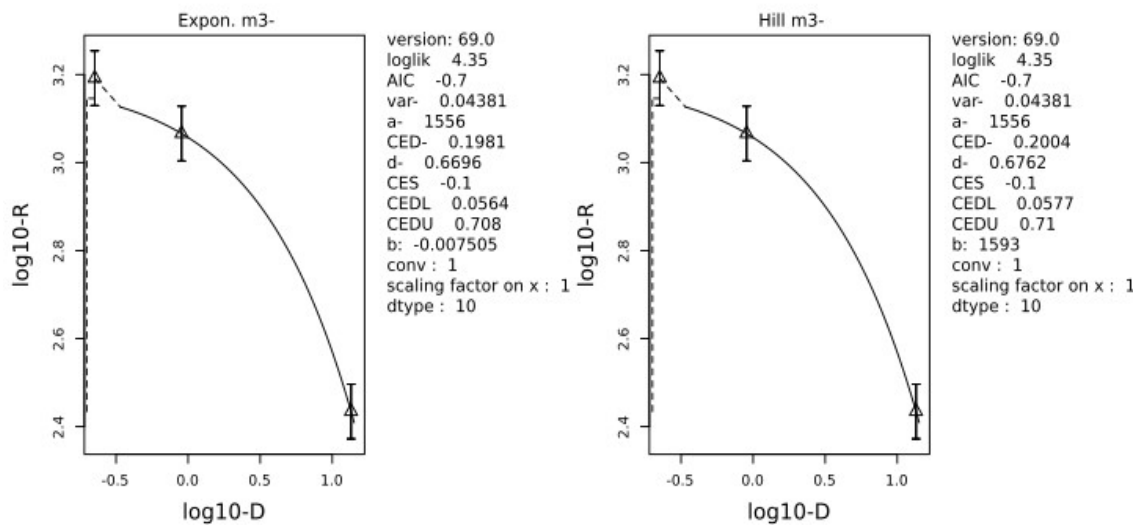
186 **Final BMD Values**

model	BMDL	BMDU	BMD
Expon. m3-	0.06	0.71	0.20
Hill m3-	0.06	0.71	0.20
LN m3-	0.09	0.73	0.25
Inv.Expon. m3-	0.12	0.75	0.29

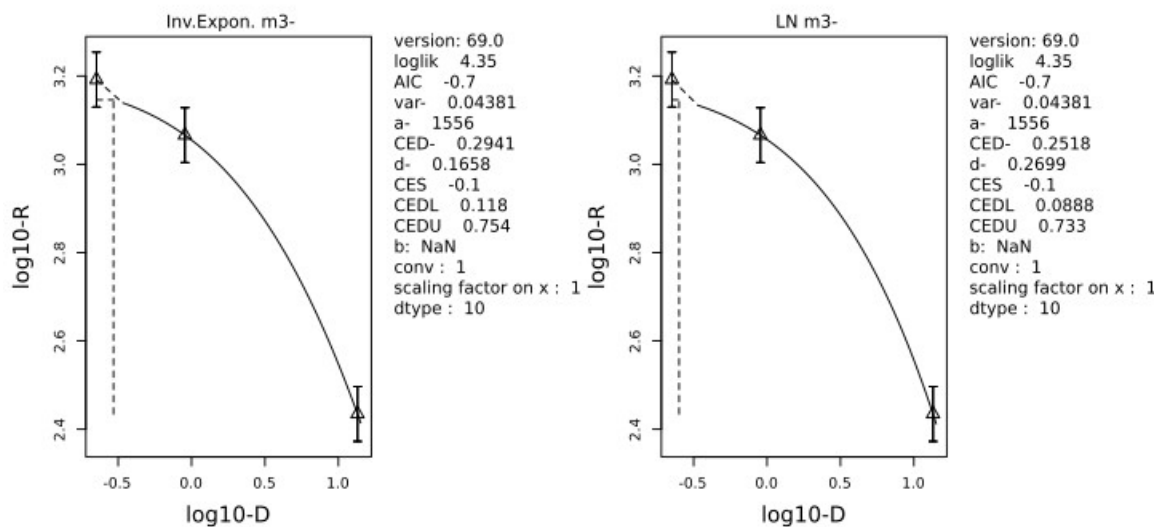
187 **Lowest BMDL and highest BMDU Values**

subgroup	bmdl.lowest	bmdu.highest
all	0.0564	0.754

188 **Visualization**



189



190

C.6. Total activity in mice exposed by gavage to HBCDDs at PND10 (Eriksson et al., 2006) – Model averaging

191 Data Description

192 The endpoint to be analysed is: Total activity.

193 Data used for analysis:

D	Total activity	SD	N
0.0	4720	580	10
0.9	4460	540	10
13.5	2480	330	10

194 Selection of the BMR

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

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

199 Results

200 Response variable: Total activity

201 Fitted Models

model	converged	loglik	npar	AIC
full model	yes	21.33	4	-34.66
null model	yes	-7.90	2	19.80
Expon. m3-	yes	21.33	4	-34.66
Expon. m5-	yes	21.33	5	-32.66
Hill m3-	yes	21.33	4	-34.66
Hill m5-	yes	21.33	5	-32.66
Inv.Expon. m3-	yes	21.33	4	-34.66
Inv.Expon. m5-	yes	21.33	5	-32.66
LN m3-	yes	21.33	4	-34.66
LN m5-	yes	21.33	5	-32.66

202 Estimated Model Parameters

203 EXP

204 estimate for var- : 0.01413

205 estimate for a- : 4685

206 estimate for CED- : 1.799

207 estimate for d- : 0.9021

208 HILL

209 estimate for var- : 0.01413

210 estimate for a- : 4685

211 estimate for CED- : 1.796

212 estimate for d- : 0.9047

213 INVEXP

214 estimate for var- : 0.01413
215 estimate for a- : 4685
216 estimate for CED- : 1.614
217 estimate for d- : 0.1701

218 **LOGN**

219 estimate for var- : 0.01413
220 estimate for a- : 4685
221 estimate for CED- : 1.689
222 estimate for d- : 0.3108

223 **Weights for Model Averaging**

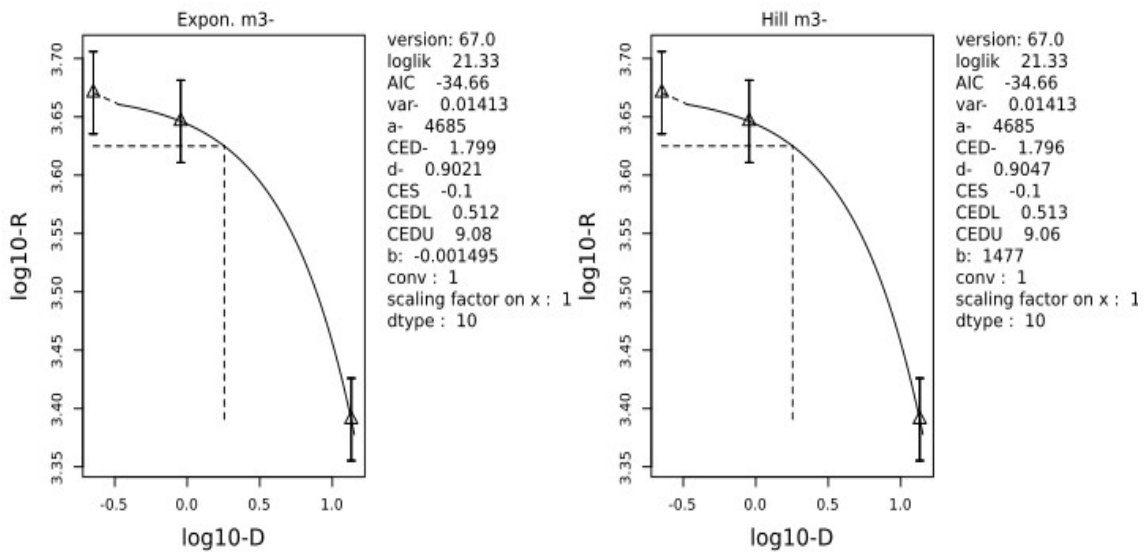
EXP	HILL	INVEXP	LOGN
0.25	0.25	0.25	0.25

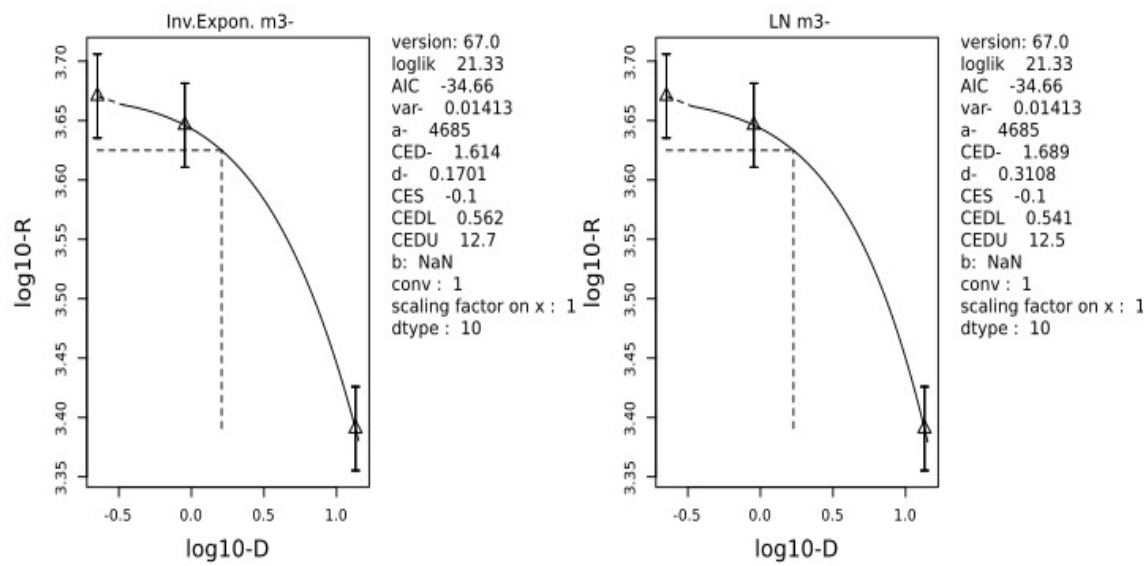
224 **Final BMD Values**

endpoint	subgroup	BMDL	BMDU
R		0.58	8.41

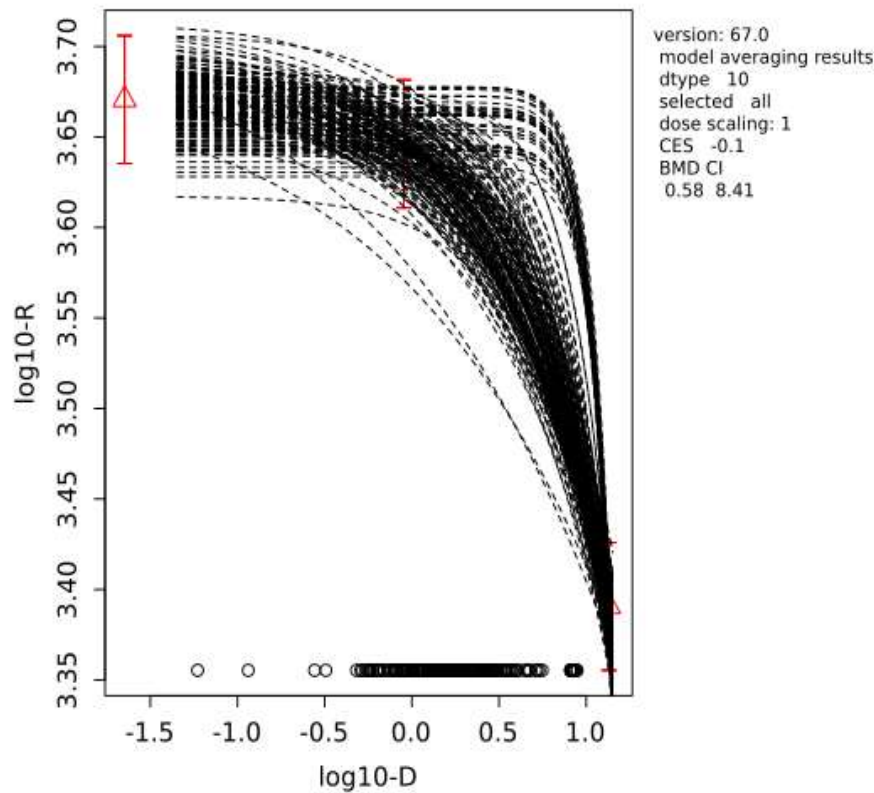
225 Confidence intervals for the BMD are based on 200 bootstrap data sets.

226 **Visualization**





**bootstrap curves
based on model averaging**



C.7. Total activity in mice exposed by gavage to HBCDDs at PND10 (Eriksson et al., 2006) – Lowest model

229 Data Description

230 The endpoint to be analyzed is: total activity.

231 Data used for analysis:

D	R	SD	N
0.0	4720	580	10
0.9	4460	540	10
13.5	2480	330	10

232 Selection of the BMR

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

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

237 Results

238 **Response variable: total activity**

239 Fitted Models

model	converged	loglik	npar	AIC
full model	yes	21.33	4	-34.66
null model	yes	-7.90	2	19.80
Expon. m3-	yes	21.33	4	-34.66
Expon. m5-	yes	21.33	5	-32.66
Hill m3-	yes	21.33	4	-34.66
Hill m5-	yes	21.33	5	-32.66
Inv.Expon. m3-	yes	21.33	4	-34.66
Inv.Expon. m5-	yes	21.33	5	-32.66
LN m3-	yes	21.33	4	-34.66
LN m5-	yes	21.33	5	-32.66

240 Estimated Model Parameters

241 EXP

242 estimate for var- : 0.01413

243 estimate for a- : 4685

244 estimate for CED- : 1.799

245 estimate for d- : 0.9021

246 HILL

247 estimate for var- : 0.01413

248 estimate for a- : 4685

249 estimate for CED- : 1.796

250 estimate for d- : 0.9047

251 INVEXP

252 estimate for var- : 0.01413
 253 estimate for a- : 4685
 254 estimate for CED- : 1.614
 255 estimate for d- : 0.1701

256 LOGN

257 estimate for var- : 0.01413
 258 estimate for a- : 4685
 259 estimate for CED- : 1.689
 260 estimate for d- : 0.3108

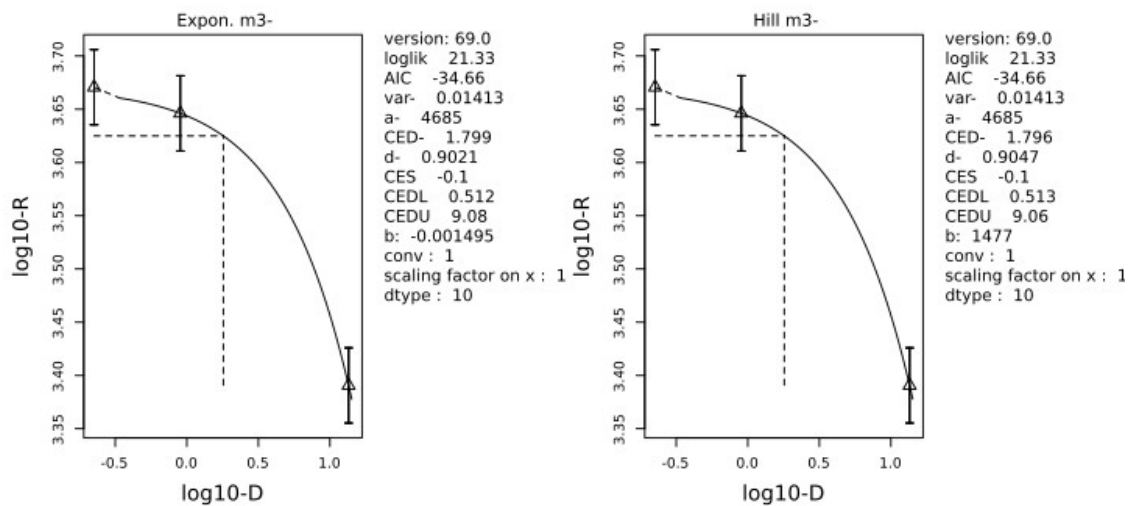
261 Final BMD Values

model	BMDL	BMDU	BMD
Expon. m3-	0.51	9.08	1.80
Hill m3-	0.51	9.06	1.80
LN m3-	0.54	12.50	1.69
Inv.Expon. m3-	0.56	12.70	1.61

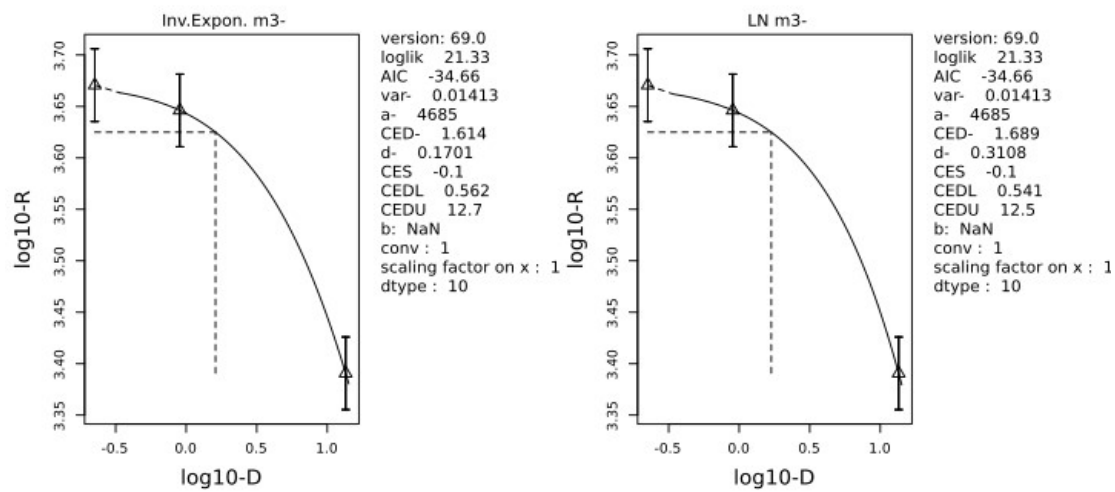
262 Lowest BMDL and highest BMDU Values

subgroup	bmdl.lowest	bmdu.highest
all	0.512	12.7

263 Visualization



264



References

- EFSA Scientific Committee, Hardy A, Benford D, Halldorsson T, Jeger MJ, Knutsen KH, More S, Mortensen A, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Silano V, Solecki R, Turck D, Aerts M, Bodin L, Davis A, Edler L, Gundert-Remy U, Sand S, Slob W, Bottex B, Abrahantes JC, Marques DC, Kass G and Schlatter JR, 2017a. Update: Guidance on the use of the benchmark dose approach in risk assessment. EFSA Journal 2017;15(1):4658, 41 pp. <https://doi.org/10.2903/j.efsa.2017.4658>
- Wheeler MW and Bailer AJ, 2008. Model averaging software for dichotomous dose response risk estimation. Journal of Statistical Software, 26, 1–15.