Annex to:

EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), Schrenk D, Bignami M, Bodin L, Chipman JK, del Mazo J, Grasl-Kraupp B, Hogstrand C, Hoogenboom LR, Leblanc J-C, Nebbia CS, Nielsen E, Ntzani E, Petersen A, Sand S, Schwerdtle T, Wallace H, Benford D, Fürst P, Rose M, Ioannidou D, Nikolič M, Ramos Bordajandi L and Vleminckx C, 2021. Scientific Opinion – Update of the risk assessment of hexabromocyclododecanes (HBCDDs) in food. EFSA Journal 2021;19(3):6421, https://doi.org/10.2903/j.efsa.2021.6421

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 Scientific Committee, 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:

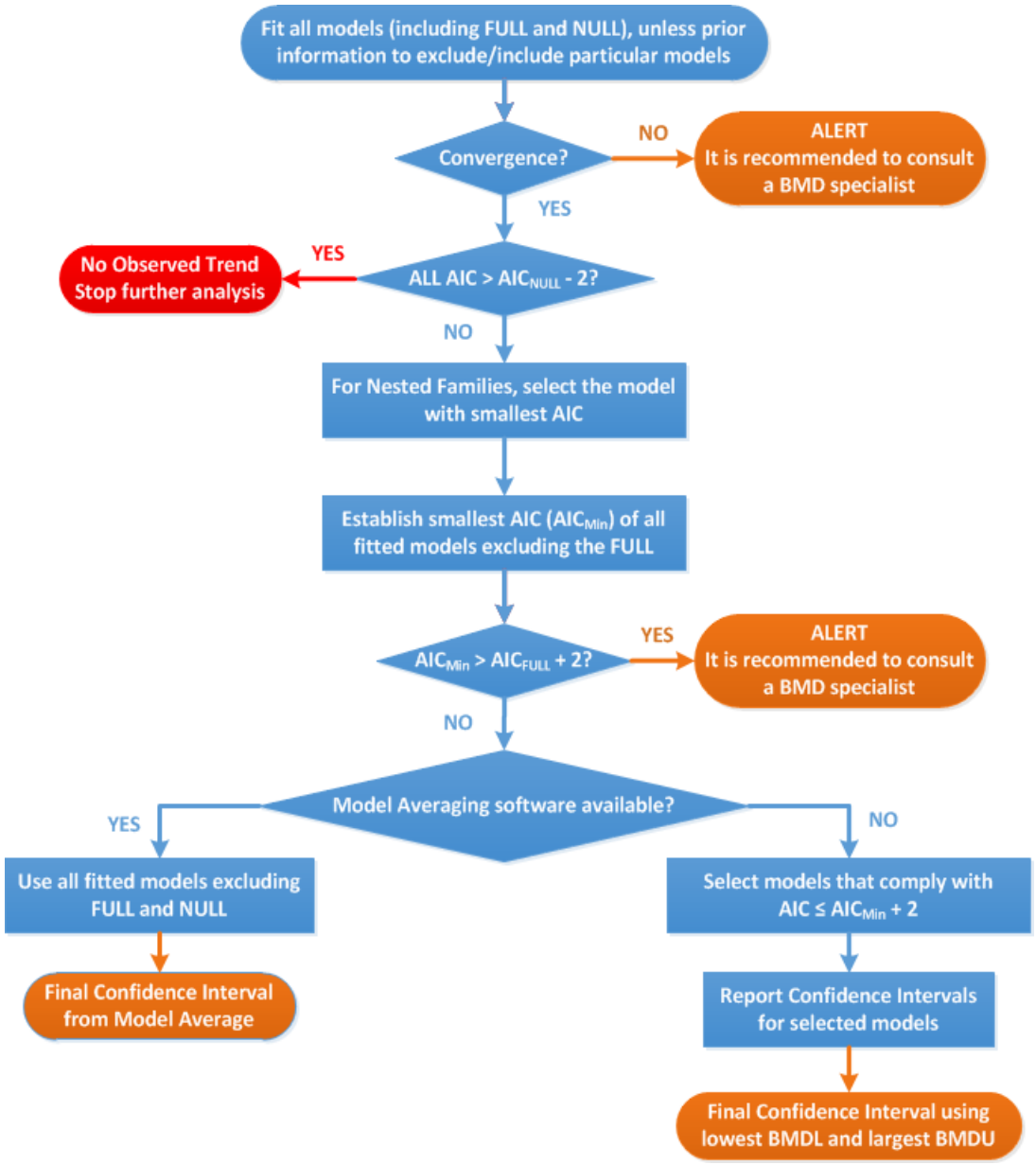
Default set of fitted models:

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 Scientific Commitee (2017) guidance:

Flowchart for selection of BMDL



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

Data description

The endpoint to be analysed is: horizontal locomotion.

Data used for analysis:

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

Selection of the BMR

The CONTAM Panel noted that the BMDLs established with a BMR = 5% for horizontal locomotion were far below the lowest dose administered and resulted in large BMD confidence interval. Thus, the CONTAM Panel decided to use a BMR of 10%.

Results

Response variable: horizontal locomotion

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

Estimated Model Parameters

EXP

estimate for var- : 0.03479
estimate for a- : 493.3
estimate for CED- : 0.3551
estimate for d- : 0.5818

HILL

estimate for var- : 0.03479
estimate for a- : 493.3
estimate for CED- : 0.3563
estimate for d- : 0.5849

INVEXP

estimate for var- : 0.03479
estimate for a- : 493.3
estimate for CED- : 0.4233
estimate for d- : 0.1256

LOGN

estimate for var- : 0.03479
estimate for a- : 493.3
estimate for CED- : 0.3942
estimate for d- : 0.2169

Weights for Model Averaging

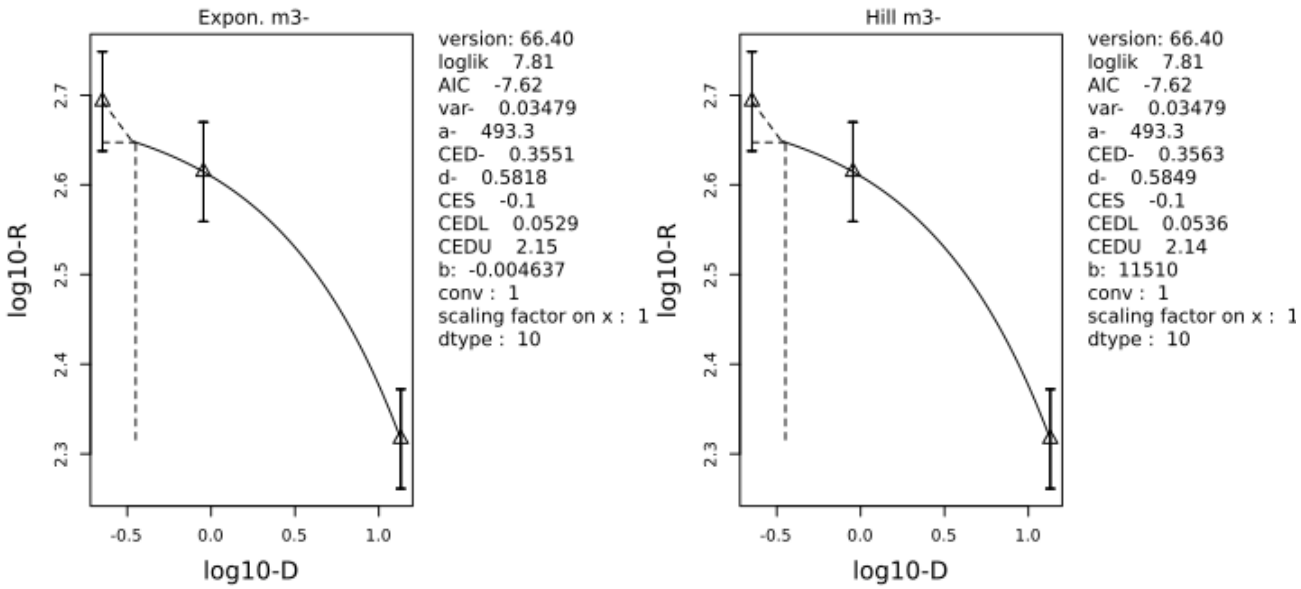
EXP	HILL	INVEXP	LOGN
0.25	0.25	0.25	0.25

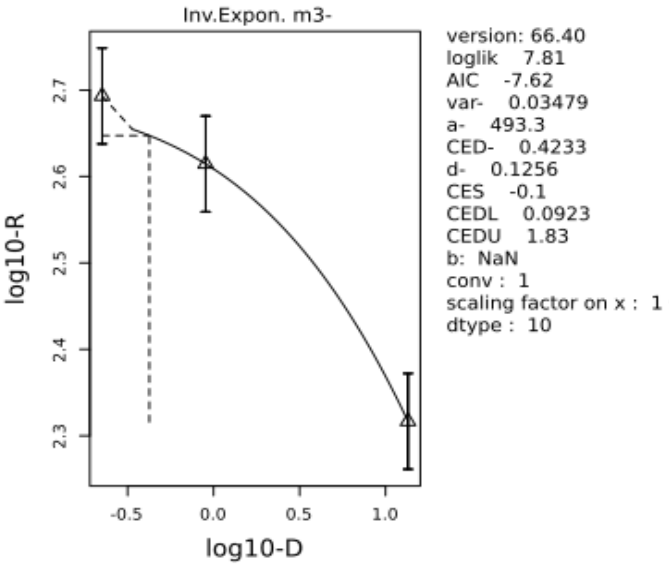
Final BMD Values

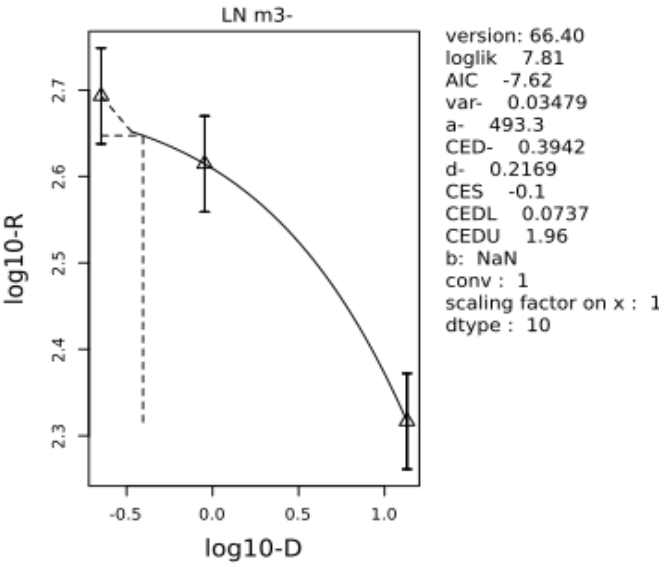
endpoint	subgroup	BMDL	BMDU
Horizontal locomotion		0.08	2.09

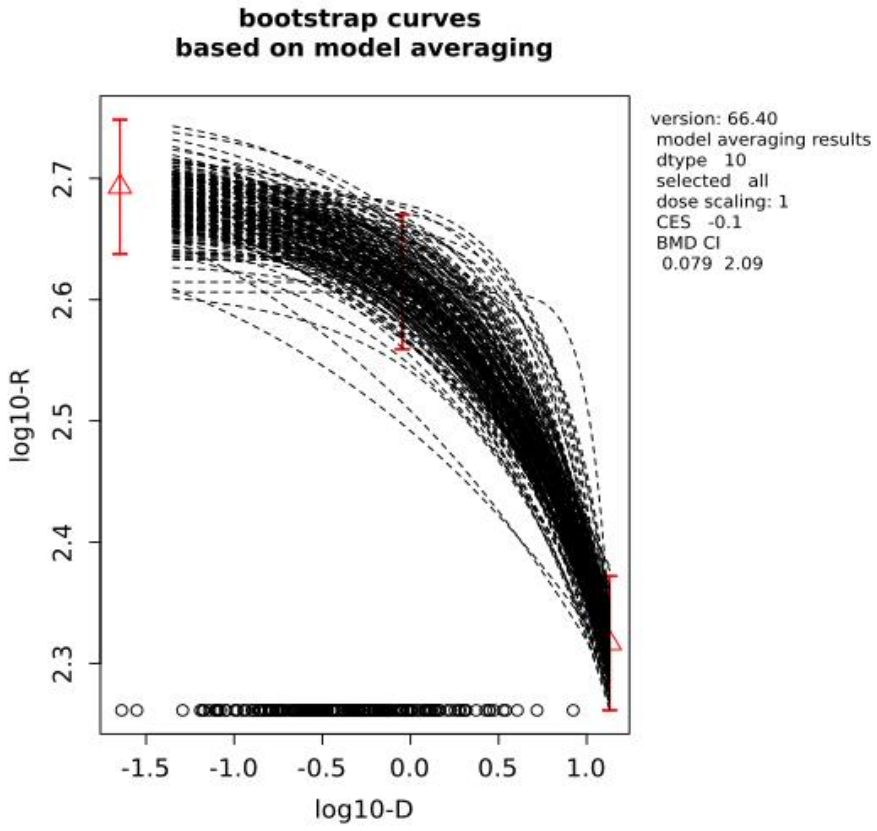
Confidence intervals for the BMD are based on 200 bootstrap data sets.

Visualization




Inv.Expon. m3-
log10-R
log10-D
version: 66.40
loglik 7.81
AIC -7.62
var- 0.03479
a- 493.3
CED- 0.4233
d- 0.1256
CES -0.1
CEDL 0.0923
CEDU 1.83
b: NaN
conv : 1
scaling factor on x : 1
dtype : 10


LN m3-
log10-R
log10-D
version: 66.40
loglik 7.81
AIC -7.62
var- 0.03479
a- 493.3
CED- 0.3942
d- 0.2169
CES -0.1
CEDL 0.0737
CEDU 1.96
b: NaN
conv : 1
scaling factor on x : 1
dtype : 10


bootstrap curves
based on model averaging
log10-R
log10-D
version: 66.40
model averaging results
dtype 10
selected all
dose scaling: 1
CES -0.1
BMD CI
0.079 2.09

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

Data Description

The endpoint to be analysed is: horizontal locomotion.

Data used for analysis:

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

Selection of the BMR

The CONTAM Panel noted that the BMDLs established with a BMR = 5% for horizontal locomotion were far below the lowest dose administered and resulted in large BMD confidence interval. Thus, the CONTAM Panel decided to use a BMR of 10%.

Results

Response variable: Horizontal locomotion

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

Estimated Model Parameters

EXP

estimate for var- : 0.03479
estimate for a- : 493.3
estimate for CED- : 0.3551
estimate for d- : 0.5818

HILL

estimate for var- : 0.03479
estimate for a- : 493.3
estimate for CED- : 0.3563
estimate for d- : 0.5849

INVEXP

estimate for var- : 0.03479
estimate for a- : 493.3
estimate for CED- : 0.4233
estimate for d- : 0.1256

LOGN

estimate for var- : 0.03479
estimate for a- : 493.3
estimate for CED- : 0.3942
estimate for d- : 0.2169

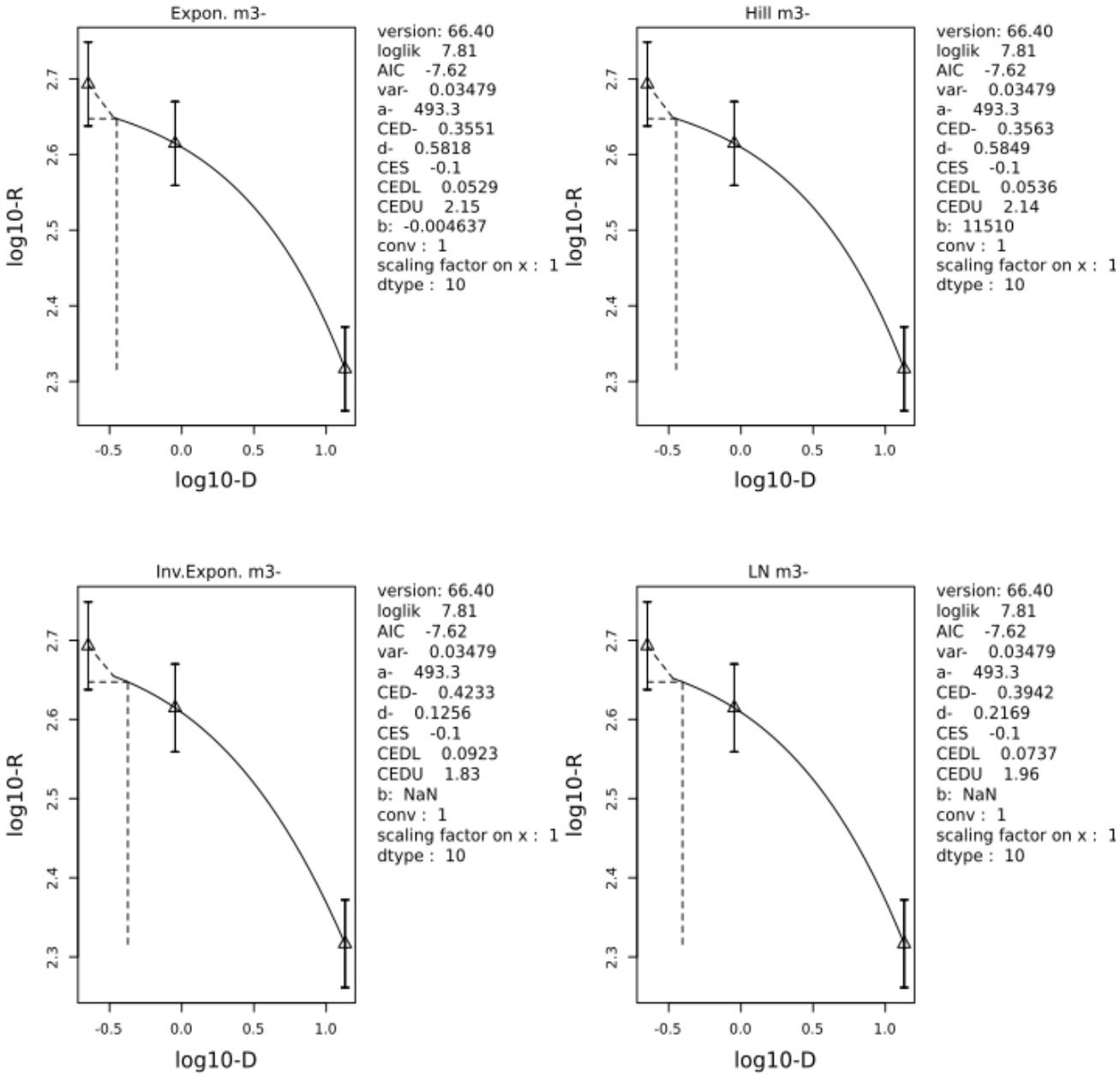
Final BMD Values

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

Lowest BMDL and highest BMDU Values

subgroup	bmdl.lowest	bmdu.highest
all	0.0529	2.15

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 analysed is: Rearing.

Data used for analysis:

D	Rearing	SD	N
0.0	1,580	280	10
0.9	1,190	250	10
13.5	282	77	10

Selection of the BMR

The CONTAM Panel noted that the BMDLs established with a BMR = 5% for rearing were far below the lowest dose administered and resulted in large BMD confidence interval. Thus, the CONTAM Panel decided to use a BMR of 10%.

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

INVEXP

estimate for var- : 0.04381
estimate for a- : 1556
estimate for CED- : 0.2941
estimate for d- : 0.1658

LOGN

estimate for var- : 0.04381
estimate for a- : 1556
estimate for CED- : 0.2518
estimate for d- : 0.2699

Weights for Model Averaging

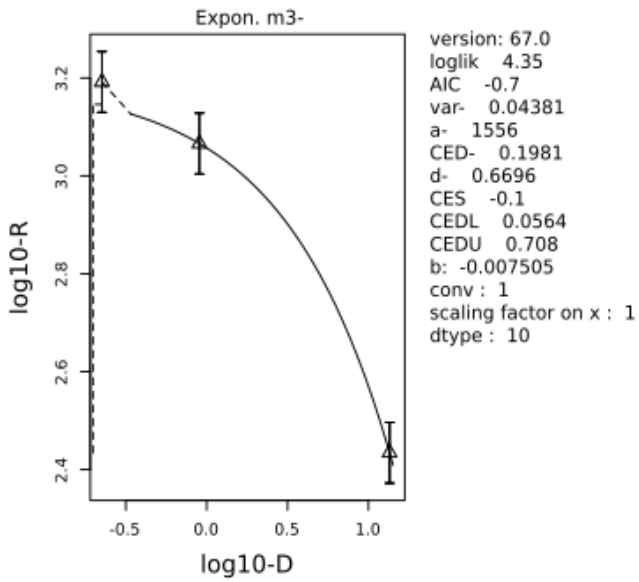
EXP	HILL	INVEXP	LOGN
0.25	0.25	0.25	0.25

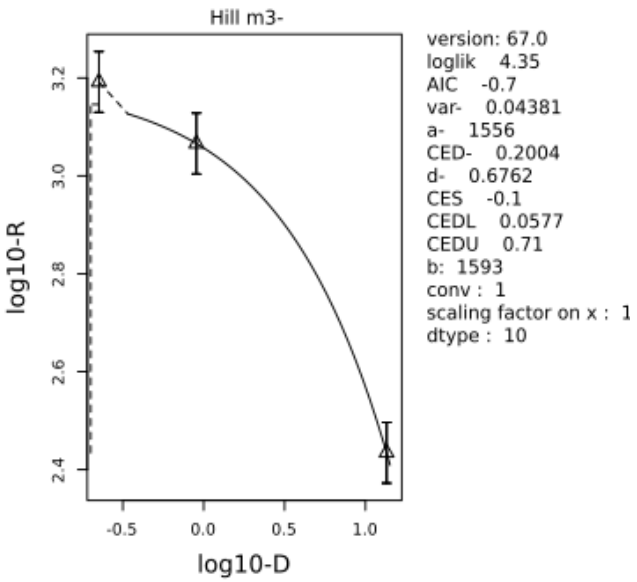
Final BMD Values

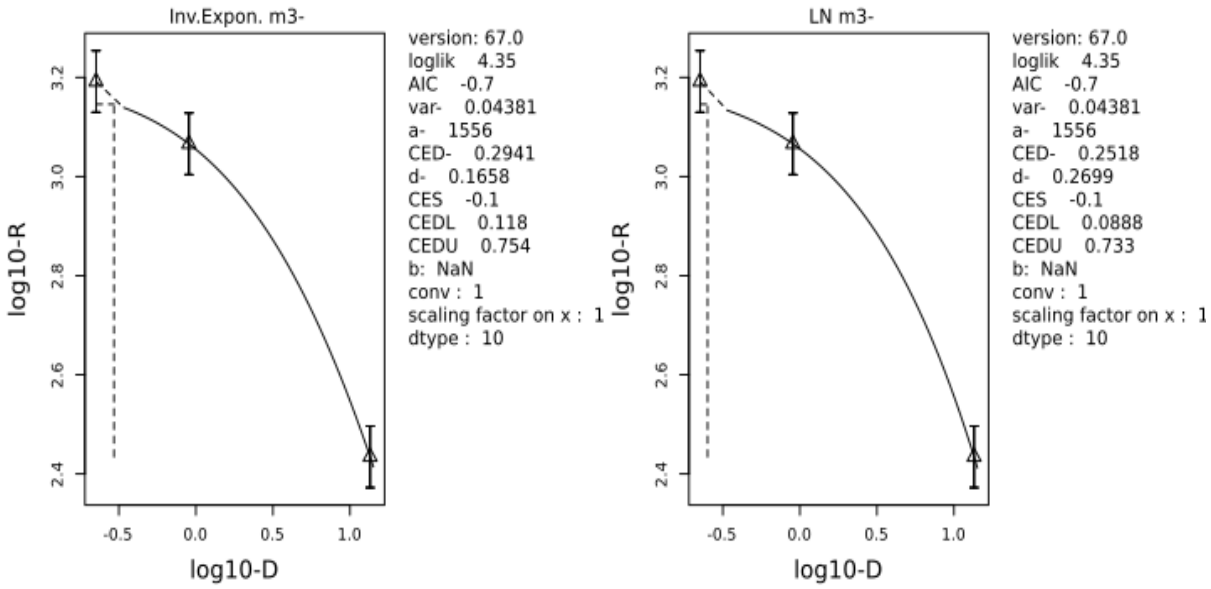
endpoint	subgroup	BMDL	BMDU
R		0.09	0.76

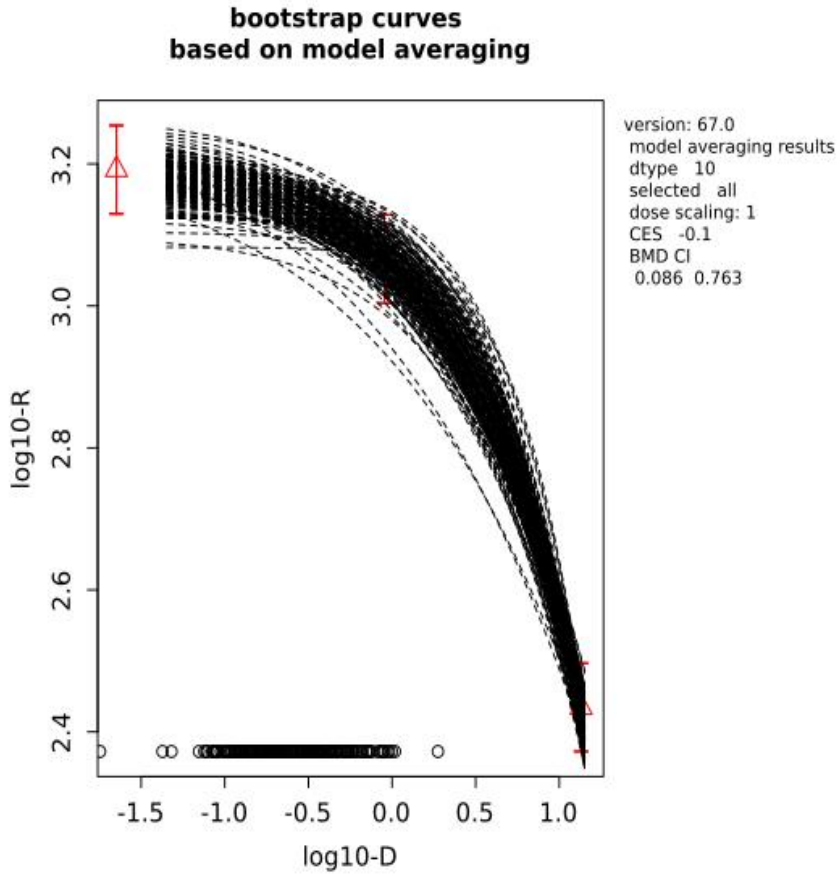
Confidence intervals for the BMD are based on 200 bootstrap data sets.

Visualization






Inv.Expon. m3-
version: 67.0
loglik 4.35
AIC -0.7
var- 0.04381
a- 1556
CED- 0.2941
d- 0.1658
CES -0.1
CEDL 0.118
CEDU 0.754
b: NaN
conv : 1
scaling factor on x : 1
dtype : 10
log10-R
log10-D
LN m3-
version: 67.0
loglik 4.35
AIC -0.7
var- 0.04381
a- 1556
CED- 0.2518
d- 0.2699
CES -0.1
CEDL 0.0888
CEDU 0.733
b: NaN
conv : 1
scaling factor on x : 1
dtype : 10
log10-R
log10-D


bootstrap curves
based on model averaging
version: 67.0
model averaging results
dtype 10
selected all
dose scaling: 1
CES -0.1
BMD CI
0.086 0.763
log10-R
log10-D

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

Data Description

The endpoint to be analysed is: Rearing.

Data used for analysis:

D	Rearing	SD	N
0.0	1,580	280	10
0.9	1,190	250	10
13.5	282	77	10

Selection of the BMR

The CONTAM Panel noted that the BMDLs established with a BMR = 5% for rearing were far below the lowest dose administered and resulted in large BMD confidence interval. Thus, the CONTAM Panel decided to use a BMR of 10%.

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

INVEXP

estimate for var- : 0.04381
estimate for a- : 1556
estimate for CED- : 0.2941
estimate for d- : 0.1658

LOGN

estimate for var- : 0.04381
estimate for a- : 1556
estimate for CED- : 0.2518
estimate for d- : 0.2699

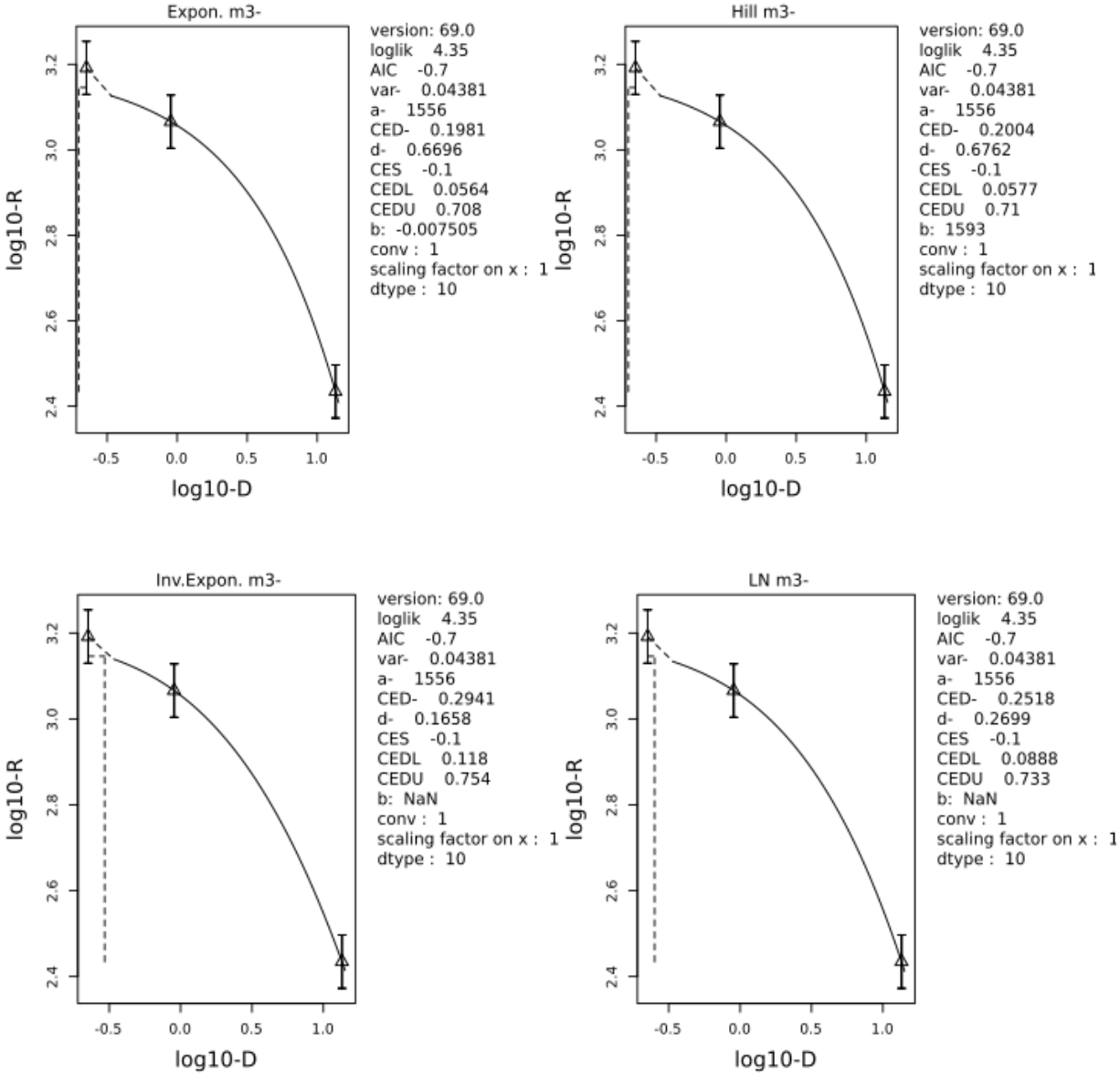
Final BMD Values

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

Lowest BMDL and highest BMDU Values

subgroup	bmdl.lowest	bmdu.highest
all	0.0564	0.754

Visualization



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

Data Description

The endpoint to be analysed is: Total activity.

Data used for analysis:

D	Total activity	SD	N
0.0	4,720	580	10
0.9	4,460	540	10
13.5	2,480	330	10

Selection of the BMR

The CONTAM Panel noted that the BMDLs established with a BMR = 5% for total activity were far below the lowest dose administered and resulted in large BMD confidence interval. Thus, the CONTAM Panel decided to use a BMR of 10%.

Results

Response variable: Total activity

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

Estimated Model Parameters

EXP

estimate for var- : 0.01413
estimate for a- : 4685
estimate for CED- : 1.799
estimate for d- : 0.9021

HILL

estimate for var- : 0.01413
estimate for a- : 4685
estimate for CED- : 1.796
estimate for d- : 0.9047

INVEXP

estimate for var- : 0.01413
estimate for a- : 4685
estimate for CED- : 1.614
estimate for d- : 0.1701

LOGN

estimate for var- : 0.01413
estimate for a- : 4685
estimate for CED- : 1.689
estimate for d- : 0.3108

Weights for Model Averaging

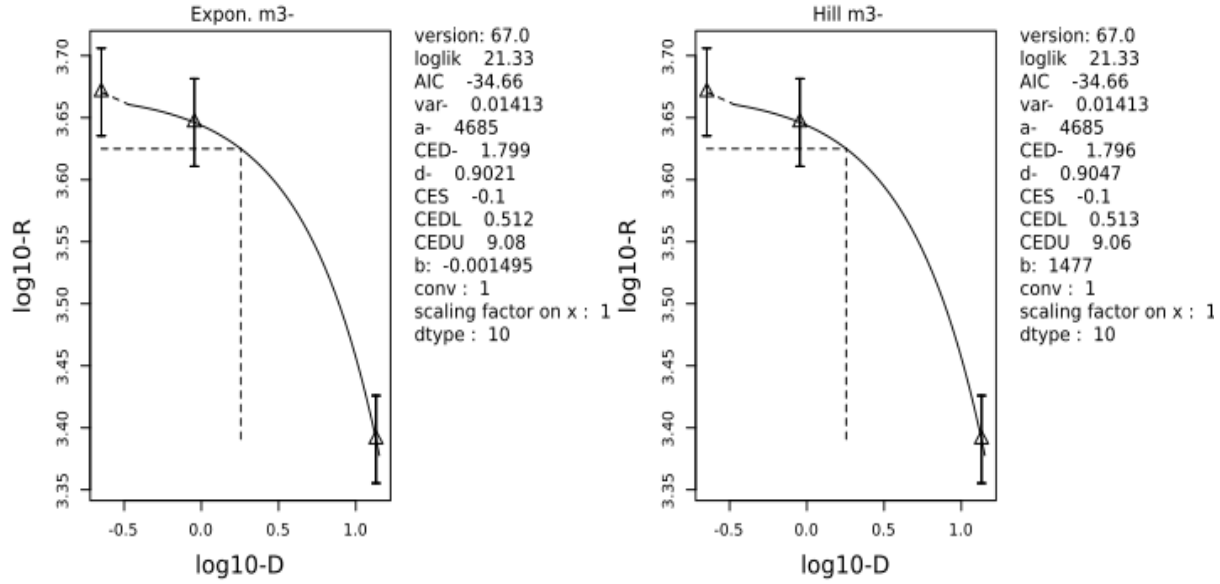
EXP	HILL	INVEXP	LOGN
0.25	0.25	0.25	0.25

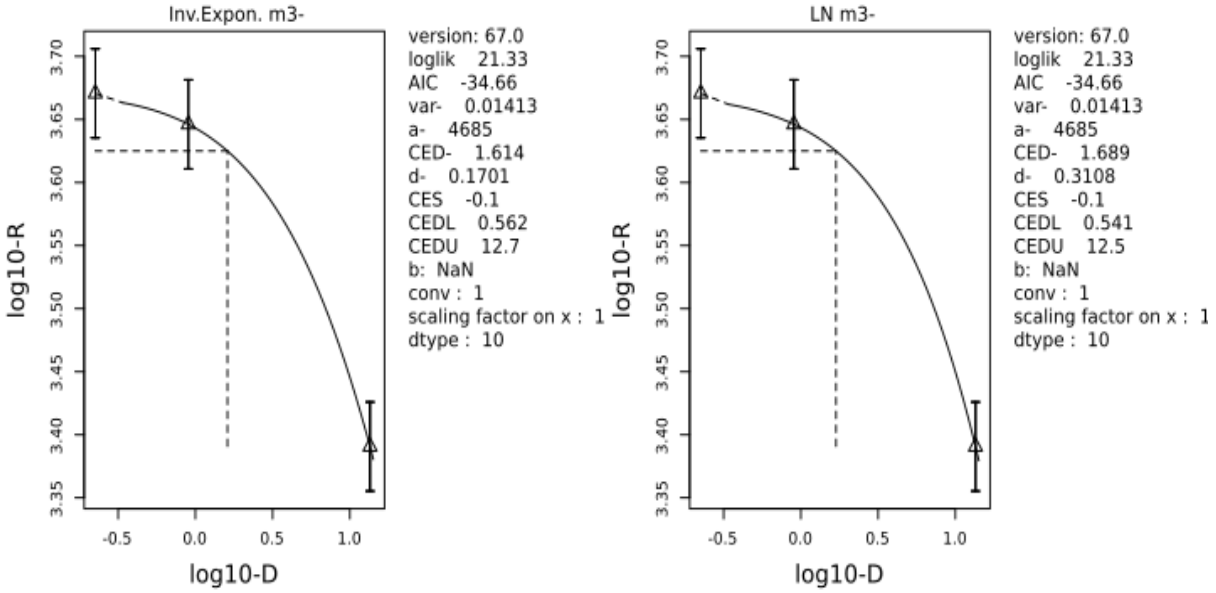
Final BMD Values

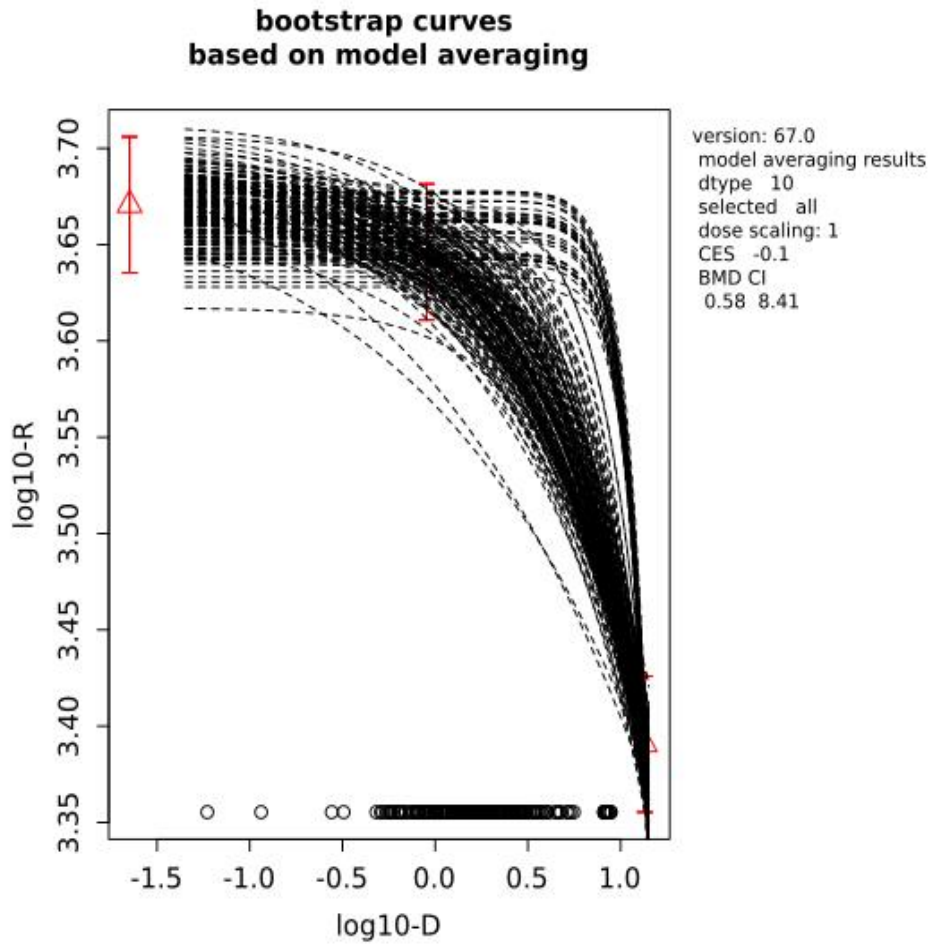
endpoint	subgroup	BMDL	BMDU
R		0.58	8.41

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

Visualization




Inv.Expon. m3-
version: 67.0
loglik 21.33
AIC -34.66
var- 0.01413
a- 4685
CED- 1.614
d- 0.1701
CES -0.1
CEDL 0.562
CEDU 12.7
b: NaN
conv : 1
scaling factor on x : 1
dtype : 10
log10-R
log10-D
LN m3-
version: 67.0
loglik 21.33
AIC -34.66
var- 0.01413
a- 4685
CED- 1.689
d- 0.3108
CES -0.1
CEDL 0.541
CEDU 12.5
b: NaN
conv : 1
scaling factor on x : 1
dtype : 10
log10-R
log10-D


bootstrap curves
based on model averaging
version: 67.0
model averaging results
dtype 10
selected all
dose scaling: 1
CES -0.1
BMD CI
0.58 8.41
log10-R
log10-D

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

Data Description

The endpoint to be analysed is: total activity.

Data used for analysis:

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

Selection of the BMR

The CONTAM Panel noted that the BMDLs established with a BMR = 5% for total activity were far below the lowest dose administered and resulted in large BMD confidence interval. Thus, the CONTAM Panel decided to use a BMR of 10%.

Results

Response variable: total activity

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

Estimated Model Parameters

EXP

estimate for var- : 0.01413
estimate for a- : 4685
estimate for CED- : 1.799
estimate for d- : 0.9021

HILL

estimate for var- : 0.01413
estimate for a- : 4685
estimate for CED- : 1.796
estimate for d- : 0.9047

INVEXP

estimate for var- : 0.01413
estimate for a- : 4685
estimate for CED- : 1.614
estimate for d- : 0.1701

LOGN

estimate for var- : 0.01413
estimate for a- : 4685
estimate for CED- : 1.689
estimate for d- : 0.3108

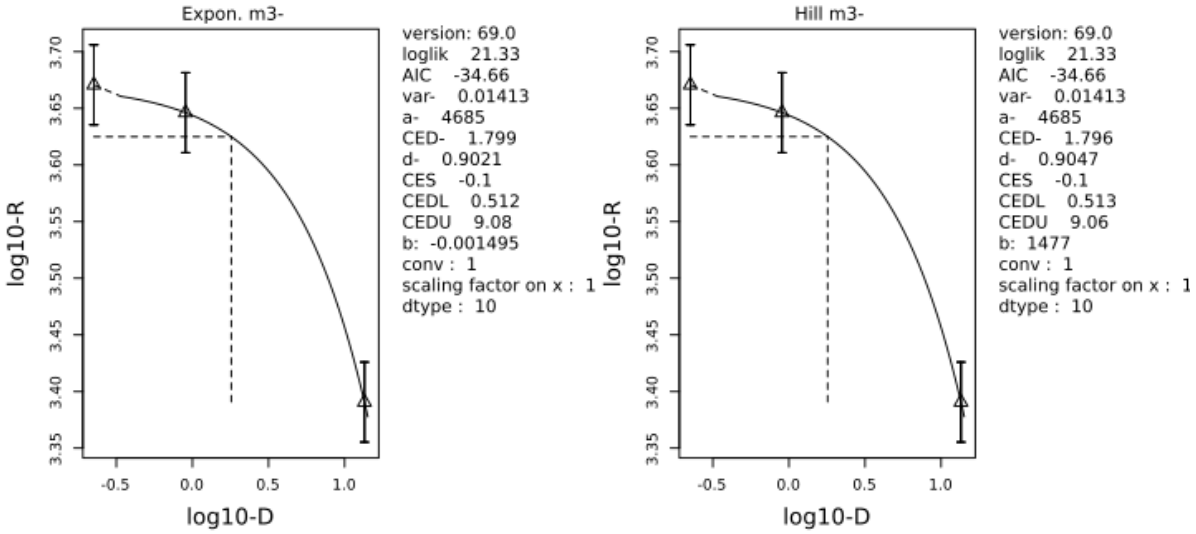
Final BMD Values

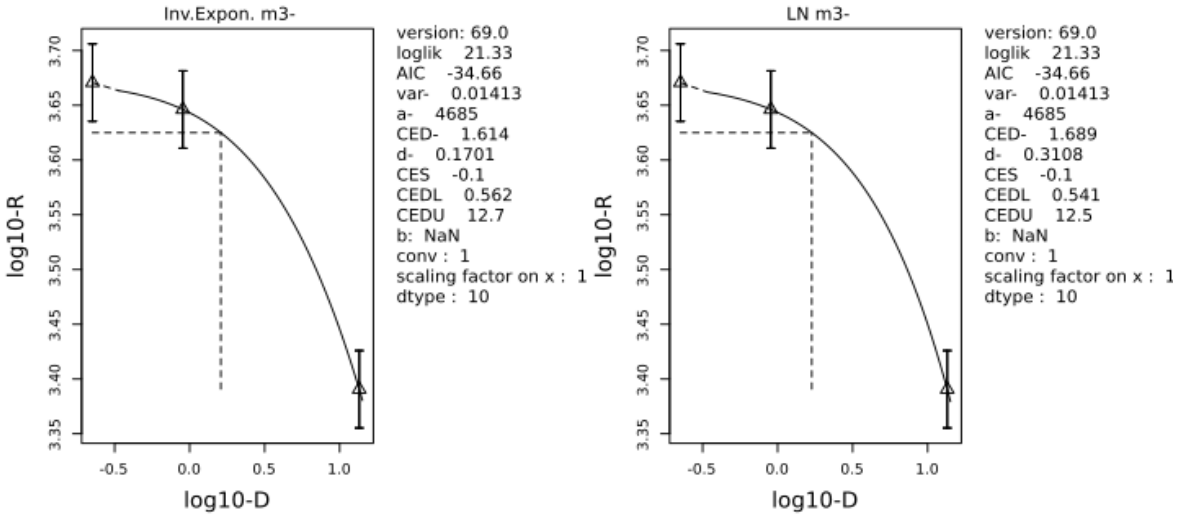
model	BMDL	BMDU	BMD
Expon. m3-	0.51	9.08	1.80
Hill m3-	0.51	9.06	1.80
LN m3-	0.54	12.50	1.69
Inv.Expon. m3-	0.56	12.70	1.61

Lowest BMDL and highest BMDU Values

subgroup	bmdl.lowest	bmdu.highest
all	0.512	12.7

Visualization





References

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