Supplementary material S5 for Lachenmeier et al. (2022) Does Cannabidiol (CBD) in Food Supplements Pose a Serious Health Risk? Consequences of the EFSA Clock Stop Regarding Novel Food Authorisation

BMDS 3.0 Analysis Report

Dziwenka et al. 2021

For

Relative liver weight – female – 90-day oral study in rats

26.08.2022 17:49:36

Analysis Info

Analysis Name: Dziwenka et al. 2021 - Relative liver weight - female

Analysis Description: C:\bmds3201\BMDS3201

Model Type: Continuous

Selected Models:

- Frequentist Dichotomous Hill (restricted)

Option Sets:

- Option Set #1
  - BMR Type: Std. Dev.
  - BMRF: 1
  - Confidence Level: 0.95
  - Distribution: Normal
  - Variance: Constant

Data

Dziwenka et al. 2021 - Relative liver weight - female			
Source: Dziwenka et al. 2021 – S9 Table			
Dose *	N	Mean	Std. Dev.
mg/kg bw/day	female	%	%
0	10	2.846	0.209
6.3	10	2.687	0.253
22.68	10	2.915	0.338
81.648	9	3.309	0.189

* Note: Dose levels adjusted from hemp oil extract to CBD assuming 25.2% CBD.

Adverse Direction: Automatic

Frequentist Exponential Restricted Option Set #1

User Input

Info	
Model	frequentist Exponential degree 2 v1.1
Dataset Name	Dziwenka et al. 2021 - Relative liver weight - female
User notes	[Add user notes here]
Dose-Response Model	M[dose] = a * exp(±1 * b * dose)

Model Options	
BMR Type	Std. Dev.
BMRF	1
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal

Model Data	
Dependent Variable	mg/kg bw/day
Independent Variable	%
Total # of Observations	4
Adverse Direction	Automatic

Model Results

Benchmark Dose	
BMD	39.38442078
BMDL	29.59131806
BMDU	59.87999972
AIC	9.274032748
Test 4 P-value	0.194112517
D.O.F.	2

Model Parameters	
# of Parameters	3
Variable	Estimate
a	2.756545111
b	0.002224073

Goodness of Fit

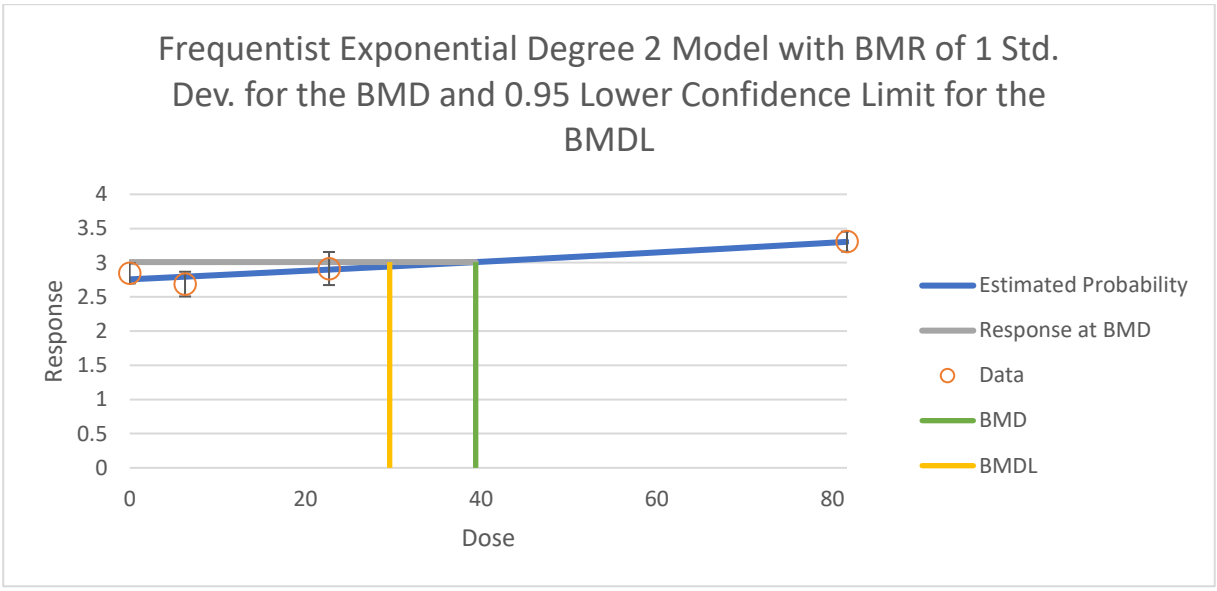
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	10	2.756545111	2.846	2.846	0.25234695	0.209	0.209	1.121001034
6.3	10	2.795440739	2.687	2.687	0.25234695	0.253	0.253	-1.358921603
22.68	10	2.899157257	2.915	2.915	0.25234695	0.338	0.338	0.198532814
81.648	9	3.305438739	3.309	3.309	0.25234695	0.189	0.189	0.042337672

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	0.002300929	5	9.99539814
A2	2.010864982	8	11.97827
A3	0.002300929	5	9.99539814
fitted	-1.637016374	3	9.27403275
R	-12.0646431	2	28.1292862

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	28.15101616	6	<0.0001
2	4.017128106	3	0.25962053
3	4.017128106	3	0.25962053
4	3.278634607	2	0.19411252


Frequentist Exponential Degree 2 Model with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
0.5
1
1.5
2
2.5
3
3.5
4
0
20
40
60
80
Estimated Probability
Response at BMD
Data
BMD
BMDL

Frequentist Exponential Restricted Option Set #1

User Input

Info	
Model	frequentist Exponential degree 3 v1.1
Dataset Name	Dziwenka et al. 2021 - Relative liver weight - female
User notes	[Add user notes here]
Dose-Response Model	M[dose] = a * exp(±1 * (b * dose)^d)

Model Options	
BMR Type	Std. Dev.
BMRF	1
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal

Model Data	
Dependent Variable	mg/kg bw/day
Independent Variable	%
Total # of Observations	4
Adverse Direction	Automatic

Model Results

Benchmark Dose	
BMD	46.6112829
BMDL	29.98277291
BMDU	79.35925662
AIC	10.99451511
Test 4 P-value	0.083309912
D.O.F.	1

Model Parameters	
# of Parameters	4
Variable	Estimate
a	2.775859475
b	0.003135788
d	1.271521575

Goodness of Fit

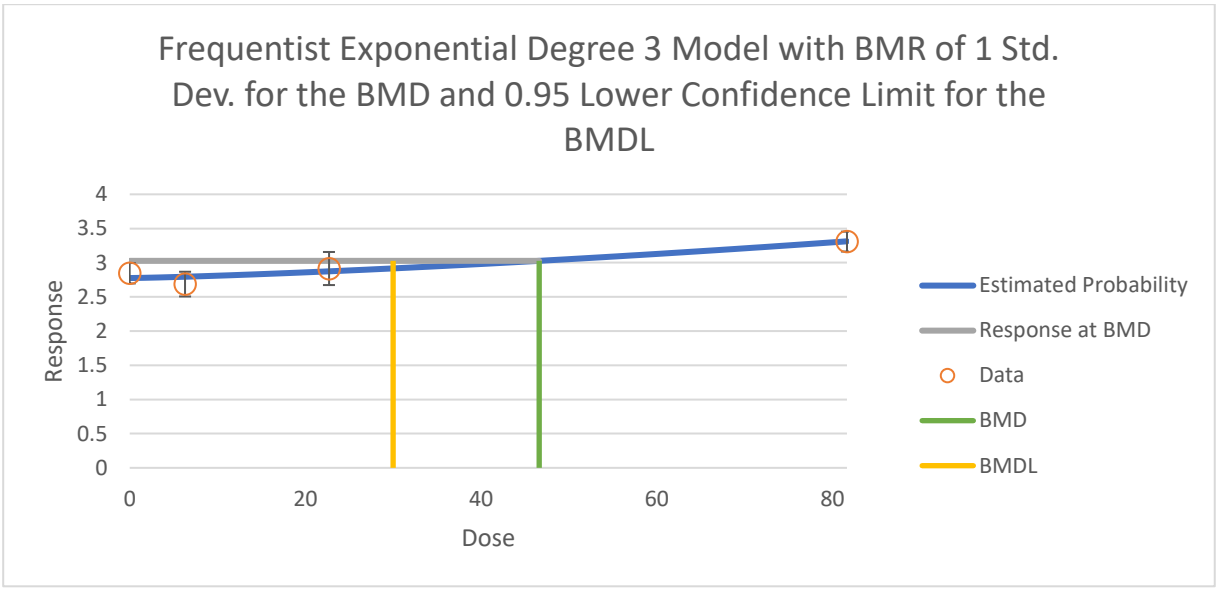
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	10	2.775859475	2.846	2.846	0.25144088	0.209	0.209	0.88213108
6.3	10	2.79481806	2.687	2.687	0.25144088	0.253	0.253	-1.355987309
22.68	10	2.873861177	2.915	2.915	0.25144088	0.338	0.338	0.517387548
81.648	9	3.312889983	3.309	3.309	0.25144088	0.189	0.189	-0.046412293

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	0.002300929	5	9.99539814
A2	2.010864982	8	11.97827
A3	0.002300929	5	9.99539814
fitted	-1.497257554	4	10.9945151
R	-12.0646431	2	28.1292862

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	28.15101616	6	<0.0001
2	4.017128106	3	0.25962053
3	4.017128106	3	0.25962053
4	2.999116966	1	0.08330991


Frequentist Exponential Degree 3 Model with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
0.5
1
1.5
2
2.5
3
3.5
4
0
20
40
60
80
Estimated Probability
Response at BMD
Data
BMD
BMDL

Frequentist Exponential Restricted Option Set #1

User Input

Info	
Model	frequentist Exponential degree 4 v1.1
Dataset Name	Dziwenka et al. 2021 - Relative liver weight - female
User notes	[Add user notes here]
Dose-Response Model	M[dose] = a * [c-(c-1) * exp(-b * dose)]

Model Options	
BMR Type	Std. Dev.
BMRF	1
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal

Model Data	
Dependent Variable	mg/kg bw/day
Independent Variable	%
Total # of Observations	4
Adverse Direction	Automatic

Model Results

Benchmark Dose	
BMD	37.48605743
BMDL	27.42039566
BMDU	58.92192718
AIC	11.35409096
Test 4 P-value	0.066851114
D.O.F.	1

Model Parameters	
# of Parameters	4
Variable	Estimate
a	2.752809075
b	3.50875E-05
c	70.81117973

Goodness of Fit

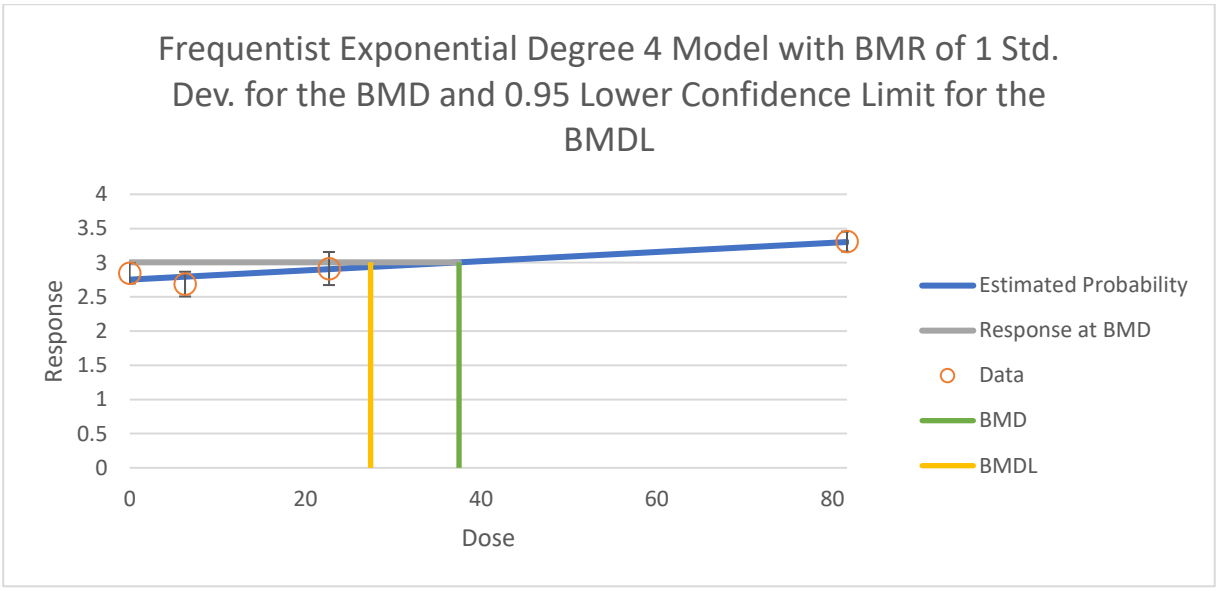
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	10	2.752809075	2.846	2.846	0.25260264	0.209	0.209	1.16663699
6.3	10	2.795285302	2.687	2.687	0.25260264	0.253	0.253	-1.355600222
22.68	10	2.905679559	2.915	2.915	0.25260264	0.338	0.338	0.116680579
81.648	9	3.302573955	3.309	3.309	0.25260264	0.189	0.189	0.076318033

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	0.002300929	5	9.99539814
A2	2.010864982	8	11.97827
A3	0.002300929	5	9.99539814
fitted	-1.677045479	4	11.354091
R	-12.0646431	2	28.1292862

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	28.15101616	6	<0.0001
2	4.017128106	3	0.25962053
3	4.017128106	3	0.25962053
4	3.358692818	1	0.06685111


Frequentist Exponential Degree 4 Model with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
0.5
1
1.5
2
2.5
3
3.5
4
0
20
40
60
80
Estimated Probability
Response at BMD
Data
BMD
BMDL

Frequentist Exponential Restricted Option Set #1

User Input

Info	
Model	frequentist Exponential degree 5 v1.1
Dataset Name	Dziwenka et al. 2021 - Relative liver weight - female
User notes	[Add user notes here]
Dose-Response Model	M[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

Model Options	
BMR Type	Std. Dev.
BMRF	1
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal

Model Data	
Dependent Variable	mg/kg bw/day
Independent Variable	%
Total # of Observations	4
Adverse Direction	Automatic

Model Results

Benchmark Dose	
BMD	77.23125874
BMDL	16.46639482
BMDU	80.59542402
AIC	14.40665766
Test 4 P-value	NA
D.O.F.	0

Model Parameters	
# of Parameters	5
Variable	Estimate
a	2.816009641
b	0.007037557
c	121.2505878
d	11.78795618

Goodness of Fit

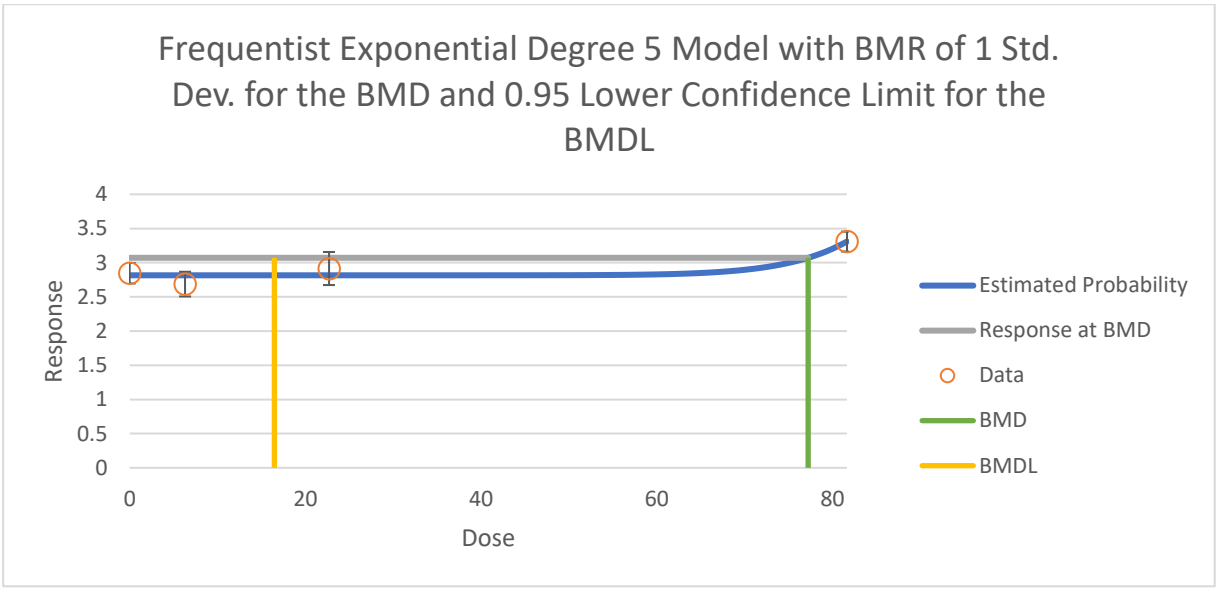
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	10	2.816009641	2.846	2.846	0.25602552	0.209	0.209	0.370423395
6.3	10	2.816009641	2.687	2.687	0.25602552	0.253	0.253	-1.593451754
22.68	10	2.816009778	2.915	2.915	0.25602552	0.338	0.338	1.222669414
81.648	9	3.309000725	3.309	3.309	0.25602552	0.189	0.189	-8.49735E-06

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	0.002300929	5	9.99539814
A2	2.010864982	8	11.97827
A3	0.002300929	5	9.99539814
fitted	-2.203328828	5	14.4066577
R	-12.0646431	2	28.1292862

Tests of Interest

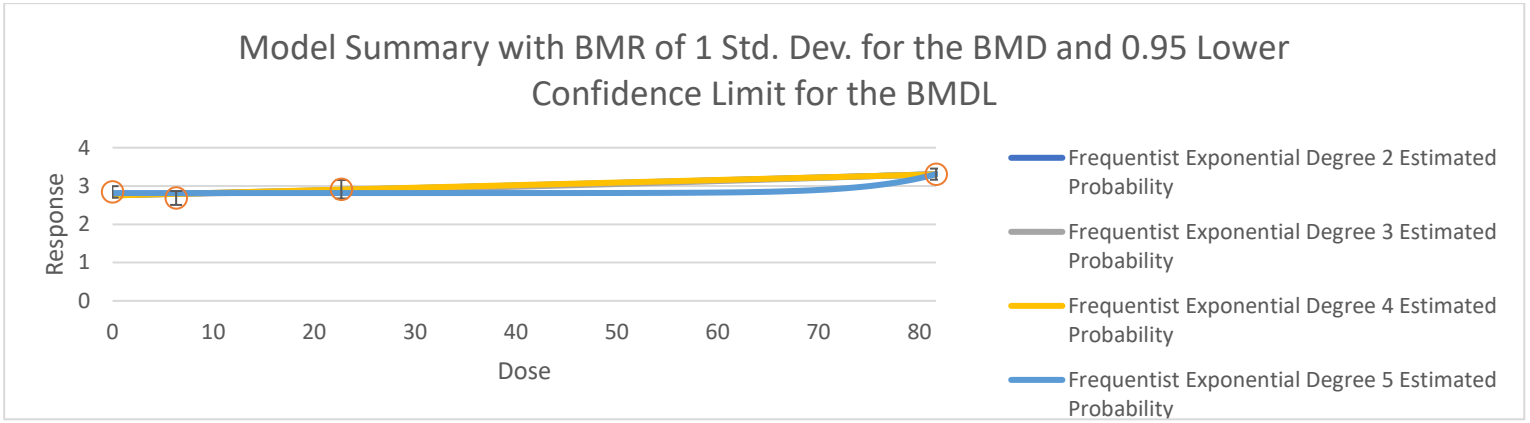
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	28.15101616	6	<0.0001
2	4.017128106	3	0.25962053
3	4.017128106	3	0.25962053
4	4.411259515	0	NA


Frequentist Exponential Degree 5 Model with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
0.5
1
1.5
2
2.5
3
3.5
4
0
20
40
60
80
Estimated Probability
Response at BMD
Data
BMD
BMDL

Summary of Results

Option set #1 (Hover for details)											
Model	Analysis Type	Restriction	RiskType	BMD	BMDL	BMDU	Test 4 P-Value	AIC	Unnormalized Log Posterior Probability	BMDS Recommendation	BMDS Recommendation Notes
Exponential 2 (CV - normal)*	**frequentist**	**Restricted**	**Std. Dev.**	**39.38442**	**29.59132**	**59.88**	**0.1941125**	**9.274032748**	**-**	**Viable - Recommended**	**Lowest AIC**
Exponential 3 (CV - normal)	frequentist	Restricted	Std. Dev.	46.61128	29.98277	79.359257	0.0833099	10.99451511	-	Questionable	Goodness of fit p-value < 0.1
Exponential 4 (CV - normal)	frequentist	Restricted	Std. Dev.	37.48606	27.4204	58.921927	0.0668511	11.35409096	-	Questionable	Goodness of fit p-value < 0.1
Exponential 5 (CV - normal)	frequentist	Restricted	Std. Dev.	77.23126	16.46639	80.595424	NA	14.40665766	-	Questionable	BMD/BMDL ratio > 3 d.f.=0, saturated model (Goodness of fit test cannot be calculated)

*Constant variance case presented (BMDS Test 2 p-value = 0.259620533885501), with the selected model in bold; scaled residuals for selected model for doses 0, 6.3, 22.68, 81.648 were 1.12100103350899, -1.35892160320108, 0.198532813627268, 4.23376715859722E-02 [units], respectively.


Model Summary with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
1
2
3
4
0
10
20
30
40
50
60
70
80
Frequentist Exponential Degree 2 Estimated Probability
Frequentist Exponential Degree 3 Estimated Probability
Frequentist Exponential Degree 4 Estimated Probability
Frequentist Exponential Degree 5 Estimated Probability