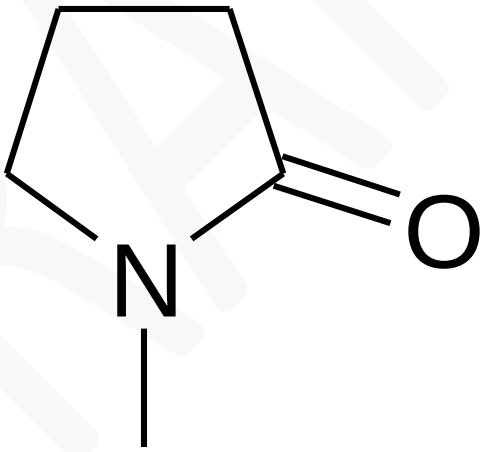
United States
Environmental Protection Agency

Office of Chemical Safety and
Pollution Prevention

Draft Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-)

CASRN: 872-50-4

Benchmark Dose Modeling Supplemental File



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1 INTRODUCTION

This supplemental file describes benchmark dose (BMD) modeling approaches and results for all endpoints considered in the derivation of points of departure (PODs) for NMP. Reduced male fertility, reduced female fecundity, and reduced fetal/pup body weights were all identified as sensitive reproductive and developmental endpoints associated with repeated dose exposures and were evaluated as the potential basis for chronic PODs. Resorptions and fetal mortality were identified as sensitive developmental endpoints that are relevant for single dose exposures and were evaluated as the potential basis for acute PODs.

BMD modeling for fetal and pup body weight changes (Section 2) and resorption/fetal death (Section 3) was performed using USEPA's BMD Software package version 2.5 (BMDS 2.5), in a manner consistent with EPA Benchmark Dose Technical Guidance. These benchmark modeling results were previously presented in EPA's risk assessment of NMP (U.S. EPA, 2015).

Subsequent BMD modeling for reduced male fertility, female fecundity, reduced litter size, and pup death (Section 4) described in a 2-generation reproductive study in rats (Exxon, 1991) was performed using USEPA's BMD Software package version 3.1.1 (BMDS 3.1.1) or 2.7 (BMDS 2.7)[1] in a manner consistent with Benchmark Dose Technical Guidance. Litter size and pup death were not the most sensitive reproductive and developmental endpoints in this study, but were evaluated for comparison with developmental effects in other studies and as supporting evidence for the reduced fertility observed in this study.

A peer-reviewed rat PBPK model for NMP (Poet et al., 2010) modified by EPA was used to calculate BMDs for each endpoint in terms of internal doses (blood concentrations) in exposed rats. PODs based on internal doses in rats can be compared to blood concentrations in people predicted by human PBPK models for each condition of use. Internal dose metrics calculated with the rat PBPK model are in units of either AUC (hr mg/L) for chronic exposures or peak blood concentration (Cmax, mg/L) for acute exposures.

[1] While EPA's preferred nested dichotomous model (NLogistic) is available in both BMDS 2.7 and 3.1.1 and, in this case, provided the best fit to the pup death endpoint, BMDS 2.7 was used to provide an evaluation of this endpoint that includes two alternative nested dichotomous models that are not currently available in BMDS 3.1.1.

2 Benchmark Dose Modeling of Fetal and Pup Body Weight Changes

BMD modeling for fetal and pup body weight changes and resorption/fetal death was performed using USEPA's BMD Software package version 2.5 (BMDS 2.5), in a manner consistent with EPA Benchmark Dose Technical Guidance. These benchmark modeling results were previously presented in EPA's (2015) risk assessment of NMP.

Continuous models were used to fit dose-response data for mean fetal/pup body weights. A BMR of 5% RD from control mean was applied in modeling pup body weight changes under the assumption that it represents a minimal biologically significant response. In adults, a 10% decrease in body weight in animals is generally recognized as a biologically significant response associated with identifying a maximum tolerated dose. During development, however, identification of a smaller (5%) decrease in body weight is consistent with the assumptions that development represents a susceptible lifestage and that the developing animal is more adversely affected by a decrease in body weight than the adult. In humans, reduced birth weight is associated with numerous adverse health outcomes, including increased risk of infant mortality as well as heart disease and type II diabetes in adults (Barker, 2007; Reyes and Mañalich, 2005). The selection of a 5% BMR is additionally supported by data from (Kavlock et al., 1995) which found that a BMR of 5% RD for fetal weight reduction was statistically similar to several other BMR measurements as well as to statistically-dervived NOAEL values. For these reasons, a BMR of 5% RD was selected for decreased pup weight. A BMR of 1 standard deviation is also shown for comparison.

Daily AUC for NMP in blood, averaged over the exposure period until the day of measurement (*e.g.* GD6-20 for Becci et al. (1982) or GD5-21 for Saillenfait et al. (2002)), was used as an appropriate dose measure for this endpoint. The doses and response data used for the modeling are presented in Table 2-2-1.

Table 2-2-1 Fetal Body Weight Data Selected for Dose-Response Modeling for NMP

Reference	Dose AUC (hr mg/L)	Number of litters	Fetal body weight (g) Mean ± Standard Deviation
Saillenfait et al. (2003)	0	24	5.671 ± 0.370
	158	20	5.623 ± 0.358
	323	19	5.469 ± 0.252
	668	25	5.393 ± 0.446
Saillenfait et al.(2002)	0	21	5.73 ± 0.5
	1144	21	5.59 ± 0.22
	2503	24	5.18 ± 0.35
	5674	25	4.02 ± 0.21
	9231	8	3.01 ± 0.39

Reference	Dose AUC (hr mg/L)	Number of litters	Fetal body weight (g) Mean ± Standard Deviation
Saillenfait et al.(2002) and (2003) pooled	0	45	5.698 ± 0.44
	158	20	5.623 ± 0.358
	323	19	5.469 ± 0.252
	668	25	5.393 ± 0.446
	1144	21	5.59 ± 0.22
	2503	24	5.18 ± 0.35
	5674	25	4.02 ± 0.21
	9231	8	3.01 ± 0.39
DuPont (1990)	0	39	7.48 ± 0.701
	51	16	7.03 ± 0.705
	268	15	7.13 ± 0.695
	633	22	6.66 ± 0.616
Becci et al. (1982)	0	24	3.45 ± 0.20
	561	22	3.49 ± 0.24
	2052	23	3.54 ± 0.29
	7986	22	2.83 ± 0.39

The best fitting model was selected based on Akaike information criterion (AIC; lower value indicates a better fit), chi-square goodness of fit p-value (higher value indicates a better fit), ratio of the BMC:BMCL (lower value indicates less model uncertainty) and visual inspection. A comparison of model fits obtained for each data set of fetal/pup body weight changes is provided in Table 2-2-2 to Table 2-2-6. The best-fitting models, based on the criteria described above, are indicated in bold. For each of the best fitting models in Sections 2.1-2.5, subsequent tables and figures show the model version number, model form, benchmark dose calculation, parameter estimates and estimated values.

2.1 Results for Saillenfait et al., 2003

Table 2-2-2 Model Predictions for Fetal Body Weights in Rats Exposed to NMP by Inhalation Using Daily Average AUC as the Dose Metric (Saillenfait et al., 2003)
BMR = 5% Relative Deviation (RD) and for Comparison 1 Standard Deviation (SD)

Model[a]	Goodness of fit		BMR = 5% RD		BMR = 1 SD		Basis for model selection
	p-value	AIC	BMD_{5RD} (hr mg/L)	$BMDL_{5RD}$ (hr mg/L)	BMD_{1SD} (hr mg/L)	$BMDL_{1SD}$ (hr mg/L)	
Linear	**0.952**	**-84.637**	**642**	**411**	747	456	Of the acceptable models based on p-value (>0.1) and visual fit the BMDLs were sufficiently close and the Linear model was selected based on lowest AIC.
Exponential (M2)	0.948	-84.629	641	405	749	451	
Exponential (M4)	0.948	-84.629	641	284	749	381	
Exponential (M3)	0.815	-82.682	653	406	745	453	
Power	0.812	-82.680	653	413	744	458	
Polynomial 3°[b] Polynomial 2°	0.789	-82.665	652	412	738	457	
Hill	N/A[c]	-80.737	649	176	889	error	
Exponential (M5)	N/A[c]	-80.737	643	168	error	error	

Notes:
[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0670), selected model in bold; scaled residuals for selected model for doses 0, 158.3, 322.6 and 668.2 hr mg/L were 0.0675, 0.316, -0.654 and 0.24, respectively.
[b] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model.
[c] No available degrees of freedom to calculate a goodness of fit value.

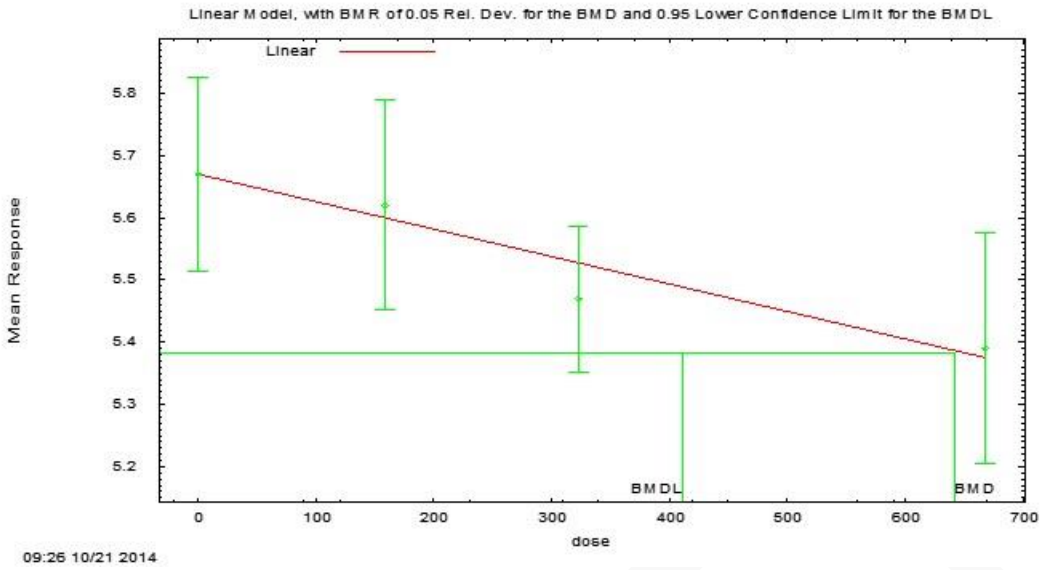


Figure 2-1 Plot of Mean Response by Dose, with Fitted Curve for Selected Model for Fetal Body Weight in Rats Exposed to NMP via Inhalation (Saillenfait et al., 2003)
BMR = 5% Relative Deviation; Daily Average AUC as Dose Shown in hr mg/L

Linear Model. (Version: 2.19; Date: 06/25/2014)
The form of the response function is: Y[dose] = beta_0 + beta_1*dose
A modeled variance is fit

Benchmark Dose Computation.
BMR = 5% Relative deviation
BMD = 642.052
BMDL at the 95% confidence level = 411.487

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	10.9507	-1.98661
rho	-7.59357	0
beta_0	5.66546	5.66303
beta_1	-0.000441199	-0.00043693

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	24	5.67	5.67	0.37	0.33	0.0675
158.3	20	5.62	5.6	0.36	0.346	0.316
322.6	20	5.47	5.52	0.25	0.363	-0.654
668.2	25	5.39	5.37	0.45	0.404	0.24

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.950356	5	-81.900712
A2	49.530515	8	-83.061031
A3	46.368255	6	-80.736511
fitted	46.318536	4	-84.637072
R	41.618363	2	-79.236727

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	15.8243	6	0.01473
Test 2	7.16032	3	0.06696
Test 3	6.32452	2	0.04233
Test 4	0.099439	2	0.9515

2.2 Results for Saillenfait et al., 2002

Table 2-2-3 Model Predictions for Fetal Body Weights in Rats Exposed to NMP by Gavage Using Daily Average AUC as the Dose Metric (Saillenfait et al., 2002)

BMR = 5% Relative Deviation (RD) and for Comparison 1 Standard Deviation (SD)

Model[a]	Goodness of fit		BMD_{5RD} (hr mg/L)	$BMDL_{5RD}$ (hr mg/L)	BMD_{1SD} (hr mg/L)	$BMDL_{1SD}$ (hr mg/L)	Basis for model selection
	p-value	AIC					
Exponential (M5)	**0.966**	**-109.73**	**1637**	**1184**	**1880**	**1400**	Of the acceptable models based on p-value (>0.1) and visual fit (Exponential (M5), Hill and Exponential (M3)) the BMDLs were sufficiently close and the Exponential (M5) model was selected based on lowest AIC.
Hill	0.962	-109.73	1660	1194	1895	1409	
Exponential (M3)	0.325	-109.49	1329	1035	1578	1245	
Linear	0.0687	-106.63	938	895	1210	1036	
Power	0.0479	-105.66	1114	904	1381	1070	
Polynomial 4°[b] Polynomial 3°[c] Polynomial 2°	0.0295	-104.68	962	895	1233	1038	
Exponential (M2)	0.00183	-98.750	741	693	1028	876	
Exponential (M4)	0.00183	-98.750	741	691	1028	876	

Notes:

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 1.26E-04), selected model in bold; scaled residuals for selected model for doses 0, 1144, 2503, 5674 and 9231 hr mg/L were -0.1399, 0.1248, -0.02274, 0.1033 and -0.1213, respectively.

[b] For the Polynomial 4° model, the b4 and b3 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model.

[c] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model.

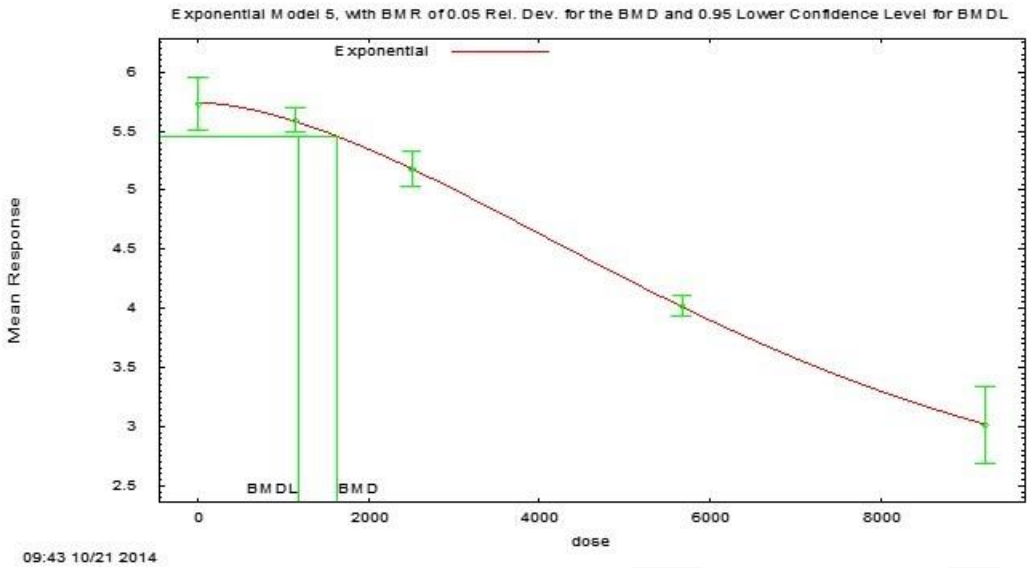


Figure 2-2 Plot of Mean Response by Dose, with Fitted Curve for Selected Model for Fetal Body Weight in Rats Exposed to NMP via Gavage (Saillenfait et al., 2002)
BMR = 5% Relative Deviation; Daily Average AUC as Dose Shown in hr mg/L

Exponential Model. (Version: 1.9; Date: 01/29/2013)
The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]
A modeled variance is fit

Benchmark Dose Computation.
BMR = 5% Relative deviation
BMD = 1637.32
BMDL at the 95% confidence level = 1184.3

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.80738	-2.38723
rho	1.00208	0.0548918
a	5.74092	6.0165
b	0.000143148	0.000073183
c	0.405685	0.000500291
d	1.67614	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	5.73	5.741	0.5	0.3577	-0.1399
1144	21	5.59	5.58	0.22	0.3527	0.1248
2503	24	5.18	5.182	0.35	0.3398	-0.02274
5674	25	4.02	4.014	0.21	0.299	0.1033
9231	8	3.01	3.021	0.39	0.2593	-0.1213

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	59.67563	6	-107.3513
A2	71.17728	10	-122.3546
A3	60.86644	7	-107.7329
R	-42.05093	2	88.10186
5	60.86544	6	-109.7309

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	226.5	8	<0.0001
Test 2	23	4	0.0001264
Test 3	20.62	3	0.0001261
Test 7a	0.001995	1	0.9644

2.3 Results for Saillenfait et al., 2002 and 2003 combined

Table 2-2-4 Model Predictions for Fetal Body Weights in Rats Exposed to NMP by Gavage or Inhalation using Daily Average AUC as the Dose Metric (Saillenfait et al. (2003; 2002))
BMR = 5% Relative Deviation (RD) and for Comparison 1 Standard Deviation (SD)

Model[a]	Goodness of fit		BMD_{5RD} (hr mg/L)	$BMDL_{5RD}$ (hr mg/L)	BMD_{1SD} (hr mg/L)	$BMDL_{1SD}$ (hr mg/L)	Basis for model selection
	p-value	AIC					
Exponential (M2) Exponential (M4)[b]	<0.0001	-169.77	828	774	1155	1030	While none of the models had an acceptable p-value (>0.1) the visual fit appears adequate and the model with the highest p-value and lowest AIC, the Exponential (M5) model was selected.
Exponential (M3)	0.0119	-187.12	1547	1253	1911	1579	
Exponential (M5)	**0.0150**	**-187.44**	**1937**	**1424**	2283	1764	
Hill	0.0138	-187.25	1962	1421	2297	1762	
Power	0.00396	-184.48	1321	1039	1696	1366	
Polynomial 7°[c] Polynomial 5°[d] Polynomial 4°[e] Polynomial 3°[f]	0.00218	-183.08	1155	978	1532	1287	
Polynomial 6°[g]	0.00218	-183.08	1155	978	1532	1287	
Polynomial 2°[h]	0.00218	-183.08	1155	978	1532	1287	
Linear	0.00164	-182.51	989	944	1343	1208	

Notes:
[a] Modeled variance case presented (BMDS Test 2 *p*-value = 1.21E-04), selected model in bold; scaled residuals for selected model for doses 0, 156.5, 319, 660.8, 1144, 2503, 5674 and 9231 hr mg/L were 1.671, 0.2153, -1.487, -2.354, 1.142, 0.2305, 0.03888 and -0.1112, respectively.
[b] For the Exponential (M4) model, the estimate of c was 0 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Polynomial 7° model, the b7, b6, b5 and b4 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Polynomial 3° model.
[d] For the Polynomial 5° model, the b5 and b4 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Polynomial 3° model.
[e] For the Polynomial 4° model, the b4 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 3° model.
[f] The Polynomial 3° model may appear equivalent to the Polynomial 6° model, however differences exist in digits not displayed in the table. This also applies to the Polynomial 2° model.
[g] The Polynomial 6° model may appear equivalent to the Polynomial 7° model, however differences exist in digits not displayed in the table. This also applies to the Polynomial 5° model. This also applies to the Polynomial 4° model. This also applies to the Polynomial 3° model. This also applies to the Polynomial 2° model.
[h] The Polynomial 2° model may appear equivalent to the Polynomial 7° model, however differences exist in digits not displayed in the table. This also applies to the Polynomial 6° model. This also applies to the Polynomial 5° model. This also applies to the Polynomial 4° model. This also applies to the Polynomial 3° model.

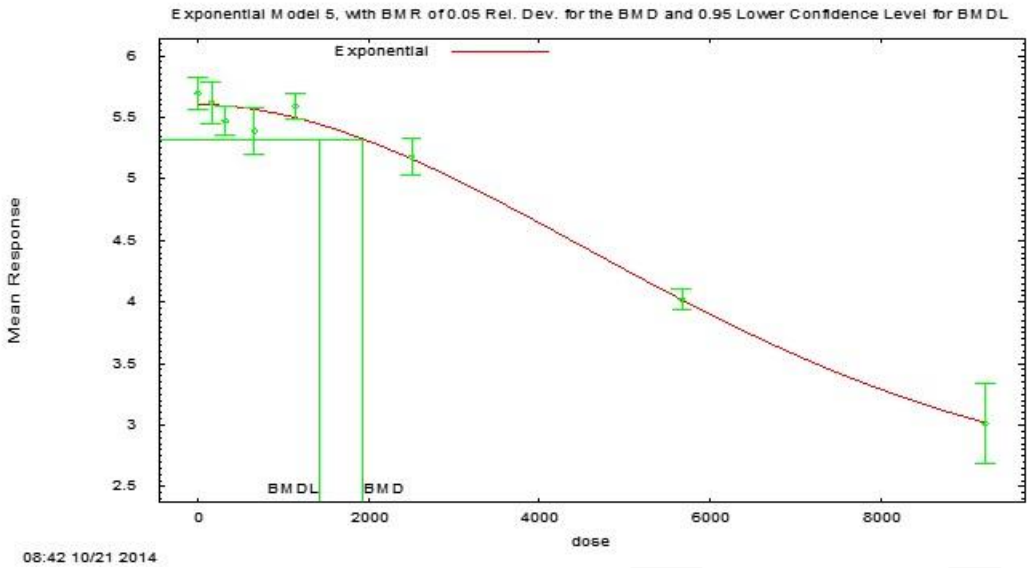


Figure 2-3 Plot of Mean Response by Dose, with Fitted Curve for Selected Model for Fetal Body Weight in Rats Exposed to NMP via Gavage or Inhalation (Saillenfait et al. (2003; 2002))
BMR = 5% Relative Deviation; Daily Average AUC as Dose Shown in hr mg/L

Exponential Model. (Version: 1.9; Date: 01/29/2013)
The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]
A modeled variance is fit

Benchmark Dose Computation.
BMR = 5% Relative deviation
BMD = 1937.29
BMDL at the 95% confidence level = 1423.77

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.03673	-2.36893
rho	1.20539	0.0584431
a	5.6045	5.9829
b	0.000147759	0.0000728823
c	0.446945	0.000503101
d	1.88381	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	45	5.698	5.604	0.4353	0.3755	1.671
156.5	20	5.62	5.602	0.36	0.3754	0.2153
319	20	5.47	5.595	0.25	0.3751	-1.487
660.8	25	5.39	5.566	0.45	0.3739	-2.354
1144	21	5.59	5.497	0.22	0.3711	1.142
2503	24	5.18	5.163	0.35	0.3574	0.2305
5674	25	4.02	4.018	0.21	0.3072	0.03888
9231	8	3.01	3.02	0.39	0.2587	-0.1112

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	104.4887	9	-190.9774
A2	119.1975	16	-206.3949
A3	105.8917	10	-191.7834
R	-48.75234	2	101.5047
5	99.71803	6	-187.4361

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	335.9	14	<0.0001
Test 2	29.42	7	0.0001214
Test 3	26.61	6	0.0001712
Test 7a	12.35	4	0.01495

2.4 Results for DuPont, 1990

Table 2-2-5 Model Predictions for Fetal Body Weights in Rats Exposed to NMP by Inhalation using Daily Average AUC as the Dose Metric (DuPont, 1990)
BMR = 5% Relative Deviation and for Comparison 1 Standard Deviation (SD)

Model[a]	Goodness of fit		BMD_{5RD} (hr mg/L)	$BMDL_{5RD}$ (hr mg/L)	BMD_{1SD} (hr mg/L)	$BMDL_{1SD}$ (hr mg/L)	Basis for model selection
	p-value	AIC					
Exponential (M2) **Exponential (M3)[b]**	**0.140**	**27.266**	**315**	**223**	594	411	Of the acceptable models based on p-value (>0.1) and visual fit the BMDLs were sufficiently close and the Exponential model was selected based on lowest AIC.
Power[c] Polynomial 3°[d] Polynomial 2°[e] **Linear**	**0.138**	**27.288**	**323**	**234**	**596**	**421**	
Exponential (M4)	0.0494	29.191	260	1.16	580	2.61	
Exponential (M5)	0.0494	29.191	260	1.30	580	3.07	
Hill	0.0597	28.875	58.5	4.71E-04	609	1.98E-05	

Notes:
[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.905), selected model in bold; scaled residuals for selected model for doses 0, 51.18, 267.9 and 633.3 hr mg/L were 0.8831, -1.718, 0.3504 and 0.0002752, respectively.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[d] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[e] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

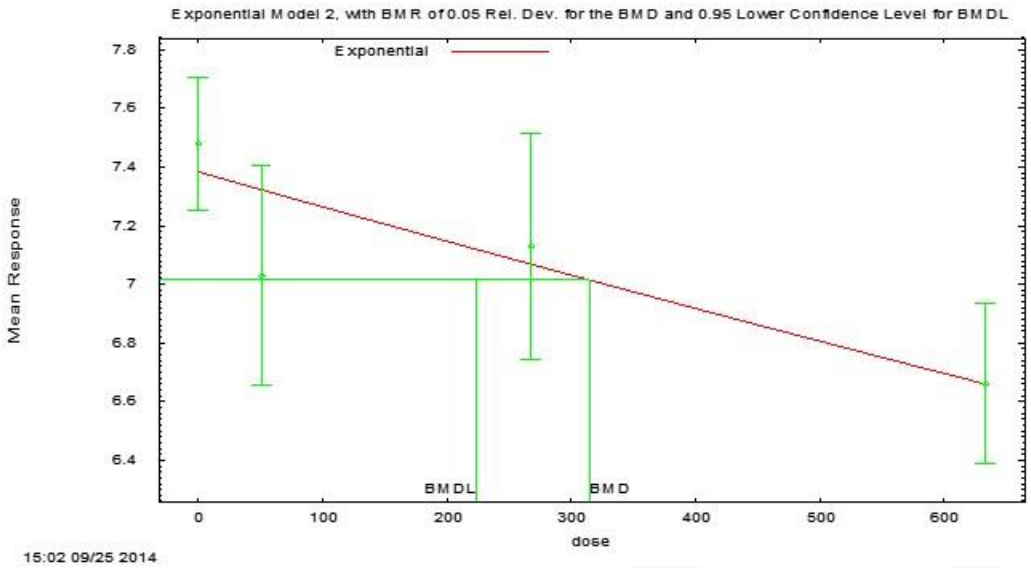


Figure 2-4 Plot of Mean Response by Dose, with Fitted Curve for Selected Model for Fetal Body Weight in Rats Exposed to NMP via Inhalation (DuPont, 1990)
BMR = 5% Relative Deviation; Daily Average AUC as Dose Shown in hr mg/L

Exponential Model. (Version: 1.9; Date: 01/29/2013)
The form of the response function is: Y[dose] = a * exp(sign * b * dose)
A constant variance model is fit

Benchmark Dose Computation.
BMR = 5% Relative deviation
BMD = 314.897
BMDL at the 95% confidence level = 223.175

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.768852	-0.811648
rho(S)	n/a	0
a	7.38373	6.90878
b	0.000162889	0.000162077
c	0	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	39	7.48	7.384	0.701	0.6808	0.8831
51.18	16	7.03	7.322	0.705	0.6808	-1.718
267.9	15	7.13	7.068	0.695	0.6808	0.3504
633.3	22	6.66	6.66	0.616	0.6808	0.0002752

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-8.66418	5	27.32836
A2	-8.383601	8	32.7672
A3	-8.66418	5	27.32836
R	-18.52227	2	41.04454
2	-10.6328	3	27.26561

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	20.28	6	0.002471
Test 2	0.5612	3	0.9053
Test 3	0.5612	3	0.9053
Test 4	3.937	2	0.1396

2.5 Results for Becci et al., 1982

Table 2-2-6 Model Predictions for Fetal Body Weights in Rats Exposed to NMP Dermally Using Daily Average AUC as the Dose Metric (Becci et al., 1982)
BMR = 5% Relative Deviation and for Comparison 1 Standard Deviation (SD)

Model[a]	Goodness of fit		BMD_{5RD} (hr mg/L)	$BMDL_{5RD}$ (hr mg/L)	BMD_{1SD} (hr mg/L)	$BMDL_{1SD}$ (hr mg/L)	Basis for model selection
	p-value	AIC					
Polynomial 3°	**0.572**	**-138.35**	**5391**	**4018**	**6015**	**4645**	Of the acceptable models based on p-value (>0.1) and visual fit the BMDLs were sufficiently close and the Polynomial 3° model was selected based on lowest AIC.
Power	0.371	-136.67	7692	3783	7864	4525	
Polynomial 2°	0.307	-137.11	4326	3919	5087	4503	
Linear	0.00557	-129.09	2452	1944	3331	2567	
Hill	N/A[b]	-134.67	7497	2302	7695	2361	

Notes:
[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0101), selected model in bold; scaled residuals for selected model for doses 0, 588.7, 2156 and 8409 hr mg/L were -0.928, -0.111, 1.08 and -0.03, respectively.
[b] No available degrees of freedom to calculate a goodness of fit value.

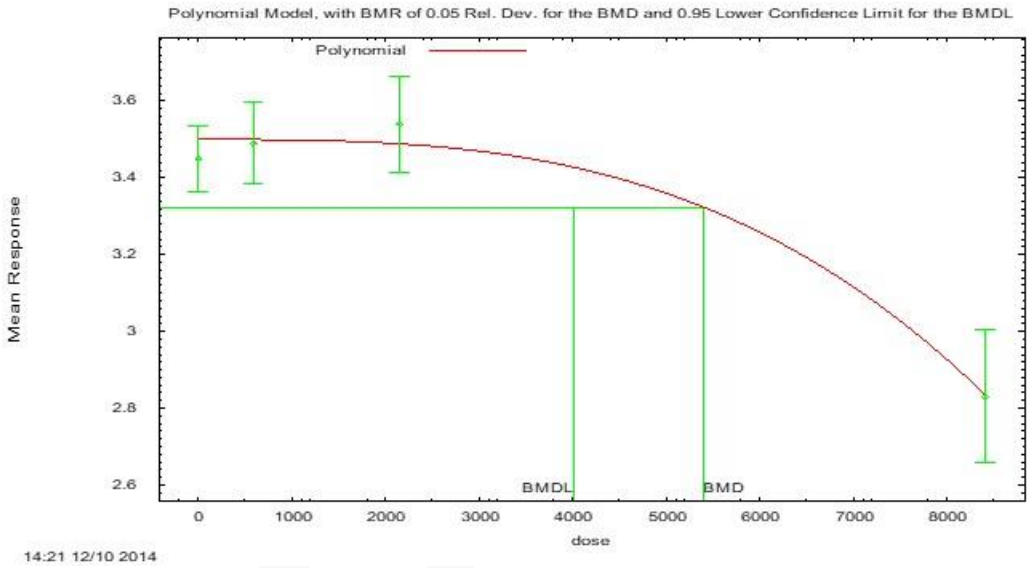


Figure 2-5 Plot of Mean Response by Dose, with Fitted Curve for Selected Model for Fetal Body Weight in Rats Exposed to NMP Dermally (Becci et al., 1982)
BMR = 5% Relative Deviation; Daily Average AUC as Dose Shown in hr mg/L

Polynomial Model. (Version: 2.19; Date: 06/25/2014)
The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …
A modeled variance is fit

Benchmark Dose Computation.
BMR = 5% Relative deviation
BMD = 5390.85
BMDL at the 95% confidence level = 4017.68

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	2.56784	-2.49546
rho	-4.31376	0
beta_0	3.49599	3.45
beta_1	-1.68014E-27	0
beta_2	0	-0.000000016108
beta_3	-1.11576E-12	-2.23106E-13

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	24	3.45	3.5	0.2	0.243	-0.928
588.7	22	3.49	3.5	0.24	0.243	-0.111
2156	23	3.54	3.48	0.29	0.244	1.08
8409	22	2.83	2.83	0.39	0.382	-0.03

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	70.088658	5	-130.177316
A2	75.754919	8	-135.509838
A3	73.734901	6	-135.469801
fitted	73.175965	4	-138.35193
R	37.76879	2	-71.537581

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	75.9723	6	<0.0001
Test 2	11.3325	3	0.01006
Test 3	4.04004	2	0.1327
Test 4	1.11787	2	0.5718

3 Benchmark Dose Modeling of Effects for Resorptions and Fetal Mortality

BMD modeling for fetal and pup body weight changes and resorption/fetal death was performed using USEPA's BMD Software package version 2.5 (BMDS 2.5), in a manner consistent with EPA Benchmark Dose Technical Guidance. These benchmark modeling results were previously presented in EPA's (2015) risk assessment of NMP.

Dichotomous models were used to fit fetal mortality incidence data and continuous models were used to fit dose-response data for mean number of resorptions. A BMR of 1% was used to address the relative severity of this endpoint (EPA, 2012). BMRs of 0.5 and 1 standard deviation are also shown for comparison. The peak NMP in maternal blood (C_{max}) was used as an appropriate dose measure for these endpoints. The doses and response data used for the modeling are presented in Table 3-3-1.

Table 3-3-1 Skeletal Malformations, Resorptions and Fetal Mortality Data Selected for Dose-Response Modeling for NMP

Reference and endpoint	Dose Cmax (mg/L)	Dose AUC (hr mg/L)	Number of litters	Response Mean ± Standard Deviation
Saillenfait et al.(2002) and (2003) Resorptions	0	0	45	3.4 ± 7.13
	15	156.5	20	4.3 ± 4.1
	30	319	20	9.9 ± 22.3
	62	660.8	25	7 ± 9.4
	120	1144	21	8.9 ± 21.2
	250	2503	24	4.5 ± 6.6
	531	5674	25	9.4 ± 8.9
	831	9231	5	91 ± 16
Sitarek et al. (2012) fetal mortality	0	0	22	0.18 ± 0.85
	76	902	24	0 ± 0
	265	3168	20	0.13 ± 0.34
	669	8245	15	0.8 ± 1.1

The best fitting model was selected based on Akaike information criterion (AIC; lower value indicates a better fit), chi-square goodness of fit p-value (higher value indicates a better fit), ratio of the BMC:BMCL (lower value indicates less model uncertainty) and visual inspection. Comparisons of model fits obtained for resorptions and fetal mortality are provided in Table 3-3-2 to Table 3-3-4. The best-fitting models, based on the criteria described above, are indicated in bold. For each of the best fitting models in Section 3.1-3.3, subsequent tables and figues show the model version number, model form, benchmark dose calculation, parameter estimates and estimated values.

3.1 Results for Saillenfait et al., 2002 and 2003 combined using C_{max}

Table 3-3-2 Model Predictions for Resorptions in Rats Exposed to NMP via Gavage or Inhalation Using C_{max} as the Dose Metric (Saillenfait et al. (2003; 2002))
BMR = 1% Relative Deviation (RD) and for Comparison 0.5 and 1 Standard Deviation (SD)

Model[a]	Goodness of fit		BMD_{1RD} (mg/L)	$BMDL_{1RD}$ (mg/L)	$BMD_{0.5SD}$ (mg/L)	$BMDL_{0.5SD}$ (mg/L)	BMD_{1SD} (mg/L)	$BMDL_{1SD}$ (mg/L)	Basis for model selection
	p-value	AIC							
Exponential (M2)	<0.0001	1288.45	1.60	1.26	424	349	530	468	While none of the models had an acceptable p-value (>0.1) the visual fit appears adequate, the lowest AIC, the Hill model was selected.
Exponential (M3)	<0.0001	1263.09	247	97.9	621	510	685	602	
Exponential (M4)	<0.0001	1364.53	0.122	0.0122	58.2	44.5	116	89.1	
Exponential (M5)	<0.0001	1265.04	326	215	593	514	648	583	
Hill	**<0.0001**	**1263.03**	**429**	**216**	558	514	582	548	
Power	<0.0001	1263.04	326	215	593	514	648	583	
Polynomial 4°	<0.0001	1276.48	128	77.6	436	419	518	504	
Polynomial 3°	<0.0001	1300.17	66.7	55.2	359	345	452	435	
Polynomial 2°	<0.0001	1336.49	19.2	3.77	247	215	349	317	
Linear	<0.0001	1362.53	0.121	0.0122	58.2	44.5	116	89.1	

Notes:
[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 15.01, 30.34, 61.86, 120, 250, 531 and 831 mg/L were -1.42, -0.619, 1.41, 0.401, 1.1, -0.599, 0.29 and -0.00443, respectively.

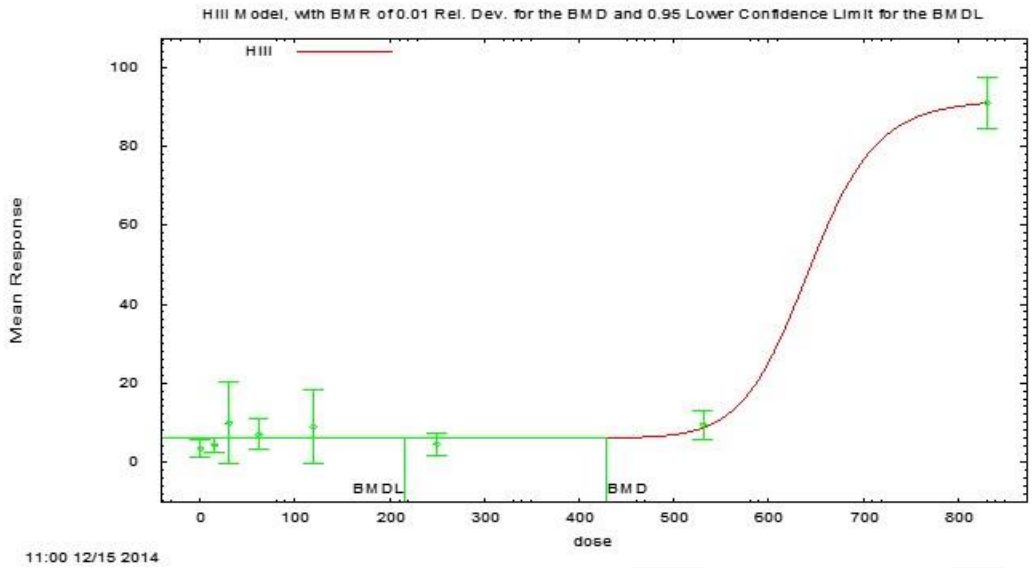


Figure 3-1 Plot of Mean Response by Dose, with Fitted Curve for Selected Model for Resorptions in Rat Exposed to NMP via Gavage or Inhalation (Saillenfait et al. (2003; 2002))
BMR = 1% Relative Deviation; C_{max} as Dose Shown in mg/L

Hill Model. (Version: 2.17; Date: 01/28/2013)
The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)
A modeled variance is fit

Benchmark Dose Computation.
BMR = 1% Relative deviation
BMD = 429.482
BMDL at the 95% confidence level = 215.783

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	4.75575	5.10412
rho	0.150826	0
intercept	6.00954	3.4
v	85.8437	87.6
n	18	1.9286
k	642.982	992.029

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	45	3.4	6.01	7.13	12.3	-1.42
15.01	20	4.3	6.01	4.1	12.3	-0.619
30.34	20	9.9	6.01	22.3	12.3	1.41
61.86	25	7	6.01	9.4	12.3	0.401
120	22	8.9	6.01	21.2	12.3	1.1
250	24	4.5	6.01	6.6	12.3	-0.599
531	25	9.4	8.67	8.9	12.7	0.29
831	25	91	91	16	15.2	-0.00443

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-624.644958	9	1267.289916
A2	-570.082153	16	1172.164306
A3	-595.035542	10	1210.071083
fitted	-626.515585	5	1263.03117
R	-806.807094	2	1617.614189

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	473.45	14	<0.0001
Test 2	109.126	7	<0.0001
Test 3	49.9068	6	<0.0001
Test 4	62.9601	5	<0.0001

3.2 Results for Saillenfait et al., 2002 and 2003 combined using AUC

Table 3-3-3 Model Predictions for Resorptions in Rats Exposed to NMP via Gavage or Inhalation Using AUC as the Dose Metric (Saillenfait et al. (2003; 2002))

BMR = 1% Relative Deviation (RD) and for Comparison 0.5 and 1 Standard Deviation (SD)

Model[a]	Goodness of fit		BMD_{1RD} (hr mg/L)	$BMDL_{1RD}$ (hr mg/L)	$BMD_{0.5SD}$ (hr mg/L)	$BMDL_{0.5SD}$ (hr mg/L)	BMD_{1SD} (hr mg/L)	$BMDL_{1SD}$ (hr mg/L)	Basis for model selection
	p-value	AIC							
Exponential (M2)	<0.0001	1286.5	19.8	15.8	4281	3524	5543	4887	While none of the models had an acceptable p-value (>0.1) the visual fit appears adequate, the lowest AIC, the Power model was selected.
Exponential (M3)	<0.0001	1263.1	2466	901	6721	5432	7486	6504	
Exponential (M4)	<0.0001	1360.1	0.720	0.0760	598	473	1196	946	
Exponential (M5)	<0.0001	1265.0	3343	2128	6394	5479	7045	6285	
Hill	<0.0001	1265.0	4177	2133	6091	5481	6478	5858	
Power	**<0.0001**	**1263.0**	**3343**	**2128**	6394	5479	7045	6285	
Polynomial 4°	<0.0001	1271.7	1432	135	4827	4537	5741	5534	
Polynomial 3°	<0.0001	1292.4	743	133	3958	3731	4986	4786	
Polynomial 2°	<0.0001	1329.7	211	148	2714	2538	3838	3589	
Linear	<0.0001	1358.1	0.720	0.0760	598	473	1196	946	

Notes:

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 156.5, 319, 660.8, 1144, 2503, 5674 and 9231 hr mg/L were -1.42, -0.62, 1.41, 0.4, 1.1, -0.603, 0.299 and -0.00462, respectively.

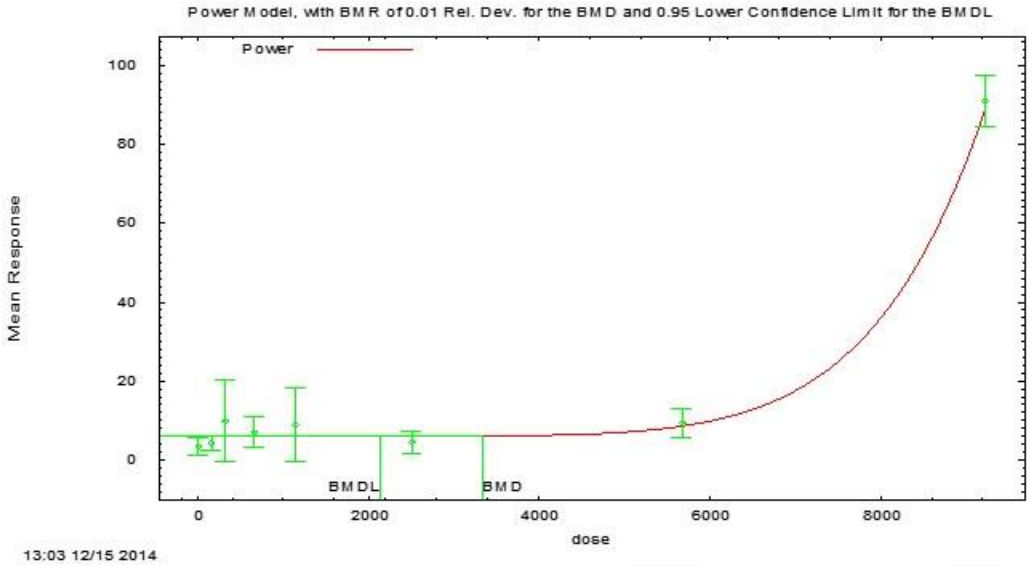


Figure 3-2 Plot of Mean Response by Dose, with Fitted Curve for Selected Model for Resorptions in Rat Exposed to NMP via Gavage or Inhalation (Saillenfait et al. (2003; 2002))
BMR = 1% Relative Deviation; AUC as Dose Shown in hr mg/L

Power Model. (Version: 2.18; Date: 05/19/2014)
The form of the response function is: Y[dose] = control + slope * dose^power
A modeled variance is fit

Benchmark Dose Computation.
BMR = 1% Relative deviation
BMD = 3343.09
BMDL at the 95% confidence level = 2127.52

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	4.75548	5.10412
rho	0.150959	0
control	6.01205	3.4
slope	4.05331E-27	0.0564664
power	7.14249	0.625198

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	45	3.4	6.01	7.13	12.3	-1.42
156.5	20	4.3	6.01	4.1	12.3	-0.62
319	20	9.9	6.01	22.3	12.3	1.41
660.8	25	7	6.01	9.4	12.3	0.4
1144	22	8.9	6.01	21.2	12.3	1.1
2503	24	4.5	6.02	6.6	12.3	-0.603
5674	25	9.4	8.64	8.9	12.7	0.299
9231	25	91	91	16	15.2	-0.00462

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-624.644958	9	1267.289916
A2	-570.082153	16	1172.164306
A3	-595.035542	10	1210.071083
fitted	-626.519051	5	1263.038102
R	-806.807094	2	1617.614189

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	473.45	14	<0.0001
Test 2	109.126	7	<0.0001
Test 3	49.9068	6	<0.0001
Test 4	62.967	5	<0.0001

3.3 Results for Sitarek et al., 2012

Table 3-3-4 Model Predictions for Fetal Mortality in Rats Exposed to NMP by Gavage Using C_{max} as the Dose Metric (Sitarek et al., 2012)

BMR = 1% Relative Deviation and for Comparison 0.5 and 1 Standard Deviation (SD)

Model[a]	Goodness of fit		BMD_{1RD} (mg/L)	$BMDL_{1RD}$ (mg/L)	$BMD_{0.5SD}$ (mg/L)	$BMD_{0.5SD}$ (mg/L)	BMD_{1SD} (mg/L)	BMD_{1SD} (mg/L)	Basis for model selection
	p-value	AIC							
Exponential (M2)	<0.0001	7701.7	0.0578	0.0403	181	0.341	185	26.4	No models provided an adequate fit and a valid BMDL estimate, therefore no model was selected.
Exponential (M3)	<0.0001	1.8E+17	1.1E+15	1.1E+15	3.9E+15	3.9E+15	3.9E+15	3.9E+15	
Exponential (M4)			error[b]	error	error[b]	error	error[b]	error	
Exponential (M5)	N/A[c]		error[b]	error	error[b]	error	error[b]	error	
Power	<0.0001	4.2143	465	83.1	634	471	658	567	
Polynomial 2°	<0.0001	11.247	31.9	15.0	471	351	666	496	
Linear	<0.0001	20.871	1.94	4.30E-05	457	241	915	482	
Hill	N/A[c]	8.2143	464	83.2	633	300	658	324	

Notes:

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001, BMDS Test 3 *p*-value = <0.0001), no model was selected as a best-fitting model.

[b] BMD or BMDL computation failed for this model.

[c] No available degrees of freedom to calculate a goodness of fit value.

4 Benchmark Dose Modeling of Male Fertility, Female Fecundity, Litter Size and Pup Death in Exxon, 1991

BMD modeling for reduced male fertility, female fecundity, and reduced litter size described in a 2-generation reproductive study in rats exposed through diet (Exxon, 1991) was performed using USEPA's BMD Software package version 3.1.1 (BMDS 3.1.1) or 2.7 (BMDS 2.7) in a manner consistent with Benchmark Dose Technical Guidance.

In the Exxon (1991) study, two generations of both sexes were dosed daily for at least ten weeks prior to mating and throughout the mating period. Target doses for the exposed groups were 50, 160 and 500 mg/kg-day. Individual litter data reported in Appendices to the Exxon (1991) report were used for the determination of dichotomous response incidence and continuous response means and standard deviations modeled in this report.

The strongest dose-responses for reproductive effects in the Exxon (1991) study were observed for reduced Male Fertility Index and Female Fecundity Index in the first (P2/F2A; Table 73 of the Exxon report) and second (P2/F2B; Table 74 of the Exxon report) litters of the P2 (F1A) 2nd generation parents.

4.1 Overall BMD Modeling Approach for Exxon 1991 Data

Benchmark dose software version 3.1.1 (BMDS 3.1.1) was used to analyze male fertility, female fecundity and litter size. The pup death endpoint was analyzed using BMDS 2.7 because it contains the larger suite of nested dichotomous models.[2] Nested dichotomous models are preferred for this endpoint because they contain an intra-litter correlation coefficient for the assessment of litter-specific responses.

Only BMDS models that use likelihood optimization and profile likelihood-based confidence intervals were used in this analysis. All continuous models applied assume normal response distribution. Also, the benchmark response levels and dose metrics for the analysis are:

- *Fertility and Fecundity for P2/F2A and P2/F2B parental rats* – estimate BMDs for 10% extra risk using PBPK estimates of average daily blood concentrations for young (50 g) rat as doses (four datasets), plus a sensitivity analysis using average daily blood concentrations for 250 g, 350 g and 450 g rats.
- *Litter Size for P2/F2A and P2/F2B* – estimate BMDs for 1 SD change from control mean using PBPK estimates of average daily blood concentrations for young (50 g) rat and GD 6-21 dams as doses (four datasets)
- *Pup death for P2/F2A and P2/F2B* - estimate BMDs for death at Day 0 and by day 4 for 10%. 5% and 1% extra risk using PBPK estimates of average daily blood concentrations for GD 6-21 dam as doses (four datasets)

Standard and non-standard forms of these models[3] (defined for each endpoint below) were run separately in BMDS 3.1.1, but EPA model selection procedures (EPA, 2012) were applied only to the results of the standard model runs when adequate fit was achieved with any standard model. Since

[2] BMDS 3.1.1 contains the same NLogistic model, which is preferred because it has received the more extensive QA testing and is deemed to be the most reliable nested model, but NCTR and RaiVR models are provided as alternatives in this report.
[3] The set of standard models are identified in accordance with EPA BMD technical guidance (EPA, 2012) and are the default models in BMDS 3.1.1. Non-standard models are the remaining (non-default) models available in BMDS 3.1.1.

adequate model fits were obtained in all cases for the standard model suites, no non-standard modeling results are shown or discussed in this report.

Model Restrictions and Model Selection

Restrictions for BMDS 3.1.1 models are defined in the BMDS 3.1.1 User Guide and are applied in accordance with EPA BMD Technical Guidance (EPA, 2012). For each BMD analysis, a single preferred model was chosen from among the preferred standard set of models (noting instances where consideration of non-standard models may be justified) in accordance with EPA BMD Technical Guidance (EPA, 2012). For continuous responses, dose group response standard deviation (SD) was modeled assuming constant variance across dose groups. If adequate fit (p>0.1) was not achieved for this variance model a non-constant variance assumption that models SD as a power function of the mean was applied (EPA, 2012). Nested dichotomous models were run two ways, with intra-litter correlation (ILC) coefficients estimated and with ILC coefficients assumed to be zero. Because potential litter-specific covariates (LSCs) such as dam BW are affected by dose, no appropriate LSC could be determined and LSCs were not estimated in the BMDS nested dichotomous model runs.

4.2 PBPK Analysis for Exxon 1991 Data

Details of the PBPK models for rats and humans are provided in Appendix I of the NMP Risk Evaluation. The models were developed to describe dosimetry in adult females during pregnancy and so were slightly adapted to estimate dosimetry in juvenile (post-weaning) rats and adult men.

Because NMP has a relatively short half-life in both rats and humans, exposures only need to be simulated for several days to a week to determine the internal dosimetry from a consistent exposure pattern, such as occurs in an animal bioassay or in the workplace (5 day/week). Therefore, adult human single-day or workplace exposures outside of pregnancy were assumed to be adequately represented by running the model for the first day or week of pregnancy, when physiological changes are minimal. Also, physiological differences between men and women were assumed to have minimal impact on the predicted dosimetry, except that a male-specific body weight (BW) and hand surface area (SA) were used to estimate dosimetry in men. Changing the BW also affects cardiac output, respiration, and metabolism, which all scale as $BW^{0.75}$ in the model. Exposures were simulated for a single day (residential consumer use) or a week (workplace, with 5 d/w exposure) and the average daily area-under-the-curve (AUC) blood concentration[4] was calculated.

For the rat, where pregnancy only lasts 21 days, the model code was modified to allow a user-specified day for the start of gestation (GSTART), so results for non-pregnant animals could be obtained; i.e., with time < GSTART. As for humans, physiological differences between males and females were assumed to not significantly impact internal dosimetry, hence the non-pregnant female model was used to simulate male dosimetry. Simulations for post-weaning juvenile animals in the Exxon (1991) bioassay were conducted by setting the (initial) BW to 50 g (and for comparison, 250 g, 350 g and 450 g). Because metabolism is scaled as $BW^{0.75}$ in the rats (as well as humans) the internal dose decreases as BW decreases, so using this BW yields the lowest estimated internal dose for post-weaning rats (weaning presumed to occur at about this BW). Using this BW in dose-response analysis for fertility and

[4] Since the 24-hour AUC can vary from day to day, in particular for workplace scenarios, a time-averaged AUC is computed as AUC_{avg} = AUC(averaging time)*(24 h)/(averaging time), where "averaging time" is typically a week. The average blood concentration is simply C_{avg} = AUC(averaging time)/(averaging time). Hence $C_{avg} = AUC_{avg}/(24\ h)$.

fecundity provides a lower bound on the internal dose that could give rise to those effects, since they could result from toxicity at any point in development or during maturity. Target exposure levels (50, 160, and 500 mg/kg/d) were used as exposure levels, exposure was simulated for one-week to go beyond any initial accumulation and the average blood concentration (C_{avg}) in the last day of exposure used as internal dose. Food consumption was assumed to occur 12 h/d, at a constant rate over the 12 h to match the target exposure. Results are given in Table 4-1.

Table 4-1 PBPK-predicted average blood concentrations (C_{avg}, mg/L) in juvenile rats

Exposure rate (mg/kg/d)	C_{avg} (50 g rat)	C_{avg} (250 g rat)	C_{avg} (350 g rat)	C_{avg} (450 g rat)
0	**0**	0	0	0
50	**13.9**	21.1	23.1	24.6
160	**48.4**	75.2	82.6	88.6
500	**181.4**	292.6	324.0	349.8

The existing PBPK model does not describe lactational dosimetry, hence the analysis did not include exposure during that period.

Since effects on litter size and pup viability could result from exposure during gestation, for these endpoints C_{avg} in the rat dam over gestation days (GDs) 6-21 days of gestation was estimated. For simulation of gestation, group-specific mean BW on GD 0 from Table 53 (P2/F2A) and Table 56 (P2/F2B) of the Exxon (1991) report were used to set the initial BW of the animals. The gestational BW gain simulated by the model depended on the number of fetuses (NUMFET), an input parameter. Since group-specific BW values were also given on GD 20 (Tables 53 and 56 of the Exxon report), a nominal NUMFET was selected for each group to match, as closely as possible, the GD 20 BW value, though the NUMFET did not necessarily match the average number actually born. This choice was made since the BW impacts the internal dose, so it was considered most important to match the BW increase. The dose rates for each exposure group were calculated as the average of measured doses for days 6-20 from Tables 67 (P2/F2A) and 69 (P2/F2B) of the Exxon (1991) report. The resulting internal doses are given in Table 4-2 and 4-3.

Table 4-2 PBPK-predicted average blood concentrations (Cavg, mg/L) during gestation for P2/F2A

GD 0 BW (kg)	GD 6-20 Exposure rate (mg/kg/d)	Predicted GD 20 BW (kg) (# fetuses simulated)	**GD 6-21 C_{avg} (mg/L)**
0.3243	52.475	0.4505 (17)	**26.12**
0.3054	166.75	0.4394 (19)	**92.55**
0.2815	494.1	0.3872 (14)	**326.1**

Table 4-3 PBPK-predicted average blood concentrations (Cavg, mg/L) during gestation for P2/F2B

GD 0 BW (kg)	GD 6-20 Exposure rate (mg/kg/d)	PredictedGD 20 BW (kg) (# fetuses simulated)	**GD 6-21 C_{avg} (mg/L)**
0.3706	49.350	0.5075 (18)	**25.25**
0.3536	156.70	0.4935 (19)	**89.03**
0.3187	466.63	0.4188 (12)	**311.9**

For human workplace and residential exposures, input parameters were specified in Excel spreadsheets. For workplace exposures, estimated air concentrations were assumed to be constant over each period of use, but the air concentration, liquid concentration (weight fraction), and duration of use varied between scenarios. Internal average blood concentrations for varying levels of protective equipment (face mask and/or gloves with varying protection factors (PFs)) were estimated assuming a five-day work week in which the exposure was repeated each day followed by two days without exposure. Residential applications were assumed to occur for a single day and air-concentration time-courses estimated for each application, along with liquid weight fraction and dermal contact duration specific to each use scenario. These inputs were read by a model script from Excel spreadsheets. For the analysis of potential for effect on male fertility, BW and hand surface area (SA) were set to male-specific values. For the analysis of potential for gestational effect, BW and SA were set to female-specific values. Residential application evaluated exposure for both adult and teenage women. Model results are written back to the Excel spreadsheet from which exposure inputs were obtained.

Since human internal doses are calculated as 24-h average AUC values, these must be divided by 24 h before comparison to C_{avg} BMD(L) values, or the C_{avg} BMD(L) values multiplied by 24 h, prior to MOE calculation.

4.3 Summary of BMD Modeling for Exxon, 1991 Data

Table 4-4 BMD Modeling Summary for Exxon (1991)

Sec.	Response	Basis for Internal Dose Calculations	Selected Model[2]	BMR	BMD[3] (mg/L)	BMDL[3] (mg/L)	BMDU[3] (mg/L)	BMD[4] 24hr AUC (h mg/L)	BMDL[4] 24hr AUC (h mg/L)
4.4.1	P2/F2A Male Rat Fertility	Young rat (50 g)	Log-Logistic	10% ER	20.5	10.9	81.7	492	262
4.4.2	P2/F2B Male Rat Fertility	Young rat (50 g)[1]	Log-Logistic	10% ER	14.2	7.64	65.1	341	183
4.4.3	P2/F2A Female Rat Fecundity	Young rat (50 g)	Log-Logistic	10% ER	35.9	16.7	179	862	401
4.4.4	P2/F2B Female Rat Fecundity	Young rat (50 g)	Log-Logistic	10% ER	17.5	8.40	58.4	420	202
4.5.1	P2/F2A Litter Size	Young rat (50 g)	Polynomial 3	1 SD	203	151	715	4872	3624
4.5.2	P2/F2B Litter Size	Young rat (50 g)	Linear	1 SD	153	99.6	332	3672	2390
4.5.3	P2/F2A Litter Size[5]	Dam (GD 6-21)	Polynomial 3	1 SD	364	274	1280	8736	6576
4.5.4	P2/F2B Litter Size[5]	Dam (GD 6-21)	Linear	1 SD	265	172	575	6360	4128
4.6.1	P2/F2A Pup Death at Day 0 (stillborn)	Dam (GD 6-21)	NLogistic - ILC	5% ER	327	205	NC	7848	4920
				1% ER	281	49.3	NC	6744	1183
4.6.2	P2/F2B Pup Death at Day 0 (stillborn)	Dam (GD 6-21)	No Model Selected	5% ER	NA	NA	NA	NA	NA
				1% ER	NA	NA	NA	NA	NA
4.6.3	P2/F2A Pup Death by Day 4	Dam (GD 6-21)	No Model Selected	5% ER	NA	NA	NA	NA	NA
				1% ER	NA	NA	NA	NA	NA
4.6.4	P2/F2B Pup Death by Day 4	Dam (GD 6-21)	No Model Selected	5% ER	NA	NA	NA	NA	NA
				1% ER	NA	NA	NA	NA	NA

[1] BMDL estimates from the selected model (Log-Logistic) for this most sensitive endpoint using internal doses based on 250 g, 350 g and 450 g rats, were 12.1, 13.4 and 14.4 mg/L, respectively (details of these results and results for the other fertility and fecundity endpoints are available in the supplemental BMDS 3.1.1 Excel Result Workbook files associated with this report).

[2] As described in Section 4.1, BMDs were derived from the standard set of models as defined in the EPA BMD technical guidance and as identified in BMDS 3.1.1 as defaults. Since the standard approach gave adequate results for all endpoints, non-standard models were not considered for BMD derivations.

[3] BMD, BMDL and BMDU values are in terms of average concentration over 24 hrs and are reported to more than 3 significant figures in the tables in Section 4.4, 4.5 and 4.6. This has been done to facilitate QC (i.e., replication of the results to a higher number of significant figures gives greater assurance that QA model runs have been performed using the same modeling options).

[4]Adjusted BMD and BMDL are in terms of 24-hour AUC blood concentration. These units are directly comparable with BMDLs previously calculated for the NMP risk evaluation

[5]Effects on litter size during gestation are of interest for acute exposure and would therefore be most appropriately evaluated based on maximum concentrations as opposed to 24hr average or AUC concentrations shown here.

NC = Not Calculated; NA = Not Applicable

4.4 Results of BMD Modeling of P2 Male and Female Fertility Indices (Exxon, 1991)

The strongest dose-responses for reproductive effects in the Exxon (1991) study were observed for reduced Male Fertility Index and Female Fecundity Index in the first (P2/F2A; Table 73 of the Exxon report) and second (P2/F2B; Table 74 of the Exxon report) litters of the P2 (F1A) 2nd generation parents. Incidence data for these effects were obtained from Appendices AF (P2/F2A parents) and AG (P2/F2B parents) of the Exxon (1991) report. Because BMDS models dichotomous data using dose-response curves that are increasing in dose-response, the results reported in Appendices AF and AG in terms of successful impregnations were inverted to obtain incidence data in terms of "number of males unsuccessful at impregnating any female" per "number of males used for mating" (Males Unsuccessful/ Males Used) and "number of females that did not get pregnant" per "number of females sperm positive (confirmed mated or confirmed pregnant)" (Females Unsuccessful/Females Mated). These ratios were derived slightly differently from the Male Fertility and Female Fecundity indices shown in Tables 73 and 74 of the Exxon (1991) report in that a confirmed pregnancy was counted as "sperm positive" regardless of whether the mating was "confirmed" (cases where this occurred are identified with footnotes in the tabular results of this Section).

Because of the existing uncertainty regarding the lifestage "window of toxicity," and the possibility that reproductive effects of concern could have been associated with early life exposures, the BMD analyses of potential reproductive effects were performed using PBPK estimates of internal doses that assume an early lifestage rat body weight of 50 g. A sensitivity analysis was performed on the P2/F2B Male Rat Fertility to determine the impact of the body weight assumption. As indicated in Footnote 1 of the table in Section 4.3, BMDL estimates for this most sensitive endpoint increased by less than 2-fold for body weight assumptions at or below 450 g. The following standard and non-standard dichotomous models and general modeling options were used to fit fertility incidence data.

Standard Dichotomous Models Applied to Fertility and Fecundity Responses:

- Gamma-restricted
- Log-Logistic-restricted
- Multistage-restricted; from degree = 1 to degree = # dose groups - 1
- Weibull-restricted
- Dichotomous Hill-unrestricted
- Logistic
- Log-Probit-unrestricted
- Probit

Non-Standard Dichotomous Models Applied to Fertility and Fecundity Responses:

- Dichotomous Hill-restricted
- LogProbit-restricted
- Gamma-unrestricted
- Log-Logistic-unrestricted
- Multistage-unrestricted
- Weibull-unrestricted

General Model Options Used for Fertility and Fecundity Dichotomous Responses:

- Benchmark Response (BMR): 0.1 (10%) Extra Risk
- Confidence Level: 0.95
- Background: Estimated

4.4.1 P2/F2A Male Fertility (Males Unsuccessful/Males Used; Exxon Appendix AF)

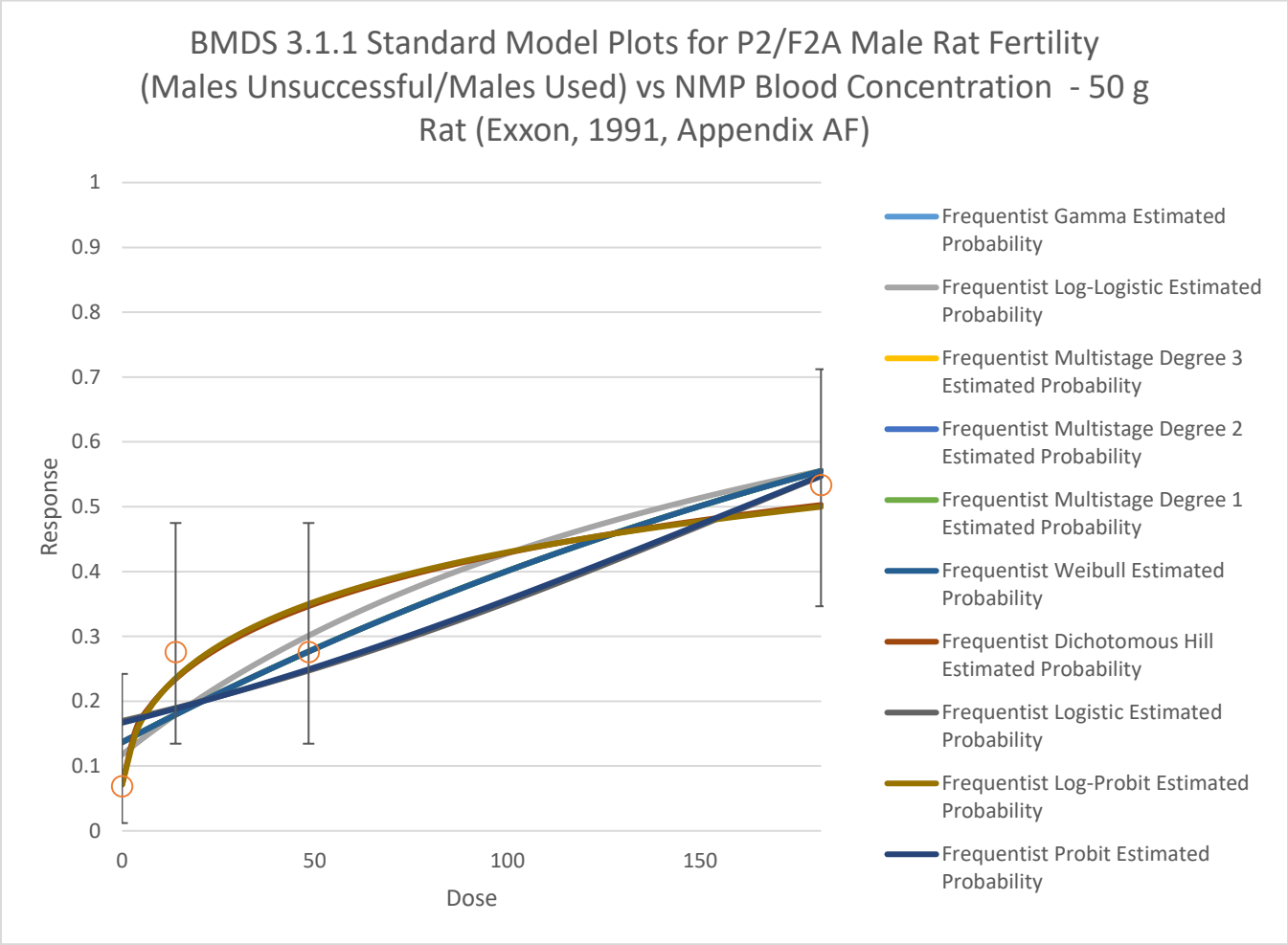
mg/L Blood - 50 g Rat	N	Incidence
0	29	2
13.9	29	8
48.4	29	8
181.4	30	16

Summary of BMDS 3.1.1 Modeling Results for P2/F2A Male Rat Fertility (Exxon, 1991)

Table 4-5 Model Predictions for Reduced Male Fertility in P2/F2A Male Rats (Exxon, 1991)

Standard Models	Restriction**	10% Extra Risk (mg/L blood – 50 g Rat)			P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL	BMDU				
Gamma	Restricted	28.8254	18.0677	106.5062	0.2212244	131.3647426	Viable - Alternate	
Log-Logistic*	**Restricted**	**20.4739**	**10.9376**	**81.73223**	**0.2674073**	**130.8745155**	**Recommended**	**Basis: Lowest BMDL In a > 3-Fold BMDL Range** Lowest AIC
Multistage Degree 3	Restricted	28.8254	18.0678	109.5157	0.221224	131.3647426	Viable - Alternate	
Multistage Degree 2	Restricted	28.8254	18.0675	91.60710	0.2212241	131.3647426	Viable - Alternate	
Multistage Degree 1	Restricted	28.8253	18.0676	56.96940	0.2212238	131.3647426	Viable - Alternate	
Weibull	Restricted	28.8254	18.0676	115.1404	0.2212239	131.3647426	Viable - Alternate	
Dichotomous Hill	Unrestricted	4.24566	0.00024	41.01537	0.3093156	131.3825536	Questionable	BMD/BMDL ratio > 20 BMD/BMDL ratio > 3 BMD 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose
Logistic	NA	51.4208	38.1985	79.82821	0.1620735	132.3326784	Viable - Alternate	
Log-Probit	Unrestricted	4.64211	0.00037	37.71069	0.2942246	131.4531168	Questionable	BMD/BMDL ratio > 20 BMD/BMDL ratio > 3 BMD 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose
Probit	NA	48.8614	36.4163	77.27841	0.1667614	132.2405329	Viable - Alternate	

*Selected Model (Green); residuals for doses 0, 13.9, 48.4, and 181.4 were -0.811610042, 1.353899534, -0.296031585 and -0.242023672, respectively.
**Restrictions defined in the BMDS 3.1.1 User Guide; NA = Not Applicable


BMDS 3.1.1 Standard Model Plots for P2/F2A Male Rat Fertility (Males Unsuccessful/Males Used) vs NMP Blood Concentration - 50 g Rat (Exxon, 1991, Appendix AF)
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
50
100
150
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 3 Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability
Frequentist Dichotomous Hill Estimated Probability
Frequentist Logistic Estimated Probability
Frequentist Log-Probit Estimated Probability
Frequentist Probit Estimated Probability

Selected Model – Log-Logistic (Restricted) - Extra Risk, BMR = 0.1

User Input

Info	
Model	Log-Logistic v1.0
Dataset Name	P2F2A Male Fertility
User notes	[Add user notes here]

Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	[Dose]
Independent Variable	[Incidence]
Total # of Observations	4

Model Results

Benchmark Dose	
BMD	20.4738478
BMDL	10.93759459
BMDU	81.7322316
AIC	130.8745155
P-value	0.267407255
D.O.F.	2
Chi^2	2.637964966

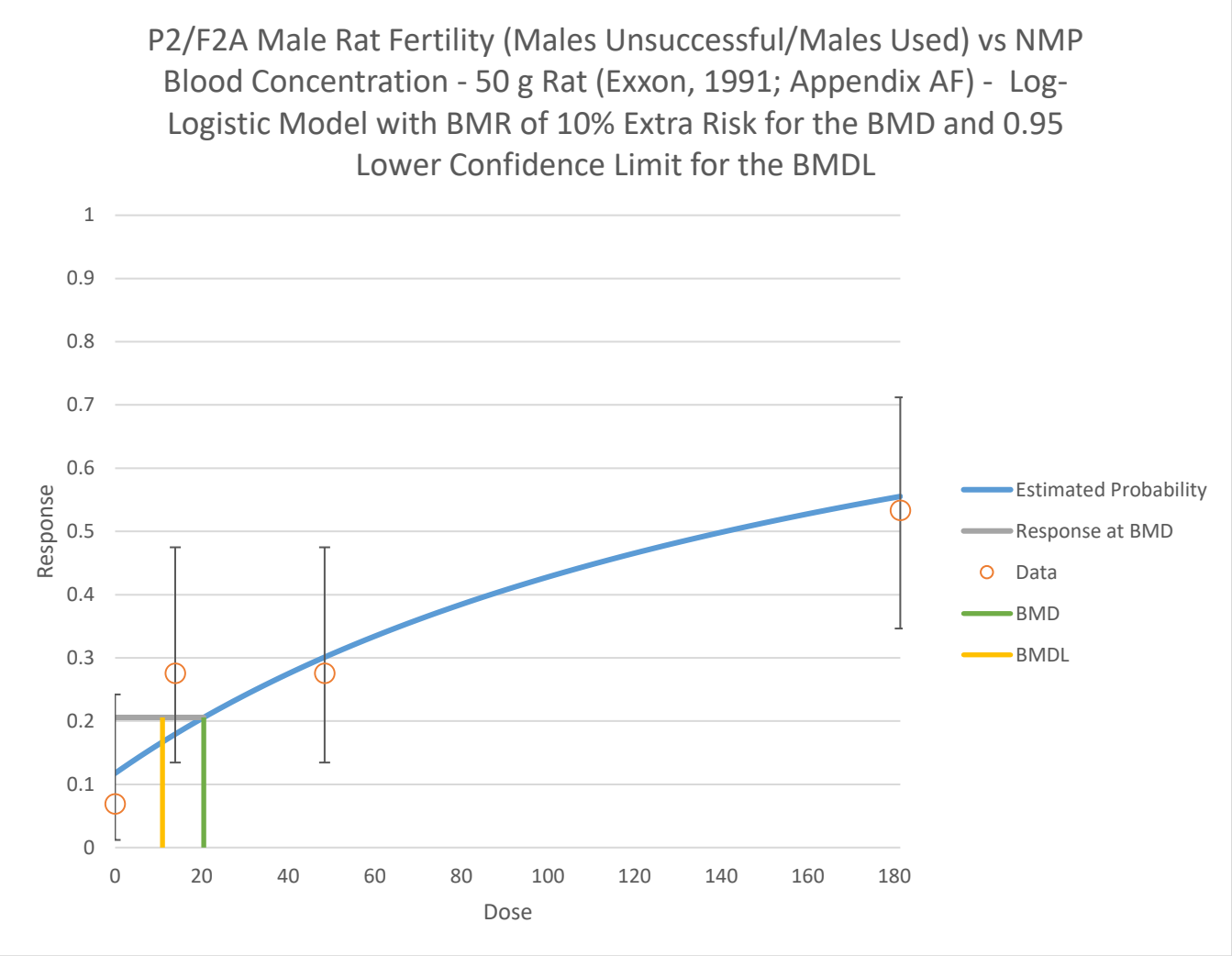
Model Parameters	
# of Parameters	3
Variable	Estimate
g	0.117496501
a	-5.216372932
b	Bounded

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.117496501	3.407398541	2	29	-0.81161
13.9	0.17939856	5.202558252	8	29	1.3538995
48.4	0.301079065	8.731292894	8	29	-0.296032
181.4	0.555291468	16.65874405	16	30	-0.242024

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-62.1675397	4	-	-	-
Fitted Model	-63.43725776	2	2.53943612	2	0.2809108
Reduced Model	-70.51432209	1	16.6935648	3	0.0008171


P2/F2A Male Rat Fertility (Males Unsuccessful/Males Used) vs NMP Blood Concentration - 50 g Rat (Exxon, 1991; Appendix AF) - Log-Logistic Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
20
40
60
80
100
120
140
160
180
Estimated Probability
Response at BMD
Data
BMD
BMDL

4.4.2 P2/F2B Male Fertility (Males Unsuccessful/Males Used; Exxon Appendix AG)

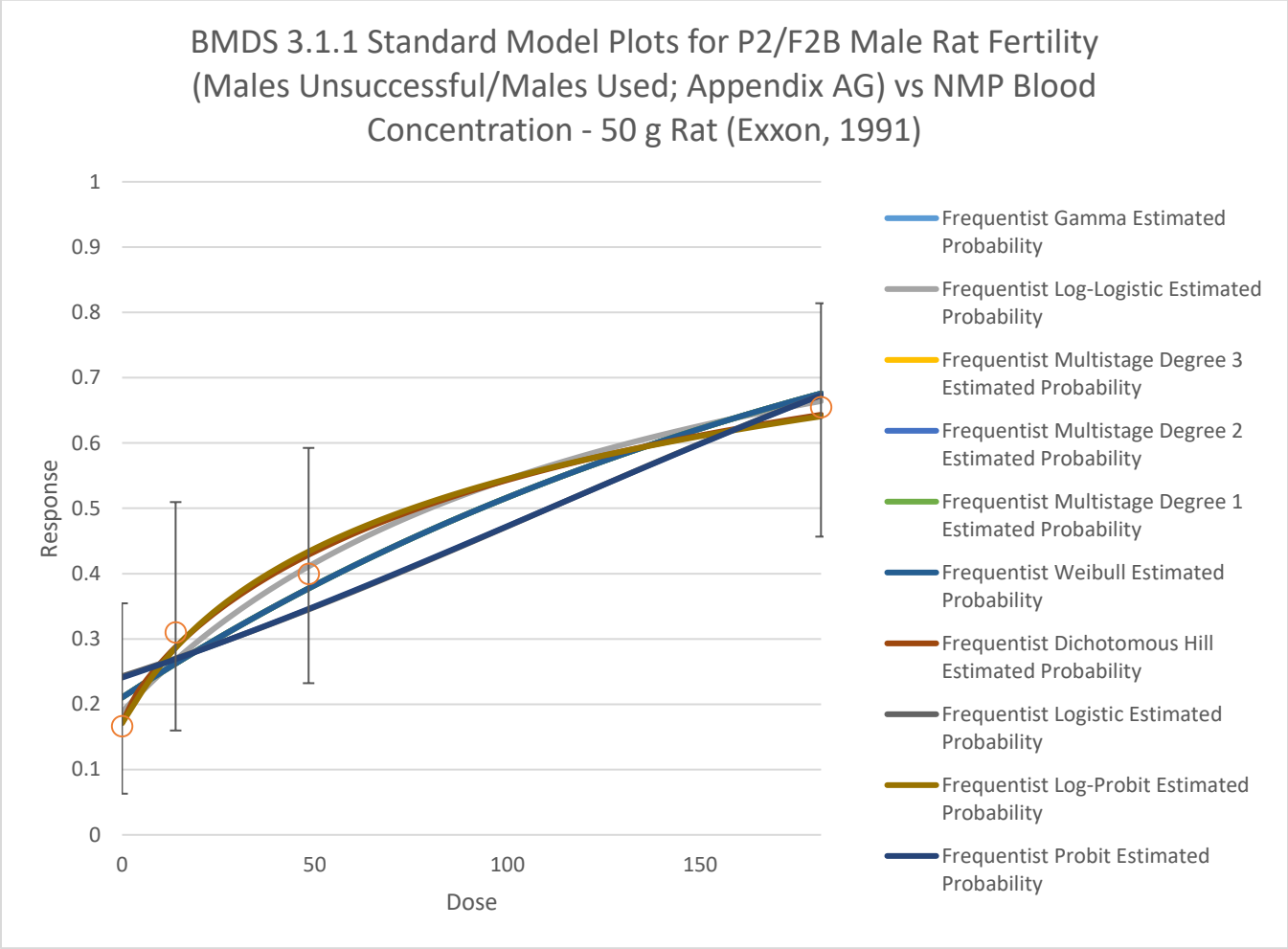
mg/L Blood - 50 g Rat	N	Incidence
0	30	5
13.9	29	9
48.4	30	12
181.4	29	19

Summary of BMDS 3.1.1 Modeling Results for P2/F2B Male Rat Fertility (Exxon, 1991)

Table 4-6 Model Predictions for Reduced Male Fertility in P2/F2B Male Rats (Exxon, 1991)

Standard Models	Restriction**	10% Extra Risk (mg/L blood – 50 g Rat)			P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL	BMDU				
Gamma	Restricted	21.4613	13.7489	76.52064	0.6666306	145.5183972	Viable - Alternate	
Log-Logistic*	**Restricted**	**14.2125**	**7.63824**	**65.11825**	**0.8248283**	**145.0806789**	**Recommended**	**Basis: Lowest BMDL In a > 3-Fold BMDL Range** Lowest AIC
Multistage Degree 3	Restricted	21.4613	13.7489	87.34237	0.6666306	145.5183972	Viable - Alternate	
Multistage Degree 2	Restricted	21.4613	13.7487	75.00523	0.6666309	145.5183972	Viable - Alternate	
Multistage Degree 1	Restricted	21.4613	13.7488	40.46712	0.6666306	145.5183972	Viable - Alternate	
Weibull	Restricted	21.4613	13.7489	80.30469	0.6666306	145.5183972	Viable - Alternate	
Dichotomous Hill	Unrestricted	8.67717	0.17104	60.82728	0.6564479	146.8984918	Questionable	BMD/BMDL ratio > 20 BMDL 10x lower than lowest non-zero dose
Logistic	NA	36.7271	27.0945	56.56066	0.4426321	146.3971535	Viable - Alternate	
Log-Probit	Unrestricted	9.26962	0.24178	59.56593	0.6161031	146.9522017	Questionable	BMD/BMDL ratio > 20 BMDL 10x lower than lowest non-zero dose
Probit	NA	35.7014	26.7157	55.32779	0.4533689	146.3437672	Viable - Alternate	

*Selected Model (Green); residuals for doses 0, 13.9, 48.4 and 181.4 were -0.300662226, 0.518709072, -0.122358174 and -0.103594189, respectively.
**Restrictions defined in the BMDS 3.1.1 User Guide; NA = Not Applicable


BMDS 3.1.1 Standard Model Plots for P2/F2B Male Rat Fertility (Males Unsuccessful/Males Used; Appendix AG) vs NMP Blood Concentration - 50 g Rat (Exxon, 1991)
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
50
100
150
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 3 Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability
Frequentist Dichotomous Hill Estimated Probability
Frequentist Logistic Estimated Probability
Frequentist Log-Probit Estimated Probability
Frequentist Probit Estimated Probability

Selected Model - Log-Logistic (Restricted) - Extra Risk, BMR = 0.1

User Input

Info	
Model	Log-Logistic v1.0
Dataset Name	P2F2B Male Fertility
User notes	[Add user notes here]

Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	[Dose]
Independent Variable	[Incidence]
Total # of Observations	4

Model Results

Benchmark Dose	
BMD	14.21245366
BMDL	7.638241538
BMDU	65.11824629
AIC	145.0806789
P-value	0.824828266
D.O.F.	2
Chi^2	0.385160154

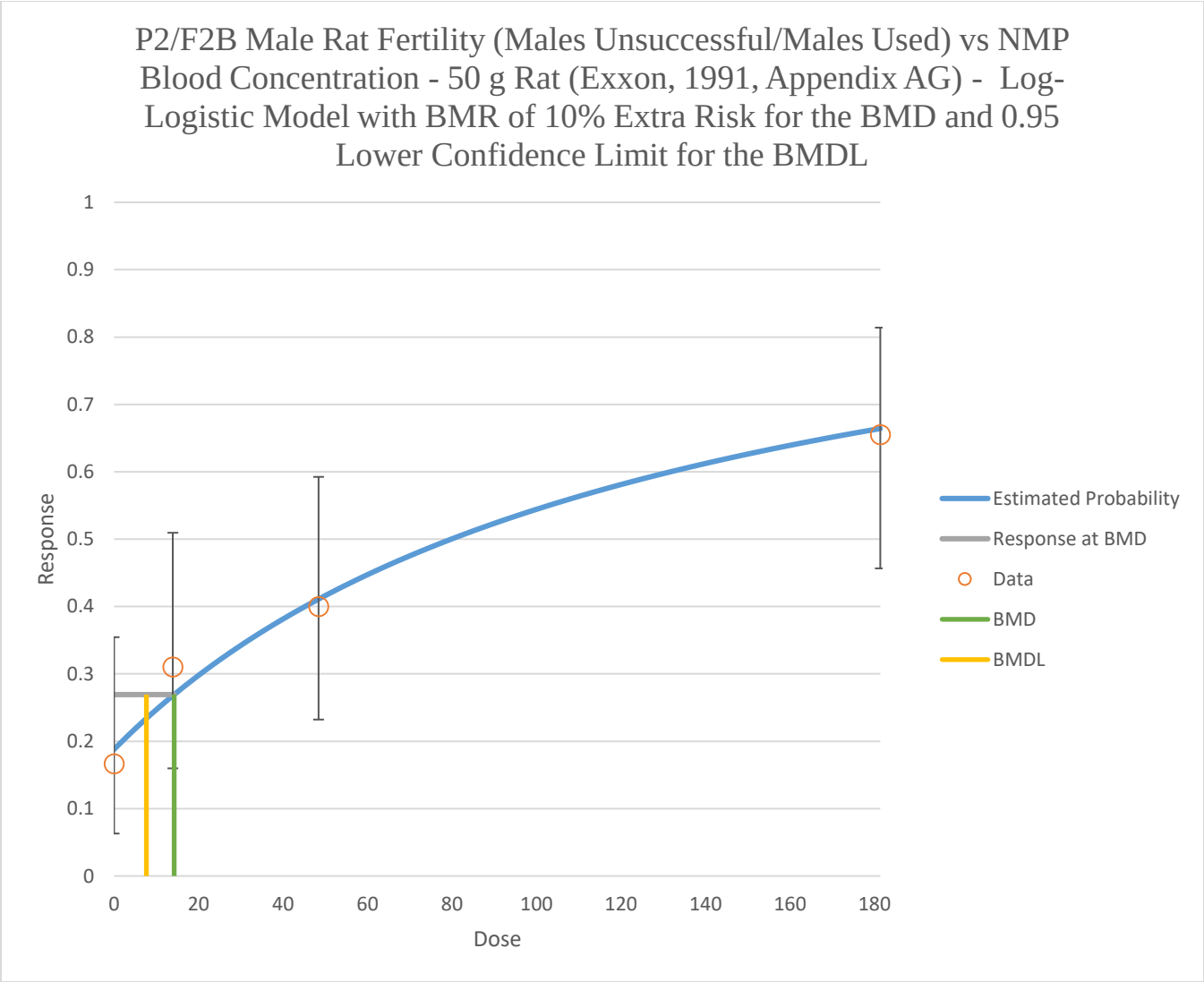
Model Parameters	
# of Parameters	3
Variable	Estimate
g	0.188119322
a	-4.851343176
b	Bounded

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.188119322	5.643579645	5	30	-0.300662
13.9	0.267697459	7.763226311	9	29	0.5187091
48.4	0.410991312	12.32973936	12	30	-0.122358
181.4	0.664257058	19.26345469	19	29	-0.103594

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-70.35048621	4	-	-	-
Fitted Model	-70.54033943	2	0.37970644	2	0.8270805
Reduced Model	-78.43743444	1	16.1738965	3	0.0010446


P2/F2B Male Rat Fertility (Males Unsuccessful/Males Used) vs NMP Blood Concentration - 50 g Rat (Exxon, 1991, Appendix AG) - Log-Logistic Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
20
40
60
80
100
120
140
160
180
Estimated Probability
Response at BMD
Data
BMD
BMDL

4.4.3 P2/F2A Female Fecundity (Females Unsuccessful/Females Mated; Exxon Appendix AF)

mg/L Blood - 50 g Rat	N	Incidence
0	29*	2
13.9	29**	6
48.4	28	7
181.4	23	9

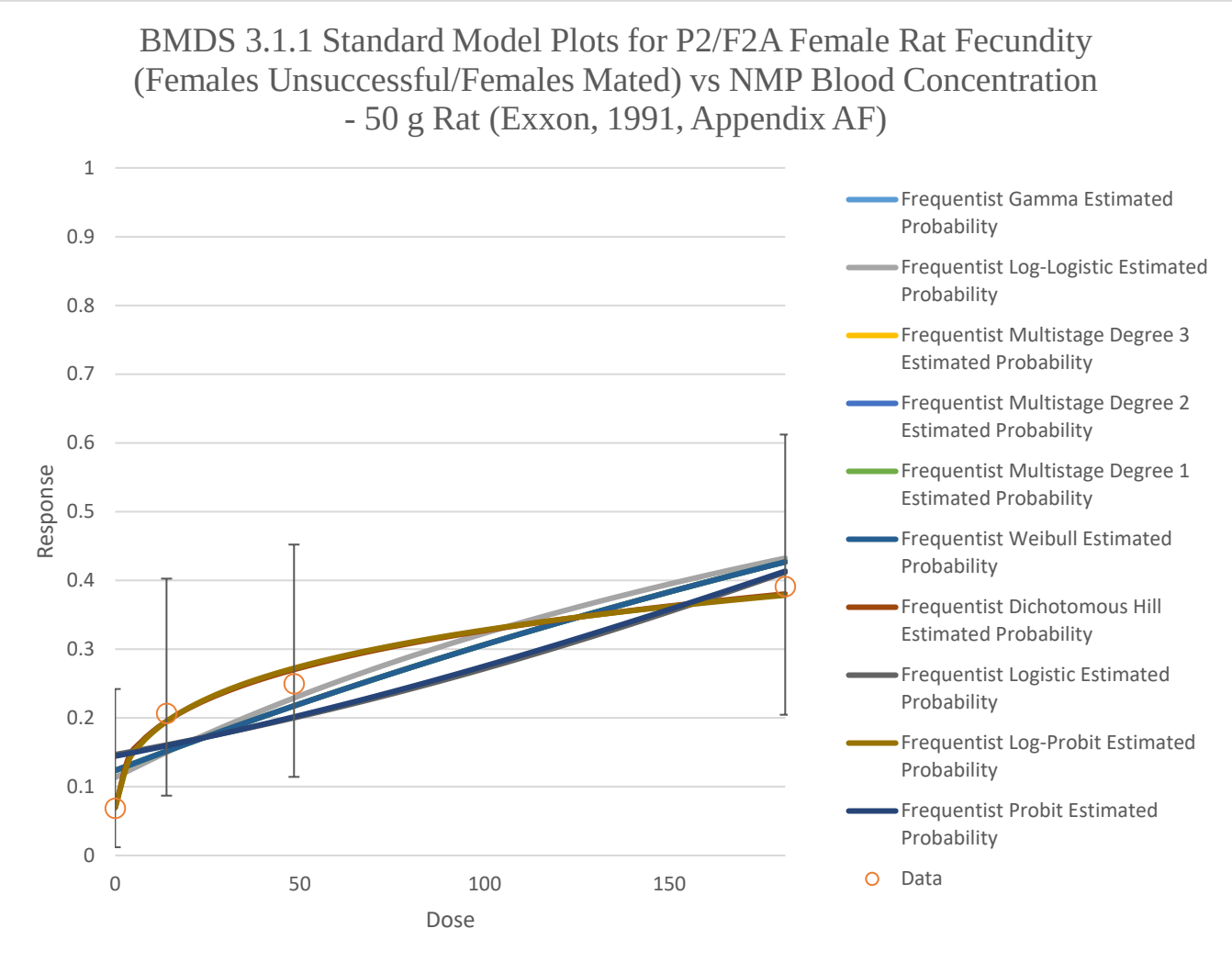
* Includes 1 presumed mating (JAB149 with JAB273) that was not "Confirmed" but resulted in pregnancy of JAB273
** Includes 1 presumed mating (JAB008 with JAB105) that was not "Confirmed" but resulted in pregnancy of JAB105

Summary of BMDS 3.1.1 Modeling Results for P2/F2A Female Rat Fecundity (Exxon, 1991)

Table 4-7 Model Predictions for Reduced Fecundity in P2/F2A Female Rats (Exxon, 1991)

Standard Models	Restriction**	10% Extra Risk (mg/L blood – 50 g Rat)			P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL	BMDU				
Gamma	Restricted	44.9690	24.2797	166.8743	0.4107328	112.2540963	Viable - Alternate	
Log-Logistic*	**Restricted**	**35.8500**	**16.7086**	**178.8394**	**0.4644837**	**111.9559685**	**Recommended**	**Basis: Lowest AIC**
Multistage Degree 3	Restricted	44.969	24.2793	152.7587	0.4107329	112.2540963	Viable - Alternate	
Multistage Degree 2	Restricted	44.9690	24.2797	145.5655	0.4107328	112.2540963	Viable - Alternate	
Multistage Degree 1	Restricted	44.9690	24.2794	139.9963	0.4107329	112.2540963	Viable - Alternate	
Weibull	Restricted	44.9690	24.2797	176.6268	0.4107328	112.2540963	Viable - Alternate	
Dichotomous Hill	Unrestricted	6.58476	0	78.86685	NA	114.5009914	Unusable	BMD computation failed; lower limit includes 0 BMDL not estimated d.f.=0 (Goodness of fit test cannot be calculated)
Logistic	NA	72.8142	49.2249	179.0743	0.3112546	112.9743842	Viable - Alternate	
Log-Probit	Unrestricted	7.04768	0	74.36506	0.7360008	112.5190346	Unusable	BMD computation failed; lower limit includes 0 BMDL not estimated
Probit	NA	69.2999	46.3835	174.6704	0.3207564	112.8954163	Viable - Alternate	

*Selected Model (Green); residuals for doses 0, 13.9, 48.4 and 181.4 were -0.754747582, 0.857664083, 0.263750831 and -0.398574381, respectively.
**Restrictions defined in the BMDS 3.1.1 User Guide; NA = Not Applicable


BMDS 3.1.1 Standard Model Plots for P2/F2A Female Rat Fecundity (Females Unsuccessful/Females Mated) vs NMP Blood Concentration - 50 g Rat (Exxon, 1991, Appendix AF)
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
50
100
150
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 3 Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability
Frequentist Dichotomous Hill Estimated Probability
Frequentist Logistic Estimated Probability
Frequentist Log-Probit Estimated Probability
Frequentist Probit Estimated Probability
Data

Selected Model – Log-Logistic - Extra Risk, BMR = 0.1

User Input

Info	
Model	Log-Logistic v1.0
Dataset Name	P2F2A Female Fecundity
User notes	[Add user notes here]

Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	mg/L Blood 50 g Rat
Independent Variable	Females Unsuccessful
Total # of Observations	4

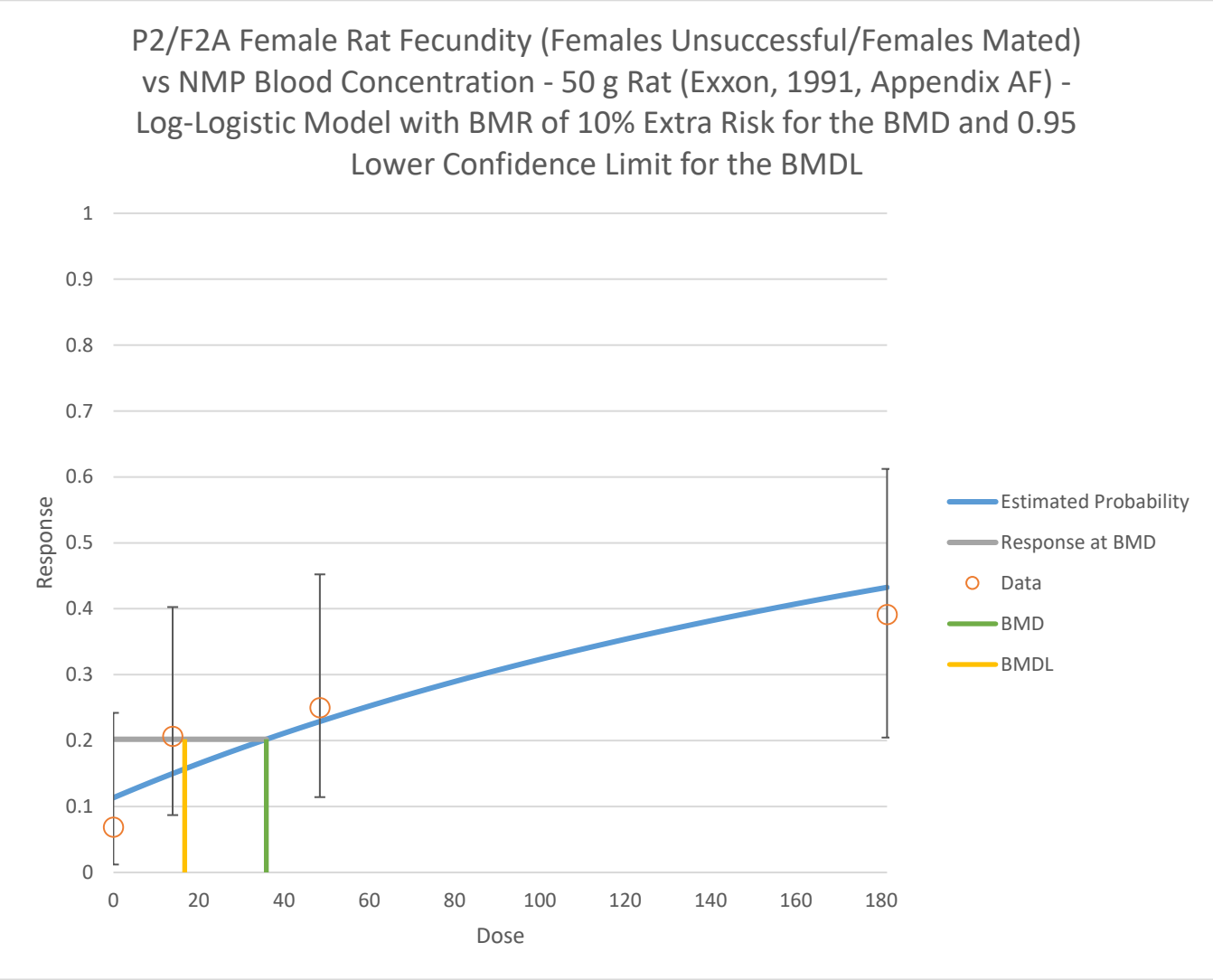
Model Results

Benchmark Dose	
BMD	35.85003887
BMDL	16.70857886
BMDU	178.8394143
AIC	111.9559685
P-value	0.464483699
D.O.F.	2
Chi^2	1.53365763

Model Parameters	
# of Parameters	3
Variable	Estimate
g	0.11340654
a	-5.776569229
b	Bounded

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.11340654	3.288789653	2	29	-0.754748
13.9	0.150024089	4.350698589	6	29	0.8576641
48.4	0.22905425	6.41351901	7	28	0.2637508
181.4	0.432477945	9.946992746	9	23	-0.398574

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-53.20227182	4	-	-	-
Fitted Model	-53.97798425	2	1.55142486	2	0.4603757
Reduced Model	-57.45827043	1	8.51199723	3	0.0365346


P2/F2A Female Rat Fecundity (Females Unsuccessful/Females Mated) vs NMP Blood Concentration - 50 g Rat (Exxon, 1991, Appendix AF) - Log-Logistic Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
20
40
60
80
100
120
140
160
180
Estimated Probability
Response at BMD
Data
BMD
BMDL

4.4.4 P2/F2B Female Fecundity (Females Unsuccessful/Females Mated; Exxon Appendix AG)

mg/L Blood - 50 g Rat	N	Incidence
0	27	2
13.9	29*	9
48.4	28	10
181.4	21**	11

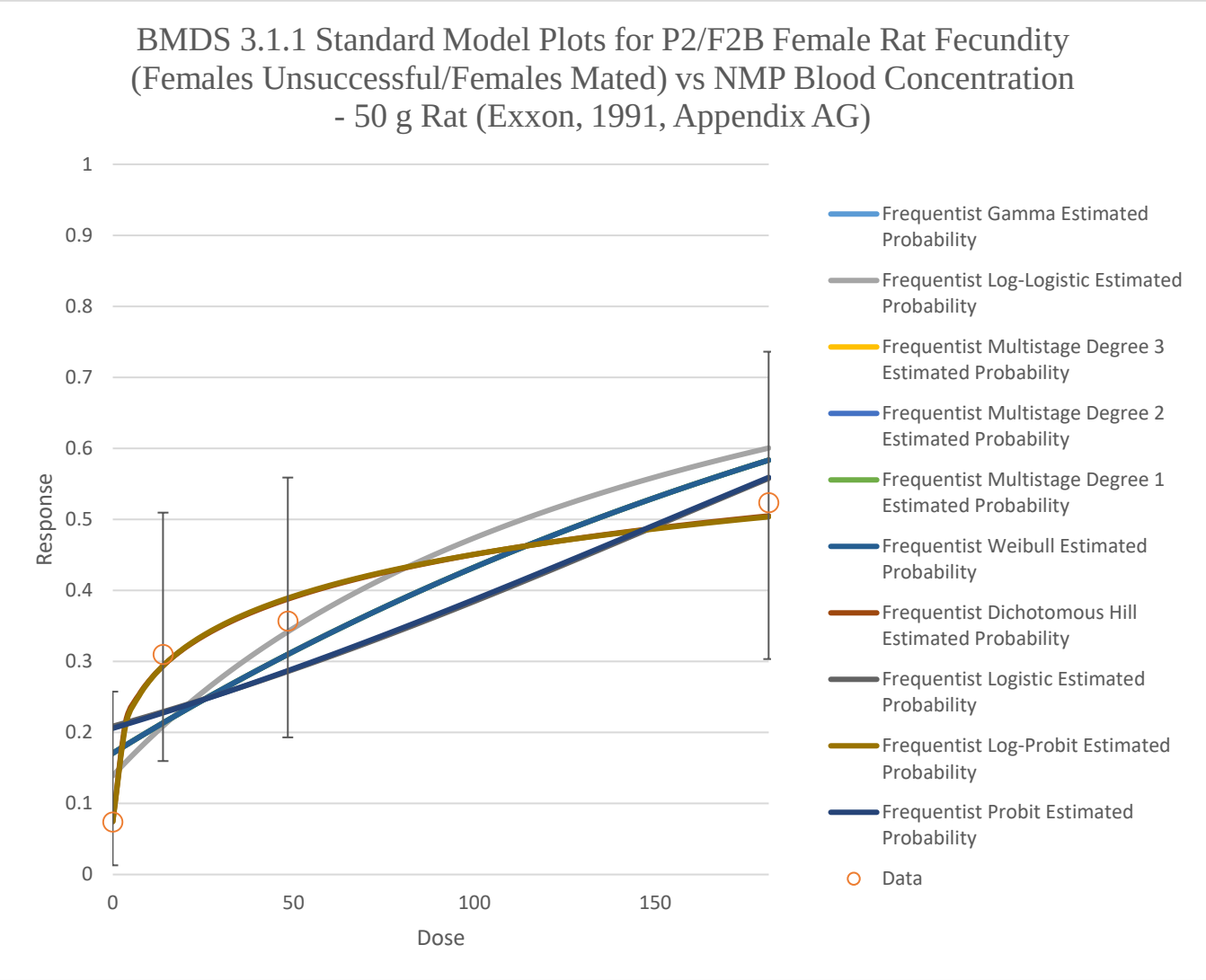
* Includes 2 presumed matings (JAB194 with JAB279; JAB201 with JAB293) not "Confirmed" but resulting in pregnancies
** Includes 1 presumed mating (JAB022 with JAB134) that was not "Confirmed" but resulted in pregnancy of JAB134

Summary of BMDS 3.1.1 Modeling Results for P2/F2B Female Rat Fecundity (Exxon, 1991)

Table 4-8 Model Predictions for Reduced Fecundity in P2/F2B Female Rats (Exxon, 1991)

Standard Models	Restriction**	10% Extra Risk (mg/L blood – 50 g Rat)			P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL	BMDU				
Gamma	Restricted	27.7596	15.9481	82.14200	0.1349299	123.9885415	Viable - Alternate	
Log-Logistic*	**Restricted**	**17.4528**	**8.39586**	**58.44882**	**0.1925123**	**123.0293723**	**Recommended**	**Basis: Lowest AIC**
Multistage Degree 3	Restricted	27.7598	15.9482	97.11740	0.1349306	123.9885415	Viable - Alternate	
Multistage Degree 2	Restricted	27.7598	15.9482	87.01075	0.1349306	123.9885415	Viable - Alternate	
Multistage Degree 1	Restricted	27.7619	15.9483	68.87117	0.134946	123.9885416	Viable - Alternate	
Weibull	Restricted	27.7600	15.9483	84.74789	0.1349318	123.9885415	Viable - Alternate	
Dichotomous Hill	Unrestricted	1.07172	0	18.13280	NA	123.9261336	Unusable	BMD computation failed; lower limit includes 0 BMDL not estimated BMD 10x lower than lowest non-zero dose d.f.=0 (Goodness of fit test cannot be calculated)
Logistic	NA	49.4825	34.0090	100.1899	0.0890178	125.2278017	Questionable	Goodness of fit p-value < 0.1
Log-Probit	Unrestricted	1.35920	0	18.12044	0.6604573	121.9394443	Unusable	BMD computation failed; lower limit includes 0 BMDL not estimated BMD 10x lower than lowest non-zero dose
Probit	NA	47.4459	32.8038	97.34369	0.0918383	125.1319918	Questionable	Goodness of fit p-value < 0.1

*Selected Model (Green); residuals for doses 0, 13.9, 48.4 and 181.4 were -0.976071189, 1.341257654, 0.170425804 and -0.717257235, respectively.
**Restrictions defined in the BMDS 3.1.1 User Guide; NA = Not Applicable


BMDS 3.1.1 Standard Model Plots for P2/F2B Female Rat Fecundity (Females Unsuccessful/Females Mated) vs NMP Blood Concentration - 50 g Rat (Exxon, 1991, Appendix AG)
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
50
100
150
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 3 Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability
Frequentist Dichotomous Hill Estimated Probability
Frequentist Logistic Estimated Probability
Frequentist Log-Probit Estimated Probability
Frequentist Probit Estimated Probability
Data

Selected Model – Log-Logistic (Restricted) - Extra Risk, BMR = 0.1

User Input

Info	
Model	Log-Logistic v1.0
Dataset Name	P2F2B Female Fecundity
User notes	[Add user notes here]

Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	[Dose]
Independent Variable	[Incidence]
Total # of Observations	4

Model Results

Benchmark Dose	
BMD	17.45276136
BMDL	8.395858147
BMDU	58.44881649
AIC	123.0293723
P-value	0.192512349
D.O.F.	2
Chi^2	3.295189957

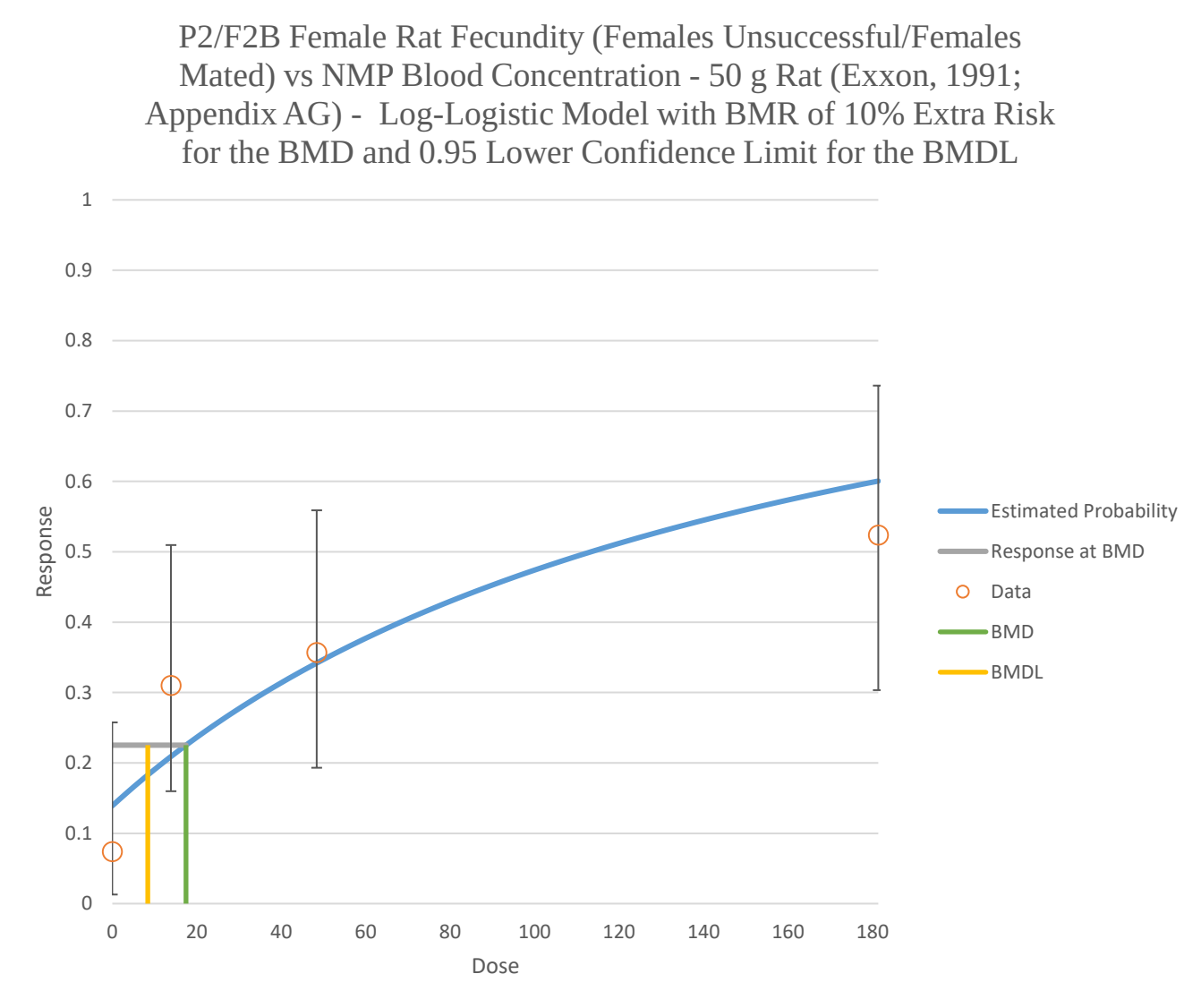
Model Parameters	
# of Parameters	3
Variable	Estimate
g	0.139072629
a	-5.056722458
b	Bounded

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.139072629	3.754960985	2	27	-0.976071
13.9	0.209064738	6.062877397	9	29	1.3412577
48.4	0.341865741	9.572240753	10	28	0.1704258
181.4	0.600472417	12.60992076	11	21	-0.717257

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-57.87277378	4	-	-	-
Fitted Model	-59.51468613	2	3.2838247	2	0.1936094
Reduced Model	-64.55874867	1	13.3719498	3	0.0038975


P2/F2B Female Rat Fecundity (Females Unsuccessful/Females Mated) vs NMP Blood Concentration - 50 g Rat (Exxon, 1991; Appendix AG) - Log-Logistic Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
20
40
60
80
100
120
140
160
180
Estimated Probability
Response at BMD
Data
BMD
BMDL

4.5 Results of BMD Modeling of P2 Litter (Exxon, 1991)

The next most sensitive dose-related reproductive effect noted in the Exxon (1991) study, other than the reduction in male fertility and female fecundity, was the reduction in litter size, which was most pronounced for the first (F2A) and 2nd (F2B) P2 rat litters. However, the Exxon (1991) study also reported a dose-related increase in pup death by postnatal day 4 that was also most pronounced in the F2A and F2B litters of the P2 parental rats. Thus, the extent to which the reduction in litter size is due to reproductive effects on the parents or gestational effects on the fetus is not clear, and the Exxon (1991) reproductive study design does not allow for a definitive investigation of that question (e.g., the number of implantations and resorptions were not identified). For these reasons, the litter size reduction effect was analyzed three ways (see Section 4.2 for PBPK modeling details):

1. Model litter size means and SD (live and stillborn pups) using BMDS continuous models against estimates of internal doses to young (50 g) parental rats (Sections 4.5.1 and 4.5.2).
2. Model litter size means and SD (live and stillborn pups) using BMDS continuous models against estimates of internal doses to P2 maternal rats during GD 6-21 (Sections 4.5.3 and 4.5.4).
3. Model pup death at day 0 (stillborn) and by postnatal day 4 per total pups born as incidence data using BMDS nested dichotomous models against estimates of internal doses to P2 maternal rats during GD 6-21 (Section 4.6).

Individual litter data that allows for the calculation of dose-specific means and standard deviations for litter size are available in Appendix AJ (for P2/F2A litters) and AK (for P2/FB litters) of the Exxon (1991) report.

Standard and nonstandard continuous models (defined below) were used to fit litter size data. BMDs were estimated for 1 SD change from control mean. Internal doses used for BMD modeling were based on PBPK estimates of average daily blood concentrations for young (50 g) rat and GD 6-21 dams.

Standard Continuous Models Applied to Litter Size Response:

- Exponential 2-restricted
- Exponential 3-restricted
- Exponential 4-restricted
- Exponential 5-restricted
- Hill-restricted
- Polynomial Degree 3-restricted
- Polynomial Degree 2-restricted
- Power-restricted
- Linear

Non-Standard Continuous Models Applied to Litter Size Response:

- Hill-unrestricted
- Polynomial Degree 3-unrestricted

- Polynomial Degree 2-unrestricted
- Power-unrestricted

General Model Options Used for Litter Size Continuous Response:

- Benchmark Response (BMR): 1 Standard Deviation (SD) Change from Control Mean
- Confidence Level: 0.95
- Background: Estimated

4.5.1 P2/F2A Litter Size - 50 g Rat (Exxon Appendix AJ, "Total Pups Born")

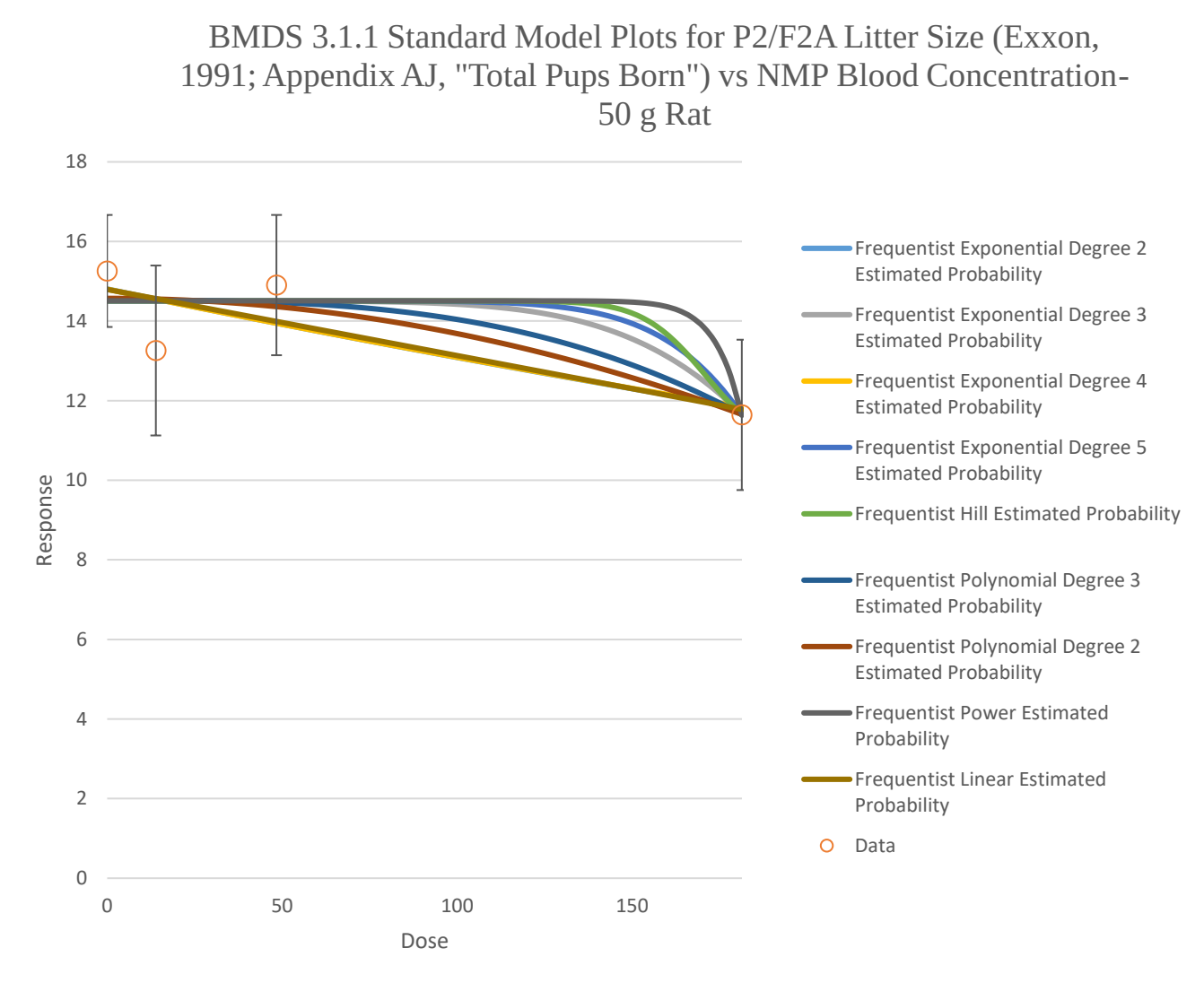
mg/L Blood – 50 g Rat	N	Mean	SD
0	27	15.2592593	3.558225
13.9	23	13.2608696	4.937955
48.4	21	14.9047619	3.871754
181.4	14	11.6428571	3.272429

Summary of BMDS 3.1.1 Modeling Results for P2/F2A Litter Size – 50 g Rat (Exxon, 1991)

Table 4-9 Model Predictions for Litter Size in P2/F2A Rats Based on Post-weaning Exposure (Exxon, 1991)

Standard Models	Restriction **	BMR = 1 Standard Deviation (mg/L blood – 50 g Rat)			P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL	BMDU				
Exponential 2 (CV)	Restricted	264.277	140.444	1032.840	0.131786 1	483.4105957	Viable - Alternate	BMD higher than maximum dose
Exponential 3 (CV)	Restricted	190.060	149.059	788.7670	0.062595 5	484.8246912	Questionable	Goodness of fit p-value < 0.1 BMD higher than maximum dose
Exponential 4 (CV)	Restricted	264.120	140.442	1032.835	0.131786 5	483.4105902	Viable - Alternate	BMD higher than maximum dose
Exponential 5 (CV)	Restricted	190.171	149.060	788.7498	NA	486.8246961	Questionable	BMD higher than maximum dose d.f.=0 (Goodness of fit test cannot be calculated)
Hill (CV)	Restricted	-9999	0	Infinity	0.062597 7	484.8246333	Unusable	BMD computation failed BMD not estimated BMDL not estimated Goodness of fit p-value < 0.1
Polynomial Degree 3 (CV)	**Restricted**	**202.696**	**150.674**	**714.9564**	**0.171851 8**	**482.8796917**	**Recommended**	**Basis: Lowest AIC** BMD higher than maximum dose
Polynomial Degree 2 (CV)	Restricted	214.035	148.914	757.4027	0.160527 3	483.016028	Viable - Alternate	BMD higher than maximum dose
Power (CV)	Restricted	183.783	182.112	698.8191	0.062598 3	484.824615	Questionable	Goodness of fit p-value < 0.1 BMD higher than maximum dose BMDL higher than maximum dose
Linear (CV)	NA	248.915	145.061	875.6812	0.136434 3	483.34127	Viable - Alternate	BMD higher than maximum dose

*Selected Model (Green); Constant variance case presented (Test 2 p-value = 0.24158); scaled residuals for doses 0, 13.9, 48.4 and 181.4 were 0.958706516, -1.509731959, 0.501737513 and -0.010801354, respectively.
**Restrictions defined in the BMDS 3.1.1 User Guide; NA = Not Applicable; CV = Constant Variance Model; NCV = Non-Constant Variance Model


BMDS 3.1.1 Standard Model Plots for P2/F2A Litter Size (Exxon, 1991; Appendix AJ, "Total Pups Born") vs NMP Blood Concentration-50 g Rat
Response
Dose
0
2
4
6
8
10
12
14
16
18
0
50
100
150
Frequentist Exponential Degree 2 Estimated Probability
Frequentist Exponential Degree 3 Estimated Probability
Frequentist Exponential Degree 4 Estimated Probability
Frequentist Exponential Degree 5 Estimated Probability
Frequentist Hill Estimated Probability
Frequentist Polynomial Degree 3 Estimated Probability
Frequentist Polynomial Degree 2 Estimated Probability
Frequentist Power Estimated Probability
Frequentist Linear Estimated Probability
Data

Selected Model – Polynomial Degree 3 (Restricted) - Extra Risk, BMR = 1 SD

User Input

Info	
Model	Polynomial degree 3 v1.1
Dataset Name	P2F2A Litter Size
User notes	[Add user notes here]
Dose-Response Model	M[dose] = g + b1*dose + b2*dose^2 + ...

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

Model Data	
Dependent Variable	[Dose]
Independent Variable	[Response]
Total # of Observations	85
Adverse Direction	Automatic

Model Results

Benchmark Dose	
BMD	202.6960934
BMDL	150.6744181
BMDU	714.956421
AIC	482.8796917
Test 4 P-value	0.171851757
D.O.F.	2

Model Parameters	
# of Parameters	5
Variable	Estimate
g	14.52128961
b1	Bounded
b2	Bounded
b3	-4.80285E-07
alpha	15.99813687

Goodness of Fit

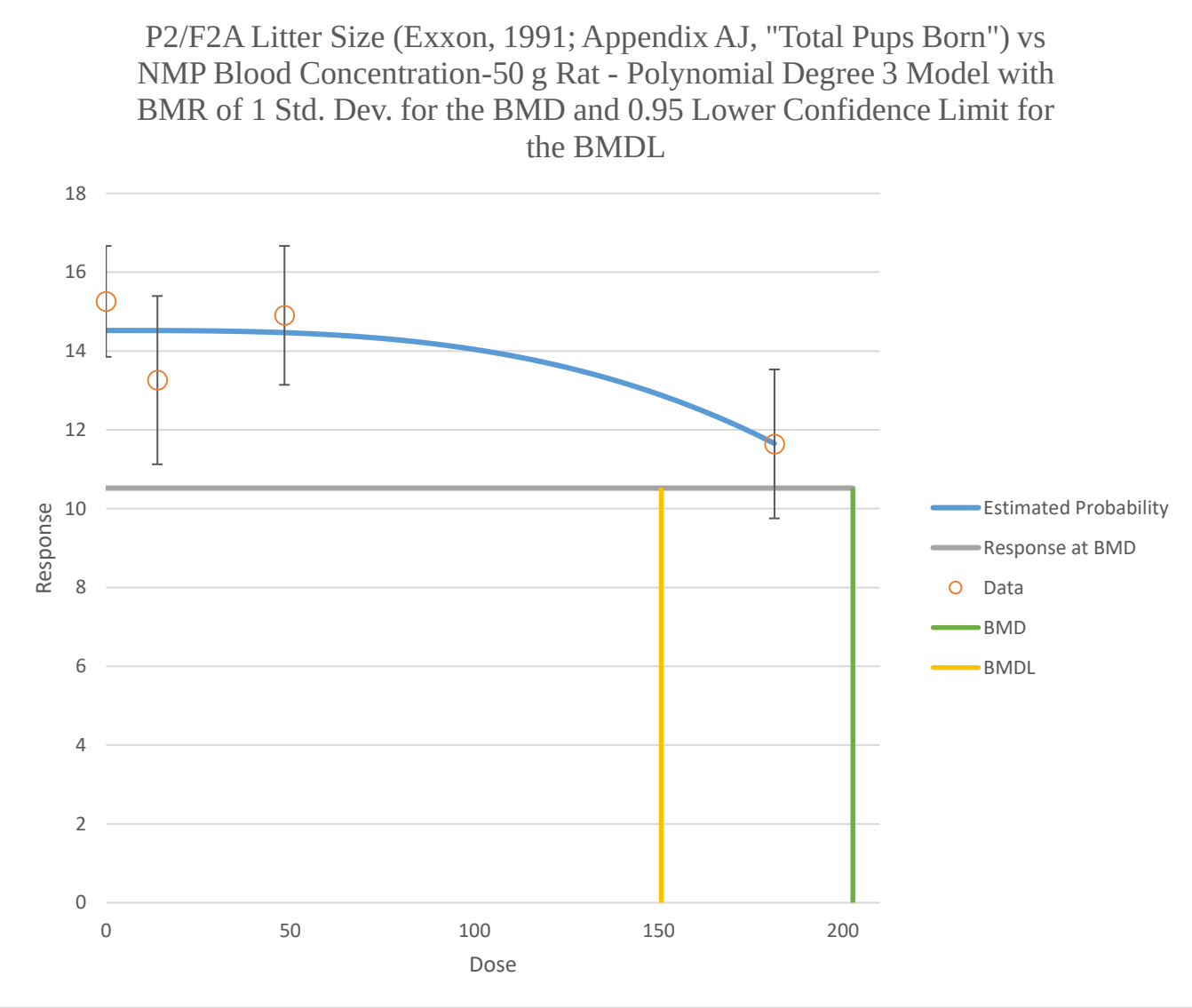
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	27	14.52128961	15.2592593	15.2592593	3.9997671	3.558225	3.558225	0.958706516
13.9	23	14.51999975	13.2608696	13.2608696	3.9997671	4.937955	4.937955	-1.509731959
48.4	21	14.466835	14.9047619	14.9047619	3.9997671	3.871754	3.871754	0.501737513
181.4	14	11.6544036	11.6428571	11.6428571	3.9997671	3.272429	3.272429	-0.01080135

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-236.6787228	5	483.357446
A2	-234.583299	8	485.166598
A3	-236.6787228	5	483.357446
fitted	-238.4398459	3	482.879692
R	-241.3113542	2	486.622708

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	13.45611034	6	0.03633832
2	4.190847665	3	0.24157981
3	4.190847665	3	0.24157981
4	3.522246101	2	0.17185176


P2/F2A Litter Size (Exxon, 1991; Appendix AJ, "Total Pups Born") vs NMP Blood Concentration-50 g Rat - Polynomial Degree 3 Model with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
2
4
6
8
10
12
14
16
18
0
50
100
150
200
Estimated Probability
Response at BMD
Data
BMD
BMDL

4.5.2 P2/F2B Litter Size - 50 g Rat (Exxon Appendix AK, "Total Pups Born")

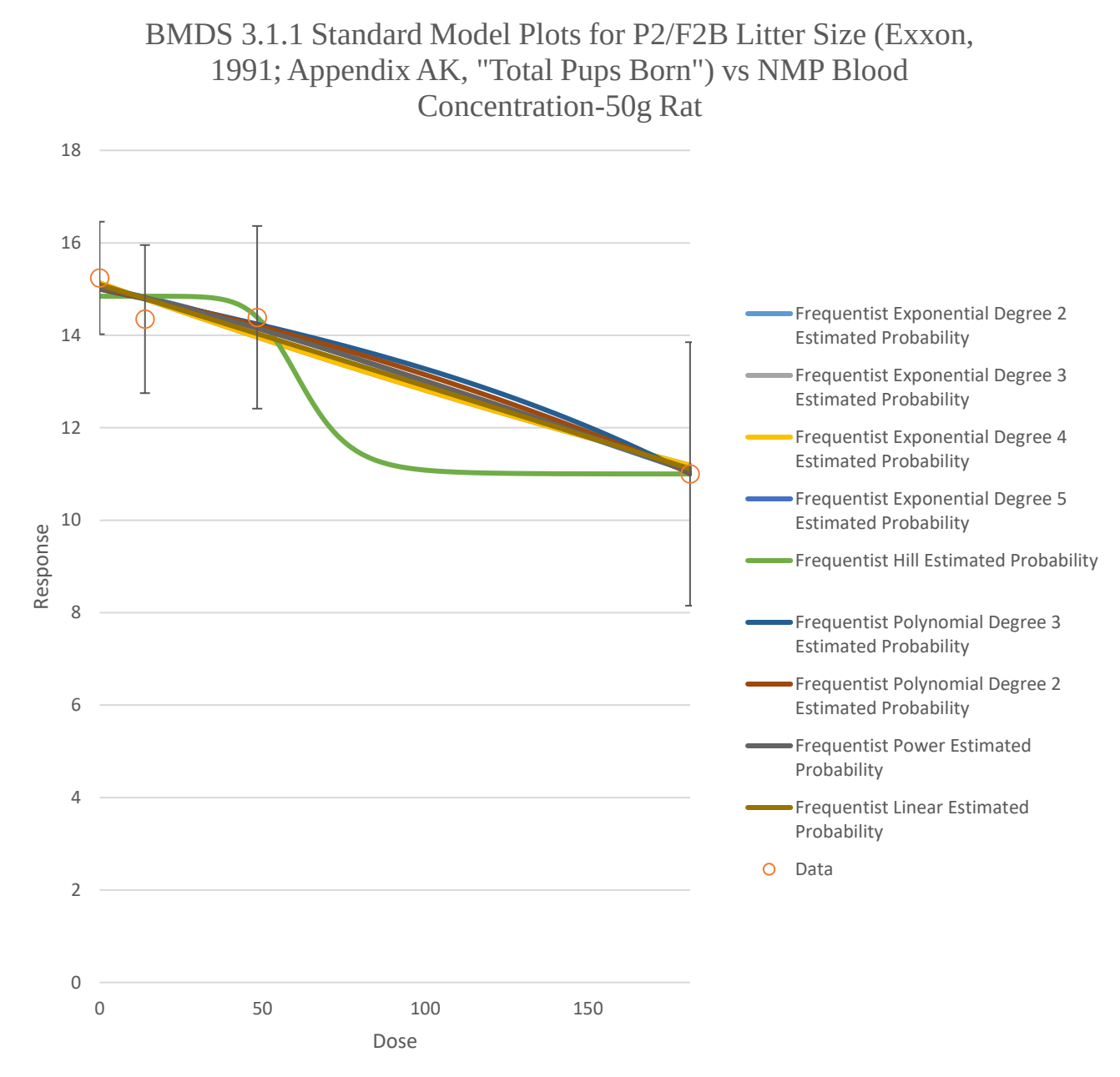
mg/L Blood – 50 g Rat	N	Mean	SD
0	25	15.24	2.947881
13.9	20	14.35	3.422449
48.4	18	14.39	3.972536
181.4	9	11	3.708099

Summary of BMDS 3.1.1 Modeling Results for P2/F2B Litter Size – 50 g Rat (Exxon, 1991)

Table 4-10 Model Predictions for Litter Size in P2/F2B Rats Based on Post-weaning Exposure (Exxon, 1991)

Standard Models	Restriction**	BMR = 1 Standard Deviation (mg/L blood – 50 g Rat)			P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL	BMDU				
Exponential 2 (CV)	Restricted	151.211	90.0144	358.8807	0.710819 6	385.221887	Viable - Alternate	
Exponential 3 (CV)	Restricted	156.952	90.5626	352.6854	0.435551 2	387.147189	Viable - Alternate	
Exponential 4 (CV)	Restricted	151.178	90.0145	358.8685	0.710823 3	385.221876 5	Viable - Alternate	
Exponential 5 (CV)	Restricted	156.962	50.8164	352.691	NA	389.147203 2	Viable - Alternate	BMD/BMDL ratio > 3 d.f.=0 (Goodness of fit test cannot be calculated)
Hill (CV)	Restricted	79.4642	51.8612	Infinity	NA	389.317859	Questionable	d.f.=0 (Goodness of fit test cannot be calculated)
Polynomial Degree 3 (CV)	Restricted	162.787	100.264	324.5483	0.478185 6	387.042212	Viable - Alternate	
Polynomial Degree 2 (CV)	Restricted	159.731	100.102	326.2531	0.467703 9	387.066609 3	Viable - Alternate	
Power (CV)	Restricted	157.000	99.7630	329.8951	0.446602 9	387.118472 9	Viable - Alternate	
Linear (CV)	NA	**153.231**	**99.6158**	**331.5177**	**0.740097 5**	**385.141160 3**	**Recommended**	**Basis: Lowest AIC**

*Selected Model (Green); Constant variance case presented (Test 2 p-value = 0.60824); scaled residuals for doses 0, 13.9, 48.4 and 181.4 were 0.209483207, -0.589116734, 0.445351928 and -0.100787718, respectively.
**Restrictions defined in the BMDS 3.1.1 User Guide; NA = Not Applicable; CV = Constant Variance Model; NCV = Non-Constant Variance Model


BMDS 3.1.1 Standard Model Plots for P2/F2B Litter Size (Exxon, 1991; Appendix AK, "Total Pups Born") vs NMP Blood Concentration-50g Rat
Response
Dose
0
2
4
6
8
10
12
14
16
18
0
50
100
150
Frequentist Exponential Degree 2 Estimated Probability
Frequentist Exponential Degree 3 Estimated Probability
Frequentist Exponential Degree 4 Estimated Probability
Frequentist Exponential Degree 5 Estimated Probability
Frequentist Hill Estimated Probability
Frequentist Polynomial Degree 3 Estimated Probability
Frequentist Polynomial Degree 2 Estimated Probability
Frequentist Power Estimated Probability
Frequentist Linear Estimated Probability
Data

Selected Model – Linear - Extra Risk, BMR = 1 SD

User Input

Info	
Model	Linear v1.1
Dataset Name	P2F2B Litter Size
User notes	[Add user notes here]
Dose-Response Model	M[dose] = g + b1*dose

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

Model Data	
Dependent Variable	[Dose]
Independent Variable	[Response]
Total # of Observations	72
Adverse Direction	Automatic

Model Results

Benchmark Dose	
BMD	153.2308251
BMDL	99.6158179
BMDU	331.5176516
AIC	385.1411603
Test 4 P-value	0.740097541
D.O.F.	2

Model Parameters	
# of Parameters	3
Variable	Estimate
g	15.09893919
beta1	-0.02197258
alpha	11.33585663

Goodness of Fit

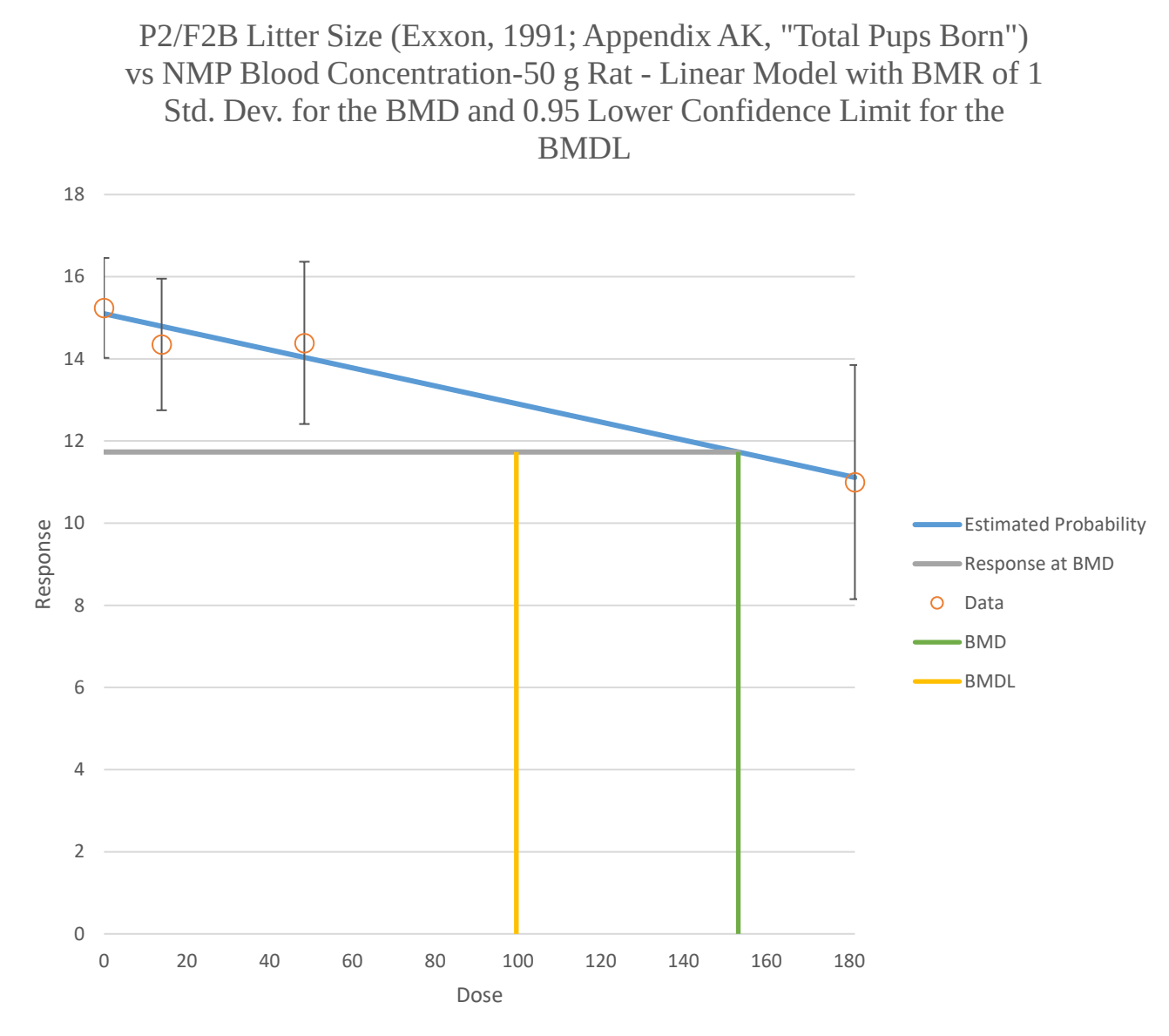
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	25	15.09893919	15.24	15.24	3.36687639	2.947881	2.947881	0.209483207
13.9	20	14.79352033	14.35	14.35	3.36687639	3.422449	3.422449	-0.58911673
48.4	18	14.03546634	14.3888889	14.3888889	3.36687639	3.972536	3.972536	0.445351928
181.4	9	11.11311326	11	11	3.36687639	3.708099	3.708099	-0.10078772

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-189.2696069	5	388.539214
A2	-188.354168	8	392.708336
A3	-189.2696069	5	388.539214
fitted	-189.5705801	3	385.14116
R	-194.2508792	2	392.501758

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	11.79342232	6	0.06673919
2	1.830877708	3	0.60823876
3	1.830877708	3	0.60823876
4	0.601946577	2	0.74009754


P2/F2B Litter Size (Exxon, 1991; Appendix AK, "Total Pups Born") vs NMP Blood Concentration-50 g Rat - Linear Model with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
2
4
6
8
10
12
14
16
18
0
20
40
60
80
100
120
140
160
180
Estimated Probability
Response at BMD
Data
BMD
BMDL

4.5.3 P2/F2A Litter Size – GD 6-21 Rat (Exxon Appendix AJ, "Total Pups Born")

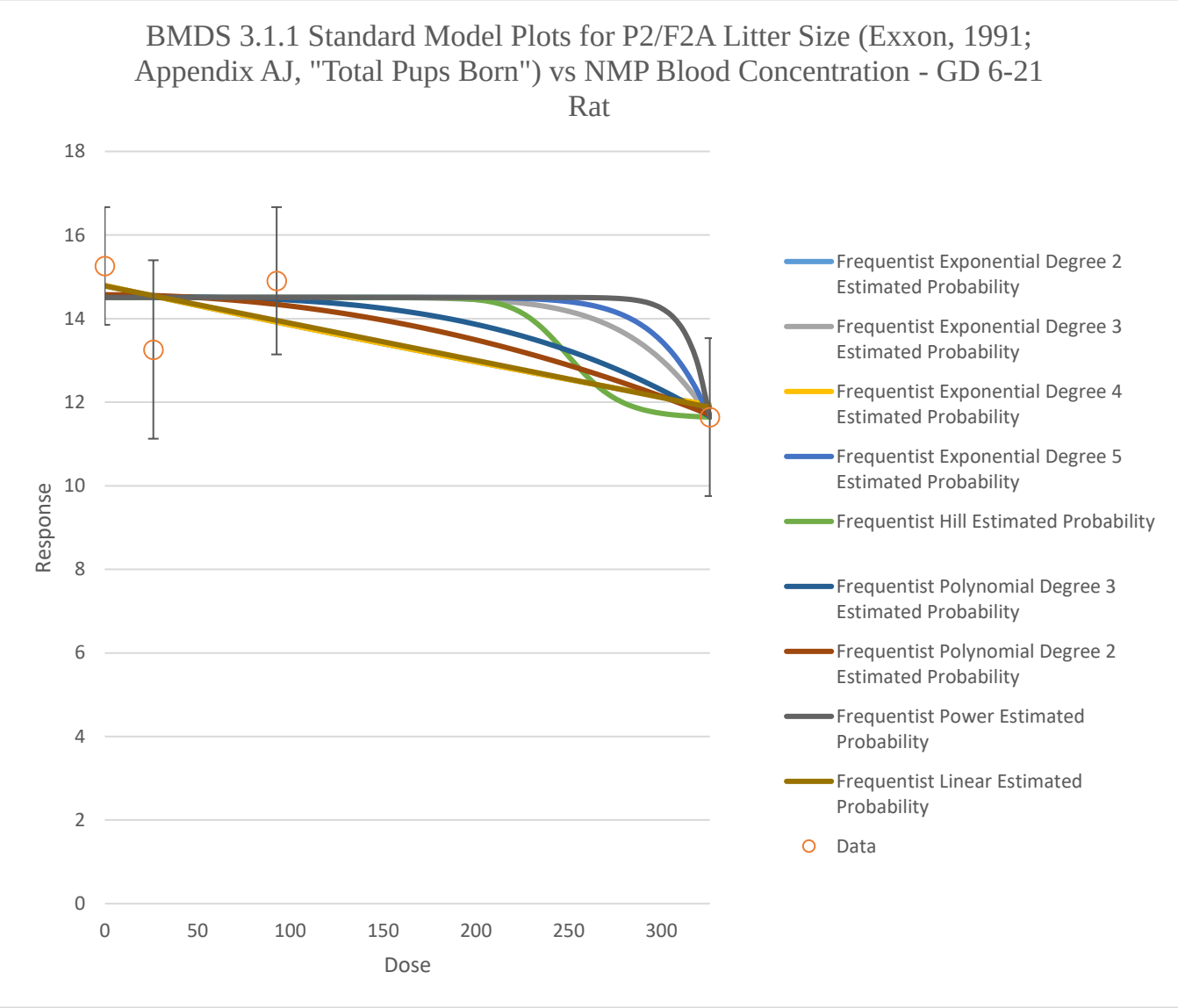
mg/L Blood – GD 6-21 Rat	N	Mean	SD
0	27	15.2592593	3.558225
26.1207	23	13.2608696	4.937955
92.5466	21	14.9047619	3.871754
326.1056	14	11.6428571	3.272429

Summary of BMDS 3.1.1 Modeling Results for P2/F2A Litter Size – GD 6-21 Rat (Exxon, 1991)

Table 4-11 Model Predictions for Litter Size in P2/F2A Rats Based on Gestational Exposure (Exxon, 1991)

Standard Models	Restriction**	BMR = 1 Standard Deviation (mg/L Blood – GD 6-21 Rat)			P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL	BMDU				
Exponential 2 (CV)	Restricted	479.877	254.430	1919.152	0.1260017	483.5003647	Viable - Alternate	BMD higher than maximum dose
Exponential 3 (CV)	Restricted	341.070	272.816	1398.651	0.0625939	484.8247334	Questionable	Goodness of fit p-value < 0.1 BMD higher than maximum dose
Exponential 4 (CV)	Restricted	479.845	254.427	1919.011	0.041809	485.5003647	Viable - Alternate	Goodness of fit p-value < 0.1 BMD higher than maximum dose
Exponential 5 (CV)	Restricted	335.907	105.778	369.6251	NA	486.8246164	Questionable	BMD/BMDL ratio > 3 BMD higher than maximum dose d.f.=0 (Goodness of fit test cannot be calculated)
Hill (CV)	Restricted	-9999	0	Infinity	NA	486.8246156	Unusable	BMD computation failed BMD not estimated BMDL not estimated d.f.=0 (Goodness of fit test cannot be calculated)
Polynomial Degree 3 (CV)	**Restricted**	**364.394**	**273.796**	**1275.735**	**0.170808**	**482.8918758**	**Recommended**	**Basis: Lowest AIC BMD higher than maximum dose**
Polynomial Degree 2 (CV)	Restricted	384.961	270.021	1364.628	0.1578744	483.0493569	Viable - Alternate	BMD higher than maximum dose
Power (CV)	Restricted	329.908	275.482	1240.389	0.0625983	484.824615	Questionable	Goodness of fit p-value < 0.1 BMD higher than maximum dose
Linear (CV)	NA	450.859	261.883	1618.656	0.1308827	483.4243533	Viable - Alternate	BMD higher than maximum dose

*Selected Model (Green); Constant variance case presented (Test 2 p-value = 0.24158); scaled residuals for doses0, 26.1207, 92.5466 and 326.1056were 0.954993534, -1.512767309, 0.511175014 and -0.013313118, respectively.
**Restrictions defined in the BMDS 3.1.1 User Guide; NA = Not Applicable; CV = Constant Variance Model; NCV = Non-Constant Variance Model


BMDS 3.1.1 Standard Model Plots for P2/F2A Litter Size (Exxon, 1991; Appendix AJ, "Total Pups Born") vs NMP Blood Concentration - GD 6-21 Rat
Response
Dose
0
2
4
6
8
10
12
14
16
18
0
50
100
150
200
250
300
Frequentist Exponential Degree 2 Estimated Probability
Frequentist Exponential Degree 3 Estimated Probability
Frequentist Exponential Degree 4 Estimated Probability
Frequentist Exponential Degree 5 Estimated Probability
Frequentist Hill Estimated Probability
Frequentist Polynomial Degree 3 Estimated Probability
Frequentist Polynomial Degree 2 Estimated Probability
Frequentist Power Estimated Probability
Frequentist Linear Estimated Probability
Data

Selected Model – Polynomial Degree 3 (Restricted) - Extra Risk, BMR = 1

User Input

Info	
Model	Polynomial degree 3 v1.1
Dataset Name	P2F2A Litter Size GD 6-21
User notes	[Add user notes here]
Dose-Response Model	M[dose] = g + b1*dose + b2*dose^2 + ...

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

Model Data	
Dependent Variable	[Dose]
Independent Variable	[Response]
Total # of Observations	85
Adverse Direction	Automatic

Model Results

Benchmark Dose	
BMD	364.3935627
BMDL	273.7956247
BMDU	1275.734624
AIC	482.8918758
Test 4 P-value	0.170808016
D.O.F.	2
Model Parameters	
# of Parameters	5
Variable	Estimate
g	14.52409502
b1	Bounded
b2	Bounded
b3	-8.26711E-08
alpha	16.00042971

Goodness of Fit

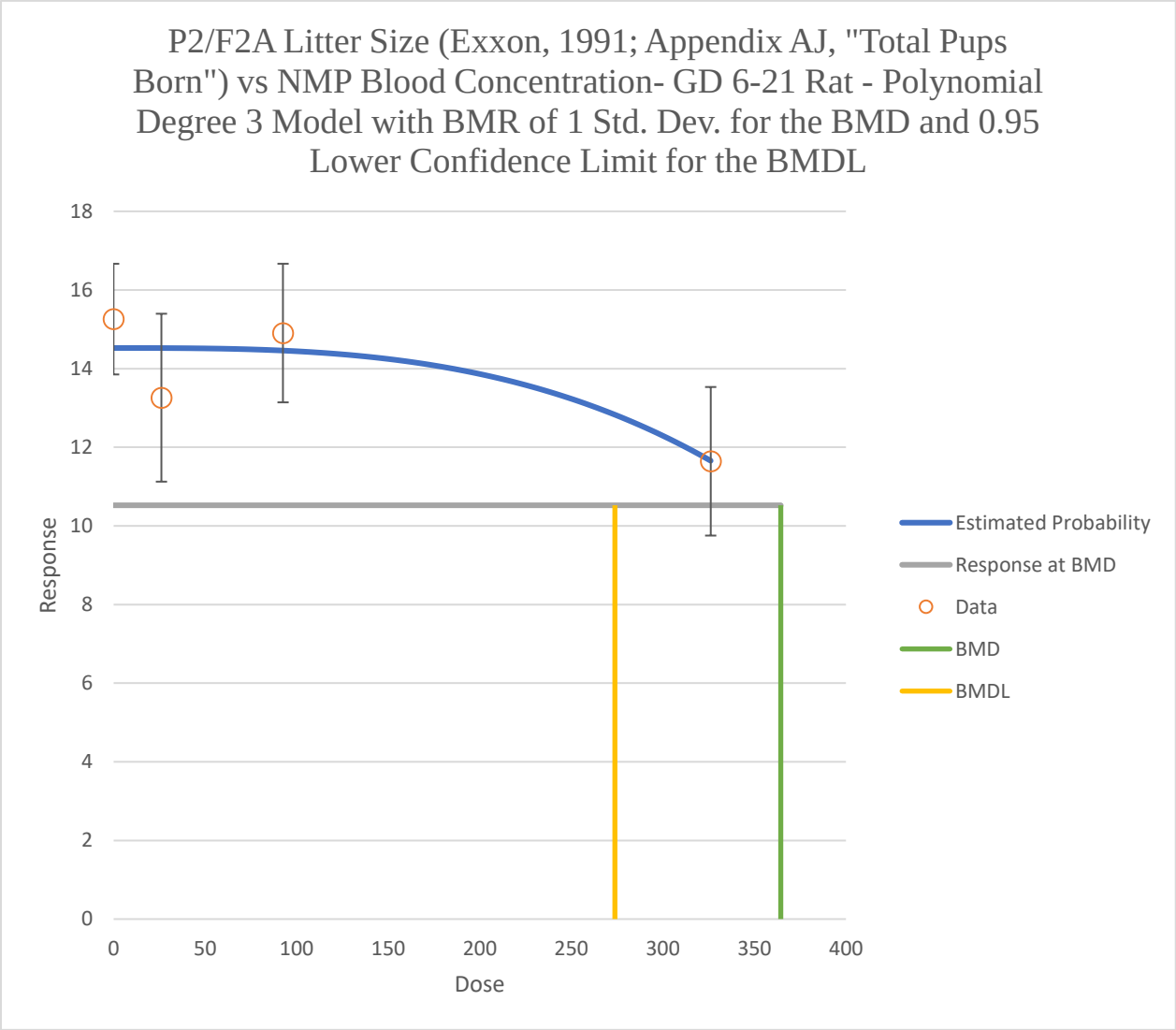
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	27	14.52409502	15.2592593	15.2592593	4.00005371	3.558225	3.558225	0.954993534
26.1207	23	14.52262166	13.2608696	13.2608696	4.00005371	4.937955	4.937955	-1.512767309
92.5466	21	14.45856578	14.9047619	14.9047619	4.00005371	3.871754	3.871754	0.511175014
326.1056	14	11.65708966	11.6428571	11.6428571	4.00005371	3.272429	3.272429	-0.013313118

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-236.6787228	5	483.357446
A2	-234.583299	8	485.166598
A3	-236.6787228	5	483.357446
fitted	-238.4459379	3	482.891876
R	-241.3113542	2	486.622708

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	13.45611034	6	0.03633832
2	4.190847665	3	0.24157981
3	4.190847665	3	0.24157981
4	3.534430134	2	0.17080802


P2/F2A Litter Size (Exxon, 1991; Appendix AJ, "Total Pups Born") vs NMP Blood Concentration- GD 6-21 Rat - Polynomial Degree 3 Model with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
2
4
6
8
10
12
14
16
18
0
50
100
150
200
250
300
350
400
Estimated Probability
Response at BMD
Data
BMD
BMDL

4.5.4 P2/F2B Litter Size – GD 6-21 Rat (Exxon Appendix AK, "Total Pups Born")

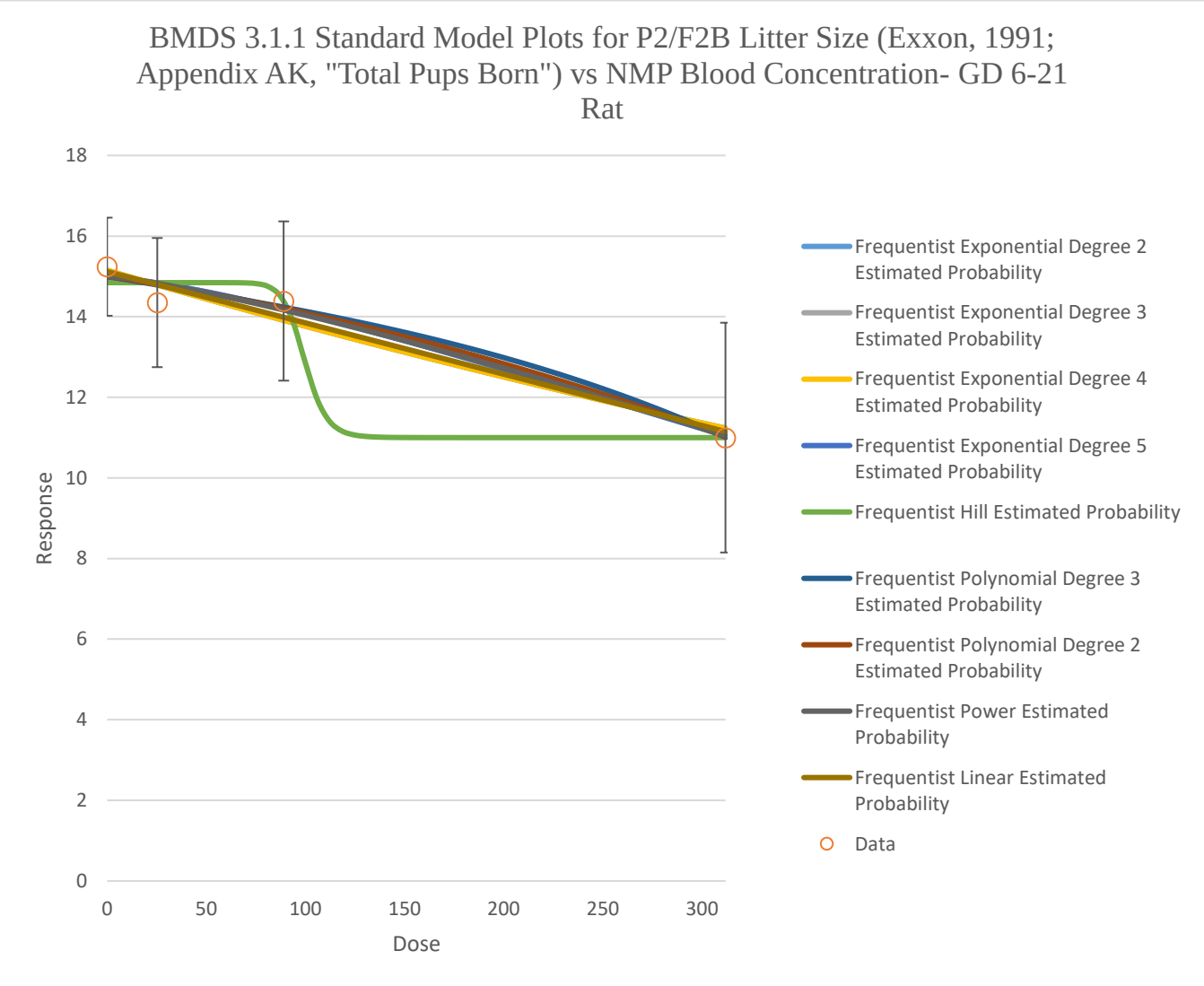
mg/L Blood – GD 6-21 Rat	N	Mean	SD
0	25	15.24	2.947881
25.25	20	14.35	3.422449
89.03	18	14.39	3.972536
311.9	9	11	3.708099

Summary of BMDS 3.1.1 Modeling Results for P2/F2B Litter Size – GD 6-21 Rat (Exxon, 1991)

Table 4-12 Model Predictions for Litter Size in P2/F2B Rats Based on Gestational Exposure (Exxon, 1991)

Standard Models	Restriction **	BMR = 1 Standard Deviation (mg/L Blood – GD 6-21 Rat)			P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL	BMDU				
Exponential 2 (CV)	Restricted	262.367	156.209	625.5100	0.6820873	385.304409	Viable - Alternate	
Exponential 3 (CV)	Restricted	273.939	157.878	606.7505	0.4253036	387.174826	Viable - Alternate	
Exponential 4 (CV)	Restricted	262.375	156.208	625.4980	0.6820873	385.304409	Viable - Alternate	
Exponential 5 (CV)	Restricted	273.909	157.876	606.7426	NA	389.174824	Questionable	d.f.=0 (Goodness of fit test cannot be calculated)
Hill (CV)	Restricted	111.061	95.2881	Infinity	NA	389.317907	Questionable	d.f.=0 (Goodness of fit test cannot be calculated)
Polynomial Degree 3 (CV)	Restricted	281.842	173.628	556.2398	0.4745885	387.050462	Viable - Alternate	
Polynomial Degree 2 (CV)	Restricted	276.875	173.241	560.2511	0.4606428	387.083541	Viable - Alternate	
Power (CV)	Restricted	273.907	172.502	568.1038	0.4351554	387.148231	Viable - Alternate	
Linear (CV)	**NA**	**264.704**	**171.883**	**574.9049**	**0.717494**	**385.203195**	**Recommended**	**Basis: Lowest AIC**

*Selected Model (Green); Constant variance case presented (Test 2 p-value = 0.60824); scaled residuals for selected model for doses 0, 25.25, 89.0333, and 311.8896 were 0.180266075, -0.593822034, 0.507945167 and -0.133410146, respectively.
**Restrictions defined in the BMDS 3.1.1 User Guide; NA = Not Applicable; CV = Constant Variance Model; NCV = Non-Constant Variance Model


BMDS 3.1.1 Standard Model Plots for P2/F2B Litter Size (Exxon, 1991; Appendix AK, "Total Pups Born") vs NMP Blood Concentration- GD 6-21 Rat
Response
Dose
0
2
4
6
8
10
12
14
16
18
0
50
100
150
200
250
300
Frequentist Exponential Degree 2 Estimated Probability
Frequentist Exponential Degree 3 Estimated Probability
Frequentist Exponential Degree 4 Estimated Probability
Frequentist Exponential Degree 5 Estimated Probability
Frequentist Hill Estimated Probability
Frequentist Polynomial Degree 3 Estimated Probability
Frequentist Polynomial Degree 2 Estimated Probability
Frequentist Power Estimated Probability
Frequentist Linear Estimated Probability
Data

Selected Model –Linear - Extra Risk, BMR = 1 SD

User Input

Info	
Model	Linear v1.1
Dataset Name	P2F2B Litter Size GD 6-21
User notes	[Add user notes here]
Dose-Response Model	M[dose] = g + b1*dose

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

Model Data	
Dependent Variable	Dose]
Independent Variable	Response]
Total # of Observations	72
Adverse Direction	Automatic

Model Results

Benchmark Dose	
BMD	264.7037947
BMDL	171.8830314
BMDU	574.9048606
AIC	385.203195
Test 4 P-value	0.717494025
D.O.F.	2

Model Parameters	
# of Parameters	3
Variable	Estimate
g	15.11856069
beta1	-0.012724921
alpha	11.34568072

Goodness of Fit

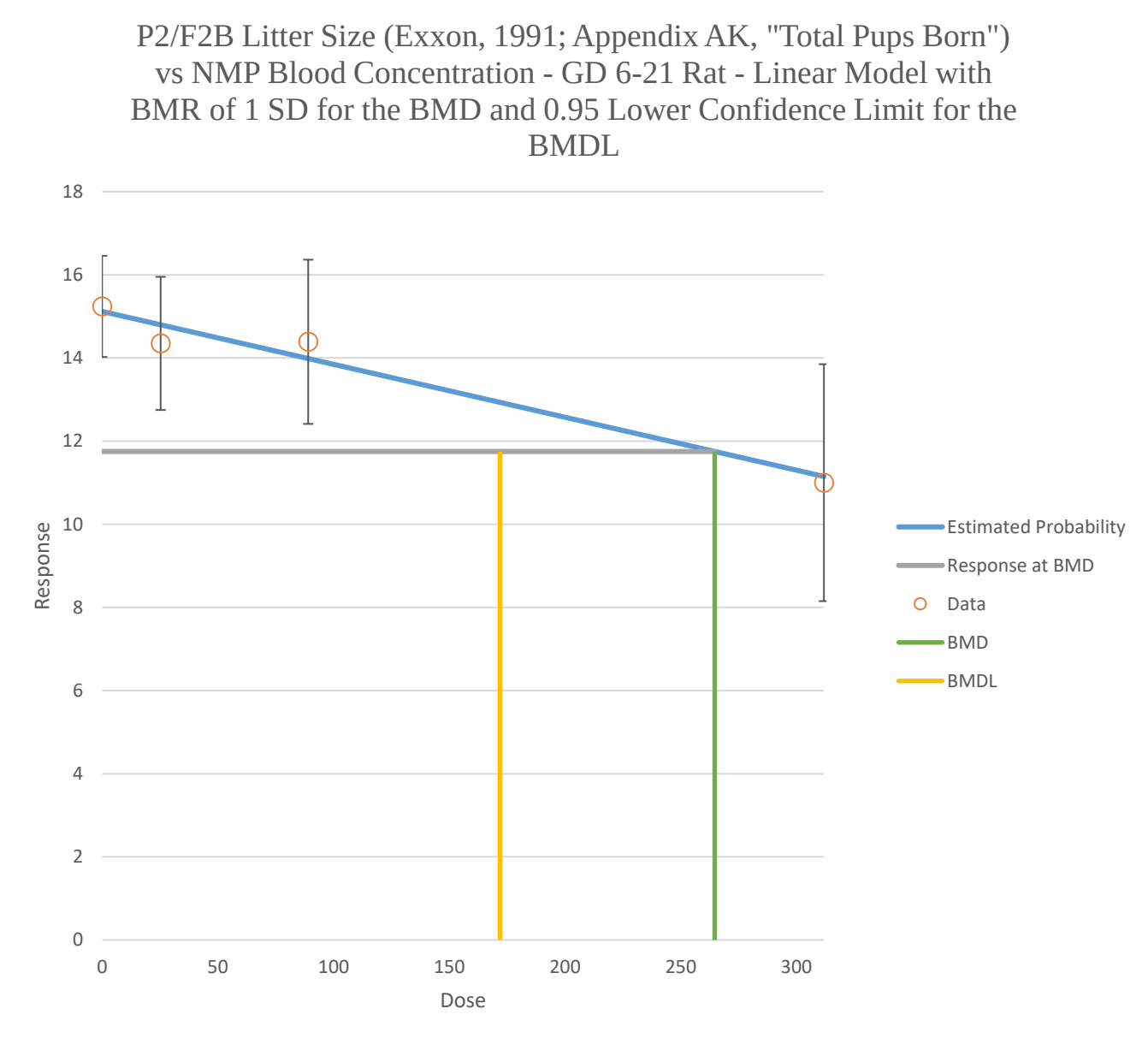
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	25	15.11856069	15.24	15.24	3.36833501	2.947881	2.947881	0.180266075
25.25	20	14.79725643	14.35	14.35	3.36833501	3.422449	3.422449	-0.59382203
89.0333	18	13.98561894	14.3888889	14.3888889	3.36833501	3.972536	3.972536	0.507945167
311.8896	9	11.14979002	11	11	3.36833501	3.708099	3.708099	-0.13341015

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-189.2696069	5	388.539214
A2	-188.354168	8	392.708336
A3	-189.2696069	5	388.539214
fitted	-189.6015975	3	385.203195
R	-194.2508792	2	392.501758

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	11.79342232	6	0.06673919
2	1.830877708	3	0.60823876
3	1.830877708	3	0.60823876
4	0.663981316	2	0.71749403


P2/F2B Litter Size (Exxon, 1991; Appendix AK, "Total Pups Born") vs NMP Blood Concentration - GD 6-21 Rat - Linear Model with BMR of 1 SD for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
2
4
6
8
10
12
14
16
18
0
50
100
150
200
250
300
Estimated Probability
Response at BMD
Data
BMD
BMDL

4.6 Results of BMD Modeling of P2 Pup Death (Exxon, 1991)

Nested dichotomous models were applied to fit pup death for the P2/F2A and P2/F2B litters. Nested dichotomous models are preferred for this endpoint because they contain an intra-litter correlation coefficient for the assessment of litter-specific responses. Details regarding pup death at day 0 (stillborn) and by day 4 are available in Appendix AJ (for P2/F2A litters) and AK (for P2/FB litters) of the Exxon (1991) report.

The pup death endpoint was analyzed using BMDS 2.7 because it contains the larger suite of nested dichotomous models. To assess intra-litter correlations (ILC) BMDS nested dichotomous models were run two ways, with ILC coefficients estimated and with ILC coefficients assumed to be zero. Because potential litter-specific covariates (LSCs) such as dam BW are affected by dose, LSCs were not assessed in the BMDS nested dichotomous model runs. The following nested dichotomouse models and general modeling options were used to the pup death incidence data.

Nested Dichotomous Models Applied to Pup Death Response[5]:

- NLogistic – Nested Logistic model with ILC coefficients assumed to be 0
- NLogistic-ILC – Nested Logistic model with ILC coefficients estimated
- NCTR - National Center for Toxicological Research model with ILC coefficients assumed to be 0
- NCTR-ILC - NCTR model with ILC coefficients estimated
- RaiVR – Rai and Van Ryzin model with ILC coefficients assumed to be 0
- RaiVR-ILC - Rai and Van Ryzin model with ILC coefficients estimated

General Model Options Used for Pup Death Nested Dichotomous Response:

- Benchmark Response (BMR): 10% (not shown in report), 5% and 1% Extra Risk
- Confidence Level: 0.95
- Background: Estimated

[5] As indicated in the tables in 2.6, the NLogistic model is generally preferred because it has received the more extensive QA testing, but the NCTR and RaiVR models are provided as alternative models.

4.6.1 P2/F2A Pups Dead at Day 0 (Stillborn Day 0/Total Pups Born; Exxon 1991 Appendix AJ)

Control			26.1207 avg. mg/L blood GD6-21			92.5466 avg. mg/L blood GD6-21			326.1056 avg. mg/L blood GD6-21		
Dam	**N**	**Stillborn**	**Dam**	**N**	**Stillborn**	**Dam**	**N**	**Stillborn**	**Dam**	**N**	**Stillborn**
JAB248	12	0	JAB029	17	0	JAB302	15	0	JAB325	13	0
JAB026	16	0	JAB032	17	0	JAB038	14	1	JAB327	12	0
JAB251	14	0	JAB279	14	2	JAB110	15	0	JAB041	13	8
JAB097	15	0	JAB104	13	1	JAB305	16	1	JAB135	7	0
JAB254	9	0	JAB282	13	0	JAB113	20	1	JAB136	4	0
JAB100	18	2	JAB285	16	1	JAB116	22	1	JAB045	14	0
JAB257	17	1	JAB288	17	0	JAB311	16	0	JAB050	12	0
JAB260	18	0	JAB035	14	1	JAB121	9	0	JAB336	11	0
JAB263	15	0	JAB107	19	0	JAB319	15	0	JAB329	11	0
JAB266	15	0	JAB292	1	1	JAB322	14	0	JAB330	8	2
JAB269	18	1	JAB295	7	0	JAB320	3	0	JAB046	14	0
JAB10	18	1	JAB347	16	0	JAB306	13	0	JAB328	14	0
JAB270	18	0	JAB298	5	0	JAB313	17	1	JAB134	16	1
JAB273	15	0	JAB348	19	1	JAB323	14	0	JAB341	14	1
JAB252	16	0	JAB293	5	0	JAB310	15	1			
JAB028	18	1	JAB037	14	1	JAB117	14	0			
JAB275	18	0	JAB349	16	0	JAB040	20	0			
JAB255	16	0	JAB278	16	1	JAB309	14	1			
JAB264	15	0	JAB105	14	0	JAB039	16	0			
JAB267	17	0	JAB297	15	0	JAB317	14	0			
JAB262	17	0	JAB106	17	0	JAB112	17	0			
JAB102	17	3	JAB281	6	0						
JAB246	2	**1**	JAB290	14	0						
JAB256	10	0									
JAB098	15	0									
JAB249	15	0									

JAB253	18	0									

Summary of BMDS 3.1.1 Modeling Results for P2/F2A Pups Dead at Day 0 (Exxon, 1991)

Table 4-13 Model Predictions for Pup Death at Day 0 in P2/F2A Rats (Exxon, 1991)

Preferred Models*	5% Extra Risk		1% Extra Risk		P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
	BMD	BMDL	BMD	BMDL				
NLogistic	326.34	240.809	280.408	50.7883	0.0007	334.364	Questionable	BMD/BMDL ratio > 3 Goodness of fit p-value < 0.1
NLogistic-ILC	**327.095**	**205.186**	**281.145**	**49.3219**	**0.1017**	**313.315**	**Recommended**	**Basis: Lowest AIC** BMD/BMDL ratio > 3 for 1% Extra Risk
Alternative Models								
NCTR	326.327	271.939	282.34	235.284	0	332.364	Questionable	Goodness of fit p-value < 0.1
NCTR-ILC	327.114	0.633785	327.114	0.633785	0.1103	311.315	Questionable	BMD/BMDL ratio > 20
RaiVR	281.131	234.276	281.131	234.276	0	332.364	Questionable	Goodness of fit p-value < 0.1
RaiVR-ILC	327.118	0.633785	280.539	0.472244	0.0867	311.315	Questionable	BMD/BMDL ratio > 20

*NLogistic is preferred because it is the more rigorously tested nested model. All nested models were restricted. Restrictions are defined in the BMDS 3.1.1 User Guide; ILC = Intra-litter Correlation Coefficients estimated; Because potential litter-specific covariates (LSCs) such as dam BW are affected by dose, LSCs were not estimated.
**Selected Model (Green); the average scaled residual for dose group nearest the BMD_{05} and BMD_{01} were -0.3523 and -0.3523, respectively.

Selected Model Results– NLogistic- ILC, BMR = 0.01 and 0.05 Extra Risk

```
================================================================
        NLogistic Model. (Version: 2.20; Date: 04/27/2015)
        Input Data File: C:/Users/jgift/BMDS2704/Data/NMP/P2F2A Dead Day 0/nln_P2F2A Day 0 Deaths_Nln-BMR01-Restrict-
noLSC.(d)
                                                    Tue Jul 30 22:03:20 2019
================================================================

BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

The probability function is:


Prob. = alpha + theta1*Rij + [1 - alpha - theta1*Rij]/

            [1+exp(-beta-theta2*Rij-rho*log(Dose))],

   where Rij is the litter specific covariate.

Restrict Power rho >= 1.



Total number of observations = 85
Total number of records with missing values = 0
Total number of parameters in model = 9
Total number of specified parameters = 2


Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
Number of Bootstrap Iterations per run: 1000
Bootstrap Seed:  1564538600

User specifies the following parameters:
   theta1 =         0
   theta2 =         0


          Default Initial Parameter Values
               alpha =      0.02553
                beta =     -66.0821
              theta1 =            0   Specified
              theta2 =            0   Specified
                rho =      10.9041
               phi1 =    0.0392728
               phi2 =            0
               phi3 =            0
               phi4 =     0.310565


                  Parameter Estimates
```

Variable	Estimate	Std. Err.
alpha	0.02553	0.00468854
beta	-66.0821	0.792172
rho	10.9041	0.0311563
phi1	0.0392728	NA
phi2	0	Bounded
phi3	0	Bounded
phi4	0.310565	NA

Log-likelihood: -151.658 AIC: 313.315

Litter Data

Dose	Lit.-Spec. Cov.	Est._Prob.	Litter Size	Expected	Scaled Observed	Residual
0.0000	2.0000	0.026	2	0.051	1	4.1730
0.0000	9.0000	0.026	9	0.230	0	-0.4236
0.0000	10.0000	0.026	10	0.255	0	-0.4400
0.0000	12.0000	0.026	12	0.306	0	-0.4686
0.0000	14.0000	0.026	14	0.357	0	-0.4928
0.0000	15.0000	0.026	15	0.383	0	-0.5036
0.0000	15.0000	0.026	15	0.383	0	-0.5036
0.0000	15.0000	0.026	15	0.383	0	-0.5036
0.0000	15.0000	0.026	15	0.383	0	-0.5036
0.0000	15.0000	0.026	15	0.383	0	-0.5036
0.0000	15.0000	0.026	15	0.383	0	-0.5036
0.0000	15.0000	0.026	15	0.383	0	-0.5036
0.0000	16.0000	0.026	16	0.408	0	-0.5136
0.0000	16.0000	0.026	16	0.408	0	-0.5136
0.0000	16.0000	0.026	16	0.408	0	-0.5136
0.0000	17.0000	0.026	17	0.434	0	-0.5230
0.0000	17.0000	0.026	17	0.434	0	-0.5230
0.0000	17.0000	0.026	17	0.434	1	0.6820
0.0000	17.0000	0.026	17	0.434	3	3.0920
0.0000	18.0000	0.026	18	0.460	0	-0.5318
0.0000	18.0000	0.026	18	0.460	1	0.6254
0.0000	18.0000	0.026	18	0.460	1	0.6254
0.0000	18.0000	0.026	18	0.460	0	-0.5318
0.0000	18.0000	0.026	18	0.460	0	-0.5318
0.0000	18.0000	0.026	18	0.460	2	1.7826
0.0000	18.0000	0.026	18	0.460	1	0.6254
0.0000	18.0000	0.026	18	0.460	0	-0.5318
26.1207	1.0000	0.026	1	0.026	1	6.1782
26.1207	5.0000	0.026	5	0.128	0	-0.3619
26.1207	5.0000	0.026	5	0.128	0	-0.3619
26.1207	6.0000	0.026	6	0.153	0	-0.3965
26.1207	7.0000	0.026	7	0.179	0	-0.4282
26.1207	13.0000	0.026	13	0.332	1	1.1748
26.1207	13.0000	0.026	13	0.332	0	-0.5836
26.1207	14.0000	0.026	14	0.357	0	-0.6056
26.1207	14.0000	0.026	14	0.357	2	2.7833
26.1207	14.0000	0.026	14	0.357	0	-0.6056
26.1207	14.0000	0.026	14	0.357	1	1.0888
26.1207	14.0000	0.026	14	0.357	1	1.0888
26.1207	15.0000	0.026	15	0.383	0	-0.6269
26.1207	16.0000	0.026	16	0.408	1	0.9376
26.1207	16.0000	0.026	16	0.408	0	-0.6474
26.1207	16.0000	0.026	16	0.408	0	-0.6474

26.1207	16.0000	0.026	16	0.408	1	0.9376
26.1207	17.0000	0.026	17	0.434	0	-0.6674
26.1207	17.0000	0.026	17	0.434	0	-0.6674
26.1207	17.0000	0.026	17	0.434	0	-0.6674
26.1207	17.0000	0.026	17	0.434	0	-0.6674
26.1207	19.0000	0.026	19	0.485	1	0.7490
26.1207	19.0000	0.026	19	0.485	0	-0.7055
92.5466	3.0000	0.026	3	0.077	0	-0.2804
92.5466	9.0000	0.026	9	0.230	0	-0.4856
92.5466	13.0000	0.026	13	0.332	0	-0.5836
92.5466	14.0000	0.026	14	0.357	0	-0.6056
92.5466	14.0000	0.026	14	0.357	1	1.0888
92.5466	14.0000	0.026	14	0.357	0	-0.6056
92.5466	14.0000	0.026	14	0.357	1	1.0888
92.5466	14.0000	0.026	14	0.357	0	-0.6056
92.5466	14.0000	0.026	14	0.357	0	-0.6056
92.5466	15.0000	0.026	15	0.383	0	-0.6269
92.5466	15.0000	0.026	15	0.383	0	-0.6269
92.5466	15.0000	0.026	15	0.383	0	-0.6269
92.5466	15.0000	0.026	15	0.383	1	1.0101
92.5466	16.0000	0.026	16	0.408	0	-0.6474
92.5466	16.0000	0.026	16	0.408	1	0.9376
92.5466	16.0000	0.026	16	0.408	0	-0.6474
92.5466	17.0000	0.026	17	0.434	1	0.8703
92.5466	17.0000	0.026	17	0.434	0	-0.6674
92.5466	20.0000	0.026	20	0.511	1	0.6938
92.5466	20.0000	0.026	20	0.511	0	-0.7239
92.5466	22.0000	0.026	22	0.562	1	0.5925
326.1056	4.0000	0.073	4	0.291	0	-0.4031
326.1056	7.0000	0.073	7	0.509	0	-0.4379
326.1056	8.0000	0.073	8	0.582	2	1.0835
326.1056	11.0000	0.073	11	0.800	0	-0.4585
326.1056	11.0000	0.073	11	0.800	0	-0.4585
326.1056	12.0000	0.073	12	0.873	0	-0.4617
326.1056	12.0000	0.073	12	0.873	0	-0.4617
326.1056	13.0000	0.073	13	0.946	8	3.4649
326.1056	13.0000	0.073	13	0.946	0	-0.4645
326.1056	14.0000	0.073	14	1.018	1	-0.0085
326.1056	14.0000	0.073	14	1.018	0	-0.4669
326.1056	14.0000	0.073	14	1.018	0	-0.4669
326.1056	14.0000	0.073	14	1.018	0	-0.4669
326.1056	16.0000	0.073	16	1.164	1	-0.0663

Scaled Residual(s) for Dose Group Nearest the BMD

Minimum scaled residual for dose group nearest the BMD = -0.4669
Minimum ABS(scaled residual) for dose group nearest the BMD = 0.0085
Average scaled residual for dose group nearest the BMD = -0.3523
Average ABS(scaled residual) for dose group nearest the BMD = 0.3523
Maximum scaled residual for dose group nearest the BMD = -0.0085
Maximum ABS(scaled residual) for dose group nearest the BMD = 0.4669
Number of litters used for scaled residual for dose group nearest the BMD = 4

Observed Chi-square = 120.2685

Bootstrapping Results

Number of Bootstrap Iterations per run: 1000

Bootstrap Chi-square Percentiles

Bootstrap Run	P-value	50th	90th	95th	99th
1	0.1020	80.1651	120.8799	132.3672	165.0942
2	0.0930	81.2319	117.9970	132.3763	160.2242
3	0.1050	81.1876	121.5273	137.2496	166.6223
Combined	0.1000	80.9778	120.2642	133.6763	165.0942

The results for three separate runs are shown. If the estimated p-values are sufficiently stable (do not vary considerably from run to run), then then number of iterations is considered adequate. The p-value that should be reported is the one that combines the results of the three runs. If sufficient stability is not evident (and especially if the p-values are close to the critical level for determining adequate fit, e.g., 0.05), then the user should consider increasing the number of iterations per run.

To calculate the BMD and BMDL, the litter specific covariate is fixed at the mean litter specific covariate of all the data: 14.035294

Benchmark Dose Computation

Specified effects = 0.01, 0.05

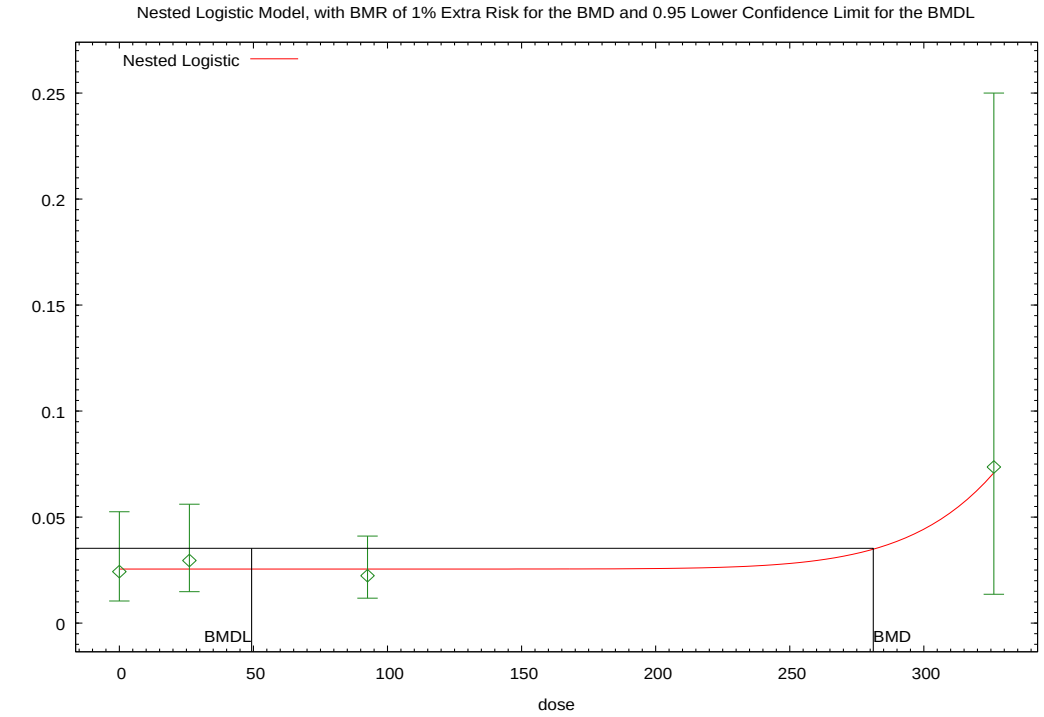
Risk Type = Extra risk

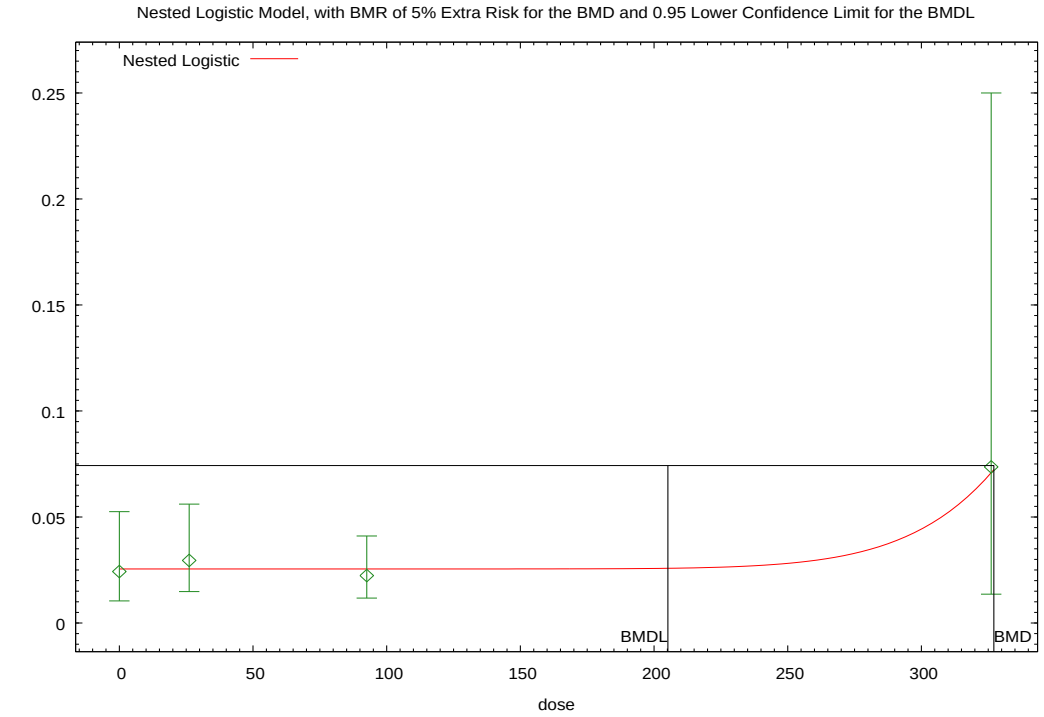
Confidence level = 0.95

BMDs = 281.145, 327.095

BMDLs = 49.3219, 205.186

Selected Model Plots– NLogistic- ILC, BMR = 0.01 and 0.05 Extra Risk





4.6.2 P2/F2B Pups Dead at Day 0 (Stillborn Day 0/Total Pups Born; Exxon 1991 Appendix AK)

Control			25.25 avg. mg/L blood GD6-21			89.03 avg. mg/L blood GD6-21			311.9 avg. mg/L blood GD6-21		
Dam	N	Stillborn	Dam	N	Stillborn	Dam	N	Stillborn	Dam	N	Stillborn
JAB245	18	3	JAB029	15	0	JAB302	19	0	JAB327	14	0
JAB248	14	0	JAB032	15	0	JAB038	14	1	JAB045	15	0
JAB026	16	0	JAB279	14	0	JAB110	15	0	JAB339	4	0
JAB251	12	0	JAB104	18	7	JAB305	15	0	JAB329	14	13
JAB097	18	0	JAB288	15	0	JAB113	16	0	JAB330	13	0
JAB254	8	0	JAB035	15	0	JAB116	5	0	JAB343D	10	0
JAB100	16	0	JAB107	6	0	JAB308	6	0	JAB337	8	0
JAB257	16	2	JAB292	12	1	JAB311	17	0	JAB328	13	0
JAB260	18	0	JAB295	7	0	JAB121	13	0	JAB134	8	5
JAB266	11	0	JAB347	15	0	JAB127	14	1			
JAB269	14	0	JAB348	19	0	JAB130	17	0			
JAB101	15	0	JAB293	19	1	JAB319	18	0			
JAB270	20	0	JAB037	15	0	JAB320	17	0			
JAB273	18	0	JAB349	16	0	JAB313	11	0			
JAB252	11	1	JAB278	11	0	JAB040	18	1			
JAB028	16	0	JAB105	18	0	JAB309	15	0			
JAB275	15	0	JAB289	15	1	JAB039	11	0			
JAB255	20	0	JAB297	13	0	JAB112	18	0			
JAB264	14	0	JAB106	16	0						
JAB262	16	1	JAB290	13	0						
JAB102	17	1									
JAB256	14	0									
JAB098	11	1									
JAB249	16	0									
JAB253	17	0									

Summary of BMDS 3.1.1 Modeling Results for P2/F2B Pups Dead at Day 0 (Exxon, 1991)

Table 4-14 Model Predictions for Pup Death at Day 0 in P2/F2B Rats (Exxon, 1991)

Standard Models*	5% Extra Risk		1% Extra Risk		P Value	AIC	BMDS Recommends **	BMDS Recommendation Notes
	BMD	BMDL	BMD	BMDL				
NLogistic	327.408	275.906	285.459	73.5614	0	246.193	Questionable	BMD/BMDL ratio > 3 Goodness of fit p-value < 0.1
NLogistic-ILC	CF	CF	CF	CF	CF	209.115	Unusable	BMD computation fail; Lower limit includes 0
Non-Standard Models								
NCTR	327.13	0.886689	285.638	0.237456	0	244.193	Questionable	BMD/BMDL ratio > 20 Goodness of fit p-value < 0.1
NCTR-ILC	324.07	0.659289	283.317	0.191833	0.256, 0.224	206.511	Questionable	BMD/BMDL ratio > 20
RaiVR	327.208	0.886689	285.513	0.514115	0	244.193	Questionable	BMD/BMDL ratio > 20 Goodness of fit p-value < 0.1
RaiVR-ILC	324.124	0.659289	283.199	0.517021	0.2407	206.511	Questionable	BMD/BMDL ratio > 20

*NLogistic is preferred because it is the more rigorously tested nested model. All nested models were restricted. Restrictions are defined in the BMDS 3.1.1 User Guide; ILC = Intra-litter Correlation Coefficients estimated; Because potential litter-specific covariates (LSCs) such as dam BW are affected by dose, LSCs were not estimated.
**No model selected as all models were questionable or unusable.

4.6.3 P2/F2A Pups Dead by Day 4 (Dead by Day 4/Total Pups Born; Exxon Appendix AJ)

Control			26.1207 avg. mg/L blood GD6-21			92.5466 avg. mg/L blood GD6-21			326.1056 avg. mg/L blood GD6-21		
Dam	**N**	**Dead by Day 4**	**Dam**	**N**	**Dead by Day 4**	**Dam**	**N**	**Dead by Day 4**	**Dam**	**N**	**Dead by Day 4**
JAB248	12	0	JAB029	17	4	JAB302	15	0	JAB325	13	9
JAB026	16	0	JAB032	17	0	JAB038	14	1	JAB327	12	12
JAB251	14	0	JAB279	14	3	JAB110	15	1	JAB041	13	13
JAB097	15	0	JAB104	13	1	JAB305	16	1	JAB135	7	0
JAB254	9	0	JAB282	13	5	JAB113	20	1	JAB136	4	0
JAB100	18	2	JAB285	16	1	JAB116	22	1	JAB045	14	2
JAB257	17	1	JAB288	17	0	JAB311	16	0	JAB050	12	12
JAB260	18	3	JAB035	14	1	JAB121	9	0	JAB336	11	11
JAB263	15	2	JAB107	19	2	JAB319	15	0	JAB329	11	1
JAB266	15	0	JAB292	1	1	JAB322	14	2	JAB330	8	8
JAB269	18	1	JAB295	7	0	JAB320	3	0	JAB046	14	0
JAB10	18	1	JAB347	16	0	JAB306	13	0	JAB328	14	14
JAB270	18	0	JAB298	5	0	JAB313	17	1	JAB134	16	16
JAB273	15	0	JAB348	19	3	JAB323	14	1	JAB341	14	14
JAB252	16	2	JAB293	5	0	JAB310	15	1			
JAB028	18	3	JAB037	14	1	JAB117	14	0			
JAB275	18	5	JAB349	16	0	JAB040	20	2			
JAB255	16	2	JAB278	16	3	JAB309	14	1			
JAB264	15	0	JAB105	14	0	JAB039	16	2			
JAB267	17	1	JAB297	15	1	JAB317	14	0			
JAB262	17	0	JAB106	17	0	JAB112	17	0			
JAB102	17	10	JAB281	6	3						
JAB246	2	2	JAB290	14	0						
JAB256	10	0									
JAB098	15	1									
JAB249	15	0									
JAB253	18	0									

Summary of BMDS 3.1.1 Modeling Results for P2/F2A Pups Dead by Day 4 (Exxon, 1991)

Table 4-15 Model Predictions for Pup Death at Day 4 in P2/F2A Rats (Exxon, 1991)

Standard Models*	5% Extra Risk		1% Extra Risk		P Value	AIC	BMDS Recommends **	BMDS Recommendation Notes
	BMD	BMDL	BMD	BMDL				
NLogistic	253.849	136.252	226.386	91.5542	0	771.038	Questionable	Goodness of fit p-value < 0.1
NLogistic-ILC	257.878	132.515	231.394	88.2173	0.0317	608.697	Questionable	Goodness of fit p-value < 0.1
Non-Standard Models								
NCTR	261.47	217.891	232.338	193.615	0	769.038	Questionable	Goodness of fit p-value < 0.1
NCTR-ILC	267.663	223.052	240.654	200.545	0.0307, 0.0303	606.697	Questionable	Goodness of fit p-value < 0.1
RaiVR	261.996	218.33	233.057	194.214	0	769.038	Questionable	Goodness of fit p-value < 0.1
RaiVR-ILC	267.488	222.907	240.412	200.344	0.0333, 0.034	606.697	Questionable	Goodness of fit p-value < 0.1

*NLogistic is preferred because it is the more rigorously tested nested model. All nested models were restricted. Restrictions are defined in the BMDS 3.1.1 User Guide; ILC = Intra-litter Correlation Coefficients estimated; Because potential litter-specific covariates (LSCs) such as dam BW are affected by dose, LSCs were not estimated.

**No model selected as all models were questionable or unusable..

4.6.4 P2/F2B Pups Dead by Day 4 (Dead by Day 4/Total Pups Born; Exxon Appendix AK)

Control			25.25 avg. mg/L blood GD6-21			89.03 avg. mg/L blood GD6-21			311.9 avg. mg/L blood GD6-21		
Dam	**N**	**Dead by Day 4**	**Dam**	**N**	**Dead by Day 4**	**Dam**	**N**	**Dead by Day 4**	**Dam**	**N**	**Dead by Day 4**
JAB245	18	18	JAB029	15	0	JAB302	19	1	JAB327	14	14
JAB248	14	0	JAB032	15	0	JAB038	14	1	JAB045	15	2
JAB026	16	0	JAB279	14	0	JAB110	15	1	JAB339	4	4
JAB251	12	0	JAB104	18	7	JAB305	15	0	JAB329	14	14
JAB097	18	0	JAB288	15	0	JAB113	16	0	JAB330	13	13
JAB254	8	0	JAB035	15	0	JAB116	5	0	JAB343 D	10	10
JAB100	16	0	JAB107	6	0	JAB308	6	1	JAB337	8	8
JAB257	16	10	JAB292	12	1	JAB311	17	1	JAB328	13	13
JAB260	18	4	JAB295	7	1	JAB121	13	1	JAB134	8	8
JAB266	11	0	JAB347	15	0	JAB127	14	1			
JAB269	14	0	JAB348	19	0	JAB130	17	1			
JAB101	15	0	JAB293	19	2	JAB319	18	0			
JAB270	20	0	JAB037	15	2	JAB320	17	0			
JAB273	18	2	JAB349	16	0	JAB313	11	0			
JAB252	11	1	JAB278	11	1	JAB040	18	1			
JAB028	16	2	JAB105	18	2	JAB309	15	0			
JAB275	15	1	JAB289	15	6	JAB039	11	0			
JAB255	20	1	JAB297	13	0	JAB112	18	0			
JAB264	14	0	JAB106	16	0						
JAB262	16	3	JAB290	13	1						
JAB102	17	2									
JAB256	14	0									
JAB098	11	3									
JAB249	16	0									
JAB253	17	3									

Summary of BMDS 3.1.1 Modeling Results for P2/F2B Pups Dead by Day 4 (Exxon, 1991)

Table 4-16 Model Predictions for Pup Death at Day 4 in P2/F2B Rats (Exxon, 1991)

Standard Models*	5% Extra Risk		1% Extra Risk		P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
	BMD	BMDL	BMD	BMDL				
NLogistic	229.655	126.176	206.373	92.1515	0	637.258	Questionable	BMD/BMDL ratio > 3 Goodness of fit p-value < 0.1
NLogistic-ILC	229.334	114.81	209.236	85.9385	0.065, 0.053	468.948	Questionable	Goodness of fit p-value < 0.1
Non-Standard Models								
NCTR	243.777	203.148	218.255	181.88	0	635.258	Questionable	Goodness of fit p-value < 0.1
NCTR-ILC	250.449	208.707	228.766	190.639	0.0623, 0.0687	466.948	Questionable	Goodness of fit p-value < 0.1
RaiVR	243.156	202.63	217.451	181.209	0	635.258	Questionable	Goodness of fit p-value < 0.1
RaiVR-ILC	250.449	208.707	228.766	190.639	0.059, 0.0603	466.948	Questionable	Goodness of fit p-value < 0.1

*NLogistic is preferred because it is the more rigorously tested nested model. All nested models were restricted. Restrictions are defined in the BMDS 3.1.1 User Guide; ILC = Intra-litter Correlation Coefficients estimated; Because potential litter-specific covariates (LSCs) such as dam BW are affected by dose, LSCs were not estimated.
**No model selected as all models were questionable or unusable.

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