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Draft Risk Evaluation for
1-Bromopropane
(*n*-Propyl Bromide)

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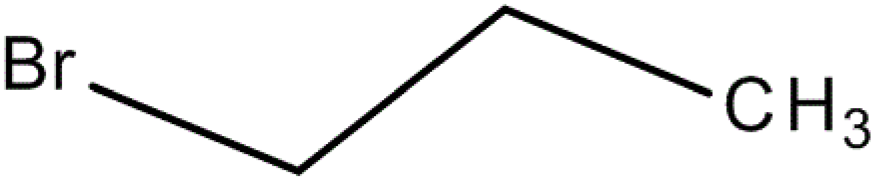
Supplemental Information on Human Health Benchmark Dose Modeling



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1 INTRODUCTION

BMD modeling was performed using USEPA's BMD Software package (BMDS), in a manner consistent with EPA Benchmark Dose Technical Guidance. BMRs were selected for each endpoint individually. The dose metric for all endpoints was the exposure concentration in ppm. Results are presented for non-cancer effects from acute exposures, then chronic exposures and cancer i.e. tumors.

2 Benchmark Dose Modeling of Non-Cancer Effects

2.1 Benchmark Dose Modeling of Non-Cancer Effects for Acute Exposures

2.1.1 Decreased Live Litter Size

EPA modeled the decreased live litter size observed in the 2-generation reproductive and developmental study by WIL Research (2001) as one endpoint relevant for calculating risks associated with acute worker and consumer scenarios. A BMR of 5% was used to address the relative severity of this endpoint (U.S. EPA, 2012). This endpoint choice is a combination of reproductive effects where a BMR 10% relative deviation would be used and developmental effects of post implantation loss which is considered a severe effect like mortality where a BMR of 1% relative deviation would be used. For comparison the modeling results with a BMR of 1 standard deviation and 1% relative deviation are also shown. The doses and response data used for the modeling are presented in Table 2-1.

Table 2-1 Litter Size Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of litters	Mean litter size	Standard Deviation
0	23	14.4	2.21
100	25	13.3	3.72
250	22	12.3	4.47
500	11	8.3	4.1

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 are provided in Table 2-2. The best-fitting model (Exponential M2), based on the criteria described above, is indicated in bold. For the best fitting model a plot of the model is shown in Figure 2-1, the model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown. Although the means were well-modeled the variances are not well modeled by the non-homogeneous variance model (the non-homogeneous variance model was used because the BMDS test 2 *p*-value = 0.0130). To investigate the effect of the poor modeling of the variances on the BMDL, the models were run using the smallest dose standard deviation (2.21), highest (4.47) and pooled (3.54) for all dose levels and the results are summarized in Table 2-4. As shown in the last column of Table 2-4 the ratios BMDLs for the lowest to the highest variance for the two best fitting models the Linear and Exponential (M2) models are 1.15 and 1.20, respectively. Overall the adjustment of the variances from most-variable to least-variable for all of the models makes little difference on the BMDL. This is strong evidence that the poor variance modeling for the original data is not substantially impacting the BMDL estimates. It is reasonable to use the non-homogeneous Exponential M2 model for the original data because it has the lowest AIC of all the model choices for the original data and therefore a BMDL of 41 ppm (40.7 ppm rounded to two significant figures) was selected for this endpoint.

Table 2-2 Summary of BMD Modeling Results for Reduced Litter Size in F_0 Generation Exposed to 1-BP by Inhalation; BMRs of 1 Standard Deviation, and 5% and 1% Relative Deviation From Control Mean.

Model[a]	**Goodness of fit**		**BMD 1SD (ppm)**	**BMDL 1SD (ppm)**	**BMD 5RD (ppm)**	**BMDL 5RD (ppm)**	**BMD 1RD (ppm)**	**BMDL 1RD (ppm)**	**Basis for model selection**
	***p*-value**	**AIC**							
Exponential (M2) **Exponential (M3)[b]**	**0.533**	**291.10**	256	158	**61.3**	**40.7**	12.0	7.97	**The Exponential (M2) model was selected based on lowest AIC from this set of models which have adequate *p*-values, adequate fit by visual inspection and the BMDLs are < 4-fold apart considered sufficiently close.**
Power[c] Polynomial 3°[d] Polynomial 2°[e] Linear	0.433	291.51	281	189	69.9	49.8	14.0	9.95	
Hill	0.722	291.96	178	error[g]	35.8	10.4	6.36	1.69	
Exponential (M4) Exponential (M5)[f]	0.622	292.08	181	69.4	40.4	17.8	7.48	3.23	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0130), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were -0.16, -0.05, 0.66, -0.76, 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.

[f] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[g] BMDL computation failed for this model.

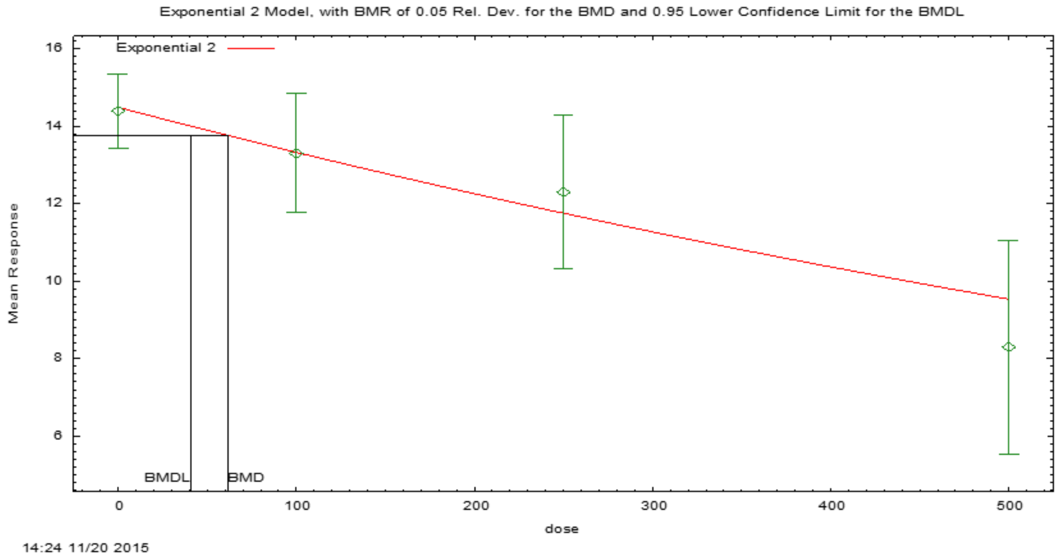

Figure 2-1 Plot of Mean Response by Dose in ppm with Fitted Curve for Exponential (M2) Model with Modeled Variance for Reduced Litter Size in F_0 Generation Exposed to 1-BP by Inhalation; BMR = 5% Relative Deviation from Control Mean.

Table 2-3 BMD Modeling Results for Reduced Litter Size in F_0 Generation Exposed to 1-BP by Inhalation; BMRs of 1 Standard Deviation, and 5% and 1% Relative Deviation From Control Mean.

Exponential Model. (Version: 1.10; Date: 01/12/2015) The form of the response function is: Y[dose] = a * exp(sign * b * dose) A modeled variance is fit
Benchmark Dose Computation. BMR = 5% Relative deviation BMD = 61.3264 BMDL at the 95% confidence level = 40.6605

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	10.4606	6.08025
rho	-3.14328	-1.44632
a	14.4915	10.5312
b	0.000836398	0.00102437
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	23	14.4	14.49	2.21	2.8	-0.1569
100	25	13.3	13.33	3.72	3.19	-0.04505
250	22	12.3	11.76	4.47	3.88	0.6554
500	11	8.3	9.54	4.1	5.4	-0.7614

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-143.3786	5	296.7571
A2	-137.9879	8	291.9758
A3	-140.9173	6	293.8347
R	-153.5054	2	311.0108
2	-141.5475	4	291.095

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	31.03	6	<0.0001
Test 2	10.78	3	0.01297
Test 3	5.859	2	0.05343
Test 4	1.26	2	0.5325

Table 2-4 BMD Modeling Results for Reduced Litter Size in F_0 Generation Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study with Variances Fixed at Smallest, Pooled and Highest Values.

Model[a]	**Smallest Standard Deviation**				**Pooled Standard Deviation**				**Largest Standard Deviation**				**Ratio BMDLs Smallest to Largest Std Dev**
	Goodness of fit		**BMD_{5RD} (ppm)**	**$BMDL_{5RD}$ (ppm)**	**Goodness of fit**		**BMD_{5RD} (ppm)**	**$BMDL_{5RD}$ (ppm)**	**Goodness of fit**		**BMD_{5RD} (ppm)**	**$BMDL_{5RD}$ (ppm)**	
	***p*-value**	**AIC**			***p*-value**	**AIC**			***p*-value**	**AIC**			
Linear	0.279	213.92	**63.5**	**53.5**	0.605	288.69	**63.5**	**49.2**	0.729	326.11	**63.5**	**46.6**	**1.15**
Exponential (M2)	0.112	215.74	**54.9**	**44.1**	0.420	289.42	**54.9**	**39.4**	0.579	326.57	**54.9**	**36.7**	**1.20**
Exponential (M4)	0.112	215.74	54.9	42.6	0.420	289.42	54.9	34.4	0.579	326.57	54.9	29.1	1.46
Polynomial 3°	0.506	213.81	96.4	58.4	0.678	289.86	96.4	51.1	0.742	327.58	96.4	47.8	1.22
Polynomial 2°	0.393	214.09	105	57.4	0.593	289.97	105	50.8	0.672	327.65	105	47.6	1.21
Power	0.303	214.43	115	56.4	0.519	290.10	115	50.5	0.609	327.74	115	47.4	1.19
Exponential (M3)	0.239	214.75	127	56.1	0.461	290.23	127	42.6	0.559	327.82	127	38.7	1.45
Exponential (M5)	0.239	214.75	127	56.1	N/A[b]	292.23	127	42.6	0.559	327.82	127	33.0	1.70
Hill	N/A[b]	216.43	115	56.4	N/A[b]	292.10	116	50.3	N/A[b]	329.74	116	47.2	1.19

[a] Constant variance case presented (BMDS Test 2 *p*-value = 1.000, BMDS Test 3 *p*-value = 1.000), no model was selected as a best-fitting model.

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

2.1.2 Post implantation loss

EPA modeled the post implantation loss observed in the F_0 generation of the 2-generation reproductive and developmental study by WIL Research (2001) as one endpoint relevant for calculating risks associated with acute worker and consumer scenarios. Post implantation loss was significantly increased in all but the lowest dose group. A BMR of 1% was used to address the relative severity of this endpoint which is considered a severe effect like mortality (U.S. EPA, 2012). The doses and response data used for the modeling were individual animal data and are shown in Table 2-5.

Table 2-5. Implantation sites and incidence of post implantation loss in pregnant female rats in the F_0 generation exposed to 0, 100, 250 ppm 1-BP by Inhalation WIL Research (2001)

Dose (ppm)	Number of Implantation Sites	Post Implantation Loss	Dam Weight at Study Week 0 (g)
0	15	0	170
0	17	0	160
0	14	0	147
0	14	0	153
0	15	1	158
0	15	0	153
0	18	2	168
0	12	0	165
0	15	0	164
0	15	1	166
0	15	0	149
0	19	0	174
0	15	0	156
0	16	1	160
0	18	1	158
0	18	0	161
0	19	0	166
0	13	0	172
0	16	0	181
0	13	0	177
0	8	0	141
0	14	1	144
0	18	1	157
100	15	0	161
100	14	0	159
100	14	2	153
100	13	1	146
100	16	1	167
100	16	0	150
100	15	0	159

Dose (ppm)	Number of Implantation Sites	Post Implantation Loss	Dam Weight at Study Week 0 (g)
100	14	1	152
100	16	0	165
100	14	0	166
100	14	3	158
100	15	1	168
100	16	1	143
100	12	3	148
100	16	2	177
100	16	0	154
100	1	0	153
100	14	0	179
100	18	0	171
100	16	0	180
100	16	1	170
100	15	0	165
100	15	1	157
100	15	0	164
100	12	0	162
250	18	1	159
250	16	2	160
250	16	5	151
250	15	1	141
250	15	2	179
250	17	0	150
250	14	1	153
250	15	0	175
250	13	0	146
250	15	0	161
250	17	1	167
250	16	1	165
250	16	1	166
250	11	3	162
250	15	0	157
250	12	1	153
250	6	2	158
250	6	0	166
250	2	0	167
250	18	2	146
250	18	2	164
250	12	4	155
500	5	0	161
500	12	0	158

Dose (ppm)	Number of Implantation Sites	Post Implantation Loss	Dam Weight at Study Week 0 (g)
500	5	1	181
500	15	2	159
500	12	1	151
500	16	0	152
500	9	1	166
500	6	0	176
500	6	1	165
500	11	0	144
500	2	0	144

The application of nested dichotomous models to these data was possible because the incidence data for post-implantation loss were available for every litter, and preferable because they can account for intra-litter correlations and litter-specific covariates. A litter specific covariate that is potentially related to the endpoint of concern but is not itself impacted by dose is needed for this analysis. In this case, dam body weight measured at week 0 and the number of implantation sites were both used as covariates and the data was modeled separately in the same format for each. In this case, dam body weight measured at week 0 was selected as the preferred litter specific covariate because it was not affected at any dose and is potentially related to the implantation loss endpoint.

Incidence of implantation loss presented a clear dose trend at lower doses but leveled off at the highest dose coincident with a reduction in implantation sites. The data were modeled with the all doses and the highest dose dropped for the purposes of this analysis because of the uncertainty associated with reduced sample size and improved model fit.

The nested modeling was performed using the nested logistic and NCTR models contained in BMDS 2.7.0.4, as follows:

- nested model for extra risk of 5% and 1%, using dam weight as a litter specific covariate, dropping the highest dose group (Table 2-6 and Table 2-7 and Figure 2-2 and Figure 2-3).
- nested model for extra risk of 5% and 1%, using number of implantation sites as a litter specific covariate, dropping the highest dose group (Table 2-8 and Table 2-9 and Figure 2-4 and Figure 2-5).
- nested model for extra risk of 5% and 1%, using dam weight as a litter specific covariate, including all dose groups (Table 2-10 and Table 2-11 and Figure 2-6 and Figure 2-7).

Table 2-6 Summary of BMDS modeling results for incidence of post implantation loss in female rats exposed to 1-BP by Inhalation (WIL Research, 2001); BMR = 5% extra risk. Dose groups = 0, 100, 250 ppm.

Model[a]	Goodness of fit		BMD_{05} (ppm)	$BMDL_{05}$ (ppm)	Basis for Model Selection
	p-value	AIC			
Litter-specific covariate = dam weight; intra-litter correlations estimated[b]					The models without intra-litter correlations estimated and without use of covariates had lowest AICs, the NCTR model was selected based on lowest AIC and BMDL.
Nlogistic (b. seed[c] = 1541098366)	0.468	412.675	181	112	
NCTR (b. seed = 1541098374)	0.469	412.658	182	90.8	
Litter-specific covariate used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1541098367)	0.15	411.498	184	123	
NCTR (b. seed = 1541098375)	0.14	411.483	185	92.3	
Litter-specific covariate not used; intra-litter correlations estimated					
Nlogistic (b. seed = 1541098368)	0.507	410.84	173	107	
NCTR (b. seed = 1541098375)	0.513	410.84	174	86.8	
Litter-specific covariate not used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1541098368)	0.136	410.377	177	118	
NCTR (b. seed = 1541098376)	**0.124**	**410.377**	**177**	**88.7**	

[a] Because the individual animal data were available, the BMDS nested dichotomous models were fitted, with the selected model in bold. All values are rounded to 3 significant figures except for AIC values.

[b] The implantation size was also used as a covariate. See Table 2-8.

[c] b. seed: bootstrap seed.

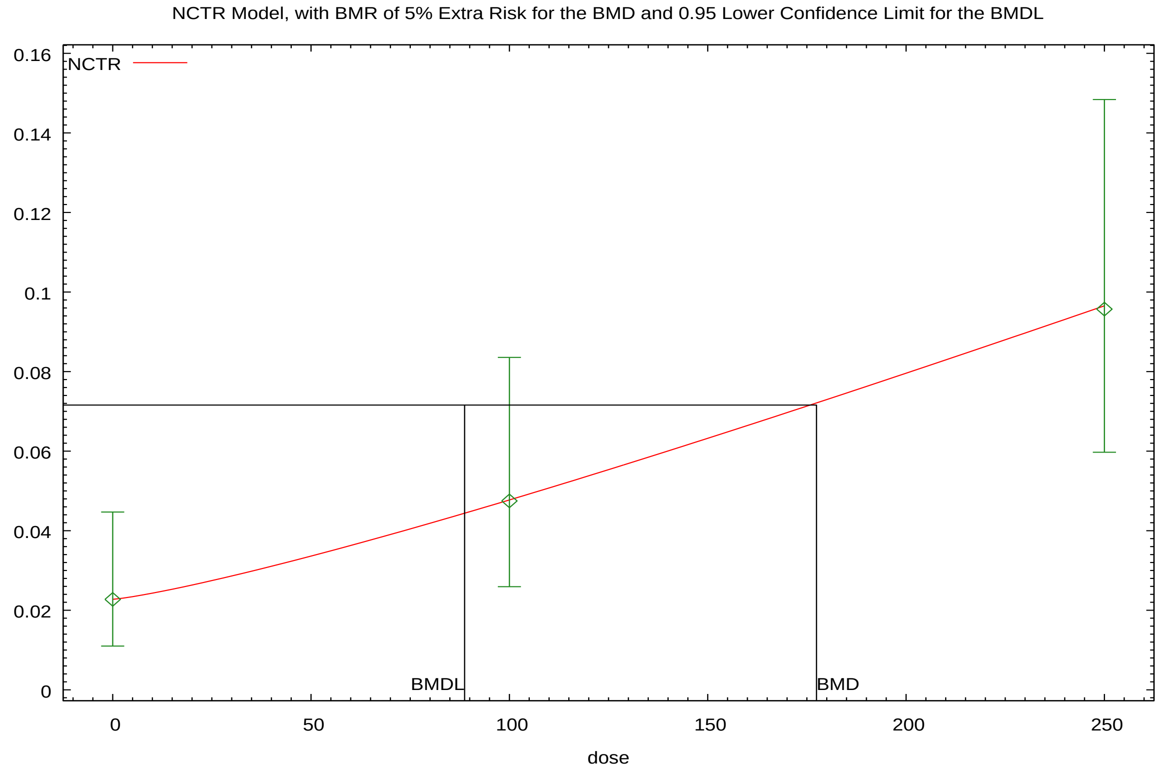

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Figure 2-2. Plot of incidence rate by dose with fitted curve for NCTR model for post implantation loss in male rats exposed to 1-BP

Table 2-7 Summary of BMDS modeling results for incidence of post implantation loss in female rats exposed to 1-BP by Inhalation (WIL Research, 2001); BMR = 1% extra risk. Dose groups = 0, 100, 250 ppm.

Model[a]	Goodness of fit		BMD_{01} (ppm)	$BMDL_{01}$ (ppm)	Basis for Model Selection
	p-value	AIC			
Litter-specific covariate = dam weight; intra-litter correlations estimated[b]					The models without intra-litter correlations estimated and without use of covariates had lowest AICs, the Nlogistic model was selected based on lowest AIC and BMDL.
Nlogistic (b. seed[c] = 1541098369)	0.482	412.675	48.9	21.5	
NCTR (b. seed = 1541098377)	0.489	412.658	48.5	24.3	
Litter-specific covariate used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1541098369)	0.146	411.498	47.5	23.6	
NCTR (b. seed = 1541098377)	0.144	411.483	47.1	23.5	
Litter-specific covariate not used; intra-litter correlations estimated					
Nlogistic (b. seed = 1541098370)	0.507	410.84	45.5	20.6	
NCTR (b. seed = 1541098378)	0.485	410.84	45.0	22.5	
Litter-specific covariate not used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1541098371)	**0.123**	**410.377**	**46.6**	**22.7**	
NCTR (b. seed = 1541098379)	0.124	410.377	46.0	23.0	

[a] Because the individual animal data were available, the BMDS nested dichotomous models were fitted, with the selected model in bold. All values are rounded to 3 significant figures except for AIC values.

[b] The implantation size was also used as a covariate. See Table 2-9.

[c] b. seed: bootstrap seed.

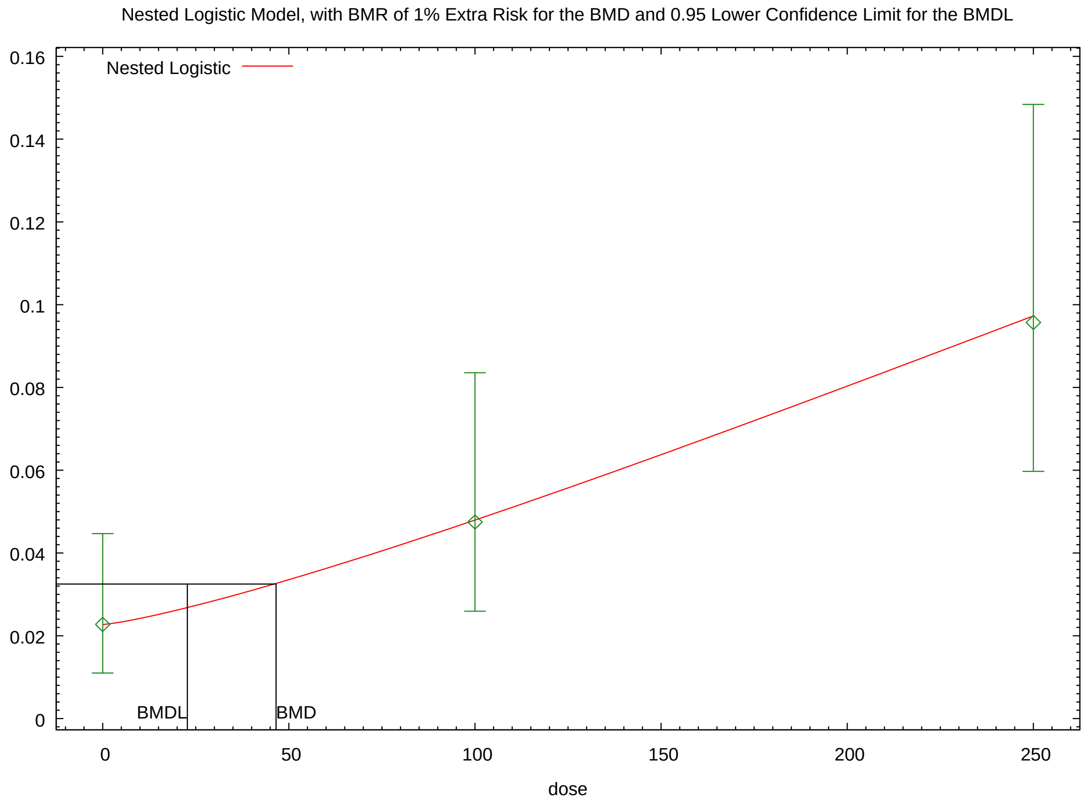

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Figure 2-3 Plot of incidence rate by dose with fitted curve for Nlogistic model for post implantation loss in male rats exposed to 1-BP

Table 2-8 Summary of BMDS modeling results for incidence of post implantation loss in female rats exposed to 1-BP by Inhalation (WIL Research, 2001); BMR = 5% extra risk. Dose groups = 0, 100, 250 ppm.

Model[a]	Goodness of fit		BMD_{05} (ppm)	$BMDL_{05}$ (ppm)	Basis for Model Selection
	p-value	AIC			
Litter-specific covariate = implantation size; intra-litter correlations estimated[b]					The models without intra-litter correlations estimated and without use of covariates had lowest AICs, the NCTR model was selected based on lowest AIC and BMDL.
Nlogistic (b. seed[c] = 1541548812)	0.579	412.889	160	105	
NCTR (b. seed = 1541548820)	0.602	412.488	153	76.7	
Litter-specific covariate used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1541548812)	0.214	411.236	159	111	
NCTR (b. seed = 1541548821)	0.242	410.586	151	75.5	
Litter-specific covariate not used; intra-litter correlations estimated					
Nlogistic (b. seed = 1541548813)	0.497	410.84	173	107	
NCTR (b. seed = 1541548821)	0.489	410.84	174	86.8	
Litter-specific covariate not used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1541548814)	0.123	410.377	177	118	
NCTR (b. seed = 1541548822)	**0.108**	**410.377**	**177**	**88.7**	

[a] Because the individual animal data were available, the BMDS nested dichotomous models were fitted, with the selected model in bold. All values are rounded to 3 significant figures except for AIC values.

[b] The implantation size was used as a covariate and yielded the same model selection results as dam weight. See Table 2-6.

[c] b. seed: bootstrap seed.

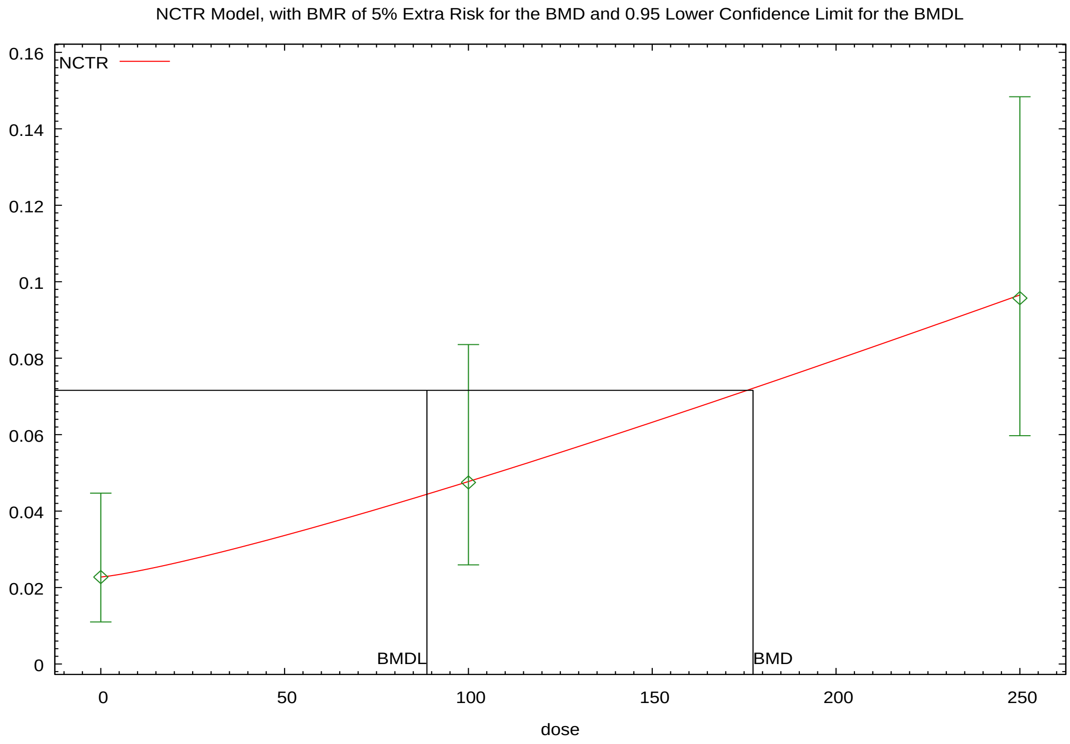

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Figure 2-4 Plot of incidence rate by dose with fitted curve for NCTR model for post implantation loss in male rats exposed to 1-BP

Table 2-9 Summary of BMDS modeling results for incidence of post implantation loss in female rats exposed to 1-BP by Inhalation (WIL Research, 2001); BMR = 1% extra risk. Dose groups = 0, 100, 250 ppm.

Model[a]	Goodness of fit		BMD$_{01}$ (ppm)	BMDL$_{01}$ (ppm)	Basis for Model Selection
	p-value	AIC			
Litter-specific covariate = implantation size; intra-litter correlations estimated[b]					The models without intra-litter correlations estimated and without use of covariates had lowest AICs, the Nlogistic model was selected based on lowest AIC and BMDL.
Nlogistic (b. seed[c] = 1541548814)	0.574	412.889	33.5	20.2	
NCTR (b. seed = 1541548823)	0.597	412.488	32.3	16.1	
Litter-specific covariate used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1541548815)	0.209	411.236	31.3	21.4	
NCTR (b. seed = 1541548824)	0.237	410.586	31.7	15.8	
Litter-specific covariate not used; intra-litter correlations estimated					
Nlogistic (b. seed = 1541548815)	0.505	410.84	45.5	20.6	
NCTR (b. seed = 1541548824)	0.506	410.84	45.0	22.5	
Litter-specific covariate not used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1541548816)	**0.128**	**410.377**	**46.6**	**22.7**	
NCTR (b. seed = 1541548825)	0.117	410.377	46.0	23.0	

[a] Because the individual animal data were available, the BMDS nested dichotomous models were fitted, with the selected model in bold. All values are rounded to 3 significant figures except for AIC values.

[b] The implantation size was used as a covariate and yielded the same model selection results as dam weight. See Table 2-7.

[c] b. seed: bootstrap seed.

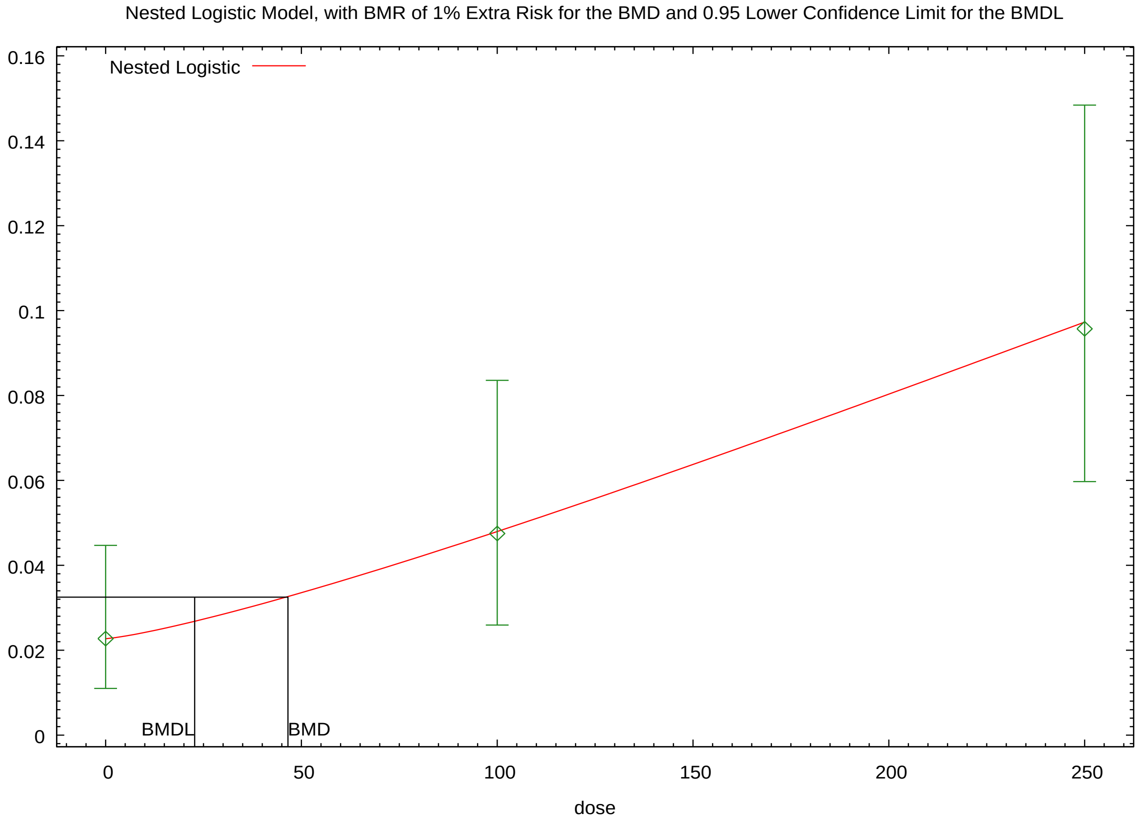

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Figure 2-5 Plot of incidence rate by dose with fitted curve for Nlogistic model for post implantation loss in male rats exposed to 1-BP

Table 2-10 Summary of BMDS modeling results for incidence of post implantation loss in female rats exposed to 1-BP by Inhalation (WIL Research, 2001); BMR = 5% extra risk. Dose groups = 0, 100, 250, 500 ppm.

Model[a]	Goodness of fit		BMD_{05} (ppm)	$BMDL_{05}$ (ppm)	Basis for Model Selection
	p-value	AIC			
Litter-specific covariate = dam weight; intra-litter correlations estimated[b]					The models with intra-litter correlations estimated and without use of covariates had p-value ≥ 0.1 and lowest AICs, the Nlogistic model was selected.
Nlogistic (b. seed[c] = 1541532427)	0.422	462.473	278	146	
NCTR (b. seed = 1541532435)	0.421	464.371	295	148	
Litter-specific covariate used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1541532428)	0.0903	460.235	293	179	
NCTR (b. seed = 1541532436)	0.093	460.173	296	148	
Litter-specific covariate not used; intra-litter correlations estimated					
Nlogistic (b. seed = 1541532428)	**0.496**	**460.864**	**229**	**135**	
NCTR (b. seed = 1541532437)	0.491	461.038	233	116	
Litter-specific covariate not used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1541532429)	0.0743	459.416	255	166	
NCTR (b. seed = 1541532438)	0.0797	459.649	261	131	

[a] Because the individual animal data were available, the BMDS nested dichotomous models were fitted, with the selected model in bold. All values are rounded to 3 significant figures except for AIC values.

[b] The dam weight at week 0 was used as a covariate.

[c] b. seed: bootstrap seed.

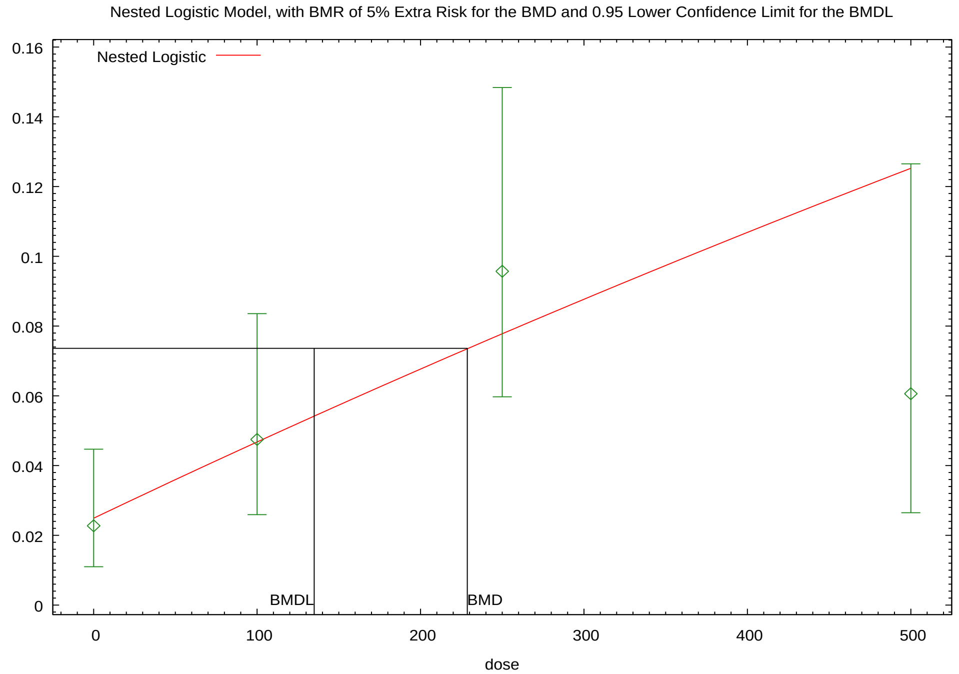

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Figure 2-6 Plot of incidence rate by dose with fitted curve for Nlogistic model for post implantation loss in male rats exposed to 1-BP

Table 2-11 Summary of BMDS modeling results for incidence of post implantation loss in female rats exposed to 1-BP by Inhalation (WIL Research, 2001); BMR = 1% extra risk. Dose groups = 0, 100, 250, 500 ppm.

Model[a]	Goodness of fit		BMD$_{01}$ (ppm)	BMDL$_{01}$ (ppm)	Basis for Model Selection
	p-value	AIC			
Litter-specific covariate = dam weight; intra-litter correlations estimated					The models with intra-litter correlations estimated and without use of covariates had p-value ≥ 0.1 and lowest AICs, the Nlogistic model was selected.
Nlogistic (b. seed[c] = 1541532430)	0.428	462.473	53.3	28.1	
NCTR (b. seed = 1541532438)	0.398	464.371	57.9	28.9	
Litter-specific covariate used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1541532430)	0.095	460.235	56.2	34.4	
NCTR (b. seed = 1541532439)	0.0967	460.173	58.0	29.0	
Litter-specific covariate not used; intra-litter correlations estimated					
Nlogistic (b. seed = 1541532431)	**0.496**	**460.864**	**43.9**	**25.9**	
NCTR (b. seed = 1541532440)	0.487	461.038	45.6	22.8	
Litter-specific covariate not used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1541532431)	0.0723	459.416	48.9	32.0	
NCTR (b. seed = 1541532441)	0.0743	459.649	51.2	25.6	

[a] Because the individual animal data were available, the BMDS nested dichotomous models were fitted, with the selected model in bold. All values are rounded to 3 significant figures except for AIC values.

[b] The dam weight at week 0 was used as a covariate.

[c] b. seed: bootstrap seed.

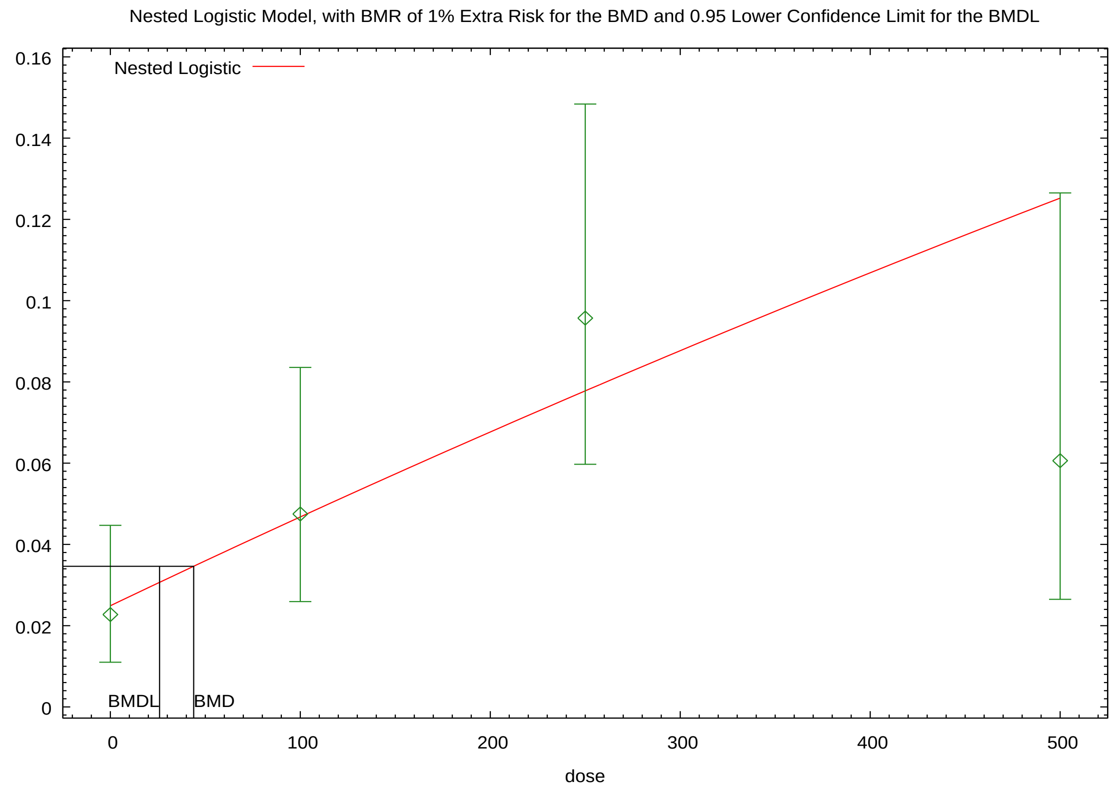

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Figure 2-7 Plot of incidence rate by dose with fitted curve for Nlogistic model for post implantation loss in male rats exposed to 1-BP

2.2 Benchmark Dose Modeling of Non-Cancer Effects for Chronic Exposures

EPA selected multiple endpoints for quantitative dose-response analysis with BMDS and calculating risks associated with chronic worker scenarios including: include liver toxicity, kidney toxicity, neurotoxicity, reproductive toxicity, and developmental toxicity. The doses, response data and BMD modeling results are presented below by effect.

2.2.1 Increased Incidence of Vacuolization of Centrilobular Hepatocytes in Males

Increased incidence of vacuolization of centrilobular hepatocytes was observed in males of the F_0 generation of the reproductive and developmental study by WIL Laboratories (2001). Dichotomous models were used to fit dose response data. A BMR of 10% added risk was choosen per EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012). The doses and response data used for the modeling are presented in Table 2-12.

Table 2-12 Incidence of Vacuolization of Centrilobular Hepatocytes Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Incidence
0	25	0
100	25	0
250	25	7
500	25	22
750	25	24

The BMD modeling results for vacuolization of centrilobular hepatocytes are summarized in Table 2-13. The best fitting model was the LogLogistic based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. For the best fitting model a plot of the model is shown in Figure 2-8. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-14.

Table 2-13 Summary of BMD Modeling Results for Vacuolization of Centrilobular Hepatocytes in Male F_0 Rats Following Inhalation Exposure to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		$BMD_{10PctAdd}$ (ppm)	$BMDL_{10PctAdd}$ (ppm)	Basis for model selection
	p-value	AIC			
LogLogistic	**0.939**	**60.974**	**188**	**143**	**LogLogistic model was selected based on the lowest AIC from this set of models which have adequate *p*-values (excluding Probit and Quantal-Linear), adequate fit by visual inspection and the BMDLs are < 1.5-fold apart considered sufficiently close.**
LogProbit	0.907	60.980	185	142	
Gamma	0.691	61.912	178	130	
Multistage 2°	0.538	63.187	129	98.5	
Weibull	0.360	64.026	158	110	
Logistic	0.146	65.548	186	142	
Probit	0.0542	66.345	177	133	
Quantal-Linear	0.0025	81.794	41.1	32.2	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 100, 250, 500, and 750 ppm were 0, -0.45, 0.12, 0.15, -0.41, respectively.

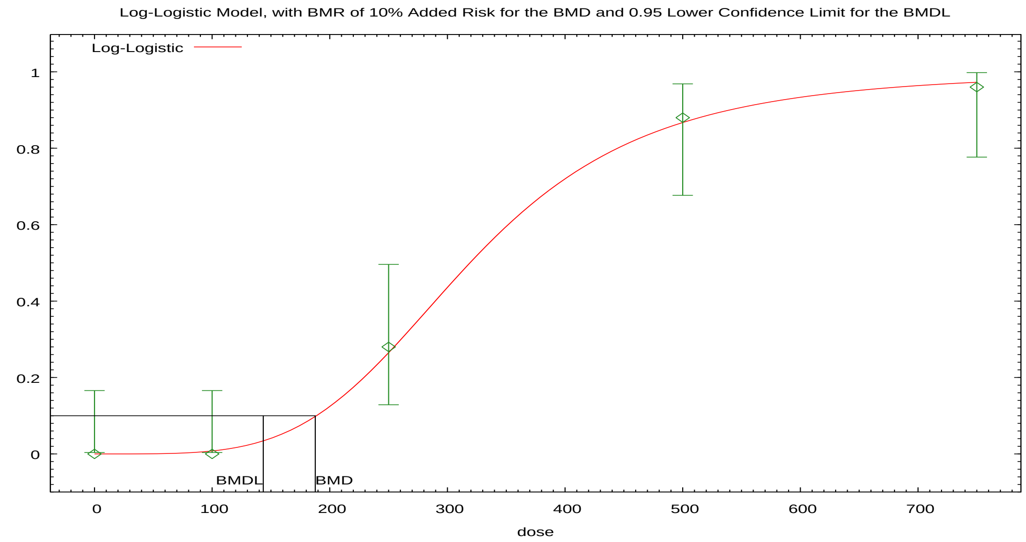

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Figure 2-8 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (LogLogistic) for Vacuolization of Centrilobular Hepatocytes in Male Rats Exposed to 1-BP Via Inhalation in ppm; BMR 10% Added Risk.

Table 2-14 BMD Modeling Results for Reduced Litter Size in F_0 Generation Exposed to 1-BP by Inhalation; BMRs of 1 Standard Deviation, and 5% and 1% Relative Deviation From Control Mean.

Logistic Model. (Version: 2.14; Date: 2/28/2013)
The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]
Slope parameter is restricted as slope >= 1

Benchmark Dose Computation.
BMR = 10% Added risk
BMD = 187.639
BMDL at the 95% confidence level = 143.489

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-2.4067E+01	-2.0600E+01
slope	4.17795	3.60147

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	*p*-value
Full model	-28.2	5			
Fitted model	-28.49	2	0.58301	3	0.9
Reduced model	-85.19	1	113.996	4	<.0001

AIC: = 60.9741

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	25	0
100	0.0079	0.199	0	25	-0.45
250	0.2693	6.731	7	25	0.12
500	0.8696	21.74	22	25	0.15
750	0.9732	24.33	24	25	-0.41

Chi^2 = 0.41   d.f = 3   *p*-value = 0.9391

2.2.2 Increased Incidence of Vacuolization of Centrilobular Hepatocytes in Males

Increased incidence of vacuolization of centrilobular hepatocytes was observed in males of the ClinTrials study (1997). Dichotomous models were used to fit dose response data. A BMR of 10% added risk was choosen per EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012). The doses and response data used for the modeling are presented in Table 2-15.

Table 2-15 Incidence of Vacuolization of Centrilobular Hepatocytes Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Incidence
0	15	0
100	15	0
200	15	0
400	15	3
800	15	6

The BMD modeling results for vacuolization of centrilobular hepatocytes are summarized in Table 2-16. The best fitting model was the LogLogistic based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. For the best fitting model a plot of the model is shown in Figure 2-9. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-17.

Table 2-16 Summary of BMD Modeling Results for Vacuolization of Centrilobular Hepatocytes in Male Rats Following Inhalation Exposure to 1-BP

Model[a]	Goodness of fit		$BMD_{10PctAdd}$ (ppm)	$BMDL_{10PctAdd}$ (ppm)	Basis for model selection
	***p*-value**	**AIC**			
Multistage 3°	**0.955**	**38.189**	**346**	**226**	**Multistage 3° model was selected based on the lowest AIC from this set of models which have adequate *p*-value, adequate fit by visual inspection and the BMDLs are < 1.5-fold apart considered sufficiently close.**
Multistage 2°	0.898	39.202	289	198	
LogProbit	0.951	39.678	345	225	
Gamma	0.919	39.874	349	227	
LogLogistic	0.903	40.003	349	224	
Weibull	0.872	40.180	351	222	
Probit	0.773	40.585	370	275	
Logistic	0.662	41.195	382	290	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 100, 200, 400, and 600 ppm were 0, -0.2, -0.56, 0.54, -0.18, respectively.

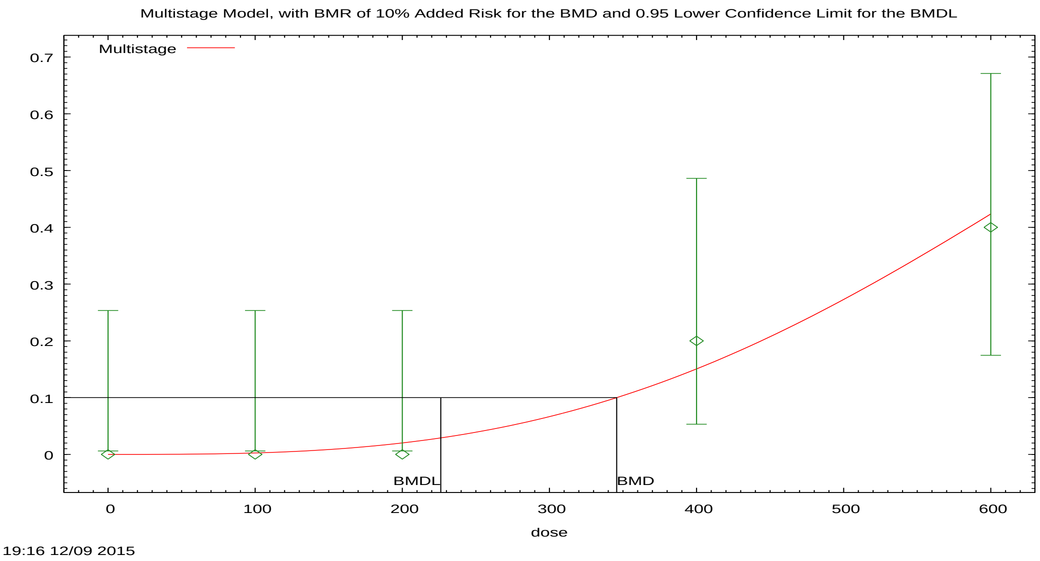

Figure 2-9 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Multistage 3°) for Vacuolization of Centrilobular Hepatocytes in Male Rats Exposed to 1-BP Via Inhalation in ppm; BMR 10% Added Risk.

Table 2-17 BMD Modeling Results for Vacuolization of Centrilobular Hepatocytes in Male Rats Exposed to 1-BP Via Inhalation; BMR 10% Added Risk.

Multistage Model. (Version: 3.4; Date: 05/02/2014)
The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.
BMR = 10% Added risk
BMD = 345.704
BMDL at the 95% confidence level = 226.133

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0	1.4788E-06
Beta(3)	2.5502E-09	0

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	*p*-value
Full model	-17.6	5			
Fitted model	-18.09	1	0.986987	4	0.91
Reduced model	-27.52	1	19.8363	4	0

AIC: = 38.1894

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	15	0
100	0.0025	0.038	0	15	-0.2
200	0.0202	0.303	0	15	-0.56
400	0.1506	2.259	3	15	0.54
600	0.4235	6.353	6	15	-0.18

Chi^2 = 0.67 d.f = 4 *p*-value = 0.9552

2.2.3 Increased Incidence of Vacuolization of Centrilobular Hepatocytes in Females

Increased incidence of vacuolization of centrilobular hepatocytes was observed in females of the F_0 generation of the reproductive and developmental study by WIL Laboratories (2001). Dichotomous models were used to fit dose response data. A BMR of 10% added risk was choosen per EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012). The doses and response data used for the modeling are presented in Table 2-18.

Table 2-18 Incidence of Vacuolization of Centrilobular Hepatocytes Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Incidence
0	25	0
100	25	0
250	25	0
500	25	6
750	25	16

The BMD modeling results for vacuolization of centrilobular hepatocytes are summarized in Table 2-19. The best fitting model was the LogProbit based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. For the best fitting model a plot of the model is shown in Figure 2-10. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in .

Table 2-19 Summary of BMD Modeling Results for Vacuolization of Centrilobular Hepatocytes in Female F_0 Rats Following Inhalation Exposure to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		$BMD_{10PctAdd}$ (ppm)	$BMDL_{10PctAdd}$ (ppm)	Basis for model selection
	p-value	AIC			
LogProbit	**0.988**	**64.438**	**415**	**322**	**LogProbit model was selected based on the lowest AIC from this set of models which have adequate *p*-values (excluding Quantal-Linear), adequate fit by visual inspection and the BMDLs are 1.5-fold apart considered sufficiently close.**
Gamma	0.965	64.648	416	320	
LogLogistic	0.945	64.843	415	320	
Weibull	0.879	65.283	411	310	
Probit	0.826	65.496	423	335	
Logistic	0.661	66.491	431	347	
Multistage 2°	0.410	68.583	279	228	
Quantal-Linear	0.0134	80.285	153	109	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 100, 250, 500, and 750 ppm were 0, 0, -0.29, 0.19, -0.11, respectively.

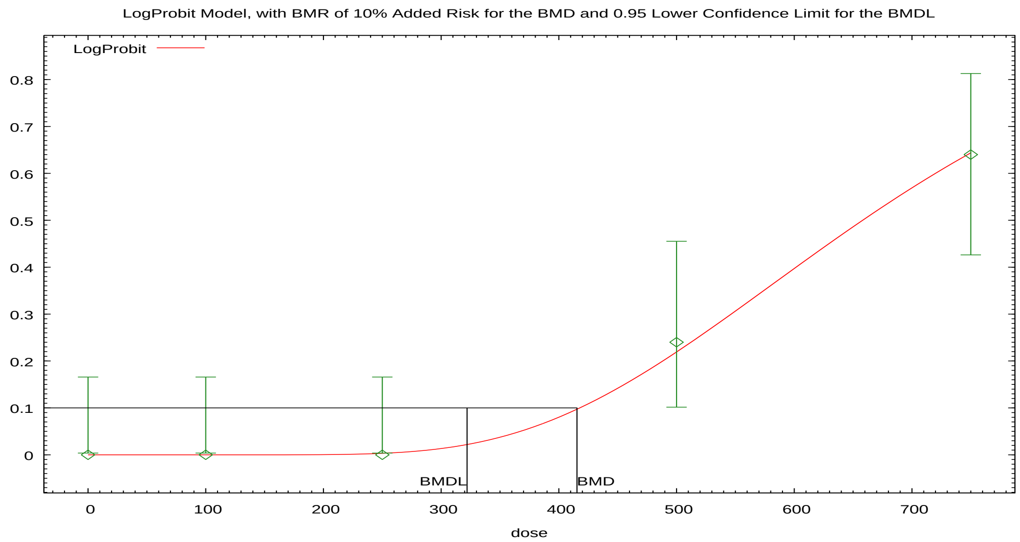

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Figure 2-10 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (LogLogistic) for Vacuolization of Centrilobular Hepatocytes in Female Rats Exposed to 1-BP Via Inhalation in ppm; BMR 10% Added Risk.

Table 2-20 BMD Modeling Results for Vacuolization of Centrilobular Hepatocytes in Female Rats Exposed to 1-BP Via Inhalation; BMR 10% Added Risk.

Probit Model. (Version: 3.3; Date: 2/28/2013)
The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),where CumNorm(.) is the cumulative normal distribution function
Slope parameter is not restricted

Benchmark Dose Computation.
BMR = 10% Added risk
BMD = 415.388
BMDL at the 95% confidence level = 322.058

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-1.8305E+01	-7.9627E+00
slope	2.82354	1.1917

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	*p*-value
Full model	-30.11	5			
Fitted model	-30.22	2	0.213311	3	0.98
Reduced model	-58.16	1	56.0935	4	<.0001

AIC: = 64.4382

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	25	0
100	0	0	0	25	0
250	0.0033	0.083	0	25	-0.29
500	0.2242	5.605	6	25	0.19
750	0.6505	16.263	16	25	-0.11

Chi^2 = 0.13 d.f = 3 *p*-value = 0.9879

2.2.4 Increased Incidence of Renal Pelvic Mineralization in Males

Increased incidence of renal pelvic mineralization was observed in males of the F_0 generation of the reproductive and developmental study by WIL Laboratories (2001). Dichotomous models were used to fit dose response data. A BMR of 10% added risk was choosen per EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012). The doses and response data used for the modeling are presented in Table 2-21.

Table 2-21 Incidence of Renal Pelvic Mineralization Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Incidence
0	25	1
100	25	0
250	25	1
500	25	2
750	25	6

The BMD modeling results for vacuolization of renal pelvic mineralization are summarized in Table 2-22. The best fitting model was the Multistage 3° based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. For the best fitting model a plot of the model is shown in Figure 2-11. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-23.

Table 2-22 Summary of BMD Modeling Results for Renal Pelvic Mineralization in Male F_0 Rats Following Inhalation Exposure to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		$BMD_{10PctAdd}$ (ppm)	$BMDL_{10PctAdd}$ (ppm)	Basis for model selection
	p-value	AIC			
Multistage 3°	**0.789**	**63.835**	**571**	**386**	**Multistage 3° model was selected based on the lowest AIC from this set of models which have adequate *p*-values, adequate fit by visual inspection and the BMDLs are 1.5-fold apart considered sufficiently close.**
Multistage 2°	0.668	64.258	527	368	
Logistic	0.629	64.260	545	434	
Probit	0.567	64.488	526	408	
Weibull	0.603	65.825	581	375	
LogLogistic	0.602	65.835	579	371	
Gamma	0.597	65.856	575	371	
LogProbit	0.597	65.894	577	355	
Quantal-Linear	0.326	66.496	507	284	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 100, 250, 500, and 750 ppm were 0.6, -0.76, 0.26, -0.18, 0.07, respectively.

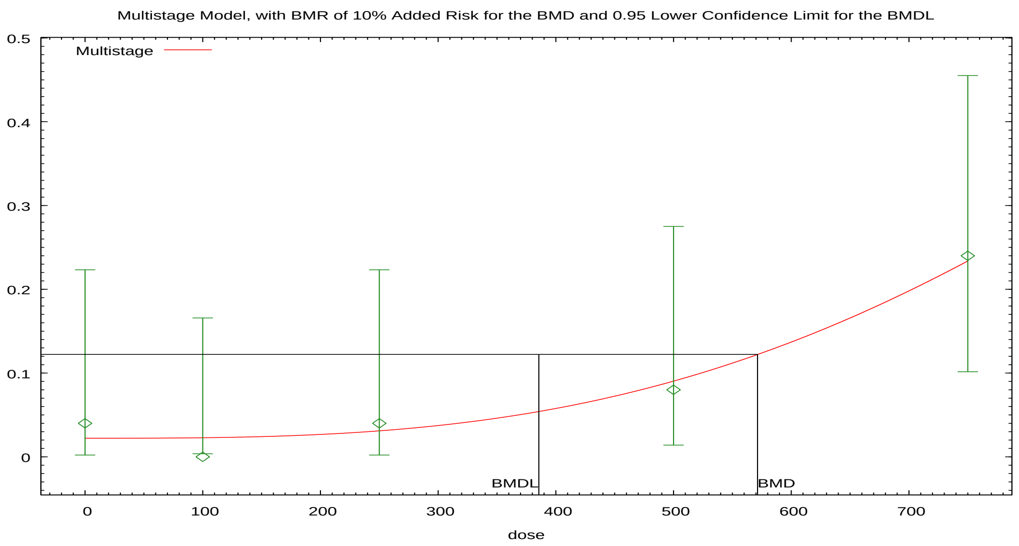

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Figure 2-11 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Multistage 3°) for Renal Pelvic Mineralization in Male Rats Exposed to 1-BP Via Inhalation in ppm; BMR 10% Added Risk.

Table 2-23 BMD Modeling Results for Renal Pelvic Mineralization in Male Rats Exposed to 1-BP Via Inhalation; BMR 10% Added Risk.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Added risk

BMD = 571.342

BMDL at the 95% confidence level = 385.532

Parameter Estimates

Variable	**Estimate**	**Default Initial Parameter Values**
Background	0.0222219	0.00963337
Beta(1)	0	0
Beta(2)	0	0
Beta(3)	5.7848E-10	5.8917E-10

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	*p*-value
Full model	-29.14	5			
Fitted model	-29.92	2	1.5483	3	0.67
Reduced model	-34.85	1	11.4055	4	0.02

AIC: = 63.8352

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0222	0.556	1	25	0.6
100	0.0228	0.57	0	25	-0.76
250	0.031	0.776	1	25	0.26
500	0.0904	2.261	2	25	-0.18
750	0.234	5.849	6	25	0.07

Chi^2 = 1.05 d.f = 3 *p*-value = 0.7887

2.2.5 Increased Incidence of Renal Pelvic Mineralization in Females

Increased incidence of renal pelvic mineralization was observed in females of the F_0 generation of the reproductive and developmental study by WIL Laboratories (2001). Dichotomous models were used to fit dose response data. A BMR of 10% added risk was choosen per EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012). The doses and response data used for the modeling are presented in Table 2-24.

Table 2-24 Incidence of Renal Pelvic Mineralization Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Incidence
0	25	2
100	25	3
250	25	5
500	24	12
750	25	14

The BMD modeling results for vacuolization of renal pelvic mineralization are summarized in Table 2-25. The best fitting model was the LogProbit based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. For the best fitting model a plot of the model is shown in Figure 2-12. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-26.

Table 2-25 Summary of BMD Modeling Results for Renal Pelvic Mineralization in Female F_0 Rats Following Inhalation Exposure to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		$BMD_{10PctAdd}$ (ppm)	$BMDL_{10PctAdd}$ (ppm)	Basis for model selection
	p-value	AIC			
Probit	**0.708**	**130.24**	**212**	**174**	**Probit model was selected based on the lowest AIC from this set of models which have adequate *p*-values, adequate fit by visual inspection and the BMDLs are < 3-fold apart considered sufficiently close.**
Quantal-Linear	0.703	130.32	113	79.3	
Logistic	0.664	130.43	228	186	
LogProbit	0.735	131.49	195	70.4	
LogLogistic	0.728	131.51	187	69.9	
Gamma	0.683	131.63	182	82.8	
Weibull	0.662	131.70	174	82.5	
Multistage 2°	0.610	131.86	164	81.6	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 100, 250, 500, and 750 ppm were -0.17, -0.15, -0.16, 0.99, -0.58, respectively.

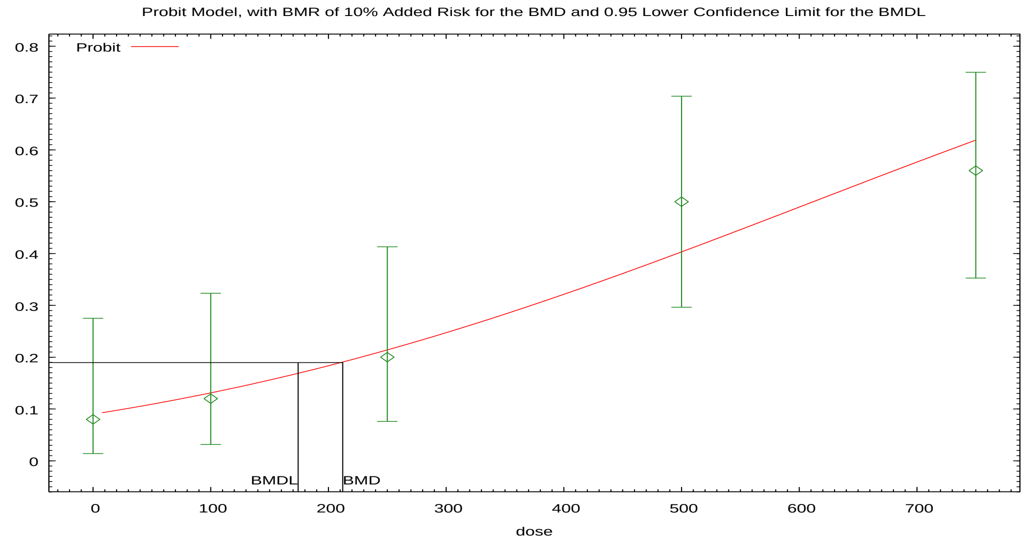

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Figure 2-12 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Probit) for Renal Pelvic Mineralization in Female Rats Exposed to 1-BP Via Inhalation in ppm; BMR 10% Added Risk.

Table 2-26 BMD Modeling Results for Renal Pelvic Mineralization in Female Rats Exposed to 1-BP Via Inhalation; BMR 10% Added Risk.

Probit Model. (Version: 3.3; Date: 2/28/2013)
The form of the probability function is: P[response] = CumNorm(Intercept+Slope*Dose),
where CumNorm(.) is the cumulative normal distribution function
Slope parameter is not restricted

Benchmark Dose Computation.
BMR = 10% Added risk
BMD = 212.127
BMDL at the 95% confidence level = 174.256

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-1.3432E+00	-1.3433E+00
slope	0.00218661	0.00218429

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	*p*-value
Full model	-62.44	5			
Fitted model	-63.12	2	1.36613	3	0.71
Reduced model	-74.7	1	24.5328	4	<.0001

AIC: = 130.239

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0896	2.24	2	25	-0.17
100	0.1304	3.26	3	25	-0.15
250	0.2129	5.321	5	25	-0.16
500	0.4013	9.632	12	24	0.99
750	0.6167	15.417	14	25	-0.58

Chi^2 = 1.39 d.f = 3 *p*-value = 0.7082

2.2.6 Decreased Seminal Vesicle Weight

Decreased relative and absolute seminal vesicle weights were observed in (Ichihara et al., 2000). Continuous models were used to fit dose-response data for both absolute and relative seminal vesicle weights. A BMR 1 standard deviation was choosen per EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012). Both absolute and relative organ weights may be relevant for reproductive organs like the seminal vesicle as described in EPA's Guidelines for Reproductive

Toxicity Risk Assessment (U.S. EPA, 1996). In this case by coincidence the BMDL was the same (38 ppm) for both absolute and relative seminal vesicle weights and therefore this endpoint is refered to as absolute/relative seminal vesicle weight in the risk evaluation and the following text and tables. The doses, response data and BMD modeling results are presented for relative and then absolute seminal vesicle weights below.

2.2.6.1 Decreased Relative Seminal Vesicle Weight

The doses and response data used for relative seminal vesicle weight are presented in Table 2-27.

Table 2-27 Relative Seminal Vesicle Weight Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Relative Weight (mg/g BW)	Standard Deviation
0	8	4.35	0.62
200	9	3.23	0.55
400	9	3.17	0.67
800	9	2.62	0.87

Comparisons of model fits obtained are provided in Table 2-28. Models with homogeneous variance were used because the BMDS Test 2 *p*-value was 0.543. The Hill model was excluded because the BMD to BMDL ratio was 7.34. Of the remaining models the best fitting model (Exponential (M4)) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The Exponential (M4) model had an acceptable BMD to BMDL ratio of 3.2 and is indicated in bold. For the best fitting model a plot of the model is shown in Figure 2-13. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-29.

Table 2-28 Summary of BMD Modeling Results for Relative Seminal Vesicle Weight in Rats Exposed to 1-BP by Inhalation

Model[a]	**Goodness of fit**		**BMD$_{10RD}$ (ppm)**	**BMDL$_{10RD}$ (ppm)**	**BMD$_{1SD}$ (ppm)**	**BMDL$_{1SD}$ (ppm)**	**Basis for model selection**
	***p*-value**	**AIC**					
Hill	0.298	13.857	57.2	6.72	101	13.7	**For models with BMD to BMDL ratios less than 5 (this excludes the Hill model), the Exponential (M4) model was selected based on the lowest BMDL because the models with adequate goodness of fit *p*-value and adequate fit by visual inspection (Exponetial M2 – M5) had BMDLs > 5-fold apart and not sufficiently close.**
Exponential (M4) **Exponential (M5)[b]**	**0.221**	**14.274**	73.1	21.4	**124**	**38.1**	
Exponential (M2) Exponential (M3)[c]	0.107	15.240	170	123	301	199	
Power[d] Polynomial 2°[e] Linear[f]	0.0604	16.386	213	165	376	267	
Polynomial 3°[g]	0.0604	16.386	213	165	376	267	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.543), selected model in bold; scaled residuals for selected model for doses 0, 200, 400, and 800 ppm were 0.15, -0.68, 0.92, -0.37, respectively.

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[b] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[c] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[d] For the Power model, the power parameter estimate was 1. 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.

[f] The Linear model may appear equivalent to the Polynomial 3° model, however differences exist in digits not displayed in the table.

[g] The Polynomial 3° model may appear equivalent to the Power model, however differences exist in digits not displayed in the table. This also applies to the Polynomial 2° model. This also applies to the Linear model.

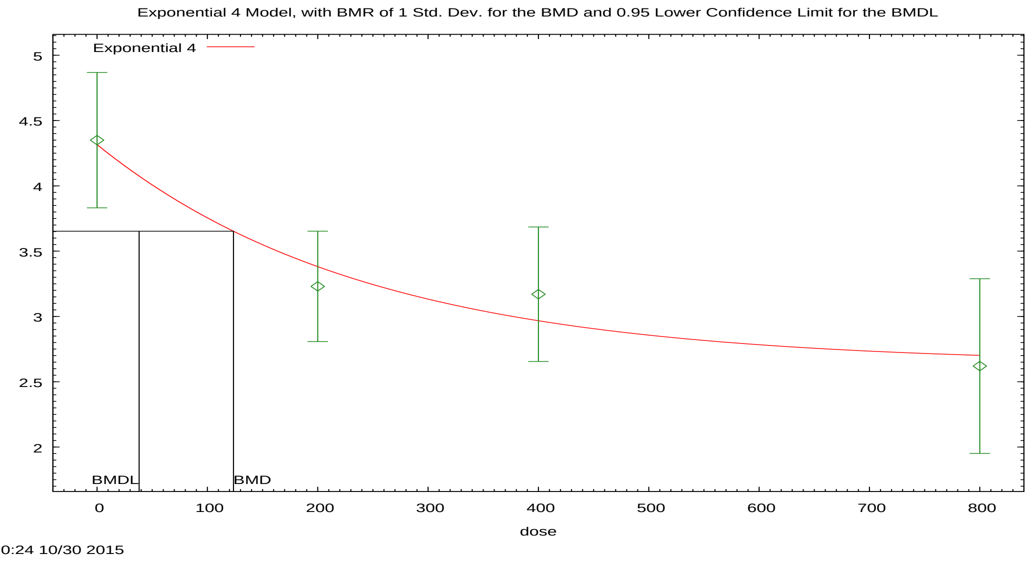

Figure 2-13 Plot of Mean Response by Dose in ppm with Fitted Curve for Exponential (M4) Model with Constant Variance for Relative Seminal Vesicle Weight; BMR = 1 Standard Deviation Change from Control Mean.

Table 2-29 BMD Modeling Results for Relative Seminal Vesicle Weight; BMR = 1 Standard Deviation Change from Control Mean.

Exponential Model. (Version: 1.10; Date: 01/12/2015)
The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]
A constant variance model is fit

Benchmark Dose Computation.
BMR = 1.0000 Estimated standard deviations from control
BMD = 123.644
BMDL at the 95% confidence level = 38.1407

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.820732	-0.863617

rho	n/a	0
a	4.31581	4.5675
b	0.00406673	0.00345735
c	0.611025	0.546303
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	8	4.35	4.32	0.62	0.66	0.1458
200	9	3.23	3.38	0.55	0.66	-0.6845
400	9	3.17	2.97	0.67	0.66	0.9177
800	9	2.62	2.7	0.87	0.66	-0.3705

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-2.386703	5	14.77341
A2	-1.313327	8	18.62665
A3	-2.386703	5	14.77341
R	-13.55019	2	31.10038
4	-3.137185	4	14.27437

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	24.47	6	0.0004272
Test 2	2.147	3	0.5425
Test 3	2.147	3	0.5425
Test 6a	1.501	1	0.2205

2.2.6.2 Decreased Absolute Seminal Vesicle Weight

The doses and response data used for the modeling are presented in Table 2-30.

Table 2-30 Absolute Seminal Vesicle Weight Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Seminal Vesicle Absolute Weight (mg)	Standard Deviation
0	8	1.88	0.27
200	9	1.38	0.26
400	9	1.27	0.25
800	9	1.00	0.36

Comparisons of model fits obtained are provided in Table 2-31. Models with homogeneous variance were used because the BMDS Test 2 *p*-value was 0.653. The best fitting model (Hill) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The Hill model had an acceptable BMD to BMDL ratio of 2.5 and is indicated in bold. For the best fitting model a plot of the model is shown in Figure 2-14. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-32.

Table 2-31 Summary of BMD Modeling Results for Seminal Vesicle Absolute Weight in Rats Exposed to 1-BP by Inhalation

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC			
Hill	**0.429**	**-47.533**	**97.3**	**38.4**	**The Hill model was selected based on the lowest AIC because the models with adequate goodness of fit *p*-value and adequate fit by visual inspection (including Hill and Exponetial M2 – M5, excluding Power, Polynomial and Linear) had BMDLs < 4-fold apart considered sufficiently close.**
Exponential (M4) Exponential (M5)[b]	0.337	-47.235	112	58.4	
Exponential (M2) Exponential (M3)[c]	0.159	-46.484	219	152	
Power[d] Polynomial 3°[e] Polynomial 2°[f] Linear	0.0576	-44.450	299	222	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.653), selected model in bold; scaled residuals for selected model for doses 0, 200, 400, and 800 ppm were 0.07, -0.43, 0.61, -0.24, respectively.

[b] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[c] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[e] 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.

[f] 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.

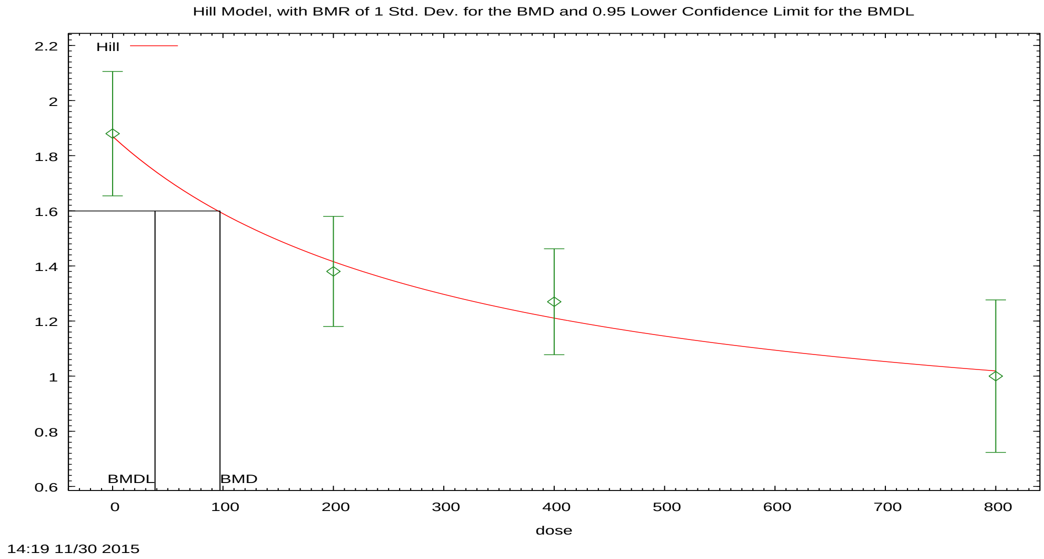

Figure 2-14 Plot of Mean Response by Dose in ppm with Fitted Curve for Hill Model with Constant Variance for Seminal Vesicle Absolute Weight; BMR = 1 Standard Deviation Change from Control Mean.

Table 2-32 BMD Modeling Results for Seminal Vesicle Absolute Weight; BMR = 1 Standard Deviation Change from Control Mean.

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 constant variance model is fit

Benchmark Dose Computation.
BMR = 1 Estimated standard deviations from the control mean
BMD = 97.2583
BMDL at the 95% confidence level = 38.4029

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0752711	0.0834806
rho	n/a	0
intercept	1.87362	1.88
v	-1.2008	-0.88
n	1	1.5698
k	328.422	176

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	8	1.88	1.87	0.27	0.27	0.0658
200	9	1.38	1.42	0.26	0.27	-0.428
400	9	1.27	1.21	0.25	0.27	0.61
800	9	1	1.02	0.36	0.27	-0.244

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	28.078773	5	-46.157546
A2	28.894036	8	-41.788073
A3	28.078773	5	-46.157546
fitted	27.766532	4	-47.533065
R	13.387326	2	-22.774652

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	31.0134	6	<0.0001
Test 2	1.63053	3	0.6525
Test 3	1.63053	3	0.6525
Test 4	0.624482	1	0.4294

2.2.7 Decreased Percent Normal Sperm Morphology

Decreased percent normal sperm morphology was observed in the F_0 generation of the reproductive and developmental study by WIL Laboratories (2001). The doses and response data used for the modeling are presented in Table 2-33.

Table 2-33 Sperm Morphology Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	% normal	Standard Deviation
0	25	99.7	0.6
100	25	99.7	0.52
250	25	99.3	0.83
500	24	98.2	2.59
750	24	90.6	8.74

Comparisons of model fits obtained are provided in Table 2-34. The best fitting model (Exponential (M2) with homogeneous variance because the BMDS Test 2 *p*-value was 0.144) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure 2-15. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-35.

Table 2-34 Summary of BMD Modeling Results for Sperm Morphology in the F_0 Generation Exposed to 1-BP by Inhalation

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC			
Exponential (M2) **Exponential (M3)[b]**	**0.787**	**-401.21**	**472**	**327**	**The Exponential (M2) model was selected based on the lowest AIC from this set of models which have adequate *p*-values, adequate fit by visual inspection and the BMDLs are < 1.5-fold apart considered sufficiently close.**
Power[c] Polynomial 3°[d] Polynomial 2°[e] Linear	0.780	-401.19	473	331	
Exponential (M4)	0.534	-399.30	459	230	
Hill	N/A[f]	-397.69	482	124	
Exponential (M5)	N/A[f]	-397.69	463	112	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.144), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were -0.05, 0.39, -0.53, 0.19, 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.

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

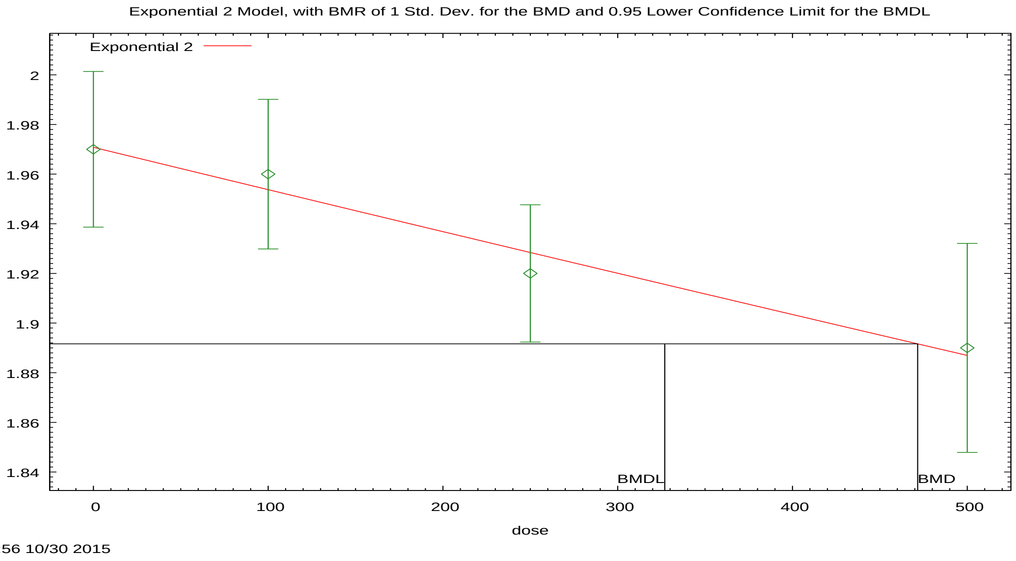

Figure 2-15 Plot of Mean Response by Dose in ppm with Fitted Curve for Exponential (M2) Model with Constant Variance for Sperm Morphology in F_0 Rats Exposed to 1-BP by Inhalation; BMR = 1 Standard Deviation Change from Control Mean.

Table 2-35 BMD Modeling Results for Sperm Morphology in F_0 Rats Exposed to 1-BP by Inhalation; BMR = 1 Standard Deviation Change from Control Mean.

Exponential Model. (Version: 1.10; Date: 01/12/2015)
The form of the response function is: Y[dose] = a * exp(sign * b * dose)
A constant variance model is fit

Benchmark Dose Computation.
BMR = 1.0000 Estimated standard deviations from control
BMD = 471.627
BMDL at the 95% confidence level = 326.935

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.07205	-5.07685
rho	n/a	0
a	1.97082	1.89939
b	0.0000869453	0.000086769
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid

0	25	1.97	1.97	0.08	0.08	-0.05174
100	25	1.96	1.95	0.07	0.08	0.3941
250	25	1.92	1.93	0.07	0.08	-0.5332
500	25	1.89	1.89	0.1	0.08	0.1908

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	203.8426	5	-397.6852
A2	206.5452	8	-397.0903
A3	203.8426	5	-397.6852
R	196.2377	2	-388.4753
2	203.6027	3	-401.2054

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	20.62	6	0.002151
Test 2	5.405	3	0.1444
Test 3	5.405	3	0.1444
Test 4	0.4799	2	0.7867

2.2.8 Decreased Percent Motile Sperm

A decrease in motile sperm was observed in the F_0 generation in the reproductive and developmental study by WIL Laboratories (2001). The doses and response data used for the modeling are presented in Table 2-36.

Table 2-36 Sperm Motility Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Mean sperm motility (% motile)	Standard Deviation
0	25	86.8	11.90
100	25	88.8	7.22
250	25	83.4	10.41
500	23	71.9	9.27
750	15	53.2	19.59

The BMD modeling results for sperm motility with non-homogeneous variance (BMDS test 2 *p*-value = 0.0001749) are summarized in Table 2-37. Although the means are sufficiently fit for some models (e.g. the Polynomial 2° model has *p*-value of 0.516) the variances are not well modeled BMDS Test 3 *p*-value = 0.0426. This result suggests that due to the poor variance modeling for the data it is not reasonable to use BMDS for this endpoint. Instead the NOAEL of 250 ppm was used.

Table 2-37 Summary of BMD Modeling Results for Sperm Motility F_0 Male Rats Following Inhalation Exposure to 1-BP

Model[a]	**Goodness of fit**		**BMD_{1SD} (ppm)**	**$BMDL_{1SD}$ (ppm)**	**Basis for model selection**
	***p*-value**	**AIC**			
Polynomial 2°	0.516	657.83	386	346	**Due to unacceptable fitting of the variances no model was selected**.
Power	0.334	659.73	399	313	
Polynomial 3°	0.330	659.76	397	315	
Exponential (M3)	0.324	659.80	402	317	
Hill	0.139	661.73	400	323	
Polynomial 4°	0.137	661.76	397	314	
Exponential (M5)	0.133	661.80	402	317	
Linear	0.00132	671.22	237	192	
Exponential (M2) Exponential (M4)[b]	2.10E-04	675.10	226	178	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 1.75E-04, BMDS Test 3 *p*-value = 0.0426), no model was selected as a best-fitting model.

[b] For the Exponential (M4) model, the estimate of c was 0 (boundary). The models in this row reduced to the Exponential (M2) model.

To investigate the effect of the poor modeling of the variances on the BMDL the observed standard deviations were considered and the standard deviation at the highest dose is much larger than at the other dose groups. The data set was investigated with the highest dose dropped. The model fits with non-homogeneous variance (BMDS test 2 *p*-value = 0.0966) are summarized in Table 2-38. Although the means are sufficiently fit for some models (e.g. the Polynomial 2° model has *p*-value of 0.676) the variances are not well modeled BMDS Test 3 *p*-value = 0.0426.

Table 2-38 Summary of BMD Modeling Results for Sperm Motility F_0 Male Rats Following Inhalation Exposure to 1-BP with the Highest Dose Dropped

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC			
Polynomial 3°	0.676	551.25	394	345	**Due to unacceptable fitting of the variances no model was selected.**
Polynomial 2°	0.676	551.25	394	302	
Hill	0.529	552.86	271	255	
Exponential (M3)	0.386	553.22	391	294	
Power	0.376	553.25	395	296	
Exponential (M5)	N/A[b]	554.86	267	253	
Linear	0.107	554.94	315	241	
Exponential (M2)[c]	0.0743	555.67	310	231	
Exponential (M4)[d]	0.0743	555.67	310	231	
Polynomial 4°	error	error	error[e]	error[e]	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0966, BMDS Test 3 *p*-value = 0.0426), no model was selected as a best-fitting model.

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

[c] The Exponential (M2) model may appear equivalent to the Exponential (M4) model, however differences exist in digits not displayed in the table.

[d] The Exponential (M4) model may appear equivalent to the Exponential (M2) model, however differences exist in digits not displayed in the table.

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

2.2.9 Decreased Left Cauda Epididymis Weight

A decrease in left cauda epididymis absolute weight was observed in the F_0 generation in the reproductive and developmental study by (WIL Research, 2001). The absolute weights are used for BMD modeling of the epididymis as described in EPA’s Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996). The doses and response data used for the modeling are presented in Table 2-39.

Table 2-39 Left Cauda Epididymis Absolute Weight Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Left Cauda Epididymis Weight (mg)	Standard Deviation
0	25	0.3252	0.03673
100	25	0.3242	0.03149
250	25	0.3050	0.03556
500	23	0.2877	0.03170
750	22	0.2401	0.03529

The BMD modeling results for left cauda epididymis absolute weight with homogeneous variance (BMDS test 2 *p*-value =0.911) are summarized in Table 2-40. The best fitting model (Polynomial 4°) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The Polynomial 4° model had an acceptable BMD to BMDL ratio of 1.4 and is indicated in bold. For the best fitting model a plot of the model is shown in Figure 2-16. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-41.

Table 2-40 Summary of BMD Modeling Results for Left Cauda Epididymis Absolute Weight F_0 Male Rats Following Inhalation Exposure to 1-BP

Model[a]	Goodness of fit		BMD$_{1SD}$ (ppm)	BMDL$_{1SD}$ (ppm)	Basis for model selection
	***p*-value**	**AIC**			
Polynomial 4°	**0.622**	**-714.88**	**438**	**313**	**The Polynomial 4° model was selected based on the lowest AIC from this set of models which have adequate *p*-values (excluding Exponential M2 and M4), adequate fit by visual inspection and the BMDLs are < 1.5-fold apart considered sufficiently close.**
Polynomial 3°	0.565	-714.69	440	316	
Polynomial 2°	0.47	-714.32	437	315	
Power	0.430	-714.14	444	317	
Exponential (M3)	0.382	-713.91	446	320	
Linear	0.133	-712.23	307	256	
Hill	0.193	-712.14	444	317	
Exponential (M5)	0.166	-711.91	446	320	
Exponential (M2)	0.0636	-710.55	289	236	
Exponential (M4)	0.0636	-710.55	289	235	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.911), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, 500, and 750 ppm were -0.21, 0.64, -0.65, 0.26, -0.04, respectively.

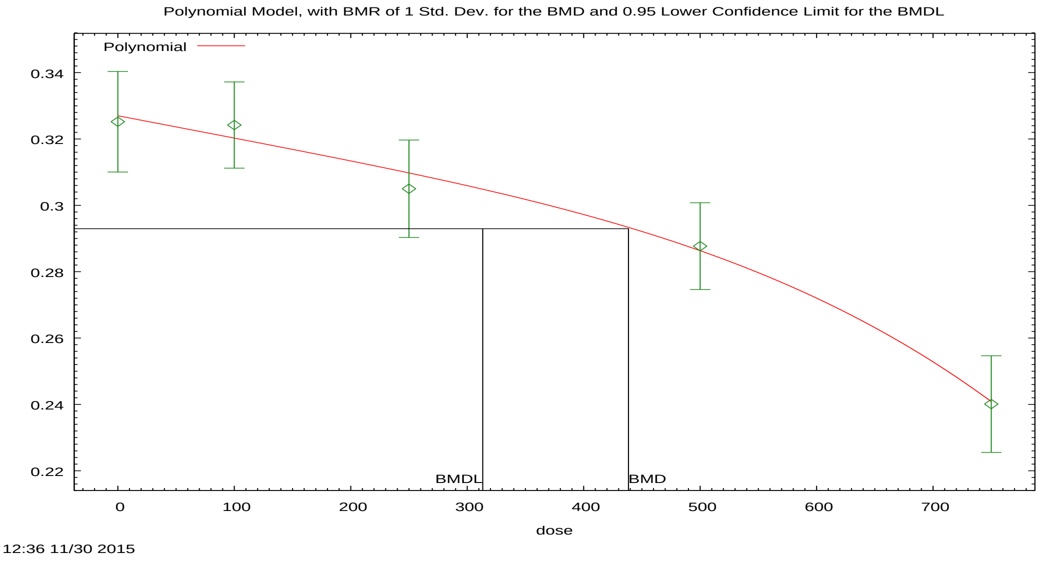

Figure 2-16 Plot of Mean Response by Dose in ppm with Fitted Curve for Polynomial 4° Model with Constant Variance for Left Cauda Epididymis Absolute Weight; BMR = 1 Standard Deviation Change from Control Mean.

Table 2-41 BMD Modeling Results for Left Cauda Epididymis Absolute Weight; BMR = 1 Standard Deviation Change from Control Mean.

Polynomial Model. (Version: 2.20; Date: 10/22/2014)
The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …
A constant variance model is fit

Benchmark Dose Computation.
BMR = 1 Estimated standard deviations from the control mean
BMD = 438.482
BMDL at the 95% confidence level = 313.325

Parameter Estimates

Variable	**Estimate**	**Default Initial Parameter Values**
alpha	0.00113284	0.0011711
rho	n/a	0
beta_0	0.326617	0.3252
beta_1	-0.0000672194	0
beta_2	0	-0.00000139519
beta_3	-6.09563E-33	0
beta_4	-1.13164E-13	-2.44944E-12

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	0.32	0.33	0.04	0.03	-0.21
100	25	0.32	0.32	0.03	0.03	0.641
250	25	0.3	0.31	0.04	0.03	-0.649
500	25	0.29	0.29	0.03	0.03	0.262
750	25	0.24	0.24	0.04	0.03	-0.044

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	361.914605	6	-711.829209
A2	362.410744	10	-704.821488
A3	361.914605	6	-711.829209
fitted	361.438986	4	-714.877972
R	322.608827	2	-641.217655

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	79.6038	8	<0.0001
Test 2	0.992278	4	0.911
Test 3	0.992278	4	0.911
Test 4	0.951238	2	0.6215

2.2.10 Decreased Right Cauda Epididymis Weight

A decrease in right cauda epididymis absolute weight was observed in the F_0 generation in the reproductive and developmental study by (WIL Research, 2001). The absolute weights are used for BMD modeling of the epididymis as described in EPA's Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996). The doses and response data used for the modeling are presented in Table 2-42.

Table 2-42 Right Cauda Epididymis Absolute Weight Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Left Cauda Epididymis Weight (mg)	Standard Deviation
0	25	0.3327	0.03631
100	25	0.3311	0.04453
250	25	0.3053	0.04188
500	23	0.2912	0.05206
750	22	0.2405	0.04804

The BMD modeling results for right cauda epididymis absolute weight with homogeneous variance (BMDS test 2 *p*-value =0.455) are summarized in Table 2-43. The best fitting model (Polynomial 4°) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The Polynomial 4° model had an acceptable BMD to BMDL ratio of 1.4 and is indicated in bold. For the best fitting model a plot of the model is shown in Figure 2-17. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-44.

Table 2-43 Summary of BMD Modeling Results for Right Cauda Epididymis Absolute Weight F_0 Male Rats Following Inhalation Exposure to 1-BP

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC			
Polynomial 4°	**0.493**	**-646.60**	**485**	**338**	**The Polynomial 4° model was selected based on the lowest AIC from this set of models which have adequate *p*-values, adequate fit by visual inspection and the BMDLs are < 1.5-fold apart considered sufficiently close.**
Polynomial 3°	0.442	-646.38	480	334	
Linear	0.296	-646.32	371	303	
Polynomial 2°	0.376	-646.06	472	327	
Power	0.340	-645.86	474	323	
Exponential (M3)	0.304	-645.63	473	317	
Exponential (M2)	0.196	-645.33	350	277	
Exponential (M4)	0.196	-645.33	350	270	
Hill	0.142	-643.85	474	323	
Exponential (M5)	0.123	-643.63	473	317	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.455), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, 500, and 750 ppm were -0.09, 0.63, -0.9, 0.44, -0.08, respectively.

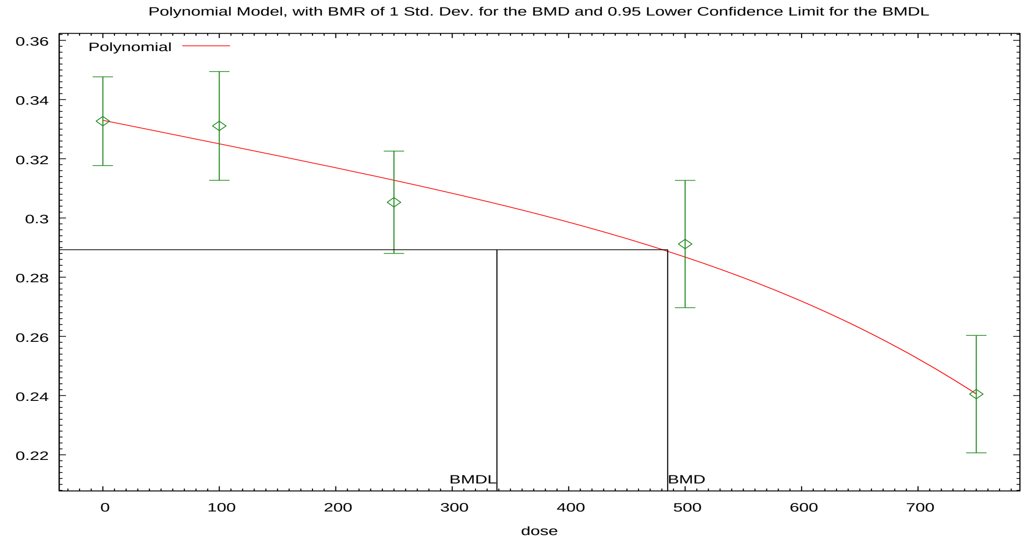

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Figure 2-17 Plot of Mean Response by Dose in ppm with Fitted Curve for Polynomial 4° Model with Constant Variance for Right Cauda Epididymis Absolute Weight; BMR = 1 Standard Deviation Change from Control Mean.

Table 2-44 BMD Modeling Results for Right Cauda Epididymis Absolute Weight; BMR = 1 Standard Deviation Change from Control Mean

Polynomial Model. (Version: 2.20; Date: 10/22/2014)
The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …
A constant variance model is fit

Benchmark Dose Computation.
BMR = 1 Estimated standard deviations from the control mean
BMD = 484.978
BMDL at the 95% confidence level = 338.42

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.00195609	0.00201467
rho	n/a	0
beta_0	0.333498	0.3327
beta_1	-0.0000793692	0
beta_2	-2.2991E-28	-0.00000198872
beta_3	-2.18866E-31	0
beta_4	-1.03676E-13	-3.6281E-12

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	0.33	0.33	0.04	0.04	-0.0902
100	25	0.33	0.33	0.04	0.04	0.627
250	25	0.3	0.31	0.04	0.04	-0.899
500	25	0.29	0.29	0.05	0.04	0.437
750	25	0.24	0.24	0.05	0.04	-0.0754

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	328.007576	6	-644.015151
A2	329.833395	10	-639.66679
A3	328.007576	6	-644.015151
fitted	327.300407	4	-646.600813
R	299.119376	2	-594.238753

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	61.428	8	<0.0001
Test 2	3.65164	4	0.4552
Test 3	3.65164	4	0.4552
Test 4	1.41434	2	0.493

2.2.11 Increased Estrus Cycle Length

An increase estrus cycle length was observed in the F_0 generation in the reproductive and developmental study by (WIL Research, 2001). The doses and response data used for the modeling are presented in Table 2-45.

Table 2-45 Estrus Cycle Length Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Estrus cycle Length (days)	Standard Deviation
0	25	4.2	0.49
100	25	4.5	1.05
250	25	4.7	0.9
500	23	5.5	2.17
750	22	5.6	1.79

The BMD modeling results for estrus cycle length with non-homogeneous variance (BMDS test 2 *p*-value = <0.0001) are summarized in Table 2-46. The means are not adequately fit for any of the models as shown by the goodness of fit where the model with the highest *p*-value is 0.0065 for the Exponential M4 and M5 models (excluding the Hill model because a BMDL could not be calculated). This result suggests that due to the poor model fit to the data it is not reasonable to use BMDS for this endpoint. Instead the NOAEL of 250 ppm was used.

Table 2-46 Summary of BMD Modeling Results for Estrus Cycle Length F$_0$ Female Rats Following Inhalation Exposure to 1-BP

Model[a]	**Goodness of fit**		**BMD$_{1SD}$ (ppm)**	**BMDL$_{1SD}$ (ppm)**	**Basis for model selection**
	***p*-value**	**AIC**			
Hill	0.00656	160.04	145	error[b]	**Due to inadequate fit of the models to the data means (shown by the goodness of fit *p*-value) no model was selected.**
Exponential (M4) Exponential (M5)[c]	0.00650	160.05	157	79.5	
Power[d] Polynomial 4°[e] Polynomial 3°[f] Polynomial 2°[g] Linear	0.00169	163.13	300	205	
Exponential (M2) Exponential (M3)[h]	7.68E-04	164.81	344	244	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001, BMDS Test 3 *p*-value = 0.506), no model was selected as a best-fitting model.

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

[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[e] 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. For the Polynomial 4° model, the b4, b3, and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[f] 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.

[g] 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.

[h] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

2.2.12 Decreased Antral Follical Count

A decreased antral follicle count was observed in the study of female reproductive function by (Yamada et al., 2003). The doses and response data used for the modeling are presented in Table 2-47. The highest dose was not included for modeling because all the rats in the highest dose group (800 ppm) were seriously ill and were sacrificed during the 8th week of the 12 week study.

Table 2-47 Antral Follicle Count Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Antral Follicle Count	Standard Deviation
0	8	30.1	22.4
200	9	12.6	4.82
400	9	7.44	6.52

The BMD modeling results for antral follical count with non-homogeneous variance (BMDS test 2 *p*-value = <0.0001) are summarized in Table 2-48. The means are not adequately fit for any of the models as shown by the goodness of fit where the model with the highest *p*-value is 0.0404 for the Exponential M2 model. This result suggests that due to the poor model fit to the data it is not reasonable to use BMDS for this endpoint. Instead the LOAEL of 200 ppm was used.

Table 2-48 Summary of BMD Modeling Results for Antral Follical Count in Female Rats Following Inhalation Exposure to 1-BP

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC			
Exponential (M4)	N/A[b]	148.31	189	0.651	**Due to inadequate fit of the models to the data means (shown by the goodness of fit *p*-value) no model was selected.**
Exponential (M2)	0.0404	150.51	270	117	
Power[c] Linear[d]	0.00496	154.21	410	233	
Polynomial 2°[e]	0.00496	154.21	410	233	
Exponential (M3)	N/A[b]	179.12	1.8E+05	754	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001, BMDS Test 3 *p*-value = 0.0545), no model was selected as a best-fitting model.
[b] No available degrees of freedom to calculate a goodness of fit value.
[c] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[d] The Linear model may appear equivalent to the Polynomial 2° model, however differences exist in digits not displayed in the table.
[e] The Polynomial 2° model may appear equivalent to the Power model, however differences exist in digits not displayed in the table. This also applies to the Linear model.

2.2.13 Decreased Male and Female Fertility Index

A decrease in the male and female fertility index was observed in the F_0 generation in the reproductive and developmental study by WIL Laboratories (2001). The doses and response data are presented in Table 2-49 as a percentage and incidence. The incidence represents the number of males that did not sire a litter which is equal to the number of nongravid females. The incidence was used for modeling as a dichotomous endpoint.

Table 2-49 Fertility Index Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Fertility Index (%)	Number Nongravid Females = Males that did not Sire a Litter
0	25	92	2
100	25	100	0
250	25	88	3
500	23	52	12
750	22	0	25

The BMD modeling results for the fertility index are summarized in Table 2-50. The best fitting models were the LogLogistic and Dichotomous-Hill based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. Dichotomous-Hill model slope parameter was at the boundary value of 18 which indicates some concern for using this model fit and so instead the LogLogistic model selected. The LogLogistic and Dichotomous-Hill models had nearly the same BMDLs with LogLogistic slightly lower (356 ppm) than Dichotomous-Hill (363 ppm). For the best fitting model a plot of the model is shown in Figure 2-18. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-51.

Table 2-50 Summary of BMD Modeling Results for Fertility Index of F_0 Rats Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		BMD_{10Pct} (ppm)	$BMDL_{10Pct}$ (ppm)	Basis for model selection
	p-value	AIC			
LogLogistic	**0.388**	**75.396**	**448**	**356**	**The LogLogistic model was selected based on the lowest AIC from this set of models which have adequate goodness of fit *p*-value (excluding Quantal-Linear, Multistage 2^0, Probit and Logistic) and adequate fit by visual inspection and the BMDLs are < 2-fold apart considered sufficiently close. The Dichotomous-Hill model had concern for the fit based on the slope parameter at the boundary and so instead the LogLogistic was selected.**
Dichotomous-Hill	0.388	75.396	448	363	
Multistage 4°	0.355	75.682	306	219	
Weibull	0.253	77.024	361	252	
Gamma	0.256	77.045	361	260	
LogProbit	0.223	77.357	461	352	
Multistage 3°	0.161	78.153	250	202	
Logistic	0.0103	80.981	238	182	
Probit	0.0031	82.358	208	159	
Multistage 2°	0.0152	85.979	173	143	
Quantal-Linear	0	106.73	68.4	52.1	

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[a] Selected model in bold; scaled residuals for selected model for doses 0, 100, 250, 500, and 750 ppm were 0.27, -1.34, 1.07, -0.01, 0.14, respectively.

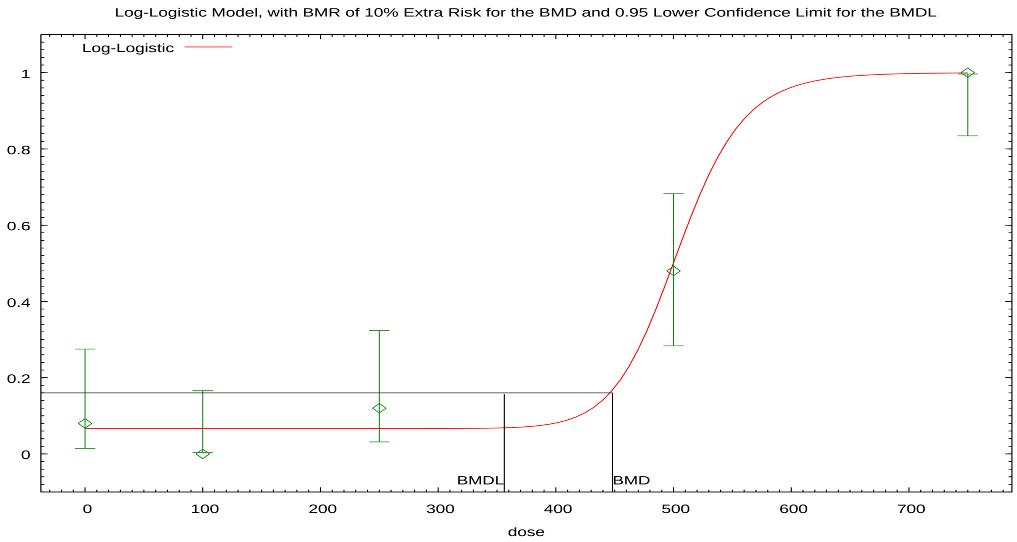

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Figure 2-18 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (LogLogistic) for Fertility Index in Rats Exposed to 1-BP Via Inhalation in ppm BMR 10% Extra Risk.

Table 2-51 BMD Modeling Results for Fertility Index in Rats Exposed to 1-BP Via Inhalation BMR 10% Extra Risk

Logistic Model. (Version: 2.14; Date: 2/28/2013)

The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 448.13

BMDL at the 95% confidence level = 356.183

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0.0666427	0.08
intercept	-1.1209E+02	-2.1668E+01
slope	18	3.62868

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	*p*-value
Full model	-33.45	5			
Fitted model	-35.7	2	4.4943	3	0.21
Reduced model	-79.79	1	92.6846	4	<.0001

AIC: = 75.3964

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0666	1.666	2	25	0.27
100	0.0666	1.666	0	25	-1.34
250	0.0666	1.666	3	25	1.07
500	0.4809	12.022	12	25	-0.01
750	0.9992	24.98	25	25	0.14

Chi^2 = 3.02 d.f = 3 *p*-value = 0.3884

2.2.14 Decreased Implantations Sites

A decrease in the number of implantations sites was observed in the F_0 generation in the reproductive and developmental study by (WIL Research, 2001). The doses and response data used for modeling are presented in Table 2-52. The highest dose group was not included because none of the dams had implantations sites.

Table 2-52 Implantations Site Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Average Numer of Sites	Standard Deviation
0	23	15.3	2.53
100	25	14.3	3.09
250	22	13.8	4.23
500	11	9.0	4.54

The BMD modeling results for the number of implantations sites are summarized in Table 2-53. The best fitting models were the Linear and Power based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. Based on the parameter estimate for the Power model it reduced to the Linear, so the Linear model was selected. For the best fitting model a plot of the model is shown in Figure 2-19. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-54.

Table 2-53 Summary of BMD Modeling Results for Implantations Sites in F_0 Rats Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	**Goodness of fit**		**BMD$_{5RD}$ (ppm)**	**BMDL$_{5RD}$ (ppm)**	**BMD$_{1SD}$ (ppm)**	**BMDL$_{1SD}$ (ppm)**	**Basis for model selection**
	***p*-value**	**AIC**					
Linear **Power**[b]	**0.936**	**284.66**	80.8	56.1	**282**	**188**	**Linear and Power models were selected based on the lowest AIC from this set of models which have adequate *p*-values, adequate fit by visual inspection and the BMDLs are < 1.5-fold apart considered sufficiently close.**
Exponential (M2)	0.901	284.74	74.1	48.1	270	166	
Exponential (M4)	0.901	284.74	74.1	37.3	270	138	
Polynomial 3°	0.741	286.64	85.5	56.2	295	188	
Polynomial 2°	0.724	286.66	84.3	56.1	289	188	
Hill	0.715	286.67	80.6	55.8	282	195	
Exponential (M3)	0.669	286.71	82.3	48.2	278	167	
Exponential (M5)	N/A[c]	288.71	82.3	48.2	278	167	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0493), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were -0.17, -0.23, 1, -1, respectively.

[b] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

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

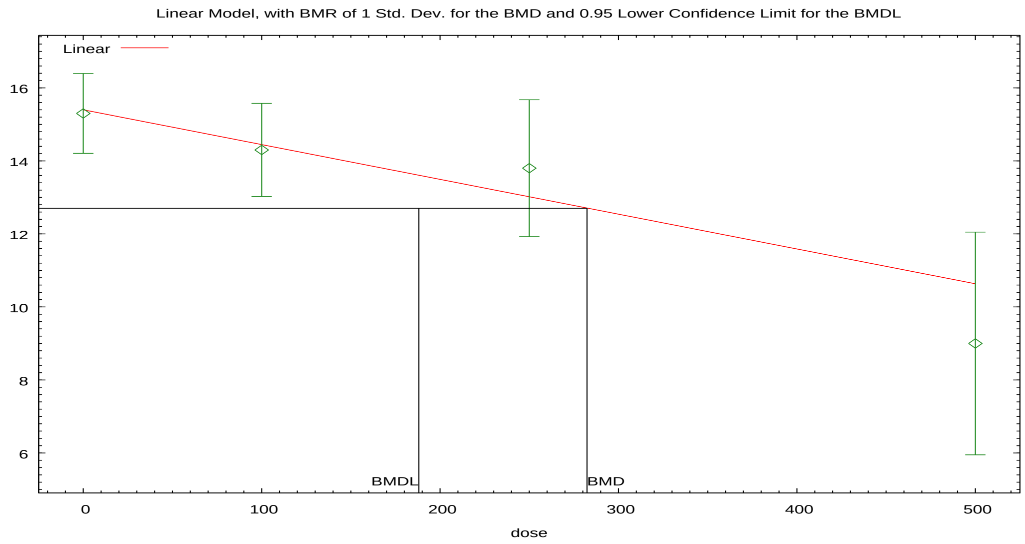

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Figure 2-19 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Linear) for Implantation Sites in Rats Exposed to 1-BP Via Inhalation in ppm BMR 1 Standard Deviation.

Table 2-54 BMD Modeling Results for Implantation Sites in Rats Exposed to 1-BP Via Inhalation in ppm BMR 1 Standard Deviation

Polynomial Model. (Version: 2.20; Date: 10/22/2014)
The form of the response function is: Y[dose] = beta_0 + beta_1*dose
A modeled variance is fit

Benchmark Dose Computation.
BMR = 1 Estimated standard deviations from the control mean
BMD = 282.359
BMDL at the 95% confidence level = 188.047

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	12.2915	2.51459
rho	-3.77194	0
beta_0	15.393	15.7286
beta_1	-0.00952791	-0.01237

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	23	15.3	15.4	2.53	2.69	-0.166
100	25	14.3	14.4	3.09	3.03	-0.231
250	22	13.8	13	4.23	3.69	1
500	11	9	10.6	4.54	5.41	-0.999

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.289933	5	290.579865
A2	-136.366566	8	288.733132
A3	-138.26616	6	288.532319
fitted	-138.332408	4	284.664816
R	-151.740933	2	307.481866

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	30.7487	6	<0.0001
Test 2	7.84673	3	0.04929
Test 3	3.79919	2	0.1496
Test 4	0.132497	2	0.9359

2.2.15 Decreased Pup Body Weight

Decreased pup body weight was observed in the 2-generation reproductive and developmental study by (WIL Research, 2001). Statistically significant decreases in pup body weight were noted for males in the F_1 generation at PND 28 and in the F_2 generation in both sexes at PNDs 14 and 21. Continuous models were used to fit-dose response data for decreased 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 per EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012). The doses, response data and BMD modeling results for decreased pup body weight are presented below at each time point.

2.2.15.1 Decreased Body Weight in F1 Male Pups at PND 28

The doses and response data from the WIL Laboratories (WIL Research, 2001) study were used for the modeling and are presented in Table 2-55.

Table 2-55 Pup Body Weight Data in F_1 Males at PND 28 for Dose-Response Modeling

	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of litters	23	24	21	10
Mean pup wt (g)	88.1	82.8	80.3	76.0
Standard deviation (g)	7.60	7.74	9.04	9.45

A comparison of the model fits obtained for pup body weight changes is provided in Table 2-56. The best fitting model was selected based on Akaike information criterion (AIC; lower values indicates a better fit), visual inspection and comparison with the BMD/BMDLs among the data for decreased pup weights at other time points. There is a large spread in BMC/L values among the models and EPA procedures allow for selecting the lowest BMDL is this case (the Hill model) however the Exponential (M2) was selected because it is in line with the results from the pup body weight decreases observed at the other time points in this data set and the Hill model has additional uncertainty of the BMD / BMDL ratio is 4-fold and the BMDL is greater than 4-fold lower than the lowest dose. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure 2-20. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table

2-57. Also a plot of the Hill model is shown in Figure 2-21 and the model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-57.

Table 2-56 Summary of BMD Modeling Results for Body Weight of F_1 Male Rat Pups on PND 28 Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	**Goodness of fit**		**BMD 1SD (ppm)**	**BMDL 1SD (ppm)**	**BMD 5RD (ppm)**	**BMDL 5RD (ppm)**	**Basis for model selection**
	***p*-value**	**AIC**					
Exponential (M2) **Exponential (M3)[b]**	**0.449**	**411.46**	334.07	228.77	**174**	**123**	**The Exponential (M2) model was selected based on the lowest AIC from this set of models which have adequate *p*-values and adequate fit by visual inspection. The Hill model has the lowest BMDL and the BMDL is > 5-fold apart from other model BMDLs not considered sufficiently close, however the BMDL is > 4-fold from the lowest dose and BMD / BMDL ratio is 4-fold and the Exponential (M2) model is in line with the result from pup body weight decreases observed in this study at other time points.**
Power[c] Polynomial 3°[d] Polynomial 2°[e] Linear	0.406	411.66	345.22	242.64	183	133	
Hill	0.578	412.17	234.74	85.21	92.2	23.2	
Exponential (M4) Exponential (M5)[f]	0.512	412.29	238.92	95.80	101	36.8	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.785), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were 0.77, -0.88, -0.17, 0.44, 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.

[f] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

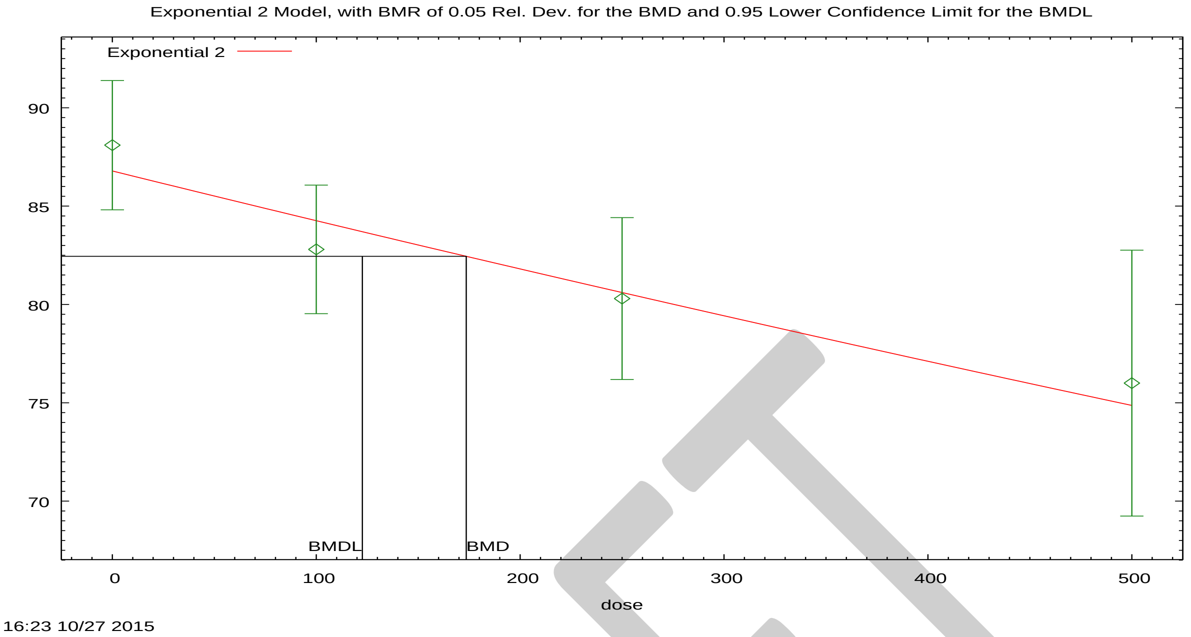

Figure 2-20 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Exponential (M2)) for Pup Body Weight in Rats Exposed to 1-BP Via Inhalation in ppm BMR 5% Relative Deviation.

Table 2-57 BMD Modeling Results for Pup Body Weight in Rats Exposed to 1-BP Via Inhalation BMR 5% Relative Deviation

Exponential Model. (Version: 1.10; Date: 01/12/2015)
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 = 173.561
BMDL at the 95% confidence level = 122.612

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	4.19824	4.17769
rho	n/a	0
a	86.7871	78.9392
b	0.000295534	0.000288601
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	23	88.1	86.79	7.6	8.16	0.7717
100	24	82.8	84.26	7.74	8.16	-0.8765
250	21	80.3	80.61	9.04	8.16	-0.1719
500	10	76	74.87	9.45	8.16	0.4398

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-201.9297	5	413.8595
A2	-201.395	8	418.7901
A3	-201.9297	5	413.8595
R	-210.4356	2	424.8712
2	-202.7313	3	411.4626

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	18.08	6	0.006033
Test 2	1.069	3	0.7845
Test 3	1.069	3	0.7845
Test 4	1.603	2	0.4486

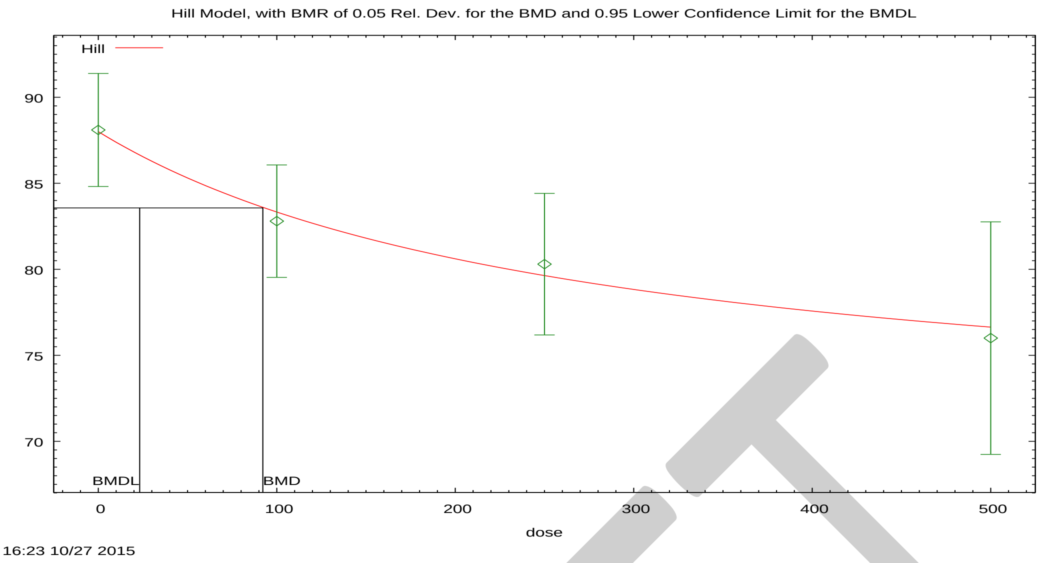

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Figure 2-21 Plot of Mean Response by Dose with Fitted Curve for the Hill Model for Pup Body Weight in Rats Exposed to 1-BP Via Inhalation in ppm BMR 5% Relative Deviation.

Table 2-58 BMD Modeling Results for Pup Body Weight in Rats Exposed to 1-BP Via Inhalation BMR 5% Relative Deviation

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 constant variance model is fit

Benchmark Dose Computation.
BMR = 5% Relative deviation
BMD = 92.1819
BMDL at the 95% confidence level = 23.1805

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	65.474	68.7399
rho	n/a	0
intercept	87.9661	88.1
v	-17.7059	-12.1
n	1	0.881973
k	278.907	145

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	23	88.1	88	7.6	8.09	0.0793
100	24	82.8	83.3	7.74	8.09	-0.299
250	21	80.3	79.6	9.04	8.09	0.398
500	10	76	76.6	9.45	8.09	-0.235

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-201.929732	5	413.859464
A2	-201.39503	8	418.790061
A3	-201.929732	5	413.859464
fitted	-202.084541	4	412.169082
R	-210.435607	2	424.871213

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.0812	6	0.006033
Test 2	1.0694	3	0.7845
Test 3	1.0694	3	0.7845
Test 4	0.309618	1	0.5779

2.2.15.2 Decreased Body Weight in F_2 Female Pups at PND 14

The doses and response data used for the modeling are presented in Table 2-59.

Table 2-59 Pup Body Weight Data in F_2 Females at PND 14 from Selected for Dose-Response Modeling

	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of litters	22	17	15	15
Mean pup wt (g)	27.6	26.9	27.3	23.7
Standard deviation (g)	2.29	2.11	3.87	3.70

The BMD modeling results for decreased pup weight in F_2 females at PND 14 with non-homogeneous variance (BMDS test 2 *p*-value = 0.0218) are summarized in Table 2-60. Although the variances are non-homogeneous and not well modeled for any of the non-homogeneous variance models the means were well-modeled (the highest *p*-value is 0.904 for the linear model with non-homogeneous variances).

Table 2-60 Summary of BMD Modeling Results for Body Weight of F_2 Female Rat Pups on PND 14 Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		BMD$_{5RD}$ (ppm)	BMDL$_{5RD}$ (ppm)
	p-value	AIC		
Linear	0.904	221.02	228	145
Exponential (M2)	0.893	221.05	224	138
Exponential (M4)	0.893	221.05	224	104
Exponential (M3)	0.715	222.96	244	139
Power	0.708	222.96	245	146
Polynomial 3°[b]	0.687	222.98	245	145
Polynomial 2°[c]	0.687	222.98	245	145
Exponential (M5)	N/A[d]	224.82	228	107
Hill	N/A[d]	224.82	226	105
Polynomial 4°	error	error	error[e]	error[e]

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0218, BMDS Test 3 *p*-value = 0.0438), no model was selected as a best-fitting model.

[b] The Polynomial 3° model may appear equivalent to the Polynomial 2° model, however differences exist in digits not displayed in the table.

[c] The Polynomial 2° model may appear equivalent to the Polynomial 3° model, however differences exist in digits not displayed in the table.

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

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

To investigate the effect of the poor modeling of the variances on the BMDL, the models were run using the smallest dose standard deviation (2.29), highest (3.87) and pooled (2.89) for all dose levels and the modeling results are summarized in Table 2-61.

Table 2-61 BMD Modeling Results for Body Weight of F2 Female Rat Pups on PND 14 Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study with Variances Fixed at Smallest, Pooled and Highest Values.

Model[a]	**Smallest Standard Deviation**				**Pooled Standard Deviation**				**Largest Standard Deviation**				**Ratio BMDLs Smallest to Largest Std Dev**
	Goodness of fit		**BMD_{5RD} (ppm)**	**BMDL_{5RD} (ppm)**	**Goodness of fit**		**BMD_{5RD} (ppm)**	**BMDL_{5RD} (ppm)**	**Goodness of fit**		**BMD_{5RD} (ppm)**	**BMDL_{5RD} (ppm)**	
	***p*-value**	**AIC**			***p*-value**	**AIC**			***p*-value**	**AIC**			
Polynomial 3°	0.518	186.54	360	274	0.661	218.16	360	183	0.793	258.09	360	145	1.9
Polynomial 2°	0.318	187.51	304	199	0.485	218.78	304	260	0.667	258.44	304	140	1.4
Power	0.331	188.16	465	247	0.441	219.93	465	200	0.564	259.96	460	148	1.7
Exponential (M3)	0.331	188.16	473	249	0.441	219.93	470	202	0.564	259.96	473	143	1.7
Hill	N/A[b]	190.16	466	248	N/A[b]	221.93	465	200	N/A[b]	261.96	442	138	1.8
Exponential (M5)	N/A[b]	190.16	470	249	N/A[b]	221.93	470	202	N/A[b]	261.96	473	139	1.8
Linear	0.0533	191.08	193	146	0.154	221.07	193	138	0.348	259.74	193	127	1.1
Exponential (M2)	0.0443	191.45	188	139	0.137	221.31	188	131	0.325	259.88	188	119	1.2
Exponential (M4)	0.0443	191.45	188	131	0.137	221.31	188	115	0.325	259.88	188	90.2	1.5

[a] Constant variance case presented (BMDS Test 2 *p*-value = 1., BMDS Test 3 *p*-value = 1.), no model was selected as a best-fitting model.
[b] No available degrees of freedom to calculate a goodness of fit value.

A comparison across the full suite of BMD models shows the BMDL is sensitive to the adjustment of the variances and for the model that fit the constant variance data best, the Polynomial 3° model the ratio of BMDLs was 1.9. This result suggests that due to the poor variance modeling for the original data it is not reasonable to use BMDS for this endpoint. Instead the NOAEL of 250 ppm was used.

2.2.15.3 Decreased Body Weight in F_2 Female Pups at PND 21

The doses and response data used for the modeling are presented in Table 2-62.

Table 2-62 Pup Body Weight Data in F_2 Females at PND 21 from Selected for Dose-Response Modeling

	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of litters	22	17	15	15
Mean pup wt (g)	46.6	44.7	45.6	39.7
Standard deviation (g)	4.05	3.80	5.60	6.13

Comparisons of model fits obtained are provided in Table 2-63. The best fitting model (Polynomial 2° with constant variance) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure 2-22. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table 2-63 Summary of BMD Modeling Results for Body Weight of F_2 Females on PND 21 Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	Basis for model selection
	p-value	AIC					
Polynomial 2°	**0.372**	**291.28**	436.24	299.79	**303**	**148**	**The Polynomial 2° model was selected based on the lowest AIC from this set of models which have adequate *p*-values, adequate fit by visual inspection and the BMDLs are < 1.5-fold apart considered sufficiently close.**
Linear	0.176	292.77	386.50	269.95	187	135	
Power	0.216	292.83	475.29	314.36	407	155	
Exponential (M3)	0.216	292.83	474.45	316.27	406	152	
Polynomial 3°	0.213	292.85	449.22	313.20	336	154	
Exponential (M2)	0.160	292.97	385.88	261.10	181	127	
Exponential (M4)	0.160	292.97	385.88	250.91	181	105	
Exponential (M5)	N/A[b]	294.83	474.45	316.27	406	152	
Hill	N/A[b]	294.83	475.10	314.77	406	150	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.144), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were 0.4, -1.06, 0.8, -0.15, respectively.

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

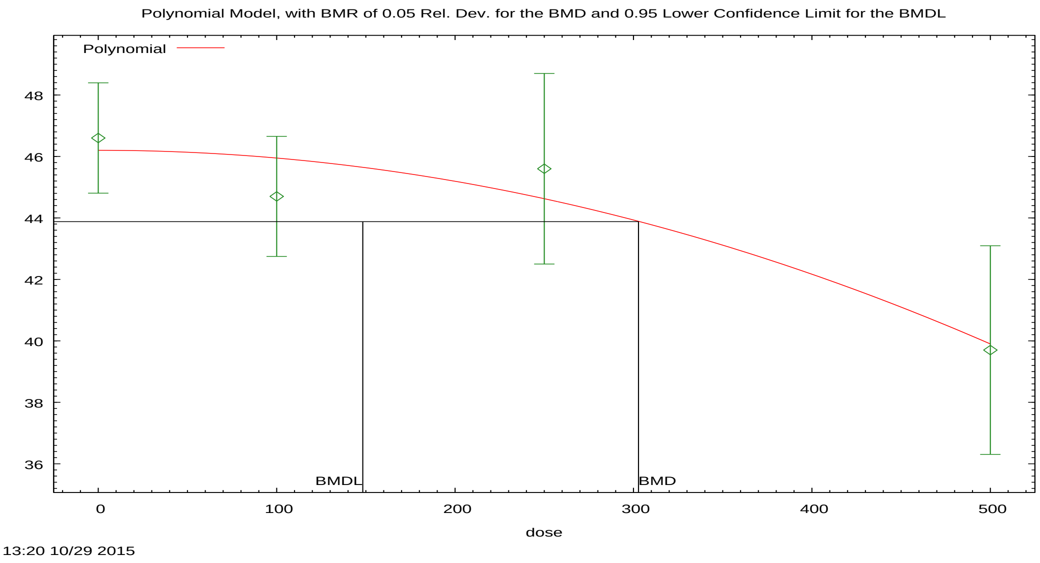

Figure 2-22 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Polynomial 2°) for Pup Body Weight in Rats Exposed to 1-BP Via Inhalation in ppm BMR = 5% Relative Deviation.

Table 2-64 BMD Modeling Results for Pup Body Weight in Rats Exposed to 1-BP Via Inhalation BMR = 5% Relative Deviation.

Polynomial Model. (Version: 2.20; Date: 10/22/2014)
The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …
A constant variance model is fit

Benchmark Dose Computation.
BMR = 5% Relative deviation
BMD = 302.794
BMDL at the 95% confidence level = 148.282

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	22.9776	23.7017
rho	n/a	0
beta_0	46.1877	45.9942
beta_1	0	0
beta_2	-0.0000251884	-0.000029911

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	46.6	46.2	4.05	4.79	0.403
100	17	44.7	45.9	3.8	4.79	-1.06
250	15	45.6	44.6	5.6	4.79	0.797
500	15	39.7	39.9	6.13	4.79	-0.154

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-141.651019	5	293.302038
A2	-138.944287	8	293.888574
A3	-141.651019	5	293.302038
fitted	-142.640988	3	291.281976
R	-150.681267	2	305.362534

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	23.474	6	0.0006523
Test 2	5.41346	3	0.1439
Test 3	5.41346	3	0.1439
Test 4	1.97994	2	0.3716

2.2.15.4 Decreased Body Weight in F_2 Male Pups at PND 14

The doses and response data used for the modeling are presented in Table 2-65.

Table 2-65 Pup Body Weight Data in F_2 Males at PND 14 from Selected for Dose-Response Modeling

	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of litters	22	17	15	16
Mean pup wt (g)	29.2	28.1	28.4	24.5
Standard deviation (g)	2.77	2.43	3.65	4.14

Comparisons of model fits obtained are provided in Table 2-66. The best fitting model (Polynomial 2° with constant variance) was selected based on Akaike information criterion

(AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure 2-23. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-67.

Table 2-66 Summary of BMD Modeling Results for Body Weight of F$_2$ Male Rat Pups on PND 14 Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	**Goodness of fit**		**BMD$_{1SD}$ (ppm)**	**BMDL$_{1SD}$ (ppm)**	**BMD$_{5RD}$ (ppm)**	**BMDL$_{5RD}$ (ppm)**	**Basis for model selection**
	***p*-value**	**AIC**					
Polynomial 2°	**0.509**	**238.45**	427.44	290.47	**288**	**136**	**The Polynomial 2° model was selected based on the lowest AIC from this set of models which have adequate *p*-values, adequate fit by visual inspection and the BMDLs are < 1.5-fold apart considered sufficiently close.**
Linear	0.236	239.99	367.99	261.73	168	124	
Polynomial 3°	0.316	240.11	439.96	300.66	314	140	
Power	0.290	240.22	457.39	297.00	358	138	
Exponential (M3)	0.289	240.23	456.58	297.67	358	134	
Exponential (M2)	0.209	240.23	365.77	251.63	161	115	
Exponential (M4)	0.209	240.23	365.77	241.42	161	95.6	
Hill	N/A[b]	242.22	457.31	296.92	358	138	
Exponential (M5)	N/A[b]	242.23	456.58	297.67	358	134	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.116), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were 0.35, -0.89, 0.64, -0.12, respectively.

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

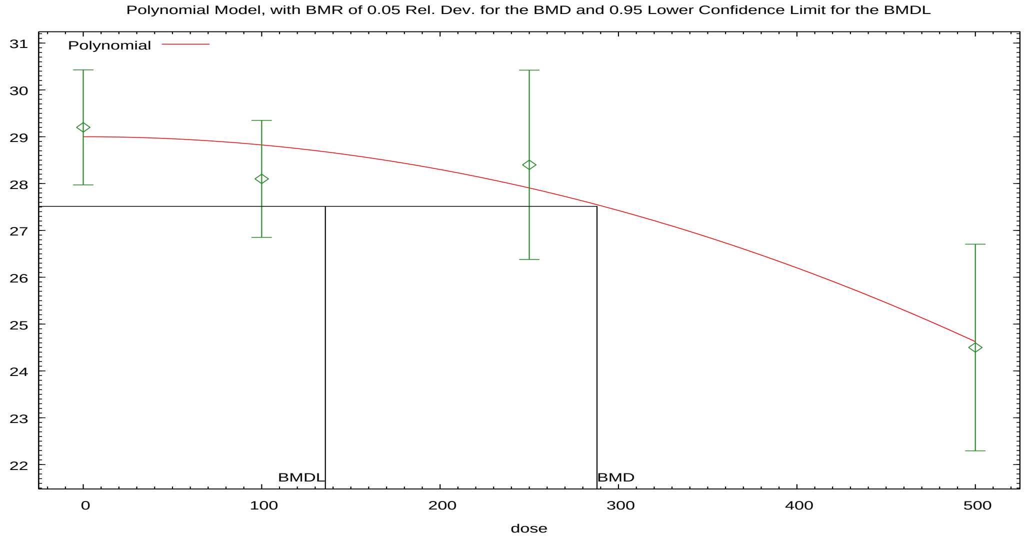

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Figure 2-23 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Polynomial 2°) for Pup Body Weight in Rats Exposed to 1-BP Via Inhalation in ppm BMR = 5% Relative Deviation.

Table 2-67 BMD Modeling Results for Pup Body Weight in Rats Exposed to 1-BP Via Inhalation in ppm BMR = 5% Relative Deviation.

Polynomial Model. (Version: 2.20; Date: 10/22/2014)
The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …
A constant variance model is fit

Benchmark Dose Computation.
BMR = 5% Relative deviation
BMD = 287.938
BMDL at the 95% confidence level = 135.688

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	10.1836	10.5942
rho	n/a	0
beta_0	28.9615	28.8658
beta_1	0	0
beta_2	-0.000017466	-0.000019675

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	29.2	29	2.77	3.19	0.35
100	17	28.1	28.8	2.43	3.19	-0.887
250	15	28.4	27.9	3.65	3.19	0.643
500	16	24.5	24.6	4.14	3.19	-0.119

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-115.551371	5	241.102743
A2	-112.600048	8	241.200097
A3	-115.551371	5	241.102743
fitted	-116.227119	3	238.454239
R	-125.255153	2	254.510306

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	25.3102	6	0.0002991
Test 2	5.90265	3	0.1164
Test 3	5.90265	3	0.1164
Test 4	1.3515	2	0.5088

2.2.15.5 Decreased Body Weight in F_2 Male Pups at PND 21

The doses and response data from the WIL Laboratories (2001) study was used for the modeling and are presented in Table 2-68.

Table 2-68 Pup Body Weight Data in F_2 Males at PND 21

	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of litters	22	17	15	16
Mean pup wt (g)	49.5	46.9	47.6	40.8
Standard deviation (g)	5.14	5.03	5.40	6.70

Comparisons of model fits obtained are provided in Table 2-69. The best fitting model (Linear with homogeneous variance) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure 2-24. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-70.

Table 2-69 Summary of BMD Modeling Results for Body Weight of F_2 Male Rat Pups on PND 21 Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	Basis for model selection
	p-value	AIC					
Linear	**0.218**	**315.14**	**344.43**	**249.00**	**155**	**116**	**The Linear model was selected based on the lowest AIC from this set of models which have adequate *p*-values, adequate fit by visual inspection and the BMDLs are < 1.5-fold apart considered sufficiently close.**
Exponential (M2)	0.194	315.38	339.42	237.32	147	107	
Exponential (M4)	0.194	315.38	339.42	220.01	147	84.8	
Polynomial 3°	0.194	315.78	418.75	271.24	273	125	
Polynomial 2°	0.153	316.14	404.48	264.17	252	122	
Power	0.150	316.17	435.13	263.67	313	122	
Exponential (M3)	0.148	316.19	436.20	257.18	318	115	
Hill	N/A[b]	318.17	435.26	262.98	314	121	
Exponential (M5)	N/A[b]	318.19	436.20	257.18	318	115	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.614), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were -0.04, -0.78, 1.44, -0.54, respectively.

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

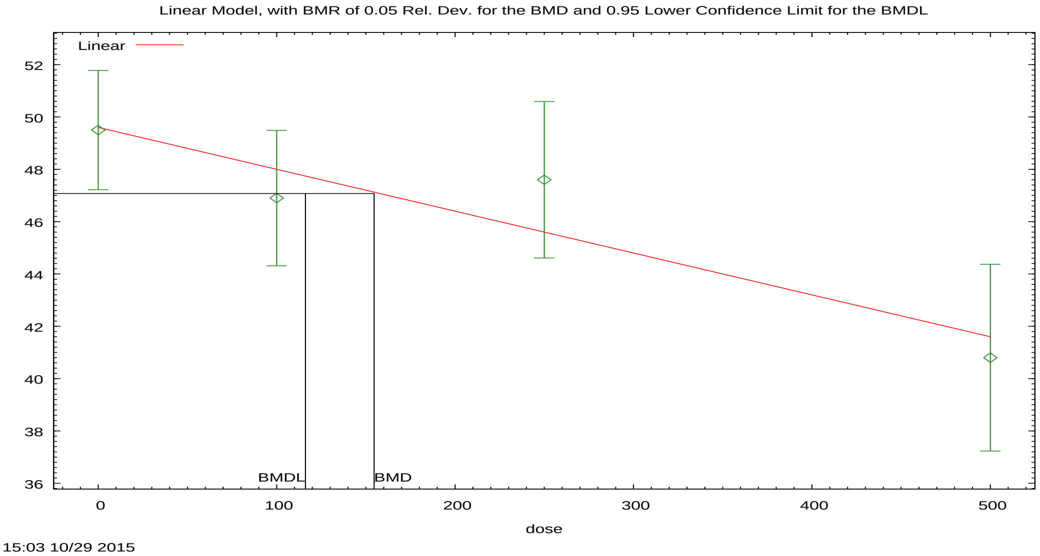

Figure 2-24 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Linear) for Pup Body Weight in Rats Exposed to 1-BP Via Inhalation in ppm BMR = 5% Relative Deviation.

Table 2-70 BMD Modeling Results for Pup Body Weight in Rats Exposed to 1-BP Via Inhalation in ppm BMR = 5% Relative Deviation

Polynomial Model. (Version: 2.20; Date: 10/22/2014)
The form of the response function is: Y[dose] = beta_0 + beta_1*dose
A constant variance model is fit

Benchmark Dose Computation.

BMR = 5% Relative deviation
BMD = 154.623
BMDL at the 95% confidence level = 116.114

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	30.4578	30.9275
rho	n/a	0
beta_0	49.5516	49.615
beta_1	-0.0160234	-0.0160705

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	49.5	49.6	5.14	5.52	-0.0439
100	17	46.9	47.9	5.03	5.52	-0.784
250	15	47.6	45.5	5.4	5.52	1.44
500	16	40.8	41.5	6.7	5.52	-0.536

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-153.048201	5	316.096402
A2	-152.146228	8	320.292456
A3	-153.048201	5	316.096402
fitted	-154.572024	3	315.144048
R	-163.858303	2	331.716606

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	23.4241	6	0.0006662
Test 2	1.80395	3	0.6141
Test 3	1.80395	3	0.6141
Test 4	3.04765	2	0.2179

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2.2.16 Decreased Brain Weight

Decreased brain weights were observed in the 2-generation reproductive and developmental study by (WIL Research, 2001). Statistically significant decreases in brain weights were noted for both sexes in the F_0 generation, F_1 generation as adults and in the F_2 generation at PNDs 21. Continuous models were used to fit-dose response data for decreased brain weights. A BMR of 5% was used because reduced brain weight is considered a more severe endpoint than other decreased organ weights. A BMR of 1 standard deviation is also shown for comparison per EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012). The doses, response data and BMD modeling results for decreased pup brain weight are presented below at each time point.

2.2.16.1 Decreased Brain Weight in F_0 Females

The doses and response data from the WIL Laboratories (2001) study was used for the modeling and are presented in Table 2-71.

Table 2-71 Brain Weight Data in F_0 Females for Dose-Response Modeling

	Concentration (ppm)				
	0	**100**	**250**	**500**	**750**
Number of animals	25	25	25	25	25
Brain wt (g)	1.96	1.92	1.94	1.89	1.86
Standard deviation (g)	0.078	0.094	0.084	0.105	0.072

Comparisons of model fits obtained are provided in Table 2-72. The best fitting model (Linear with homogeneous variance) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure 2-25. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-73.

Table 2-72 Summary of BMD Modeling Results for Brain Weight of F_0 Females Following Inhalation Exposure to 1-BP

Model[a]	Goodness of fit		BMD$_{1SD}$ (ppm)	BMDL$_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC			
Linear	**0.444**	**-480.77**	**711**	**509**	**The Linear model was selected based on the lowest AIC from this set of models which have adequate *p*-values, adequate fit by visual inspection and the BMDLs are < 1.2-fold apart considered sufficiently close.**
Exponential (M2)	0.441	-480.75	711	504	
Exponential (M4)	0.441	-480.75	711	434	
Polynomial 4°[b] Polynomial 3°	0.273	-478.85	717	511	
Polynomial 2°	0.271	-478.84	718	511	
Power	0.263	-478.77	715	509	
Exponential (M3)	0.261	-478.76	716	504	
Exponential (M5)	0.101	-476.76	716	504	
Hill	0.100	-476.75	error[c]	error[c]	

---

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.340), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, 500, and 750 ppm were 0.41, -1.2, 1.01, -0.12, -0.1, respectively.

[b] 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.

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

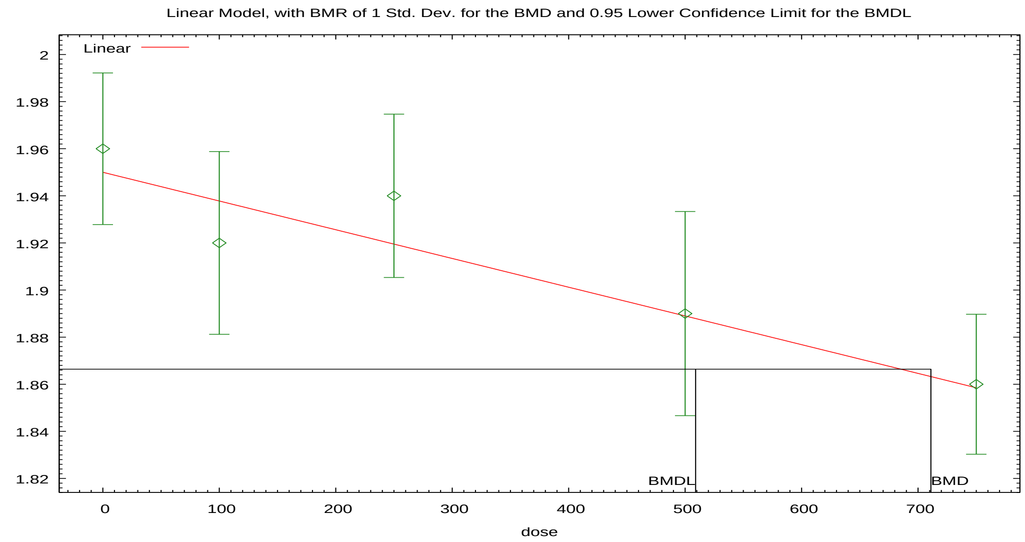

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Figure 2-25 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Linear) for Brain Weight in F_0 Female Rats Exposed to 1-BP Via Inhalation in ppm BMR = 1 Standard Deviation.

Table 2-73 BMD Modeling Results for Brain Weight in F_0 Female Rats Exposed to 1-BP Via Inhalation in ppm BMR = 1 Standard Deviation

Polynomial Model. (Version: 2.20; Date: 10/22/2014)
The form of the response function is: Y[dose] = beta_0 + beta_1*dose
A constant variance model is fit

Benchmark Dose Computation.
BMR = 1 Estimated standard deviations from the control mean
BMD = 711.056
BMDL at the 95% confidence level = 508.985

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.00749034	0.007637
rho	n/a	0
beta_0	1.95295	1.95295
beta_1	-0.000121716	-0.000121716

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	1.96	1.95	0.08	0.09	0.407
100	25	1.92	1.94	0.09	0.09	-1.2
250	25	1.94	1.92	0.08	0.09	1.01
500	25	1.89	1.89	0.1	0.09	-0.121
750	25	1.86	1.86	0.07	0.09	-0.096

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	244.723276	6	-477.446552
A2	246.984613	10	-473.969225
A3	244.723276	6	-477.446552
fitted	243.383815	3	-480.76763
R	234.782134	2	-465.564268

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	24.405	8	0.001959
Test 2	4.52267	4	0.3399
Test 3	4.52267	4	0.3399
Test 4	2.67892	3	0.4438

2.2.16.2 Decreased Brain Weight in F_0 Males

The doses and response data from the WIL Laboratories (2001) study was used for the modeling and are presented in Table 2-74.

Table 2-74 Brain Weight Data in F_0 Males for Dose-Response Modeling

	Concentration (ppm)				
	0	100	250	500	750
Number of animals	25	25	25	25	25
Brain wt (g)	2.19	2.15	2.08	2.1	2.05
Standard deviation (g)	0.091	0.114	0.087	0.177	0.091

The BMD modeling results for decreased brain weight in F_0 males with non-homogeneous variance (BMDS test 2 *p*-value = 0.000386) are summarized in Table 2-75. Although the variances are non-homogeneous and not well modeled for any of the non-homogeneous variance models the means were well-modeled (the highest *p*-value is 0.618 for the Exponential (M4) model with non-homogeneous variances).

Table 2-75 Summary of BMD Modeling Results for Brain Weight of F_0 Males Following Inhalation Exposure to 1-BP

Model[a]	**Goodness of fit**		**BMD$_{5RD}$ (ppm)**	**BMDL$_{5RD}$ (ppm)**
	***p*-value**	**AIC**		
Exponential (M4)	0.618	-408.61	372	159
Hill	0.340	-406.66	354	107
Exponential (M5)	0.152	-405.52	115	102
Exponential (M2) Exponential (M3)[b]	0.0868	-405.00	636	453
Power[c] Polynomial 4°[d] Polynomial 2°[e] Linear[f]	0.0804	-404.83	644	463
Polynomial 3°[g]	0.0804	-404.83	644	463

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 3.86E-04, BMDS Test 3 *p*-value = 5.66E-04), no model was selected as a best-fitting model.

[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 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. For the Polynomial 4° model, the b4, 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.

[f] The Linear model may appear equivalent to the Polynomial 3° model, however differences exist in digits not displayed in the table.

[g] The Polynomial 3° model may appear equivalent to the Power model, however differences exist in digits not displayed in the table. This also applies to the Polynomial 4° model. This also applies to the Polynomial 2° model. This also applies to the Linear model.

To investigate the effect of the poor modeling of the variances on the BMDL, the models were run using the smallest dose standard deviation (0.091), highest (0.177) and the pooled (0.0907) for all dose levels and the modeling results are summarized in Table 2-76.

Table 2-76 BMD Modeling Results for Brain Weight of F_0 Male Rats Following Inhalation Exposure to 1-BP in a Two-Generation Study with Variances Fixed at Smallest, Pooled and Highest Values.

Model[a]	Smallest Standard Deviation				Pooled Standard Deviation				Largest Standard Deviation				Ratio BMDLs Smallest to Largest Std Dev
	Goodness of fit		BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	Goodness of fit		BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	Goodness of fit		BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	
	p-value	AIC			*p*-value	AIC			*p*-value	AIC			
Exponential (M4)	0.0893	-477.73	375	164	0.108	-467.70	375	159	0.553	-303.82	375	78.7	2.1
Hill	0.0423	-476.44	289	106	0.0513	-466.35	289	106	0.315	-302.00	289	70.4	1.5
Exponential (M5)	0.0398	-476.34	246	104	0.0484	-466.26	246	103	0.309	-301.97	246	82.4	1.3
Exponential (M2)	0.0238	-475.11	669	515	0.0332	-465.43	669	510	0.503	-304.65	669	420	1.2
Exponential (M3)	0.0238	-475.11	669	515	0.0332	-465.43	669	510	0.503	-304.65	669	420	1.2
Power	0.0223	-474.96	674	523	0.0312	-465.29	674	518	0.496	-304.62	674	430	1.2
Polynomial 4°	0.0223	-474.96	674	523	0.0312	-465.29	674	518	0.496	-304.62	674	430	1.2
Polynomial 2°	0.0223	-474.96	674	523	0.0312	-465.29	674	518	0.496	-304.62	674	430	1.2
Linear	0.0223	-474.96	674	523	0.0312	-465.29	674	518	0.496	-304.62	674	430	1.2
Polynomial 3°	0.0223	-474.96	674	523	0.0312	-465.29	674	518	0.496	-304.62	674	430	1.2

[a] Constant variance case presented (BMDS Test 2 *p*-value = 1., BMDS Test 3 *p*-value = 1.), no model was selected as a best-fitting model.

A comparison across the full suite of BMD models shows the BMDL is sensitive to the adjustment of the variances and for the model that fit the constant variance data best, the Exponential (M4) model the ratio of BMDLs was 2.1. This result suggests that due to the poor variance modeling for the original data it is not reasonable to use BMDS for this endpoint. Instead the NOAEL of 100 ppm was used.

2.2.16.3 Decreased Brain Weight in F_1 Females as Adults

The doses and response data used for the modeling are presented in Table 2-77.

Table 2-77 Brain Weight Data in F_1 Females as Adults from Selected for Dose-Response Modeling

	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of animals	25	25	25	25
Brain wt (g)	1.97	1.96	1.92	1.89
Standard deviation (g)	0.076	0.073	0.067	0.102

Comparisons of model fits obtained are provided in Table 2-78. The best fitting model (Exponential (M2) with homogeneous variance) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure 2-26. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-79.

Table 2-78 Summary of BMD Modeling Results for Brain Weight of F_1 Female Rats as Adults Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	**Goodness of fit**		**BMD 1SD (ppm)**	**BMDL 1SD (ppm)**	**BMD 5RD (ppm)**	**BMDL 5RD (ppm)**	**BMD 1RD (ppm)**	**BMDL 1RD (ppm)**	**Basis for model selection**
	***p*-value**	**AIC**							
Exponential (M2) **Exponential (M3)[b]**	**0.787**	**-401.21**	472	327	590	416	**116**	**81.5**	**The Exponential (M2) model was selected based on the lowest AIC from this set of models which have adequate *p*-values, adequate fit by visual inspection and the BMDLs are < 3-fold apart considered sufficiently close.**
Power[c] Polynomial 3°[d] Polynomial 2°[e] Linear	0.780	-401.19	473	331	589	419	118	83.8	
Exponential (M4)	0.534	-399.30	459	230	619	363	94.7	35.1	
Hill	N/A[f]	-397.69	482	230	error[g]	error[g]	138	33.1	
Exponential (M5)	N/A[f]	-397.69	463	112	error[g]	0	141	37.6	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.144), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were -0.05, 0.39, -0.53, 0.19, respectively.

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[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.

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

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

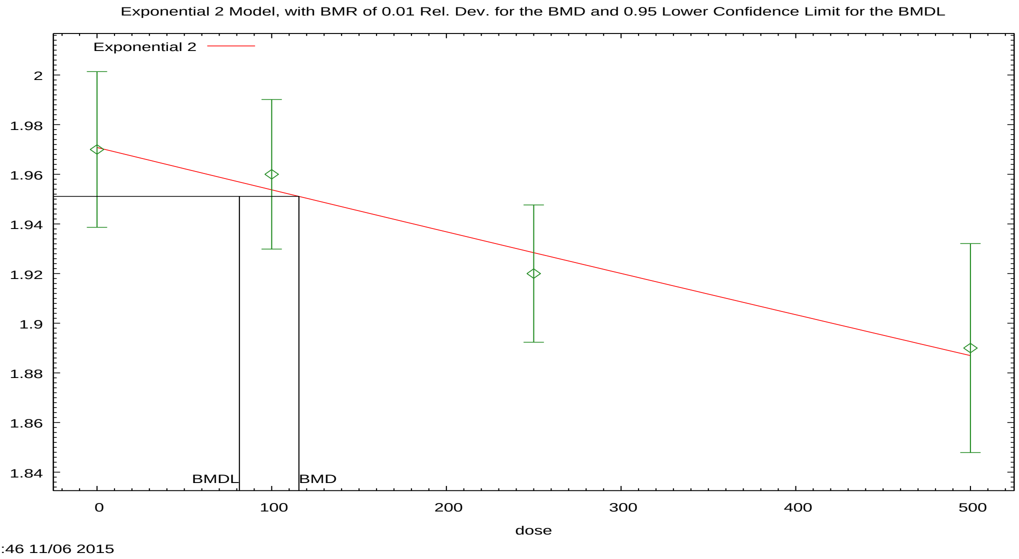

Figure 2-26 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Exponential (M2)) for Brain Weight in F_1 Female Rats as Adults Exposed to 1-BP Via Inhalation in ppm BMR = 1% Relative Deviation.

Table 2-79 BMD Modeling Results for Brain Weight in F_1 Female Rats as Adults Exposed to 1-BP Via Inhalation BMR = 1% Relative Deviation.

Exponential Model. (Version: 1.10; Date: 01/12/2015)
The form of the response function is: Y[dose] = a * exp(sign * b * dose)
A constant variance model is fit

Benchmark Dose Computation.
BMR = 1% Relative deviation
BMD = 115.594
BMDL at the 95% confidence level = 81.5083

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.07205	-5.07685
rho	n/a	0
a	1.97082	1.89939
b	0.0000869453	0.000086769
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	1.97	1.97	0.08	0.08	-0.05174
100	25	1.96	1.95	0.07	0.08	0.3941
250	25	1.92	1.93	0.07	0.08	-0.5332
500	25	1.89	1.89	0.1	0.08	0.1908

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	203.8426	5	-397.6852
A2	206.5452	8	-397.0903
A3	203.8426	5	-397.6852
R	196.2377	2	-388.4753
2	203.6027	3	-401.2054

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	20.62	6	0.002151
Test 2	5.405	3	0.1444
Test 3	5.405	3	0.1444
Test 4	0.4799	2	0.7867

2.2.16.4 Decreased Brain Weight in F_1 Males as Adults

The doses and response data used for the modeling are presented in Table 2-80.

Table 2-80 Brain Weight Data in F_1 Males as Adults from Selected for Dose-Response Modeling

	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of animals	24	25	25	24
Brain wt (g)	2.21	2.11	2.12	2.01
Standard deviation (g)	0.092	0.111	0.109	0.079

The data were not adequately fit by any of the models, the means goodness of fit *p*-values were less than 0.05 for all of the models. Comparisons of model fits obtained are provided in Table 2-81. Since no model was selected a plot of the model, BMD and BMDL calculations and other output are not presented. BMRs other than 5% relative deviation are not shown because the fit to the means are not different and therefore also inadequate. Instead the LOAEL of 100 ppm was used because there was no NOAEL observed in the WIL Laboratories (2001) study.

Table 2-81 Summary of BMD Modeling Results for Brain Weight of F_1 Male Rats as Adults Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	**Goodness of fit**		**BMD_{5RD} (ppm)**	**$BMDL_{5RD}$ (ppm)**
	***p*-value**	**AIC**		
Exponential (M2) Exponential (M3)[b]	0.0320	-346.71	308	245
Power[c] Polynomial 3°[d] Polynomial 2°[e] Linear	0.0312	-346.66	314	252
Hill	0.00968	-344.90	265	112
Exponential (M4) Exponential (M5)[f]	0.00932	-344.84	279	144

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.310, BMDS Test 3 *p*-value = 0.310), no model was selected as a best-fitting model.

[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.

[f] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

2.2.16.5 Decreased Brain Weight in F_2 Females at PND 21

The doses and response data used for the modeling are presented in Table 2-82.

Table 2-82 Brain Weight Data in F_2 Females at PND 21 from Selected for Dose-Response Modeling

	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of animals	22	17	15	15
Brain wt (g)	1.3957	1.3903	1.3673	1.3089
Standard deviation (g)	0.06491	0.08882	0.12231	0.1004

Comparisons of model fits obtained are provided in Table 2-83. The best fitting model (Exponential (M2) with non-homogeneous variance) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure 2-27. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-84.

Table 2-83 Summary of BMD Modeling Results for Brain Weight of F_2 Female Rats at PND 21 Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	**Goodness of fit**		**BMD$_{1SD}$ (ppm)**	**BMDL$_{1SD}$ (ppm)**	**BMD$_{5RD}$ (ppm)**	**BMDL$_{5RD}$ (ppm)**	**BMD$_{1RD}$ (ppm)**	**BMDL$_{1RD}$ (ppm)**	**Basis for model selection**
	***p*-value**	**AIC**							
Exponential (M2) **Exponential (M3)**[b]	**0.634**	**-257.31**	454	260	426	256	**83.4**	**50.1**	**The Exponential (M2) model was selected based on the lowest AIC from this set of models which have adequate *p*-values, adequate fit by visual inspection and the BMDLs are < 4-fold apart considered sufficiently close.**
Power	0.621	-257.27	456	266	427	261	85.3	52.1	
Polynomial 3°[c] Linear[d]	0.566	-257.27	456	266	427	261	85.3	52.1	
Polynomial 2°[e]	0.566	-257.27	456	266	427	261	85.3	52.1	
Exponential (M4)	0.702	-256.08	643	130	1149	170	48.5	12.6	
Hill	N/A[f]	-254.41	error[g]	error[g]	error[g]	error[g]	85.7	6.27	
Exponential (M5)	N/A[f]	-254.41	error[g]	0	error[g]	0	81.2	14.9	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0643), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were -0.31, 0.32, 0.34, -0.32, 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 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.

[d] The Linear model may appear equivalent to the Polynomial 2° model, however differences exist in digits not displayed in the table.

[e] The Polynomial 2° model may appear equivalent to the Polynomial 3° model, however differences exist in digits not displayed in the table. This also applies to the Linear model.

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

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

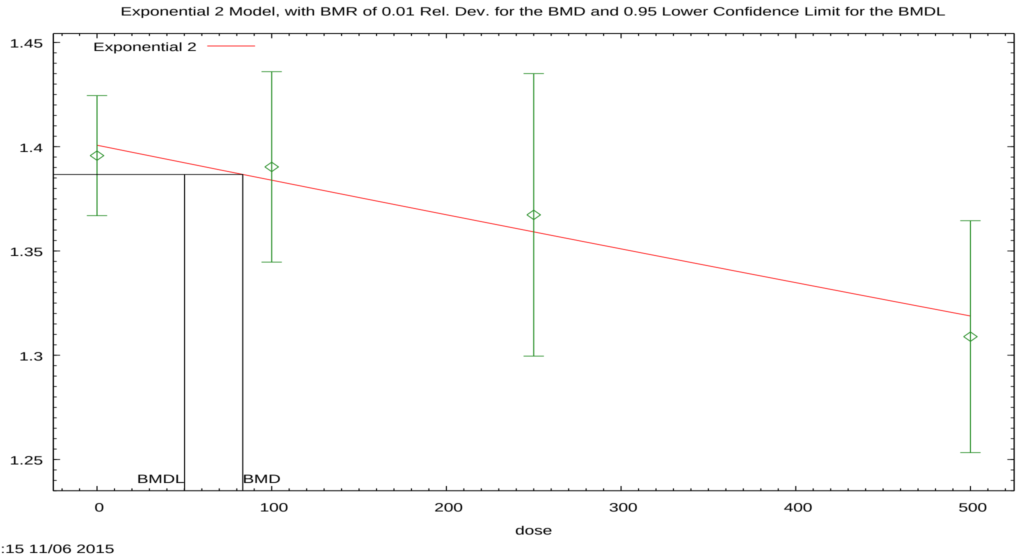

Figure 2-27 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Exponential (M2)) for Brain Weight in F_2 Female Exposed to 1-BP Via Inhalation in ppm BMR = 1% Relative Deviation.

Table 2-84 BMD Modeling Results for Brain Weight in F_2 Female Exposed to 1-BP Via Inhalation BMR = 1% Relative Deviation.

Exponential Model. (Version: 1.10; Date: 01/12/2015) The form of the response function is: Y[dose] = a * exp(sign * b * dose) A modeled variance is fit **Benchmark Dose Computation.** BMR = 1% Relative deviation BMD = 83.4282 BMDL at the 95% confidence level = 50.1098

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.0282712	-1.99881
rho	-15.3239	-8.92906
a	1.40066	1.33604
b	0.000120467	0.000129477
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	1.4	1.4	0.06	0.07	-0.3121
100	17	1.39	1.38	0.09	0.08	0.3231
250	15	1.37	1.36	0.12	0.09	0.3377
500	15	1.31	1.32	0.1	0.12	-0.3236

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	131.2578	5	-252.5155
A2	134.8828	8	-253.7656
A3	133.1137	6	-254.2275
R	126.819	2	-249.638
2	132.6574	4	-257.3148

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	16.13	6	0.01309
Test 2	7.25	3	0.06434
Test 3	3.538	2	0.1705
Test 4	0.9127	2	0.6336

2.2.16.6 Decreased Brain Weight in F_2 Males at PND 21

The doses and response data from the WIL Laboratories (2001) study was used for the modeling are presented in Table 2-85.

Table 2-85 Brain Weight Data in F_2 Males at PND 21 for Dose-Response Modeling

	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of animals	22	17	15	16
Brain wt (g)	1.4728	1.4253	1.4668	1.3629
Standard deviation (g)	0.07836	0.07679	0.05971	0.09581

Comparisons of model fits obtained are provided in Table 2-86. The best fitting model (Power with homogeneous variance) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure 2-28. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-87.

Table 2-86 Summary of BMD Modeling Results for Brain Weight of F_2 Male Rats as Adults Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	**Goodness of fit**		**BMD $_{1SD}$ (ppm)**	**BMDL $_{1SD}$ (ppm)**	**BMD $_{5RD}$ (ppm)**	**BMDL $_{5RD}$ (ppm)**	**BMD $_{1RD}$ (ppm)**	**BMDL $_{1RD}$ (ppm)**	**Basis for model selection**
	***p*-value**	**AIC**							
Power	**0.137**	**-279.68**	495	395	493	374	**451**	**97.6**	**The Power model was selected based adequate goodness of fit *p*-value (> 0.1 which excludes all other models) and adequate fit by visual inspection. Also, note if Polynomial 3° model *p*-value was rounded up to 0.1 and included the Power model would be selected based on lowest AIC for models with BMDLs < 1.5-fold apart considered sufficiently close**
Polynomial 3°	0.0961	-278.97	472	353	459	331	269	67.1	
Polynomial 2°	0.0647	-278.18	459	383	440	370	197	166	
Exponential (M3)	0.0463	-277.68	495	396	493	376	450	102	
Hill	0.0463	-277.68	495	281	493	error[b]	450	error[b]	
Linear	0.0306	-276.68	430	293	393	274	78.6	54.8	
Exponential (M2)	0.0294	-276.60	431	289	393	269	76.9	52.8	
Exponential (M4)	0.0294	-276.60	431	278	393	250	76.9	36.9	
Exponential (M5)	N/A[c]	-275.68	495	272	493	376	449	102	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.337), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were 0.99, -1.62, 0.52, 0, respectively.

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

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

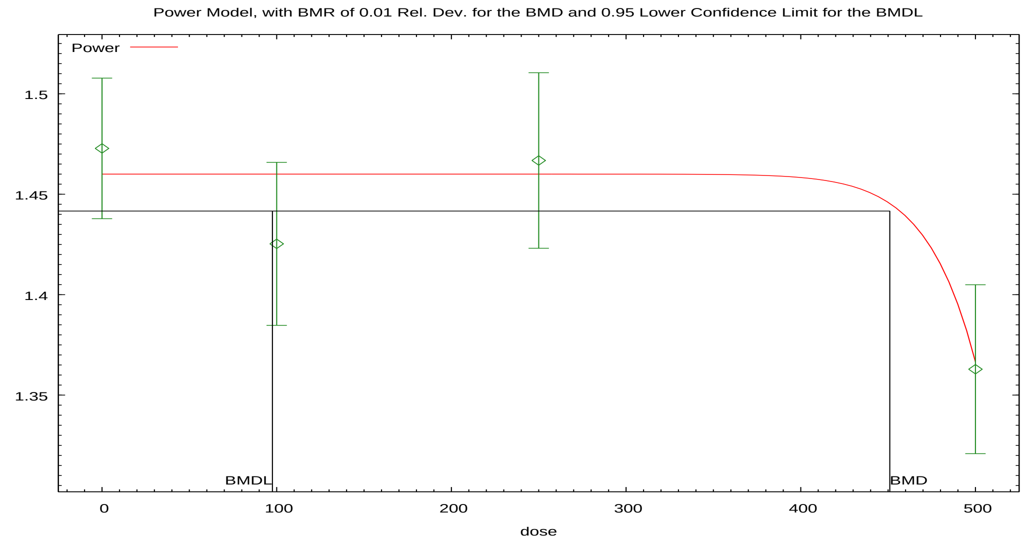

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Figure 2-28 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Power) for Brain Weight in Rats Exposed to 1-BP Via Inhalation in ppm BMR = 1% Relative Deviation.

Table 2-87 BMD Modeling Results for Brain Weight in Rats Exposed to 1-BP Via Inhalation in ppm BMR = 1% Relative Deviation

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

Benchmark Dose Computation.
BMR = 1% Relative deviation
BMD = 450.983
BMDL at the 95% confidence level = 97.5507

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.00621258	0.00622577
rho	n/a	0
control	1.45618	1.3629
slope	-2.44527E-50	0.0048117
power	18	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	1.47	1.46	0.08	0.08	0.989
100	17	1.43	1.46	0.08	0.08	-1.62
250	15	1.47	1.46	0.06	0.08	0.522
500	16	1.36	1.36	0.1	0.08	-0.00000182

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	144.826466	5	-279.652932
A2	146.516124	8	-277.032248
A3	144.826466	5	-279.652932
fitted	142.841294	3	-279.682588
R	135.116612	2	-266.233223

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	22.799	6	0.0008667
Test 2	3.37932	3	0.3368
Test 3	3.37932	3	0.3368
Test 4	3.97034	2	0.1374

2.2.17 Decreased Hang Time

EPA selected decreased time hanging from a suspended bar from the (Honma et al., 2003) study as a relevant endpoint for calculating risks associated with chronic worker scenarios. Since this is a continuous endpoint and in the absence of a basis for selecting a BMR a default selection of 1 standard deviation was used in accordance with EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012). The doses and response data used for the modeling are presented in Table 2-88.

Table 2-88 Hang Time from a Suspended Bar Data for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Mean traction time (sec)	Standard Deviation
0	5	25.2	15.25
10	5	23.8	7.53
50	5	15.2	5.54
200	5	5.2	3.42
1000	5	4.4	3.65

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 are provided in Table 2-89. The best-fitting model (Exponential M4), based on the criteria described above, is indicated in bold. For the best fitting model a plot of the model is shown in Figure 2-29. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below in Table 2-90.

Table 2-89 Summary of BMD Modeling Results for Hang Time from a Suspended Bar; BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC			
Exponential (M4)	**0.955**	**122.13**	**36.9**	**18.2**	**The Exponential (M4) model was selected based on the lowest AIC from this set of models which have adequate *p*-values (including Exponential M4 and M5 and excluding Exponential M2 and M3, Power, Polynomial and Linear models), adequate fit by visual inspection and BMDLs (excluding Hill model) are the same for Exponential M4 and M5.**
Exponential (M5)	0.766	124.12	37.7	18.2	
Hill	0.467	124.57	45.0	error[b]	
Exponential (M2)[c]	0.00443	133.13	47.4	20.8	
Exponential (M3)[d]	0.00443	133.13	47.4	20.8	
Power[e]	2.22E-04	139.47	799	525	
Polynomial 2°[f] Linear[g]	2.22E-04	139.47	799	525	
Polynomial 3°	<0.0001	188.00	-9999	error[b]	
Polynomial 4°	N/A[h]	192.45	-9999	error[b]	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.00293), selected model in bold; scaled residuals for selected model for doses 0, 10, 50, 200, and 1000 ppm were -0.34, 0.12, 0.44, -0.07, -0.17, respectively.
[b] BMD or BMDL computation failed for this model.

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[c] The Exponential (M2) model may appear equivalent to the Exponential (M3) model, however differences exist in digits not displayed in the table.

[d] The Exponential (M3) model may appear equivalent to the Exponential (M2) model, however differences exist in digits not displayed in the table.

[e] The Power model may appear equivalent to the Polynomial 2° model, however differences exist in digits not displayed in the table. This also applies to the Linear model.

[f] 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.

[g] The Linear model may appear equivalent to the Power model, however differences exist in digits not displayed in the table.

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

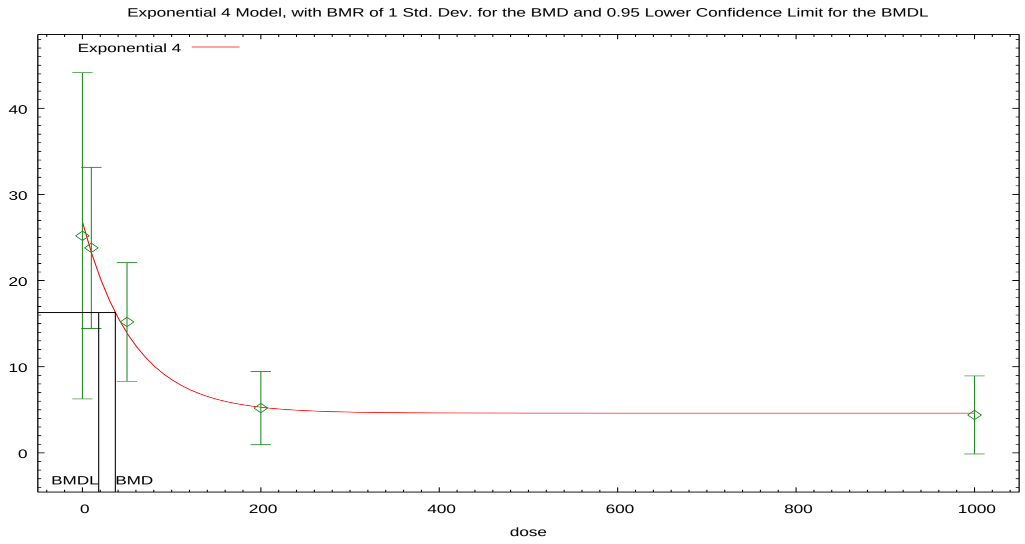

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Figure 2-29 Plot of Mean Response by Dose in ppm with Fitted Curve for Exponential (M4) Model with Modeled Variance for Hang Time from a Suspended Bar; BMR = 1 Standard Deviation Change from Control Mean.

Table 2-90 BMD Modeling Results for Hang Time from a Suspended Bar; BMR = 1 Standard Deviation Change from Control Mean

Exponential Model. (Version: 1.10; Date: 01/12/2015)
The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]
A modeled variance is fit

Benchmark Dose Computation.
BMR = 1.0000 Estimated standard deviations from control
BMD = 36.9173
BMDL at the 95% confidence level = 18.2429

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.107405	0.415293
rho	1.46448	1.29675
a	26.8244	26.46
b	0.0174245	0.00510395
c	0.172048	0.15837
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	5	25.2	26.82	15.25	10.54	-0.3447
10	5	23.8	23.27	7.53	9.5	0.1241
50	5	15.2	13.91	5.54	6.51	0.4434
200	5	5.2	5.3	3.42	3.21	-0.0668
1000	5	4.4	4.62	3.65	2.9	-0.1656

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-62.64066	6	137.2813
A2	-54.60856	10	129.2171
A3	-56.01777	7	126.0355
R	-73.64274	2	151.2855
4	-56.06343	5	122.1269

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	38.07	8	<0.0001
Test 2	16.06	4	0.002934
Test 3	2.818	3	0.4205
Test 6a	0.09133	2	0.9554

3 Benchmark Dose Modeling of Tumors

EPA selected 1-BP-induced tumors observed in mice and rats in the chronic inhalation bioassay by NTP (2011) for BMD modeling with EPA's BMDS. The three tumor sites were selected for modeling were alveolar/bronchiolar adenomas and carcinomas (i.e. lung tumors) in female mice, adenomas of the large intestine in female rats, and keratoacanthoma and squamous cell carcinomas of the skin in male rats. None of the tumor sites occurred in the same strain and sex therefore combined tumor modeling was not conducted. Three approaches were applied to model individual tumor sites; multistage modeling, frequentist model-averaging and Bayesian model averaging.

All of the models in the BMDS suite of dichotomous models were applied the gamma, logistic, log-logistic, multistage, probit, log-probit, quantal-linear and Weibull models. BMRs of 10% and 0.1% (1 in 1,000) both added nad extra risk were modeled and the 95% lower confidence limit was calculated. Models were determined to be adequate or not in a manner consistent with EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012). Briefly the AIC, goodness of fit *p*-values (0.1 or greater) and a visual assessment of fit are important criteria.

In agreement with U.S. EPA's long-standing approach all three tumor types from the NTP study (NTP, 2011) were dose-response modeled with multistage models using the typical constrained model coefficients ≥0 (EPA, 2012). Under U.S. EPA's 2005 cancer guidelines (U.S. EPA 2005), quantitative risk estimates from cancer bioassay data were calculated by modeling the data in the observed range to estimate a BMCL for a BMR of 10% extra risk, which is generally near the low end of the observable range for standard cancer bioassay data. Also the results for a BMR of 0.1% added risk are presented for comparison.

In addition to the multistage modeling model averaging methods were applied, frequentist (Wheeler and Bailer, 2007) and Bayesian (USEPA 2018 BMDS software) to assess the impact of model uncertainty. A model-averaging (MA) technique (Wheeler and Bailer, 2007) was applied using the multistage, log-probit and Weibull models based on the observation that those 3 models performed better in bias and coverage than other combinations of models (Wheeler and Bailer, 2007). The model averaging applied statistics (bootstrapping technique) to weigh, based on fit, the models providing acceptable fit to the experimental dataset (as evidenced by a chi-square goodness-of-fit value > 0.10). Model-averaging software was restricted to avoid supralinear models, which exhibit properties at the low dose that are not considered biologically plausible. The resulting model-average benchmark concentrations (MA BMCs) associated with 0.1% added risk and their 95% lower confidence limits (MA BMCLs) are shown the Frequentist Model-Average (BMDS 2.6) row for each of the three cancer datasets.

Since the 2016 Draft Risk Assessment (U.S. EPA, 2016), the EPA has conducted additional modeling, using the BMDS (Version 3.0) and more details are available in the supplemental file. All dichotomous frequentist and Bayesian[1] models in the BMD software (BMDS Version 3.0), were fit to the incidence data for each of the three tumor types. The benchmark response (BMR) levels used were 0.1% and 10% added and extra risk. The BMR used in the 2016 Draft Risk Assessment (U.S. EPA, 2016) was 0.1% added risk. The BMR of 10% extra risk which is generally near the low end of the observable range for standard cancer bioassay data was used. The

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[1] The Bayesian dichotomous models used in BMDS 3.0 are identical to the frequentist parametric models but incorporate prior information (e.g., parameter distributions) that is used in the model fit (see the BMDS 3.0 User Guide for details; https://www.epa.gov/bmds/benchmark-dose-software-bmds-version-30-user-guide-readme).

Bayesian models and Bayesian model averaging solve issues associated with strict frequentist parameter bounds by replacing them with “soft bounds” defined by mildly informative prior density for the individual parameters of the models included in the analysis. Thus, in the cases where there are limited data, the shapes of the models are limited to dose-response shapes that are frequently seen in practice. In addition, because parameters are restricted through their prior density, the U.S. EPA BMDS 3.0 Bayesian model averaging approach allows for consideration of a large suite of models across many different study designs without typical model “degeneracy” or “overparameterization” concerns of previous model averaging approaches (BMDS 3.0 User Guide). The resulting model-average benchmark concentrations (MA BMCs) associated with 0.1% added risk (AR) and 10% extra risk (ER) and their 95% lower confidence limits (BMCLs) are shown in the Bayesian Model-Average (BMDS 3.0) row for each of the three cancer datasets.

3.1 Lung Tumors in Female Mice

The doses and response data from the NTP (2011) study that were used for the modeling are presented in Table 3-1.

Table 3-1 Incidence of Lung Tumors in Female Mice

Dose (ppm)	Number of animals	Number of Animals with Tumors
0	50	1
62.5	50	9
125	50	8
250	50	14

Comparisons of model fits obtained from BMD modeling of the NTP (2011) study are provided in Table 3-2. A summary of all the dichotomous models and all three modeling approachs are shown for comparison with the BMDS results in Table 3-2. Detailed output of the multistage, frequestist model average and Bayesian model average results are also shown below.

Table 3-2 Summary of BMDS 3.0 modeling results for lung tumors in female mice exposed to 1-BP by inhalation for 2 years (NTP, 2011); BMRs = 10% and 0.1% extra and added risk, doses are in ppm

Frequentist Model	Restriction***	10% Extra Risk		10% Added Risk		0.1% Extra Risk		0.1% Added Risk		P Value	AIC	BMDS Recommendation Notes
		BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL			
Dichotomous Hill	Restricted	37.97524	CF	39.13867	CF	0.262433	CF	0.267937	CF	0.2913697	167.35319	Lower limit includes zero
Gamma	Restricted	78.59758	54.06762	81.47433	54.97972	0.74636	0.513424	0.772227	0.521665	0.2183691	166.9715428	
Log-Logistic	Restricted	69.93796	46.26665	72.25183	46.99549	0.630072	0.416817	0.64879	0.422752	0.2824931	166.5219996	Lowest AIC
Log-Probit	Restricted	135.5751	91.5552	142.1972	93.75467	22.21672	15.00317	22.7714	15.19065	0.0392364	170.9591691	Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05
Multistage Degree 3	Restricted	78.59758	54.05654	81.47433	54.96919	0.74636	0.513402	0.772228	0.521634	0.2183691	166.9715428	Converges to Degree 1
Multistage Degree 2	Restricted	78.59758	54.05354	81.47433	54.96921	0.74636	0.513407	0.772228	0.521634	0.2183691	166.9715428	Converges to Degree 1
Multistage Degree 1 (Quantal Linear)**	Restricted	78.59758	54.06143	81.47433	54.96919	0.74636	0.5134	0.772228	0.521634	0.2183691	166.9715428	All Multistage models converged to Degree 1
Weibull	Restricted	65.43007	41.33211	66.06867	41.67007	4.083719	0.997165	4.121506	1.005019	3.896E-08	197.0272423	Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05
Dichotomous Hill	Unrestricted	28.47259	CF	29.82262	CF	0.00191	CF	0.001991	CF	CF	169.1046753	Lower limit includes zero
Logistic	Unrestricted	136.7186	107.335	144.6373	113.6071	1.996488	1.492227	2.156856	1.643332	0.0888649	169.5064951	Goodness of fit p-value < 0.1
Log-Probit	Unrestricted	29.35781	CF	30.64006	CF	0.038238	CF	0.039098	CF	0.3429581	167.1324257	Lower limit includes zero
Probit	Unrestricted	129.2628	100.3938	136.6598	105.8843	1.801609	1.349556	1.937322	1.474752	0.0955787	169.2319294	Goodness of fit p-value < 0.1
Frequentist Model Average (multistage, log-probit and Weibull)	Restricted	--	--	--	--	--	--	0.849	0.634	0.1298	NA	
Bayesian Model										**BMA model Posterior Probabilities**	**Unnormalized Log Posterior Probabilities**	
Dichotomous Hill	Priors	64.34544	14.5245	67.31868	15.29848	0.752301	0.006834	0.779298	0.007215	0.166806	-87.09741015	NB
Gamma	Priors	98.64837	50.08382	104.1892	52.11979	1.716614	0.088742	1.80595	0.093472	0.056914	-88.17269343	NB
Logistic	Priors	150.9715	111.2937	162.4684	118.824	2.063819	1.503801	2.27159	1.670964	0.195845	-86.93691547	NB
Log-Logistic	Priors	73.78165	29.87163	77.34186	31.35776	0.751037	0.008745	0.783528	0.009254	0.079815	-87.8345243	NB
Log-Probit	Priors	97.84488	45.04163	102.5082	46.68855	8.25872	0.636263	8.460435	0.652272	0.012133	-89.71830101	NB
Multistage Degree 3	Priors	78.73632	57.42297	81.69198	58.98483	0.839515	0.572085	0.873569	0.587588	NA	-96.25255595	NB
Multistage Degree 2	Priors	74.67602	54.67322	77.5899	56.14487	0.773638	0.538379	0.804686	0.552757	0.000911	-92.30719837	NB
Multistage Degree 1	Priors	70.96872	51.75386	74.00783	53.1925	0.673917	0.491566	0.701235	0.50454	NA	-87.07030802	NB
Probit	Priors	136.3017	102.8982	145.3018	109.0151	1.838917	1.363377	1.995304	1.496475	0.199328	-86.91928526	NB
Quantal Linear	Priors	82.46298	56.36126	86.78205	58.07897	0.783066	0.535205	0.82187	0.550684	0.240282	-86.73242779	NB
Weibull	Priors	95.40995	43.42538	100.647	45.41124	1.445756	0.034791	1.520816	0.036836	0.047966	-88.3437562	NB

Bayesian Model Average (BMA) results	Priors	104.6183	39.4122	111.1076	41.12461	1.412281	0.080929	1.511725	0.084815	Probabilities Sum to 1	NA	NB

**Best Multistage; scaled residuals for doses 0, 62.5, 125, and 250 were -0.529882976, 1.548678296, -0.413499804, and -0.439288554, respectively.

***Restrictions and parameter priors defined in the BMDS 3.0 User Guide; CF = Computation failed; NA = Not available in BMDS 3.0; NA = Not Applicable

3.1.1 Summary of Multistage Model

3.1.1.1 Selected Frequentist Multistage - Multistage 1 Restricted; Extra Risk, BMR = 0.001 and 0.1, doses are in ppm

Table 3-3 Lung Tumors in Female Mice, Selected Frequentist Multistage - Multistage 1 Restricted; Extra Risk, BMR = 0.001 and 0.1 User Input

Info	
Model	frequentist Multistage degree 1 v1.0
Dataset Name	1-BP - Lung Tumors - F Mice
User notes	NTP (2011) Lung Tumors in Female Mice from 1-BP

Options	
Risk Type	Extra Risk
BMR	0.001 and 0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	PPM
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Table 3-4 Lung Tumors in Female Mice, Selected Frequentist Multistage - Multistage 1 Restricted; Extra Risk, BMR = 0.001 and 0.1 Model Results

BMR 0.001 Benchmark Dose	
BMD	0.746360281
BMDL	0.513400221
BMDU	1.377878074
BMR 0.1 Benchmark Dose	
BMD	78.59757869
BMDL	54.06142797
BMDU	145.0923735
AIC	166.9715428
P-value	0.218369111
D.O.F.	2
Chi^2	3.043136955

Model Parameters		
# of Parameters	3	
Variable	Estimate	Std Error
Background	0.033480124	0
Beta1	0.001340506	0
Beta2	0	0

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.033480124	1.674006202	1	50	-0.529883
62.5	0.111157329	5.557866469	9	50	1.5486783
125	0.182591778	9.129588912	8	50	-0.4135
250	0.308698954	15.43494771	14	50	-0.439289

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-80.10278985	0	-	-	-
Fitted Model	-81.4857714	2	2.7659631	2	0.2508296
Reduced Model	-87.93397588	1	15.6623721	3	0.0013298

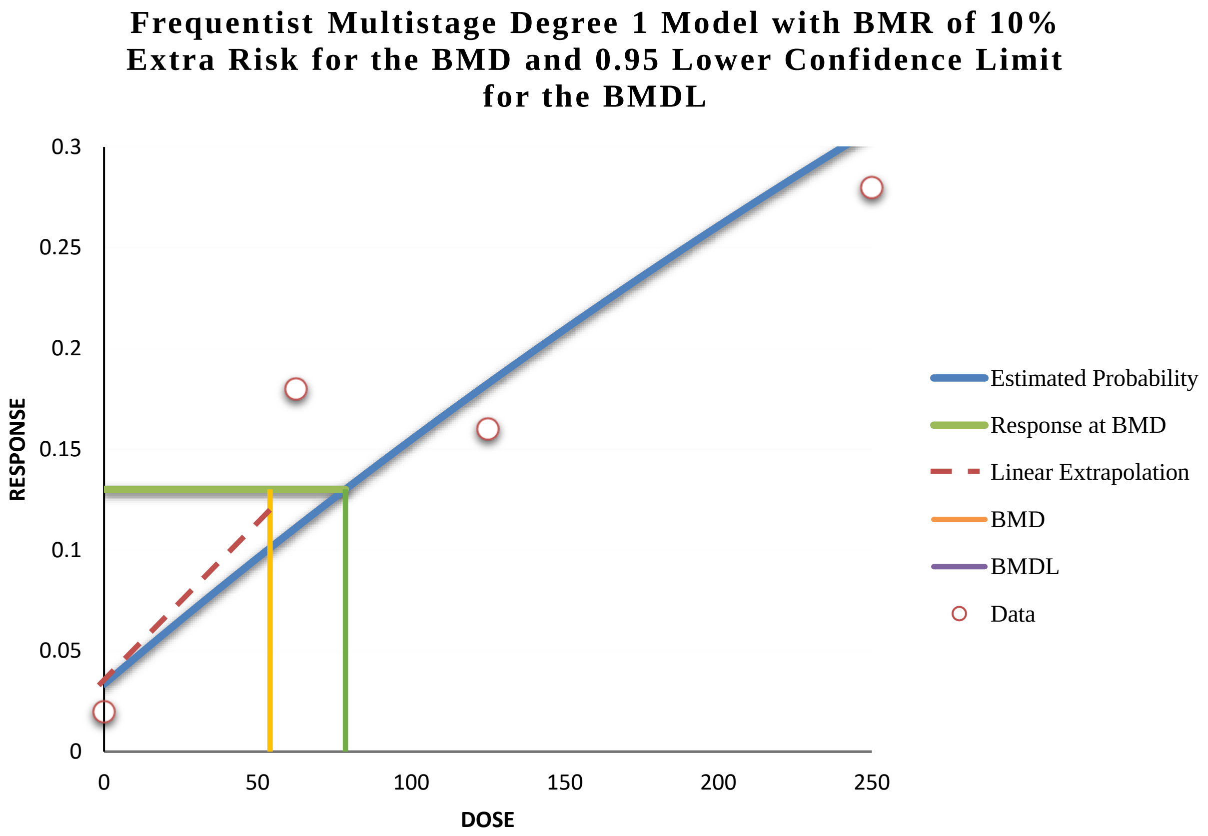

Figure 3-1 Plot of Results for Lung Tumors in Female Mice Frequentist Multistage Degree 1 Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL

3.1.1.2 Selected Frequentist Multistage - Multistage 1 Restricted; Added Risk, BMR = 0.001 and 0.1, doses are in ppm

Table 3-5 Lung Tumors in Female Mice, Selected Frequentist Multistage - Multistage 1 Restricted; Added Risk, BMR = 0.001 and 0.1 User Input

Info	
Model	frequentist Multistage degree 1 v1.0
Dataset Name	1-BP - Lung Tumors - F Mice
User notes	NTP (2011) Lung Tumors in Female Mice from 1-BP

Options	
Risk Type	Added Risk
BMR	0.001 and 0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	PPM
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Table 3-6 Lung Tumors in Female Mice, Selected Frequentist Multistage - Multistage 1 Restricted; Added Risk, BMR = 0.001 and 0.1 Model Results

BMR 0.001 Benchmark Dose	
BMD	0.772227533
BMDL	0.521640376
BMDU	1.495515393
BMR 0.1 Benchmark Dose	
BMD	81.47432888
BMDL	54.97974829
BMDU	158.2503904
AIC	166.9715428
P-value	0.218369111
D.O.F.	2
Chi^2	3.043136955

Model Parameters		
# of Parameters	3	
Variable	Estimate	Std Error
Background	0.033480124	0
Beta1	0.001340506	0
Beta2	0	0

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.033480124	1.674006202	1	50	-0.529883
62.5	0.111157329	5.557866469	9	50	1.5486783
125	0.182591778	9.129588912	8	50	-0.4135
250	0.308698954	15.43494771	14	50	-0.439289

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-80.10278985	0	-	-	-
Fitted Model	-81.4857714	2	2.7659631	2	0.2508296
Reduced Model	-87.93397588	1	15.6623721	3	0.0013298

3.1.2 Summary of Frequentist Model Averaging

Table 3-7 Lung Tumors in Female Mice, Summary of Frequentist Model Averaging

Model Averaging Fit Statistics

Model	Weight	-2log(L)	AIC	BIC
Multistage, 3°	0.245	162.97	170.97	184.16
Weibull	0.665	162.97	168.97	178.87
Log-Probit	0.091	166.96	172.96	182.85

Average-Model Benchmark Dose Estimate:
Nominally Specified Confidence Level:0.950
Weighting Criterion: AIC
BMD Calculation: Added Risk
BMR: 0.001000
BMD: 0.849148762733
BMDL(BCa):0.400888479370
BMDL(Percentile):0.634308392327
Acceleration: 0.043517
Bootstrap Resamples: 5000
Random Seed: 102210

Average-Model Goodness of Fit Test
Test Statistic: 3.274559
Bootstrap *p*-value: 0.129800

Parameter Estimates

Model	Parameter	Estimate	Standard Error
Multistage, 3°	gamma	0.03348013	0.02882729
	beta(1)	0.001340506	0.0003669969
	beta(2)	0	N/A
	beta(3)	0	N/A
Weibull	gamma	0.033480	0.028840
	alpha	1.0	N/A
	beta	0.001341	0.000367
Log-Probit	gamma	0.079419089201	0.034577
	alpha	-6.191081	0.272037
	beta	1.0	N/A

3.1.3 Summary of Bayesian Model Averaging

3.1.3.1 Bayesian Model Averaging – Extra Risk, BMR = 0.001 and 0.1, doses are in ppm

Table 3-8 Lung Tumors in Female Mice, Bayesian Model Averaging – Extra Risk, BMR = 0.001 and 0.1 User Inputs

Info	
Model	Bayesian Model Averaging v1.0
Dataset Name	1-BP - Lung Tumors - F Mice
User notes	NTP (2011) Lung Tumors in Female Mice from 1-BP

Model Options	
Risk Type	Extra Risk
BMR	0.001 and 0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	PPM
Independent Variable	[Incidence]
Total # of Observation	4

Table 3-9 Lung Tumors in Female Mice, Bayesian Model Averaging – Extra Risk, BMR = 0.001 and 0.1 Model Results

BMR 0.001 Benchmark Dose	
BMD	1.412280907
BMDL	0.08092889
BMDU	6.929373369
BMR 0.1 Benchmark Dose	
BMD	104.618334
BMDL	39.41220045
BMDU	220.1845944

MA - Individual Models		**BMR 0.001**			**BMR 0.1**		
Model	Posterior Probability	BMD	BMDL	BMDU	BMD	BMDL	BMDU
Dichotomous Hill	0.166805588	0.752300664	0.00683358	11.23398263	64.34543431	14.5244971	165.5205
Gamma	0.056914248	1.716613537	0.088741617	15.75845852	98.64837676	50.0838161	206.6454
Logistic	0.195845027	2.06381944	1.503801206	3.924900666	150.9715021	111.293748	313.7542
Log-Logistic	0.07981527	0.751036569	0.008744945	12.44686637	73.78164679	29.8716258	150.8161
Log-Probit	0.012133111	8.258719929	0.636263227	106.3076332	97.84487635	45.0416319	232.3484
Multistage	0.000911231	0.773638254	0.538378954	1.237213961	74.67601448	54.976739	100.7804
Probit	0.199328433	1.838917378	1.363377436	2.949863905	136.3016963	102.89821	237.678
Quantal Linear	0.240281547	0.783066032	0.535204832	1.367988414	82.46298134	56.3612543	144.0599
Weibull	0.047965545	1.445755828	0.034791225	21.79520577	95.40994465	43.4253775	190.5838

3.1.3.2 Bayesian Model Averaging – Added Risk, BMR = 0.001 and 0.1, doses are in ppm

Table 3-10 Lung Tumors in Female Mice, Bayesian Model Averaging – Added Risk, BMR = 0.001 and 0.1 User Inputs

Info	
Model	Bayesian Model Averaging v1.0
Dataset Name	1-BP - Lung Tumors - F Mice
User notes	NTP (2011) Lung Tumors in Female Mice from 1-BP

Model Options	
Risk Type	Added Risk
BMR	0.001 and 0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	PPM
Independent Variable	[Incidence]
Total # of Observation	4

Table 3-11 Lung Tumors in Female Mice, Bayesian Model Averaging – Added Risk, BMR = 0.001 and 0.1 Model Results

BMR 0.001 Benchmark Dose	
BMD	1.511725049
BMDL	0.084814979
BMDU	7.349459454

BMR 0.1 Benchmark Dose	
BMD	111.1076087
BMDL	41.12460837
BMDU	242.2282994

MA - Individual Models		**BMR 0.001**			**BMR 0.001**		
Model	Posterior Probability	BMD	BMDL	BMDU	BMD	BMDL	BMDU
Dichotomous Hill	0.166805588	0.779298134	0.00721453	11.78462	67.3186779	15.2984811	179.9472
Gamma	0.056914248	1.805950073	0.09347239	16.61692	104.1891947	52.1197878	225.3164
Logistic	0.195845027	2.271589823	1.67096395	4.486674	162.4683738	118.824027	351.2111
Log-Logistic	0.07981527	0.783527736	0.00925409	13.02672	77.34185457	31.3577577	160.9768
Log-Probit	0.012133111	8.460435085	0.6522715	107.9432	102.5081798	46.6885529	244.554
Multistage	0.000911231	0.804685755	0.55281934	1.312665	77.5898993	56.0719296	106.9866
Probit	0.199328433	1.995303668	1.49647507	3.303659	145.3018337	109.015137	262.5193
Quantal Linear	0.240281547	0.821870286	0.55068434	1.494455	86.78204566	58.078967	158.1819
Weibull	0.047965545	1.52081612	0.036836	22.85683	100.6470174	45.4112366	204.8545

3.2 Large Intestine Adenomas in Female Rats

The doses and response data from the NTP (2011) study that were used for the modeling are presented in Table 3-12.

Table 3-12 Incidence of Large Intestine Adenomas in Female Rats

Dose (ppm)	Number of animals	Number of Animals with Tumors
0	50	0
125	50	1
250	50	2
500	50	5

Comparisons of model fits obtained from BMD modeling of the NTP (2011) study are provided in Table 3-13. A summary of all the dichotomous models and all three modeling approaches are shown for comparison with the the BMDS results in Table 3-13. Detailed output of the multistage, frequestist model average and Bayesian model average results are also shown below.

Table 3-13 Summary of BMDS 3.0 modeling results for large intestine adenomas in female rats exposed to 1-BP by inhalation for 2 years (NTP, 2011); BMRs = 10% and 0.1% extra and added risk, doses are in ppm

Frequentist Model	**Restriction****	**10% Extra Risk**		**10% Added Risk**		**0.1% Extra Risk**		**0.1% Added Risk**		**P Value**	**AIC**	**BMDS Recommendation Notes**
		BMD	**BMDL**	**BMD**	**BMDL**	**BMD**	**BMDL**	**BMD**	**BMDL**			
Dichotomous Hill	Restricted	507.1886	233.2808	507.1886	CF	12.49015	2.02E-05	12.49015	0.000691	0.8834656	65.12821578	BMD10 higher than max dose
Gamma	Restricted	507.0328	328.131	507.0328	328.1311	12.23436	3.132948	12.23436	3.132948	0.9899304	63.12698036	BMD10 higher than max dose
Log-Logistic	Restricted	507.1886	326.4527	507.1886	326.4527	12.49014	2.967884	12.49015	2.967884	0.989315	63.12821578	BMD10 higher than max dose
Log-Probit	Restricted	477.1922	330.2017	478.8704	330.202	78.19758	54.11022	78.34071	54.11038	0.6315053	64.24003983	
Multistage Degree 3	Restricted	500.7362	330.5708	CF	CF	6.557897	3.138036	6.557897	3.138036	0.9988974	63.10882433	BMD10 higher than max dose
Multistage Degree 2	Restricted	502.9252	330.2656	CF	CF	7.437661	3.136283	7.437661	3.136283	0.9958358	63.11496834	BMD10 higher than max dose
Multistage Degree 1 (Quantal Linear)*	Restricted	555.3227	326.7021	555.3227	326.7336	5.273328	3.102597	5.273328	3.102597	0.9885628	61.23428391	BMD10 higher than max dose Lowest AIC
Weibull	Restricted	301.4129	228.7688	301.7364	284.8074	105.7531	45.34816	105.8608	45.36294	2.024E-14	126.9988592	Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05
Dichotomous Hill	Unrestricted	507.1886	326.4527	507.1886	326.4527	12.49015	CF	12.49015	CF	0.989315	63.12821578	BMD10 higher than max dose
Logistic	Unrestricted	502.6164	401.8342	504.1957	403.3183	21.75435	11.15261	21.92247	11.40486	0.7220677	64.14445439	BMD10 higher than max dose
Log-Probit	Unrestricted	513.5019	319.158	513.5019	319.158	22.53697	3.05E-10	22.53697	3.05E-10	0.9787434	63.15005452	BMD10 higher than max dose
Probit	Unrestricted	498.6988	387.1642	500.1934	388.3664	20.22219	10.09325	20.35123	10.29972	0.7579644	63.98223935	
Frequentist Model Average	Restricted	--	--	--	--	--	--	13.5	5.005	0.824	NA	Average of: multistage, log-probit and Weibull
Bayesian Model										**BMA model Posterior Probabilities**	**Unnormalized Log Posterior Probability**	
Dichotomous Hill	Priors	580.7885	363.9277	586.8591	366.3746	32.1626	1.943651	32.44390	1.970037	0.220739	-34.83201879	NB
Gamma	Priors	574.6022	370.815	581.0418	373.6548	36.78534	7.612838	37.14127	7.691739	0.039040	-36.56441487	NB
Logistic	Priors	748.2903	435.647	758.8572	439.4368	17.09404	9.77774	17.53697	10.10689	0.209018	-34.88658014	NB
Log-Logistic	Priors	443.7372	317.9377	447.3434	320.2013	34.7643	3.044037	35.01854	3.079371	0.009846	-37.941941	NB
Log-Probit	Priors	496.108	365.0003	500.2088	367.391	138.4617	37.032	139.0559	37.23307	0.019907	-37.23793011	NB
Multistage Degree 3	Priors	281.6332	214.8912	283.5637	216.3168	3.58622	2.361475	3.617773	2.380263	NA	-55.95416186	NB
Multistage Degree 2	Priors	292.2843	214.7176	294.6334	216.4783	3.394427	2.261514	3.425026	2.27977	3.7871E-08	-50.41033757	NB
Multistage Degree 1	Priors	326.0742	223.1094	329.3273	224.9746	3.096391	2.118664	3.125683	2.135989	NA	-43.07798951	NB
Probit	Priors	560.3876	401.1173	563.8816	403.0099	16.40803	9.430684	16.60386	9.66788	0.488955	-34.03672885	NB
Quantal Linear	Priors	518.8844	308.1564	525.4594	311.1072	4.92731	2.926244	4.986506	2.952824	0.003797	-38.89483963	NB
Weibull	Priors	482.3999	345.5124	486.5647	347.9023	36.57184	4.415083	36.87119	4.466438	0.008698	-38.06592312	NB
Bayesian Model Average (BMA) results	Priors	601.4568	392.3594	607.1436	394.7824	23.56684	7.783059	23.84832	7.975868	Probabilities Sum to 1	NA	NB

*Best overall and Multistage; scaled residuals for doses 0, 125, 250 and 500 were -0.000872639, -0.160645981, -0.212777056, and 0.234051055, respectively.
**Restrictions and parameter priors are defined in the BMDS 3.0 User Guide; CF = Computation failed; NA = Not available in BMDS 3.0; NA = Not Applicable

3.2.1 Summary of Multistage Model

3.2.1.1 Selected Frequentist Multistage - Multistage 1 Restricted; Extra Risk, BMR = 0.001 and 0.1, doses are in ppm

Table 3-14 Large Intestine Adenomas in Female Rats, Selected Frequentist Multistage - Multistage 1 Restricted; Extra Risk, BMR = 0.001 and 0.1 User Input

Info	
Model	frequentist Multistage degree 1 v1.0
Dataset Name	1-BP Large Intestine Adenomas - F Rats
User notes	NTP (2011) Large Intestine Adenomas in Female Rats from 1-BP

Model Options	
Risk Type	Extra Risk
BMR	0.001 and 0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	PPM
Independent Variable	[Incidence]
Total # of Observation	4

Table 3-15 Large Intestine Adenomas in Female Rats, Selected Frequentist Multistage - Multistage 1 Restricted; Extra Risk, BMR = 0.001 and 0.1 Model Results

BMR 0.001 Benchmark Dose	
BMD	5.273328163
BMDL	3.102597277
BMDU	10.04488819
BMR 0.1 Benchmark Dose	
BMD	555.3227114
BMDL	326.7020652
BMDU	1058.027014
AIC	61.23428391
P-value	0.988562772
D.O.F.	3
Chi^2	0.125861864

Model Parameters		
# of Parameters	3	
Variable	Estimate	Std Error
Background	0	0
Beta1	0.000189728	0
Beta2	0	0

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	7.61499E-07	0	50	-0.000873
125	0.023437055	1.171852759	1	50	-0.160646
250	0.0463248	2.316240014	2	50	-0.212777
500	0.0905036	4.525179979	5	50	0.2340511

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-29.55331182	0	-	-	-
Fitted Model	-29.61714195	1	0.12766026	3	0.988323
Reduced Model	-33.58882955	1	8.07103545	3	0.0445662

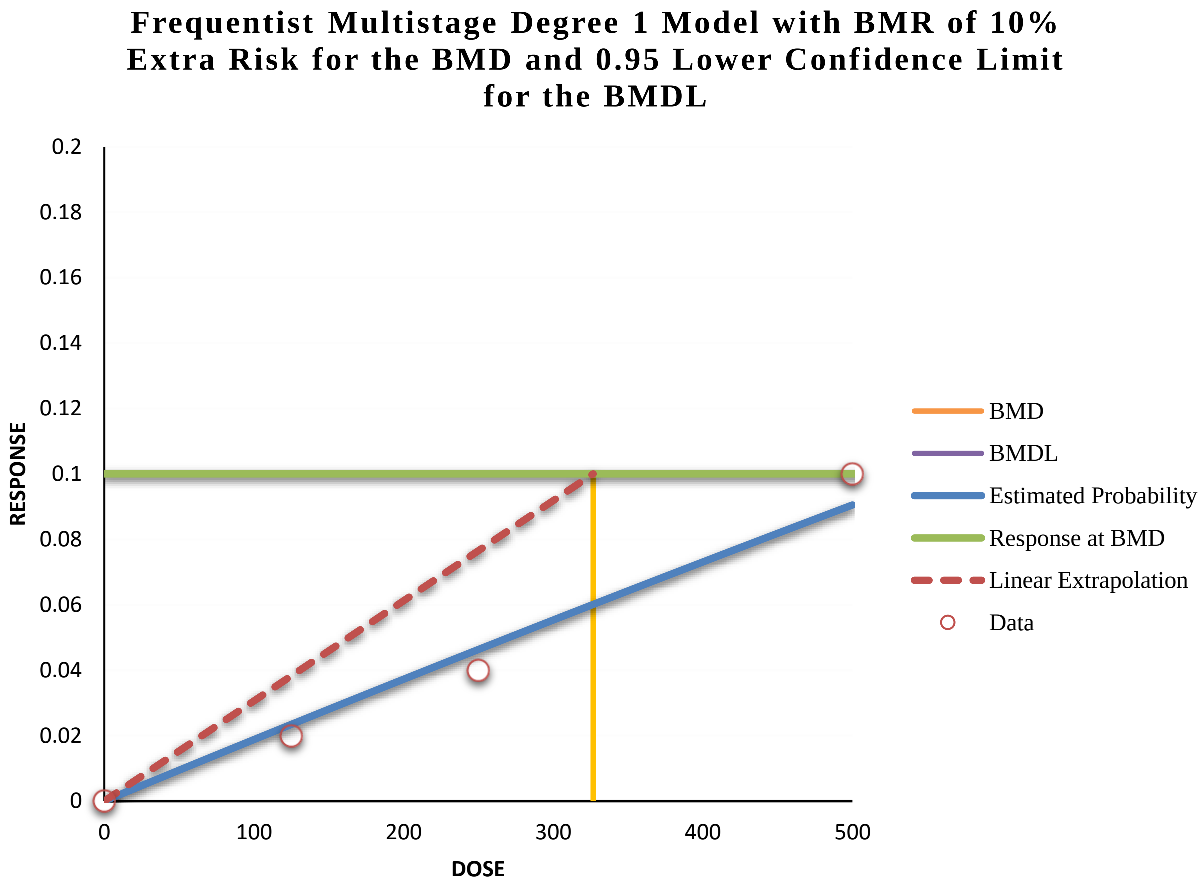

Figure 3-2 Plot of Results for Large Intestine Adenomas in Female Rats Frequentist Multistage Degree 1 Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL

3.2.1.2 Selected Frequentist Multistage - Multistage 1 Restricted; Added Risk, BMR = 0.001 and 0.1, doses are in ppm

Table 3-16 Large Intestine Adenomas in Female Rats, Selected Frequentist Multistage - Multistage 1 Restricted; Added Risk, BMR = 0.001 and 0.1 User Input

Info	
Model	frequentist Multistage degree 1 v1.0
Dataset Name	1-BP Large Intestine Adenomas - F Rats
User notes	NTP (2011) Large Intestine Adenomas in Female Rats from 1-BP

Model Options	
Risk Type	Added Risk
BMR	0.001 and 0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	PPM
Independent Variable	[Incidence]
Total # of Observation	4

Table 3-17 Large Intestine Adenomas in Female Rats, Selected Frequentist Multistage - Multistage 1 Restricted; Added Risk, BMR = 0.001 and 0.1 Model Results

BMR 0.001 Benchmark Dose	
BMD	5.273328163
BMDL	3.102597277
BMDU	11.28247793
BMR 0.1 Benchmark Dose	
BMD	555.322731
BMDL	326.7335971
BMDU	1188.88287
AIC	61.23428391
P-value	0.988562772
D.O.F.	3
Chi²	0.125861864

Model Parameters		
# of Parameters	3	
Variable	Estimate	Std Error
Background	0	0
Beta1	0.000189728	0
Beta2	0	0

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	7.61499E-07	0	50	-0.000873
125	0.023437055	1.171852759	1	50	-0.160646
250	0.0463248	2.316240014	2	50	-0.212777
500	0.0905036	4.525179979	5	50	0.2340511

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-29.55331182	0	-	-	-
Fitted Model	-29.61714195	1	0.12766026	3	0.988323
Reduced Model	-33.58882955	1	8.07103545	3	0.0445662

3.2.2 Summary of Frequentist Model Averaging

Table 3-18 Large Intestine Adenomas in Female Rats, Summary of Frequentist Model Averaging

Model Averaging Fit Statistics

Model	Weight	-2log(L)	AIC	BIC
Multistage, 3°	0.191	59.11	67.11	80.30
Weibull	0.514	59.13	65.13	75.02
Log-Probit	0.295	60.24	66.24	76.13

Average-Model Benchmark Dose Estimate:
Nominally Specified Confidence Level:0.950
Weighting Criterion: AIC
BMD Calculation: Added Risk
BMR: 0.001000
BMD: 13.472617282689
BMDL(BCa): 2.445277845095
BMDL(Percentile): 5.005030327500
Acceleration: -0.149668
Bootstrap Resamples: 5000
Random Seed: 331201

Average-Model Goodness of Fit Test
Test Statistic: 0.139777
Bootstrap *p*-value: 0.824400

Parameter Estimates

Model	Parameter	Estimate	Standard Error
Multistage, 3°	gamma	0.0	N/A
	beta(1)	0.0001525544	0.00006655318
	beta(2)	0	N/A
	beta(3)	2.307482E-10	N/A
Weibull	gamma	0.0	N/A
	alpha	1.238098	0.739784
	beta	0.000047	0.000206
Log-Probit	gamma	0.006136953057	0.011787
	alpha	-7.449471	0.263198
	beta	1.0	N/A

3.2.3 Summary of Bayesian Model Averaging

3.2.3.1 Bayesian Model Averaging – Extra Risk, BMR = 0.001 and 0.1, doses are in ppm

Table 3-19 Large Intestine Adenomas in Female Rats, Bayesian Model Averaging – Extra Risk, BMR = 0.001 and 0.1 User Inputs

Info	
Model	Bayesian Model Averaging v1.0
Dataset Name	1-BP Large Intestine Adenomas - F Rats
User notes	NTP (2011) Large Intestine Adenomas in Female Rats from 1-BP

Model Options	
Risk Type	Extra Risk
BMR	0.001 and 0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	PPM
Independent Variable	[Incidence]
Total # of Observation	4

Table 3-20 Large Intestine Adenomas in Female Rats, Bayesian Model Averaging – Extra Risk, BMR = 0.001 and 0.1 Model Results

BMR 0.001 Benchmark Dose	
BMD	23.5668422
BMDL	7.783059031
BMDU	103.7795544
BMR 0.1 Benchmark Dose	
BMD	601.4567771
BMDL	392.359376
BMDU	1236.80985

MA - Individual Models		BMR 0.001			BMR 0.1		
Model	Posterior Probability	BMD	BMDL	BMDU	BMD	BMDL	BMDU
Dichotomous Hill	0.220739084	32.16260672	1.943651238	140.386492	580.7885528	363.927722	-9999*
Gamma	0.039039943	36.78534552	7.61283841	119.1831902	574.6021867	370.8150089	1205.82664
Logistic	0.20901793	17.09404029	9.777739644	85.90026945	748.2903004	435.6470108	-9999*
Log-Logistic	0.00984594	34.76430476	3.044036916	128.055945	443.7371492	317.9377317	710.2971673
Log-Probit	0.019906973	138.4616643	37.03200072	298.4407544	496.1079955	365.0002778	766.8138146
Multistage	3.78705E-08	3.394427244	2.261513844	5.397694651	292.2843099	215.5684978	386.8899941
Probit	0.488955424	16.40802808	9.430683218	39.76662457	560.3876114	401.1173546	-9999*
Quantal Linear	0.003796807	4.927310627	2.926244168	9.784449823	518.8843608	308.1564009	1030.379176
Weibull	0.00869786	36.57183424	4.415083211	123.5612407	482.3999405	345.5123901	809.5982075

* these model outputs -9999 indicate a BMDU was not identified

3.2.3.2 Bayesian Model Averaging – Added Risk, BMR = 0.001 and 0.1, doses are in ppm

Table 3-21 Large Intestine Adenomas in Female Rats, Bayesian Model Averaging – Added Risk, BMR = 0.001 and 0.1 User Inputs

Info	
Model	Bayesian Model Averaging v1.0
Dataset Name	1-BP Large Intestine Adenomas - F Rats
User notes	NTP (2011) Large Intestine Adenomas in Female Rats from 1-BP

Model Options	
Risk Type	Added Risk
BMR	0.001 and 0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	PPM
Independent Variable	[Incidence]
Total # of Observation	4

Table 3-22 Large Intestine Adenomas in Female Rats, Bayesian Model Averaging – Added Risk, BMR = 0.001 and 0.1 Model Results

BMR 0.001 Benchmark Dose	
BMD	23.84832328
BMDL	7.975867949
BMDU	95.10070086
BMR 0.1 Benchmark Dose	
BMD	607.1436084
BMDL	394.782424
BMDU	1228.752732

MA - Individual Models		**BMR 0.001**			**BMR 0.1**		
Model	Posterior Probability	BMD	BMDL	BMDU	BMD	BMDL	BMDU
Dichotomous Hill	0.220739084	32.44390339	1.97003712	141.4284	586.859107	366.374612	-9999*
Gamma	0.039039943	37.14127466	7.69173913	120.7405	581.0417533	373.654813	-9999*
Logistic	0.20901793	17.53697172	10.1068914	57.47345	758.8571906	439.436793	-9999*
Log-Logistic	0.00984594	35.01853719	3.07937129	128.7793	447.3433793	320.201248	721.1831
Log-Probit	0.019906973	139.0558928	37.2330733	299.1879	500.2087951	367.39105	778.8816
Multistage	3.78705E-08	3.425025847	2.27973261	5.453989	294.6333885	216.422349	405.7088
Probit	0.488955424	16.60385728	9.6678799	39.83995	563.8816357	403.009892	1407.68
Quantal Linear	0.003796807	4.986505955	2.95282365	9.981385	525.4594088	311.107248	1052.267
Weibull	0.00869786	36.87119484	4.46643773	124.3649	486.5646958	347.902298	822.9395

* these model outputs -9999 indicate a BMDU was not identified

3.3 Keratoacanthoma and Squamous Cell Carcinomas in Male Rats

The doses and response data from the NTP (2011) study that were used for the modeling are presented in Table 3-23.

Table 3-23 Incidence of Keratoacanthoma and Squamous Cell Carcinomas in Male Rats

Dose (ppm)	**Number of animals**	**Number of Animals with Tumors**
0	50	1
125	50	4
250	50	6
500	50	8

Comparisons of model fits obtained from BMD modeling of the NTP (2011) study are provided in Table 3-24. A summary of all the dichotomous models and all three modeling approaches are shown for comparison with the the BMDS results in Table 3-24. Detailed output of the multistage, frequestist model average and Bayesian model average results are also shown below.

Table 3-24 Summary of BMDS 3.0 modeling results for keratoacanthoma & squamous cell carcinomas in male rats exposed to 1-BP by inhalation for 2 years (NTP, 2011); BMRs = 10% and 0.1% extra and added risk, doses are in ppm

Frequentist Model	**Restriction *****	**10% Extra Risk**		**10% Added Risk**		**0.1% Extra Risk**		**0.1% Added Risk**		***P* Value**	**AIC**	**BMDS Recommendation Notes**
		BMD	**BMDL**	**BMD**	**BMDL**	**BMD**	**BMDL**	**BMD**	**BMDL**			
Dichotomous Hill	Restricted	241.9508	CF	250.0001	CF	3.236715	CF	3.290924	CF	CF	126.3403356	BMD Lower limit includes zero
Gamma	Restricted	303.843	185.275	312.2107	187.7474	2.885284	1.759366	2.960561	1.781668	0.8021847	122.7789055	
Log-Logistic	Restricted	294.0892	173.3592	302.2094	175.6876	2.649453	1.561794	2.715178	1.580743	0.8427402	122.6810603	Lowest AIC
Log-Probit	Restricted	399.4465	261.7774	411.4748	265.8007	65.45737	42.89751	66.4724	43.24036	0.312975	124.8422642	
Multistage Degree 3	Restricted	303.843	185.2034	312.2107	187.6895	2.885284	1.759338	2.960561	1.781575	0.8021847	122.7789055	Converges to Degree 1
Multistage Degree 2	Restricted	303.843	185.206	312.2107	187.6879	2.885284	1.759315	2.960561	1.781575	0.8021847	122.7789055	Converges to Degree 1
Multistage Degree 1**	Restricted	303.843	185.2037	312.2107	187.6903	2.885284	1.759336	2.960561	1.781575	0.8021847	122.7789055	All Multistage models converged to Multistage Degree 1
Weibull	Restricted	210.3339	150.19	211.7953	150.9278	35.05038	12.46708	35.28128	12.52632	5.148E-12	173.1717353	Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05
Dichotomous Hill	Unrestricted	241.9507	CF	250	CF	3.236742	CF	3.290951	CF	CF	126.3403356	BMD Lower limit includes zero
Logistic	Unrestricted	408.5802	301.9481	420.7805	310.1677	7.203864	4.997068	7.542471	5.311385	0.4706516	123.9898837	
Log-Probit	Unrestricted	258.4618	CF	267.409	CF	1.230169	CF	1.252142	CF	0.9131073	124.3521934	BMD Lower limit includes zero
Probit	Unrestricted	394.6247	285.4619	406.5746	292.8437	6.509137	4.502717	6.797135	4.762942	0.5034012	123.8228047	
Frequentist Model Average	Restricted	--	--	--	--	--	--	3.73	2.26	0.7077	NA	Average of: multistage, log-probit and Weibull
Bayesian Model										**BMA model Posterior Probabilities**	**Unnormalized Log Posterior Probability**	
Dichotomous Hill	Priors	355.5078	147.56	369.5556	152.9072	8.094685	0.153672	8.357178	0.160579	0.203424	-64.32163349	NB
Gamma	Priors	389.7621	222.3436	404.6563	228.1034	15.30021	1.588847	15.82102	1.643549	0.054140	-65.64536621	NB
Logistic	Priors	528.4769	325.7855	553.3675	337.3084	8.149692	5.110528	8.702688	5.475214	0.321293	-63.86457516	NB
Log-Logistic	Priors	300.2942	168.0456	309.8314	172.937	8.166761	0.220277	8.399582	0.229138	0.029647	-66.24756569	NB
Log-Probit	Priors	407.5987	226.62	420.3065	232.0305	82.22845	9.177505	83.54719	9.343584	0.019221	-66.6809488	NB
Multistage Degree 3	Priors	216.2644	160.9627	220.8948	163.8834	2.47565	1.663083	2.537335	1.695316	NA	-79.02131211	NB
Multistage Degree 2	Priors	213.6458	156.4551	218.7139	159.4762	2.319659	1.581474	2.378462	1.612377	1.1126E-05	-74.13536451	NB
Multistage Degree 1	Priors	218.2195	153.9162	224.3367	157.1083	2.072206	1.461724	2.127236	1.490495	NA	-67.77973593	NB
Probit	Priors	434.7017	297.0376	450.8228	305.801	6.767236	4.568947	7.121577	4.849836	0.302901	-63.92352293	NB
Quantal Linear	Priors	295.3006	185.6616	306.2603	190.0876	2.804166	1.763037	2.902711	1.802915	0.045837	-65.81184537	NB
Weibull	Priors	352.5042	206.0483	364.4752	211.6823	12.68129	0.624409	13.08899	0.649286	0.023527	-66.47877309	NB
Bayesian Model Average (BMA) results	Priors	433.4563	220.5825	451.3116	227.1573	9.392749	1.425164	9.805706	1.473828	Probabilities Sum to 1	NA	NB

**Best Multistage; scaled residuals for doses 0, 125, 250 and 500 were -0.243246539, 0.375234935, 0.313277121, and -0.37778312, respectively.

***Restrictions and parameter priors are defined in the BMDS 3.0 User Guide; CF = Computation failed; NA = Not available in BMDS 3.0; NA = Not Applicable

3.3.1 Summary of Multistage Model

3.3.1.1 Selected Frequentist Multistage - Multistage 1 Restricted; Extra Risk, BMR = 0.001 and 0.1, doses are in ppm

Table 3-25 Keratoacanthoma and Squamous Cell Carcinomas in Male Rats, Selected Frequentist Multistage - Multistage 1 Restricted; Extra Risk, BMR = 0.001 and 0.1 User Input

Info	
Model	frequentist Multistage degree 1 v1.0
Dataset Name	1-BP K and SCC - M Rats
User notes	NTP (2011) Keratoacanthoma and Squamous Cell Carcinomas in Male Rats

Model Options	
Risk Type	Extra Risk
BMR	0.001 and 0.1
Confidence Level	0.95
Background	Estimated

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

Table 3-26 Keratoacanthoma and Squamous Cell Carcinomas in Male Rats, Selected Frequentist Multistage - Multistage 1 Restricted; Extra Risk, BMR = 0.001 and 0.1 Model Results

BMR 0.001 Benchmark Dose	
BMD	2.885283902
BMDL	1.759336336
BMDU	7.747724524
BMR 0.1 Benchmark Dose	
BMD	303.8429907
BMDL	185.2037126
BMDU	815.6993114
AIC	122.7789055
P-value	0.802184708
D.O.F.	2
Chi^2	0.440832776

Model Parameters		
# of Parameters	3	
Variable	**Estimate**	**Std Error**
Background	0.025413861	0
Beta1	0.00034676	0
Beta2	0	0

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.025413861	1.270693055	1	50	-0.243247
125	0.066754831	3.337741571	4	50	0.3752349
250	0.106342159	5.317107955	6	50	0.3132771
500	0.180550282	9.027514105	8	50	-0.377783

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-59.17016779	0	-	-	-
Fitted Model	-59.38945275	2	0.43856993	2	0.8030928
Reduced Model	-62.79117005	1	7.24200452	3	0.0645715

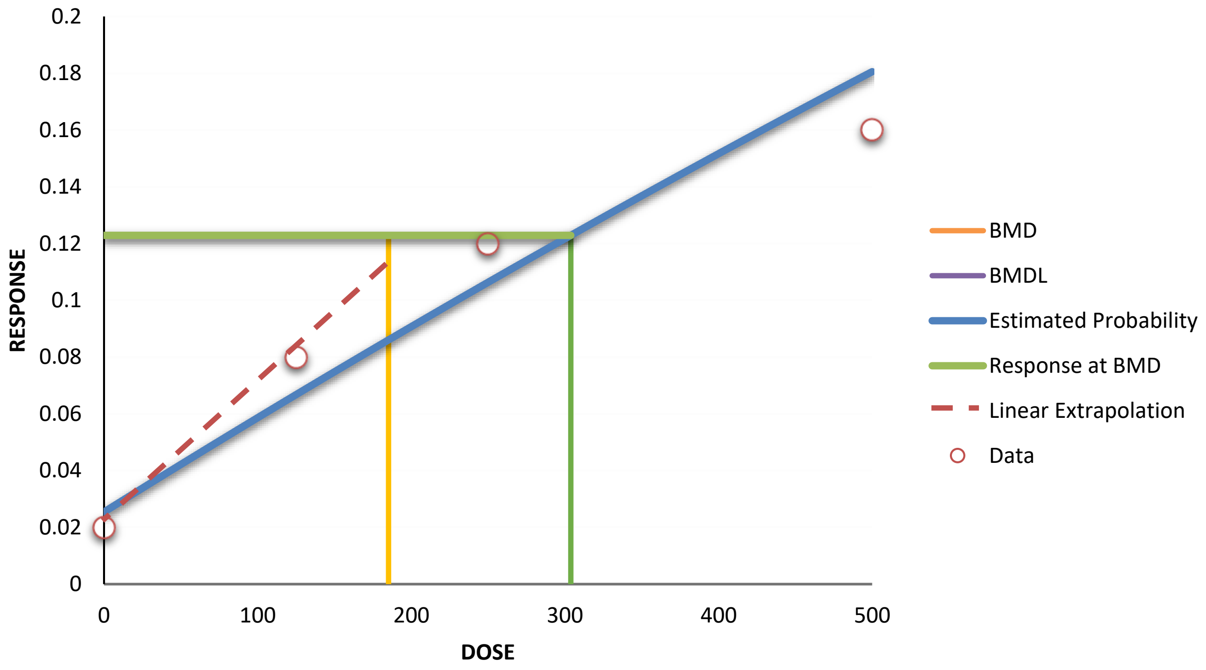
Frequentist Multistage Degree 1 Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL

Figure 3-3 Plot of Results for Keratoacanthoma and Squamous Cell Carcinomas in Male Rats Frequentist Multistage Degree 1 Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL

3.3.1.2 Selected Frequentist Multistage - Multistage 1 Restricted; Added Risk, BMR = 0.001 and 0.1, doses are in ppm

Table 3-27 Keratoacanthoma and Squamous Cell Carcinomas in Male Rats, Selected Frequentist Multistage - Multistage 1 Restricted; Added Risk, BMR = 0.001 and 0.1 User Input

Info	
Model	frequentist Multistage degree 1 v1.0
Dataset Name	1-BP K and SCC - M Rats
User notes	NTP (2011) Keratoacanthoma and Squamous Cell Carcinomas in Male Rats

Model Options	
Risk Type	Added Risk
BMR	0.001 and 0.1
Confidence Level	0.95
Background	Estimated

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

Table 3-28 Keratoacanthoma and Squamous Cell Carcinomas in Male Rats, Selected Frequentist Multistage - Multistage 1 Restricted; Added Risk, BMR = 0.001 and 0.1 Model Results

BMR 0.001 Benchmark Dose	
BMD	2.960560843
BMDL	1.781575063
BMDU	8.258328982
BMR 0.1 Benchmark Dose	
BMD	312.2107498
BMDL	187.7473751
BMDU	872.7938309
AIC	122.7789055
P-value	0.802184708
D.O.F.	2
Chi^2	0.440832776

Model Parameters		
# of Parameters	3	
Variable	Estimate	Std Error
Background	0.025413861	0
Beta1	0.00034676	0
Beta2	0	0

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.025413861	1.270693055	1	50	-0.243247
125	0.066754831	3.337741571	4	50	0.3752349
250	0.106342159	5.317107955	6	50	0.3132771
500	0.180550282	9.027514105	8	50	-0.377783

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-59.17016779	0	-	-	-
Fitted Model	-59.38945275	2	0.43856993	2	0.8030928
Reduced Model	-62.79117005	1	7.24200452	3	0.0645715

3.3.2 Summary of Frequentist Model Averaging

Table 3-29 Keratoacanthoma and Squamous Cell Carcinomas in Male Rats, Summary of Frequentist Model Averaging

Model Averaging Fit Statistics

Model	Weight	-2log(L)	AIC	BIC
Multistage, 3°	0.213	118.78	126.78	139.97
Weibull	0.580	118.78	124.78	134.67
Log-Probit	0.207	120.84	126.84	136.74

Average-Model Benchmark Dose Estimate:
Nominally Specified Confidence Level:0.950
Weighting Criterion: AIC
BMD Calculation: Added Risk
BMR: 0.001000
BMD: 3.732432783338
BMDL(BCa): 1.505273123061
BMDL(Percentile): 2.260265766150
Acceleration: 0.030873
Bootstrap Resamples: 5000
Random Seed: 257515

Average-Model Goodness of Fit Test
Test Statistic: 0.707725
Bootstrap *p*-value: 0.586800

Parameter Estimates

Model	Parameter	Estimate	Standard Error
Multistage, 3°	gamma	0.02541313	0.02238034
	beta(1)	0.0003467654	0.0001309450
	beta(2)	0	N/A
	beta(3)	0	N/A
Weibull	gamma	0.025414	0.022401
	alpha	1.0	N/A
	beta	0.000347	0.000131
Log-Probit	gamma	0.050387778679	0.025518
	alpha	-7.271630	0.311627
	beta	1.0	N/A

3.3.3 Summary of Bayesian Model Averaging

3.3.3.1 Bayesian Model Averaging – Extra Risk, BMR = 0.001 and 0.1, doses are in ppm

Table 3-30 Keratoacanthoma and Squamous Cell Carcinomas in Male Rats, Bayesian Model Averaging – Extra Risk, BMR = 0.001 and 0.1 User Inputs

Info	
Model	Bayesian Model Averaging v1.0
Dataset Name	1-BP Large Intestine Adenomas - F Rats
User notes	NTP (2011) Large Intestine Adenomas in Female Rats from 1-BP

Model Options	
Risk Type	Extra Risk
BMR	0.001 and 0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	PPM
Independent Variable	[Incidence]
Total # of Observation	4

Table 3-31 Keratoacanthoma and Squamous Cell Carcinomas in Male Rats, Bayesian Model Averaging – Extra Risk, BMR = 0.001 and 0.1 Model Results

BMR 0.001 Benchmark Dose	
BMD	9.392749294
BMDL	1.425164286
BMDU	55.04451692
BMR 0.1 Benchmark Dose	
BMD	433.4563002
BMDL	220.582515
BMDU	1556.137562

MA - Individual Models		BMR 0.001			BMR 0.1		
Model	Posterior Probability	BMD	BMDL	BMDU	BMD	BMDL	BMDU
Dichotomous Hill	0.203424469	8.094685152	0.153671514	86.83353662	355.5077612	147.5600451	192683.5175
Gamma	0.054139392	15.30020591	1.588847255	82.10273087	389.7621334	222.343564	928.3482432
Logistic	0.321292879	8.149691857	5.11052832	31.40190989	528.4768939	325.7855475	2252.007484
Log-Logistic	0.029647049	8.166761138	0.220277332	67.28941947	300.2942502	168.0455804	513.0673647
Log-Probit	0.019220539	82.22845197	9.177505039	271.9267905	407.5987339	226.6199589	689.7653341
Multistage	1.11264E-05	2.319659106	1.581473509	3.680806607	213.6458308	156.4551443	296.4730561
Probit	0.302900793	6.767235696	4.568947013	15.09856433	434.7017109	297.0376015	1098.289967
Quantal Linear	0.0458366	2.804165939	1.763036591	5.545045715	295.3006327	185.6615543	583.9366913
Weibull	0.023527152	12.68129051	0.624408538	81.15071058	352.504164	206.0482651	624.6541739

* these model outputs -9999 indicate a BMDU was not identified

3.3.3.2 Bayesian Model Averaging – Added Risk, BMR = 0.001 and 0.1, doses are in ppm

Table 3-32 Keratoacanthoma and Squamous Cell Carcinomas in Male Rats, Bayesian Model Averaging – Added Risk, BMR = 0.001 and 0.1 User Inputs

Info	
Model	Bayesian Model Averaging v1.0
Dataset Name	1-BP Large Intestine Adenomas - F Rats
User notes	NTP (2011) Large Intestine Adenomas in Female Rats from 1-BP

Model Options	
Risk Type	Added Risk
BMR	0.001 and 0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	PPM
Independent Variable	[Incidence]
Total # of Observation	4

Table 3-33 Keratoacanthoma and Squamous Cell Carcinomas in Male Rats, Bayesian Model Averaging – Added Risk, BMR = 0.001 and 0.1 Model Results

BMR 0.001 Benchmark Dose	
BMD	9.805706222
BMDL	1.47382787
BMDU	51.07468367
BMR 0.1 Benchmark Dose	
BMD	451.311646
BMDL	227.1572948
BMDU	1229.189038

MA - Individual Models		BMR 0.001			BMR 0.1		
Model	Posterior Probability	BMD	BMDL	BMDU	BMD	BMDL	BMDU
Dichotomous Hill	0.203424469	8.357177489	0.16057906	89.33856338	369.5555627	152.9071629	-9999
Gamma	0.054139392	15.82102291	1.64354872	85.22485197	404.6563208	228.1033844	983.3875895
Logistic	0.321292879	8.702687919	5.475214217	31.09874949	553.3674359	337.3084068	-9999
Log-Logistic	0.029647049	8.399581537	0.229138095	68.88824701	309.8314404	172.9370356	540.1743054
Log-Probit	0.019220539	83.54718983	9.343584068	274.2274106	420.3065038	232.0304662	722.1497893
Multistage	1.11264E-05	2.378462348	1.612394466	3.807670902	218.7139392	159.5782638	296.4761257
Probit	0.302900793	7.121576462	4.84983623	16.27391949	450.8228302	305.8009446	1167.158008
Quantal Linear	0.0458366	2.90271081	1.802915474	5.884175655	306.2603176	190.0876462	621.7316389
Weibull	0.023527152	13.08898814	0.649286201	83.21873099	364.4751906	211.6823345	659.6490741

* these model outputs -9999 indicate a BMDU was not identified

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