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Office of Chemical Safety and
Pollution Prevention

Draft Benchmark Dose Modeling Results for 1,3-Butadiene

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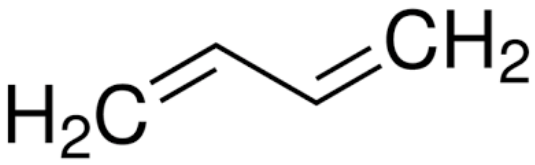

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1 BENCHMARK DOSE MODELING RESULTS

EPA performed benchmark dose (BMD) modeling using EPA's BMD modeling software (BMDS Version 3.3.2) for dichotomous, dichotomous nested, and continuous data for the non-cancer health domains that were identified during hazard identification and that received a judgment of "likely" ("evidence indicates that 1,3-butadiene exposure likely causes [health effect]") during evidence integration, including maternal and related developmental effects (maternal body weight, fetal body weight, fetal malformations), male reproductive system effects (dominant lethal effects), and hematological effects (endpoints related to anemia effects). EPA conducted BMD modeling in a manner consistent with EPA's *Benchmark Dose (BMD) Technical Guidance* (U.S. EPA, 2012).

EPA used dichotomous models to fit quantal data (*e.g.*, overall incidences of fetal malformations), dichotomous-nested models to fit dichotomous-nested data (*e.g.*, incidences of fetal malformations per litter, taking into account litter-specific covariates and intralitter correlations), and continuous models to fit continuous data (*e.g.*, body weights), as recommended by EPA's *BMD Technical Guidance* (U.S. EPA, 2012). All data sets identified for BMD modeling were from inhalation exposure studies and administered concentrations were modeled in units of ppm. The BMDs/BMDLs (benchmark dose lower 95 percent confidence limits) are provided based on a daily exposure (*i.e.*, 24 hours per day, seven days per week) for easier comparison across all hazard endpoints and thus, concentrations were adjusted as needed before BMD modeling. EPA modeled endpoints that had statistically significant pairwise changes between individual doses and controls or significant dose-response trends. EPA also considered potential biologically significant changes from controls where possible and/or changes that appeared to exhibit a dose-response relationship upon visual inspection. Multiple health endpoints may have been modeled from each study, depending on the relevance of the data to adverse health outcomes and to identify sensitive health endpoints for each domain.

If a data set did not provide an adequate fit when applying the models, the data at the highest dose(s) were omitted and the models refit to the remaining data to attempt to obtain an adequate fit, particularly in the response region of interest. Dropping the highest dose results in the loss of degrees of freedom and, for continuous data, may result in loss of information for modeling the variances; however, data at the highest doses may be least informative of responses in the lower dose region of interest. This document does not present results of modeling exercises in which none of the models in the BMD suite provided an adequate fit to the full or reduced data sets. For non-cancer endpoints, if BMD modeling was not possible or available models did not fit the data, EPA used no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs) during point of departure (POD) selection for the risk evaluation.

EPA relied on the BMD guidance and other information to choose benchmark responses (BMRs) appropriate for each endpoint. Although the *BMD Technical Guidance* (U.S. EPA, 2012) doesn't recommend default BMRs, it describes how various BMD modeling results compare with NOAEL values, and the guidance does recommend calculating 10 percent extra risk (ER) for quantal data and one standard deviation (SD) for continuous data to compare modeling results across endpoints. EPA also modeled percent relative deviations (RD) for certain continuous endpoints and additional percent ER for certain dichotomous endpoints. EPA's choice of BMRs for the 1,3-butadiene health endpoints is described in more detail in the following sections that present BMD modeling results for each health domain.

When modeling dose-response relationships, the data can be modeled as either ER or additional risk. EPA modeled the data as ER. EPA's *BMD Technical Guidance* defines ER as "a measure of the

proportional increase in risk of an adverse effect adjusted for the background incidence of the same effect." Mathematically, ER is equal to [P(d) − P(0)]/[1 − P(0)]. P(d) is the probability of the effect at dose d, and P(0) is the probability of risk with no exposure to a hazard (U.S. EPA, 2012).[1]

Non-cancer endpoints selected for modeling were based on both dichotomous and continuous measurement data. For dichotomous data, the Dichotomous Hill, Gamma, Logistic, Log-Logistic, Log-Probit, Multistage, Probit, Weibull, and Quantal Linear dichotomous models available within the software were fit using the selected BMR(s). Adequacy of model fit was judged based on the $\chi 2$ goodness-of-fit p-value ($p > 0.1$), magnitude of scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. Among all models providing adequate fit, the lowest BMDL was selected if the BMDLs estimated from different models varied > 3-fold; otherwise, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) was selected.

For dichotomous nested data, the Nested Logistic model available within the software was fit using the selected BMR(s). The model was applied with and without a litter-specific covariate (lsc), such as litter size, to determine whether or not the litter-specific covariate contributes to a better explanation of the observation. The model was also run with and without intralitter correlation (ilc) to estimate the degree to which observations within the same litter are correlated. The forms of the model include lsc+ilc+, lsc+ilc-, lsc-ilc+, and lsc-ilc-. Adequacy of model fit was judged based on the $\chi 2$ goodness-of-fit p-value ($p > 0.1$), magnitude of scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. Among the forms of the models providing adequate fit, the model form with the lowest AIC was selected.

For continuous measurement data, the Exponential, Hill, Linear, Polynomial, and Power continuous models available within the software were fit employing the selected BMR(s). An adequate fit was judged based on the chi-square goodness-of-fit p-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was constant. If a constant variance model was deemed appropriate based on the statistical test provided in BMDS (*i.e.*, Test 2; p-value > 0.05 [note: this is a change from previous versions of BMDS, which required variance p-value > 0.10 for adequate fit]), the final BMD results were estimated from a constant variance model. If the test for homogeneity of variance was rejected (p-value < 0.05), the model was run again while modeling the variance as a power function of the mean to account for this nonconstant variance. If this nonconstant variance model also did not adequately fit the data (*i.e.*, Test 3; p-value < 0.05), the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMDL was selected if the BMDLs estimated from different models varied > 3-fold; otherwise, the BMDL from the model with the lowest AIC was selected.

1.1 Maternal and Related Developmental Toxicity

1.1.1 Maternal Body Weight Effects

Two gestational inhalation exposure studies were identified for BMD modeling that showed significant changes in body weight (Hazleton Labs, 1981) or body weight gain (Battelle PNL, 1987), (Hazleton Labs, 1981).

[1] EPA's *BMD Technical Guidance* also uses the terms, excess incidence and excess risk, which are defined more generally as increased risk or incidence above control or background responses. These terms can refer to either additional or extra risk (U.S. EPA, 2012).

1.1.1.1 Maternal Absolute Body Weight Gain (GD 11-16) in CD-1 Mice Exposed via Inhalation on GD 6-15 (Battelle PNL, 1987)

Maternal absolute body weight gains were significantly decreased for gestation days (GD) 11-16 in pregnant CD-1 mice exposed to 1,3-butadiene by inhalation on GD 6-15 (six hours per day) (Battelle PNL, 1987). First, the exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day rather than six hours per day. Then, continuous models were fit to the dose-response data.

A BMR of one SD was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentrations and response data used for the modeling are presented in Table 1-1.

Table 1-1. Decreased Maternal Body Weight Gain (GD 11-16) in Pregnant CD-1 Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,3-Butadiene from a Gestational Inhalation Exposure Study (GD6-15)

Adjusted Concentration (ppm)	Number of Animals	Mean (g)	SD (g)
0	18	13.3	2.5
10.0	19	12.7	1.7
49.95	21	11.4	2.3
250	20	10.6	1.8

The BMD modeling results for decreased maternal body weight gain in pregnant mice are summarized in Table 1-2. The constant variance model provided adequate fit to the variance data. With the constant variance model applied, only the Exponential 5 model provided an adequate fit to the means (test 4 p-value > 0.1). The goodness-of-fit test for the means (test 4) could not be calculated for the Hill model because the model was saturated (degree of freedom = 0). The Exponential 5 model was selected as the only adequately fitting model.

Table 1-2. Summary of BMD Modeling Results for Decreased Maternal Body Weight Gain (GD 11-16) in Pregnant CD-1 Mice Following Inhalation Exposure to 1,3-Butadiene During Gestation (GD 6-15) (Constant Variance Model)[a]

Model	Goodness of Fit (Means)		BMD 1SD (ppm)	BMDL 1SD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC			
Exponential 3	0.0873	343.7	229	151	The constant variance model provided an adequate fit to the variance data. With the constant variance model applied, only the Exponential 5 model provided an adequate fit to the means (test 4 p-value > 0.1); therefore, this model was selected.
Exponential 5	**0.9773**	**340.8**	**58.2**	**10.4**	
Hill	NA	342.8	60.1	12.1	
Polynomial Degree 3	0.0764	344.0	236	163	
Polynomial Degree 2	0.0764	344.0	238	163	
Power	0.0764	344.0	237	163	
Linear	0.0764	344.0	237	163	

[a] Selected model in bold.

The Plot of the Exponential 5 model with a BMR of one SD is shown in Figure 1-1. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 1-2.

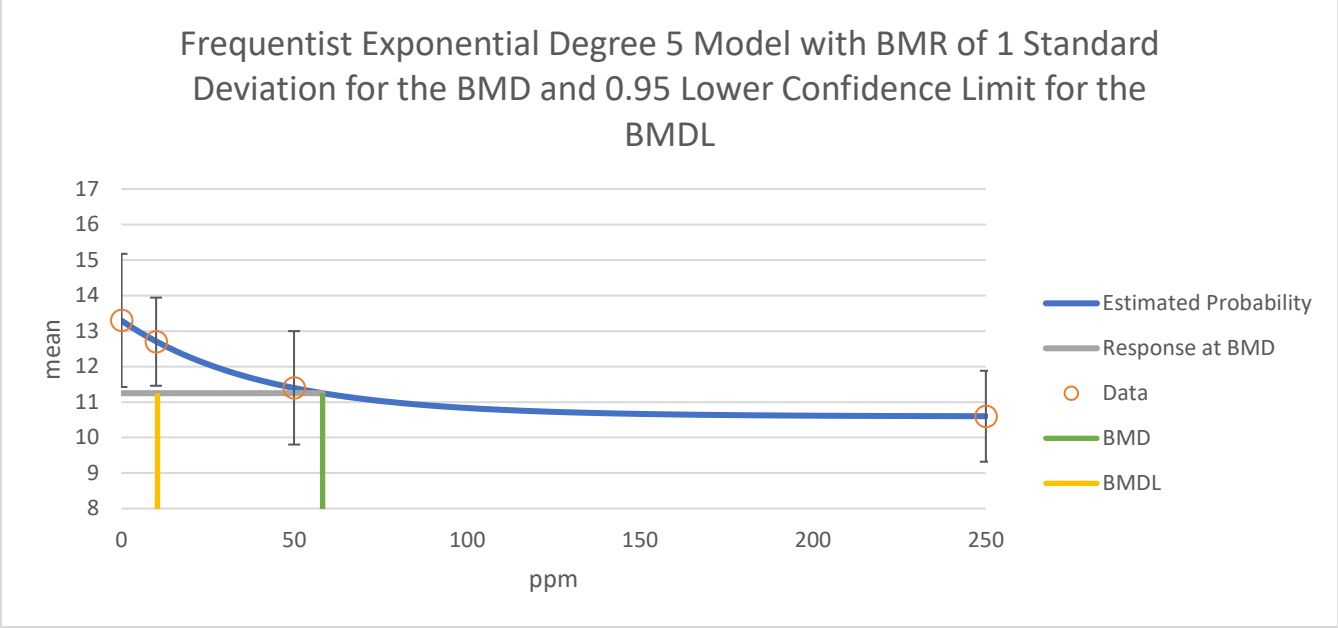

Figure 1-1. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 5, Constant Variance Model) for Decreased Maternal Body Weight Gain (GD 11-16) in CD-1 Mice Exposed to 1,3-Butadiene via Inhalation During Gestation (GD 6-15) and BMR of 1SD

Summary:

BMD	58.1705
BMDL	10.426
BMDU	-9999
AIC	340.821
Log Likelihood	166.411
P-Value	0.97725
Model DOF	1

Model Parameters:

Variable	Estimate	Bounded	Std Error	Lower CI	Upper CI
a	13.2932	no	0.419152	12.4717	14.1147
b	0.0243461	no	0.0141892	-0.00346414	0.0521564
c	0.797055	no	0.0519408	0.695253	0.898858
d	1	yes	NA	NA	NA
log-alpha	1.42906	no	0.160125	1.11523	1.7429

Goodness of Fit:

Dose	Size	Observed Mean	Calculated Mean	Estimated Mean	Scaled Residual
0	18	13.3	13.3	13.2932	0.0140662
10	19	12.7	12.7	12.7103	-0.0218884
49.95	21	11.4	11.4	11.395	0.0111534
250	20	10.6	10.6	10.6016	-0.003439

Dose	Size	Observed SD	Calculated SD	Estimated SD
0	18	2.5	2.5	2.04323
10	19	1.7	1.7	2.04323
49.95	21	2.3	2.3	2.04323
250	20	1.8	1.8	2.04323

Likelihoods of Interest:

Model	Log Likelihood	# Params	AIC
A1	-166.41	5	342.821
A2	-164.446	8	344.892
A3	-166.41	5	342.821
fitted	-166.411	4	340.821
reduced	-175.578	2	355.157

Tests of Interest:

Name	Loglikelihood Ratio	Test DOF	P-Value
Test 1	22.2649	6	0.00108403
Test 2	3.92873	3	0.269264
Test 3	3.92873	3	0.269264
Test 4	0.000813187	1	0.97725

Figure 1-2. Details Regarding the Selected Model (Exponential 5, Constant Variance Model) for Decreased Maternal Body Weight Gain (GD 11-16) in CD-1 Mice Exposed to 1,3-Butadiene Via Inhalation During Gestation (GD 6-15) and BMR of 1SD

1.1.1.2 Maternal Extragestational Weight Gain (Gravid Uterus Adjusted) for GD 0-18 in CD-1 Mice Exposed via Inhalation on GD 6-15 (Battelle PNL, 1987)

Maternal extragestational body weight gains (gravid uterus adjusted) were significantly decreased for GD 0 to 18 in pregnant CD-1 mice exposed to 1,3-butadiene by inhalation on GD 6 to 15 (six hours per day) (Battelle PNL, 1987). First, the exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day rather than six hours per day. Then, continuous models were fit to the dose-response data.

A BMR of one SD was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentrations and response data used for the modeling are presented in Table 1-3.

Table 1-3. Decreased Maternal Extragestational Body Weight Gain (Gravid Uterus Adjusted) for GD 0-18 in Pregnant CD-1 Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,3-Butadiene from a Gestational Inhalation Exposure Study (GD 6-15)

Adjusted Concentration (ppm)	Number of Animals	Mean (g)	SD (g)
0	18	7.60	2.04
10.0	19	6.99	1.66
49.95	21	6.20	1.74
250	20	5.91	1.25

The BMD modeling results for decreased maternal extragestational uterine-adjusted body weight gain in pregnant mice for GD 0 to 18 are summarized in Table 1-4. The constant variance model provided adequate fit to the variance data. With the constant variance model applied, only the Exponential 3 model provided adequate fit to the means (test 4 p-value > 0.1). The goodness-of-fit test for the means (test 4) could not be calculated for the Hill model because the model was saturated (degree of freedom = 0) and the BMD computation failed for the Exponential 5 model. The Exponential 3 model was selected as it was the only adequately fitting model. The BMD was higher than the maximum tested concentration.

Table 1-4. Summary of BMD Modeling Results for Decreased Maternal Extragestational Body Weight Gain (Gravid Uterus Adjusted) for GD 0-18 in Pregnant CD-1 Mice Following Inhalation Exposure to 1,3-Butadiene During Gestation (GD 6-15) (Constant Variance Model)[a]

Model	Goodness of Fit (Means)		BMD 1SD (ppm)	BMDL 1SD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC			
Exponential 3	**0.1013**	**309.4**	**337**	**193**	The constant variance model provided an adequate fit to the variance data. With the constant variance model applied, only the Exponential 3 model provided adequate fit to the means (test 4 p-value > 0.1);
Exponential 5	-	-	-	-	
Hill	NA	308.8	150	10.5	
Polynomial Degree 3	0.0926	309.6	337	206	
Polynomial Degree 2	0.0926	309.6	336	206	
Power	0.0926	309.6	337	206	

Model	Goodness of Fit (Means)		BMD 1SD (ppm)	BMDL 1SD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC			
Linear	0.0926	309.6	337	206	therefore, this model was selected.
[a] Selected model in bold.					

The Plot of the Exponential 3 model with a BMR of one SD is shown in Figure 1-3. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 1-4.

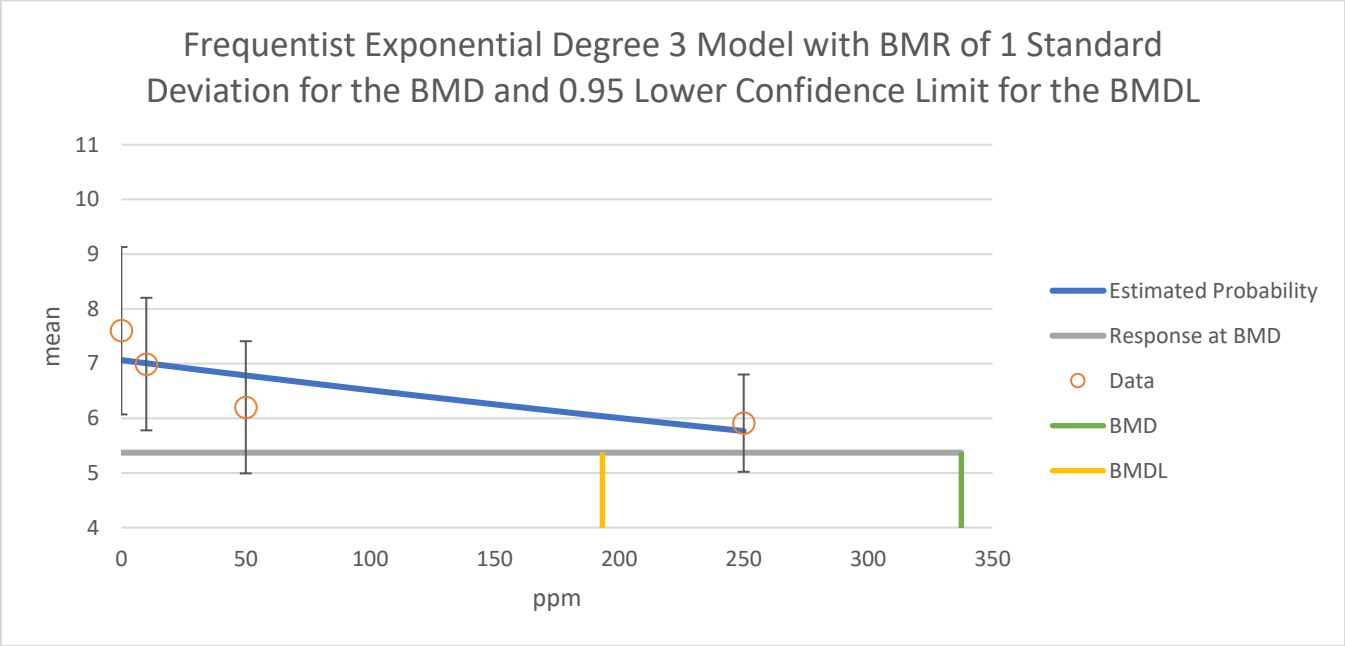

Figure 1-3. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 3, Constant Variance Model) for Decreased Maternal Extragestational Body Weight Gain (Gravid Uterus Adjusted) for GD 0-18 in Pregnant CD-1 Mice Following Inhalation Exposure to 1,3-Butadiene During Gestation (GD 6-15) and BMR of 1SD

Summary:

BMD	337.469
BMDL	193.268
BMDU	964.39
AIC	309.403
Log Likelihood	151.701
P-Value	0.101305
Model DOF	2

Model Parameters:

Variable	Estimate	Bounded	Std Error	Lower CI	Upper CI
a	7.06261	no	0.249034	6.57452	7.55071
b	0.000811587	no	0.000315489	0.00019324	0.00142993
d	1	yes	NA	NA	NA
log-alpha	1.0519	no	0.16013	0.738052	1.36575

Goodness of Fit:

Dose	Size	Observed Mean	Calculated Mean	Estimated Mean	Scaled Residual
0	18	7.6	7.6	7.06261	1.34742
10	19	6.99	6.99	7.00553	-0.0400003
49.95	21	6.2	6.2	6.78203	-1.5763
250	20	5.91	5.91	5.76565	0.381507

Dose	Size	Observed SD	Calculated SD	Estimated SD
0	18	2.04	2.04	1.69207
10	19	1.66	1.66	1.69207
49.95	21	1.74	1.74	1.69207
250	20	1.25	1.25	1.69207

Likelihoods of Interest:

Model	Log Likelihood	# Params	AIC
A1	-149.412	5	308.823
A2	-147.181	8	310.362
A3	-149.412	5	308.823
fitted	-151.701	3	309.403
reduced	-155.191	2	314.383

Tests of Interest:

Name	Loglikelihood Ratio	Test DOF	P-Value
Test 1	16.0209	6	0.0136424
Test 2	4.46142	3	0.215758
Test 3	4.46142	3	0.215758
Test 4	4.57924	2	0.101305

Figure 1-4. Details Regarding the Selected Model (Exponential 3, Constant Variance Model) for Decreased Maternal Extragestational Body Weight Gain (Gravid Uterus Adjusted) for GD 0-18 in Pregnant CD-1 Mice Following Inhalation Exposure to 1,3-Butadiene During Gestation (GD 6-15)

1.1.1.3 Maternal Absolute Body Weight Gain for GD 6 to 15 in Sprague-Dawley Rats Exposed via Inhalation on GD 6 to 15 (Hazleton Labs, 1981)

Maternal absolute body weight gains were significantly decreased for GD 6 to 15 in pregnant Sprague-Dawley Rats exposed to 1,3-butadiene by inhalation on GD 6 to 15 (six hours per day) (Hazleton Labs, 1981). First, the exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day rather than six hours per day. Then, continuous models were fit to the dose-response data.

A BMR of one SD was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentrations and response data used for the modeling are presented in in Table 1-5.

Table 1-5. Decreased Maternal Absolute Body Weight Gain (GD 6-15) in Pregnant Sprague-Dawley Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,3-Butadiene from a Gestational Inhalation Exposure Study (GD 6-15)

Adjusted Concentration (ppm)	Number of Animals	Mean (g)	SD (g)
0.70	36	44	9
50.5	22	38	7.7
248	23	31	9.3
1912	23	24	9.3

The BMD modeling results for decreased absolute maternal body weight gain in pregnant rats are summarized in Table 1-6. The constant variance model provided adequate fit to the variance data. With the constant variance model applied, only the Exponential 5 and Hill models provided adequate fit to the means (test 4 p-value > 0.1). The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Hill).

Table 1-6.Summary of BMD Modeling Results for Decreased Maternal Absolute Body Weight Gain (GD 6-15) in Pregnant Sprague-Dawley Rats Following Inhalation Exposure to 1,3-Butadiene During Gestation (GD 6-15) (Constant Variance Model)

Model	Goodness of Fit (Means)		BMD 1SD (ppm)	BMDL 1SD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC			
Exponential 3	<0.0001	769.8	912.0	671.9	The constant variance model provided an adequate fit to the variance data. With the constant variance model applied, only the Exponential 5 and Hill models provided adequate fit to the means (test 4 p-value > 0.1). The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model
Exponential 5	0.3349	754.2	130.0	72.76	
Hill	**0.7012**	**753.4**	**101.3**	**48.93**	
Polynomial Degree 3	<0.0001	771.7	1111	880.6	
Polynomial Degree 2	<0.0001	771.7	1128	880.0	
Power	<0.0001	771.7	1111	880.6	

Model	Goodness of Fit (Means)		BMD 1SD (ppm)	BMDL 1SD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC			
Linear	<0.0001	771.7	1111	880.6	with the lowest AIC was selected (Hill).
[a] Selected model in bold.					

The Plot of the Hill model with a BMR of one SD is shown in Figure 1-5. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 1-6.

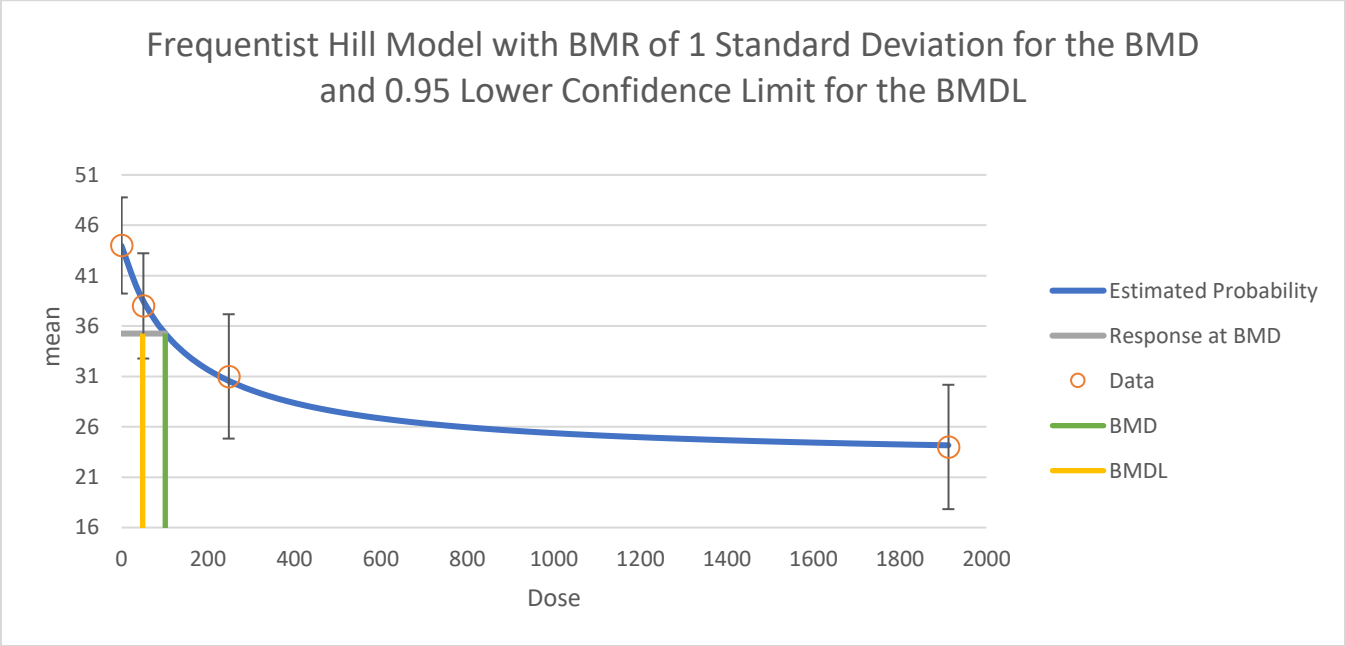

Figure 1-5. Plot of Response by Dose with Fitted Curve for the Selected Model (Hill, Constant Variance Model) for Decreased Maternal Absolute Body Weight Gain (GD 6-15) in Pregnant Sprague-Dawley Rats Following Inhalation Exposure to 1,3-Butadiene During Gestation (GD 6-15) and BMR of 1SD

Summary:

BMD	101.284
BMDL	48.9096
BMDU	222.75
AIC	753.441
Log Likelihood	372.721
P-Value	0.701154
Model DOF	1

Model Parameters:

Variable	Estimate	Bounded	Std Error	Lower CI	Upper CI
g	43.9677	no	1.44972	41.1263	46.8091
v	-21.3234	no	2.55912	-26.3392	-16.3076
k	146.566	no	69.7788	9.80241	283.33
n	1	yes	NA	NA	NA
alpha	75.931	no	799.531	-1491.12	1642.98

Goodness of Fit:

Dose	Size	Observed Mean	Calculated Mean	Estimated Mean	Scaled Residual
0.7	36	44	44	43.8664	0.0920115
50.5	22	38	38	38.5034	-0.270972
248	23	31	31	30.5651	0.239333
1912	23	24	24	24.1625	-0.089432

Dose	Size	Observed SD	Calculated SD	Estimated SD
0.7	36	9	9	8.71384
50.5	22	7.7	7.7	8.71384
248	23	9.3	9.3	8.71384
1912	23	9.3	9.3	8.71384

Likelihoods of Interest:

Model	Log Likelihood	# Params	AIC
A1	-372.647	5	755.294
A2	-372.116	8	760.232
A3	-372.647	5	755.294
fitted	-372.721	4	753.441
reduced	-402.981	2	809.961

Tests of Interest:

Name	Loglikelihood Ratio	Test DOF	P-Value
Test 1	61.729	6	2.00324e-11
Test 2	1.06172	3	0.786321
Test 3	1.06172	3	0.786321
Test 4	0.147274	1	0.701154

Figure 1-6. Details Regarding the Selected Model (Hill, Constant Variance Model) for Decreased Maternal Absolute Body Weight Gain (GD 6-15) in Pregnant Sprague-Dawley Rats Following Inhalation Exposure to 1,3-Butadiene During Gestation (GD 6-15)

1.1.1.4 Maternal Body Weight Gain (Gravid Uterus Adjusted) for GD 0 to 20 in Sprague-Dawley Rats Exposed via Inhalation on GD 6 to 15 (Hazleton Labs, 1981)

Maternal body weight gains (gravid uterus adjusted) were significantly decreased for GD 0 to 20 in pregnant Sprague-Dawley Rats exposed to 1,3-butadiene by inhalation on GD 6 to 15 (six hours per day) (Hazleton Labs, 1981). First, the exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day rather than six hours per day. Then, continuous models were fit to the dose-response data.

A BMR of one SD was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentrations and response data used for the modeling are presented in Table 1-7.

Table 1-7. Decreased Maternal Body Weight Gain (Gravid Uterus Adjusted) for GD 0-20 in Pregnant Sprague-Dawley Rats and Associated Doses Selected for Dose-Response Modeling for 1,3-Butadiene From a Gestational Exposure Study (GD 6-15)

Adjusted Concentration (ppm)	Number of Animals	Mean (g)	SD (g)
0.70	36	58.7	12.3
50.5	22	58.4	12
248	23	49.2	11.3
1912	23	45.4	11.5

The BMD modeling results for decreased uterine-adjusted body weight gain in pregnant rats are summarized in Table 1-8. Both the constant and nonconstant variance models provide adequate fit to the variance data; however, with either variance model applied, none of the models provided adequate fit to the means (test 4 p-value < 0.1). The goodness-of-fit test for the means (Test 4) could not be calculated for the Exponential 5 and Hill models because the models were saturated (degree of freedom = 0). The full data set is not suitable for BMD modeling. With the highest concentration dropped from the data set, the constant variance model provided an adequate fit to the variance data. With the constant variance model applied, only the Linear model provided adequate fit to the means (test 4 p-value > 0.1). The goodness-of-fit test for the means (test 4) could not be calculated for all other models because the models were saturated (degree of freedom = 0). The Linear model was selected as it was the only adequately fit model. The predicted BMD for the Linear model was higher than the maximum concentration modeled.

Table 1-8. Summary of BMD Modeling Results for Decreased Maternal Body Weight Gain (Gravid Uterus Adjusted) for GD 0-20 in Pregnant Sprague-Dawley Rats Following Inhalation Exposure to 1,3-Butadiene in a Gestational Exposure Study (GD 6-15)[a]

Model	Goodness of Fit (Means)		BMD 1SD (ppm)	BMDL 1SD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC			
Full Data set (Constant Variance Model)					For the full data set, both the constant and nonconstant variance
Exponential 3	0.0264	818.5	1878	1251	

Model	Goodness of Fit (Means)		BMD 1SD (ppm)	BMDL 1SD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC			
Exponential 5	NA	815.3	302.6	267.9	models provide adequate fit to the variance data; however, with either variance model applied, none of the models provided adequate fit to the means (test 4 p-value < 0.1). The full data set is not suitable for BMD modeling. With the highest concentration dropped from the data set, The constant variance model provided an adequate fit to the variance data. With the constant variance model applied, only the Linear model provided adequate fit to the means (test 4 p-value > 0.1); therefore, this model was selected.
Hill	NA	815.3	349.8	69.52	
Polynomial Degree 3	0.0229	818.8	1939	1354	
Polynomial Degree 2	0.0229	818.8	1928	1354	
Power	0.0229	818.8	1925	1354	
Linear	0.0229	818.8	1925	1354	
Highest Concentration Dropped (Constant Variance Model)					
Exponential 3	NA	636.6	275	192	
Exponential 5	NA	638.6	278	259	
Hill	NA	638.6	284	58.3	
Polynomial Degree 2	NA	636.6	275	197	
Power	NA	636.6	273	248	
Linear	**0.5895**	**634.9**	**295**	**193**	

[a] Selected model in bold.

The Plot of the Linear model (with the highest concentration dropped from the data set) with a BMR of one SD is shown in Figure 1-7. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 1-8.

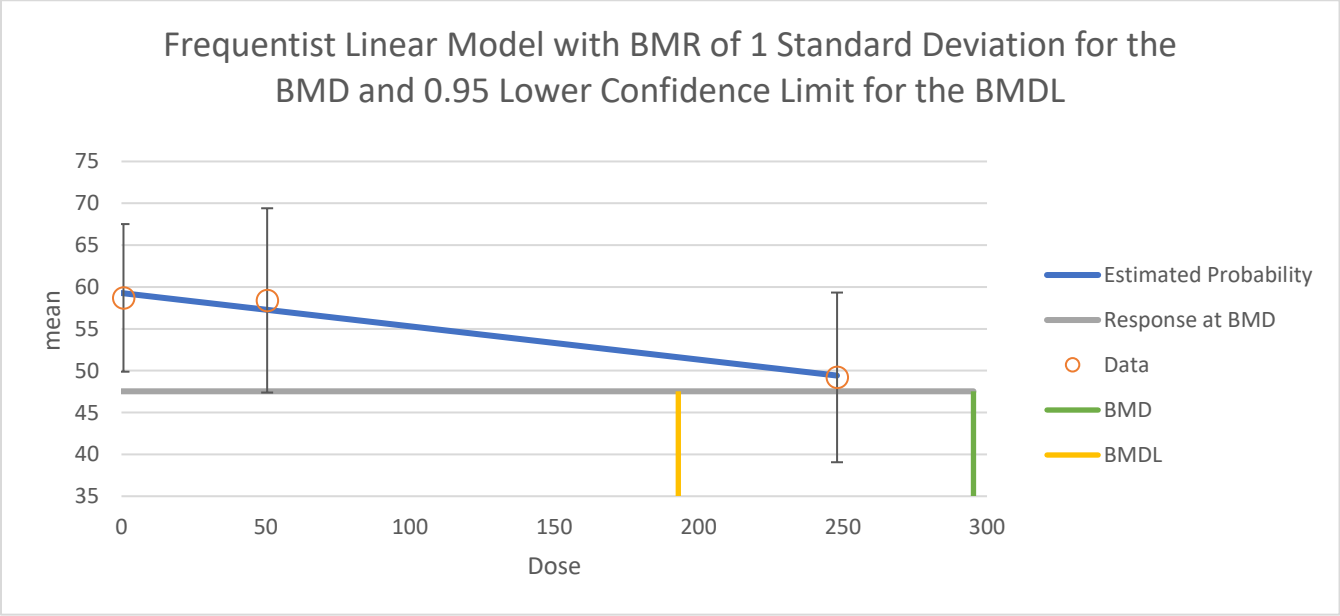

Figure 1-7. Plot of Response by Dose with Fitted Curve for the Selected Model (Linear, Constant Variance Model) for Decreased Maternal Body Weight Gain (Gravid Uterus Adjusted) for

GD 0-20 in Pregnant Sprague-Dawley Rats Following Inhalation Exposure to 1,3-Buadiene During Gestation (GD 6-15) and BMR of 1SD (Highest Concentration Dropped)

Summary:

BMD	295.301
BMDL	192.995
BMDU	628.047
AIC	634.906
Log Likelihood	314.453
P-Value	0.589491
Model DOF	1

Model Parameters:

Variable	Estimate	Bounded	Std Error	Lower CI	Upper CI
g	59.2789	no	1.67431	55.9973	62.5605
b1	-0.0397638	no	0.0124258	-0.0641179	-0.0154096
alpha	137.881	no	2987.34	-5717.19	5992.96

Goodness of Fit:

Dose	Size	Observed Mean	Calculated Mean	Estimated Mean	Scaled Residual
0.7	36	58.7	58.7	59.2511	-0.281588
50.5	22	58.4	58.4	57.2708	0.451037
248	23	49.2	49.2	49.4175	-0.088831

Dose	Size	Observed SD	Calculated SD	Estimated SD
0.7	36	12.3	12.3	11.7423
50.5	22	12	12	11.7423
248	23	11.3	11.3	11.7423

Likelihoods of Interest:

Model	Log Likelihood	# Params	AIC
A1	-314.307	4	636.615
A2	-314.188	6	640.376
A3	-314.307	4	636.615
fitted	-314.453	3	634.906
reduced	-319.275	2	642.55

Tests of Interest:

Name	Loglikelihood Ratio	Test DOF	P-Value
Test 1	10.1738	4	0.0375992
Test 2	0.238836	2	0.887437
Test 3	0.238836	2	0.887437
Test 4	0.291139	1	0.589491

Figure 1-8. Details Regarding the Selected Model (Linear, Constant Variance Model) for Decreased Maternal Body Weight Gain (Gravid Uterus Adjusted) for GD 0-20 in Pregnant Sprague-Dawley Rats Following Inhalation Exposure to 1,3-Buadiene During Gestation (GD 6-15) (Highest Concentration Dropped)

1.1.1.5 Maternal Body Weight (Gravid Uterus Adjusted) on GD 20 in Sprague-Dawley Rats Exposed via Inhalation on GD 6 to 15 (Hazleton Labs, 1981)

Maternal body weights (gravid uterus adjusted) were significantly decreased on GD 20 in pregnant Sprague-Dawley Rats exposed to 1,3-butadiene by inhalation on GD 6 to 15 (six hours per day) (Hazleton Labs, 1981). First, the exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day rather than six hours per day. Then, continuous models were fit to the dose-response data.

A BMR of one SD was chosen according to EPA *BMD Technical Guidance* (U.S. EPA, 2012). A BMR of 10 percent RD was also selected because EPA considers a 10 percent change in body weight to be biologically significant. The doses and response data used for the modeling are presented in Table 1-9.

Table 1-9. Decreased Maternal Body Weight (Gravid Uterus Adjusted) on GD 20 in Pregnant Sprague-Dawley Rats and Associated Doses Selected for Dose-Response Modeling for 1,3-Butadiene from a Gestational Exposure Study (GD 6-15)

Adjusted Concentration (ppm)	Number of Animals	Mean (g)	SD (g)
0.70	36	297.9	15.7
50.5	22	296.3	16.2
248	23	288.8	14
1912	23	283.9	13.6

The BMD modeling results for decreased maternal uterine- adjusted body weight in rats are summarized in Table 1-10. The constant variance model provided an adequate fit to the variance data. With the constant variance model applied, the Exponential 3, Polynomial 3-degree, Power, and Linear models provided adequate fit to the means (test 4 p-value > 0.1); the BMD computation failed for the Exponential 5 and Hill models. BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Exponential 3). With a BMR of one SD, the predicted BMD for the Exponential 3 model was higher than the maximum modeled concentration, and with a BMR of 10 percent RD, both the BMD and BMDL were higher than the maximum modeled concentration.

Table 1-10. Summary of BMD Modeling Results for Decreased Maternal Body Weight (Gravid Uterus Adjusted) on GD 20 in Pregnant Sprague-Dawley Rats Following Inhalation Exposure to 1,3-Butadiene During Gestation (GD 6-15) (Constant Variance Model)[a]

Model	Goodness of Fit (Means)		BMD 1SD (ppm)	BMDL 1SD (ppm)	BMD 10%RD (ppm)	BMDL 10%RD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC					
Exponential 3	**0.1494**	**864.2**	**2321**	**1528**	**4701**	**1995**	The constant variance model provided an adequate fit to the variance data. With the constant variance model applied, the
Exponential 5	-	-	-	-	-	-	
Hill	-	-	-	-	-	-	
Polynomial Degree 3	0.1450	864.3	2308	1540	4281	2410	

Model	Goodness of Fit (Means)		BMD 1SD (ppm)	BMDL 1SD (ppm)	BMD 10%RD (ppm)	BMDL 10%RD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC					
Polynomial Degree 2	0.0251	867.4	2190	1446	3145	2537	Exponential 3, Polynomial 3-degree, Power, and Linear models provided adequate fit to the means (test 4 p-value > 0.1). BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Exponential 3).
Power	0.1471	864.3	2319	1543	4573	1992	
Linear	0.1471	864.3	2319	1543	4573	3078	

[a] Selected model in bold.

Plots of the Exponential 3 model with BMRs of one SD and ten percent RD are shown in Figure 1-9 and Figure 1-10. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 1-11 (BMD and BMDL shown are for BMR of one SD; the rest is applicable to both BMRs).

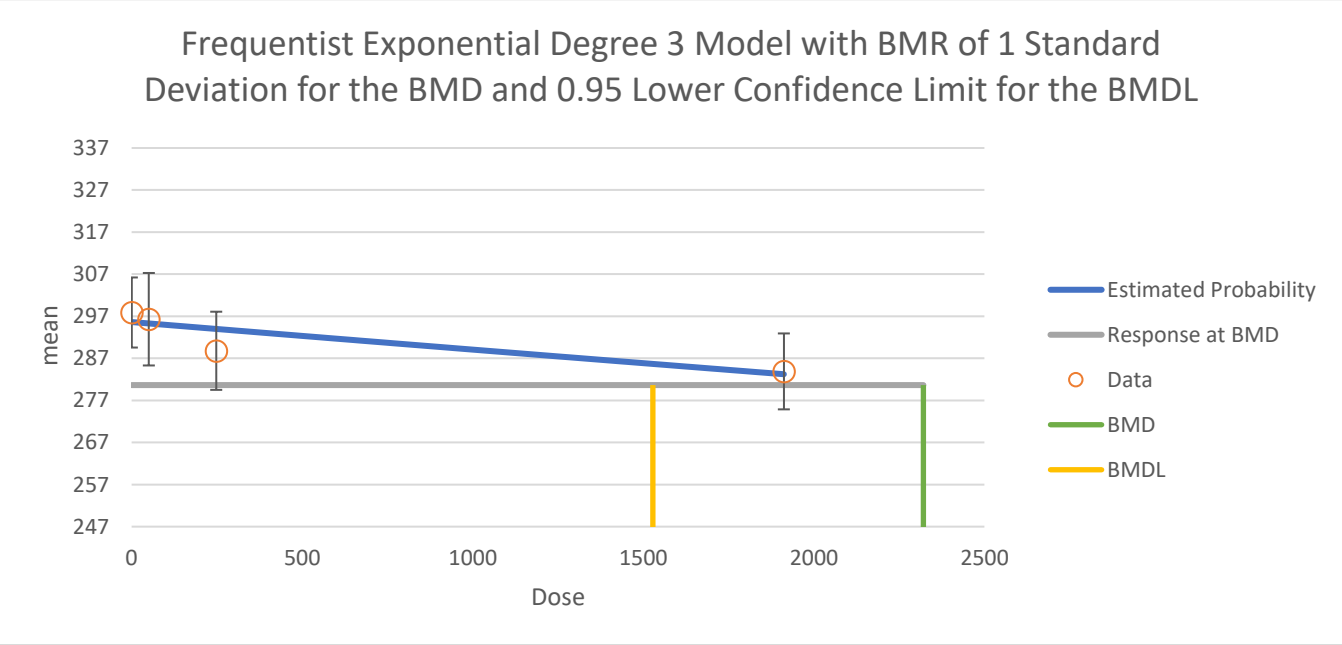

Figure 1-9. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 3, Constant Variance Model) for Decreased Maternal Body Weight on GD 20 in Pregnant Sprague-Dawley Rats Following Inhalation Exposure to 1,3-Butadiene During Gestation (GD 6-15) and BMR of 1SD

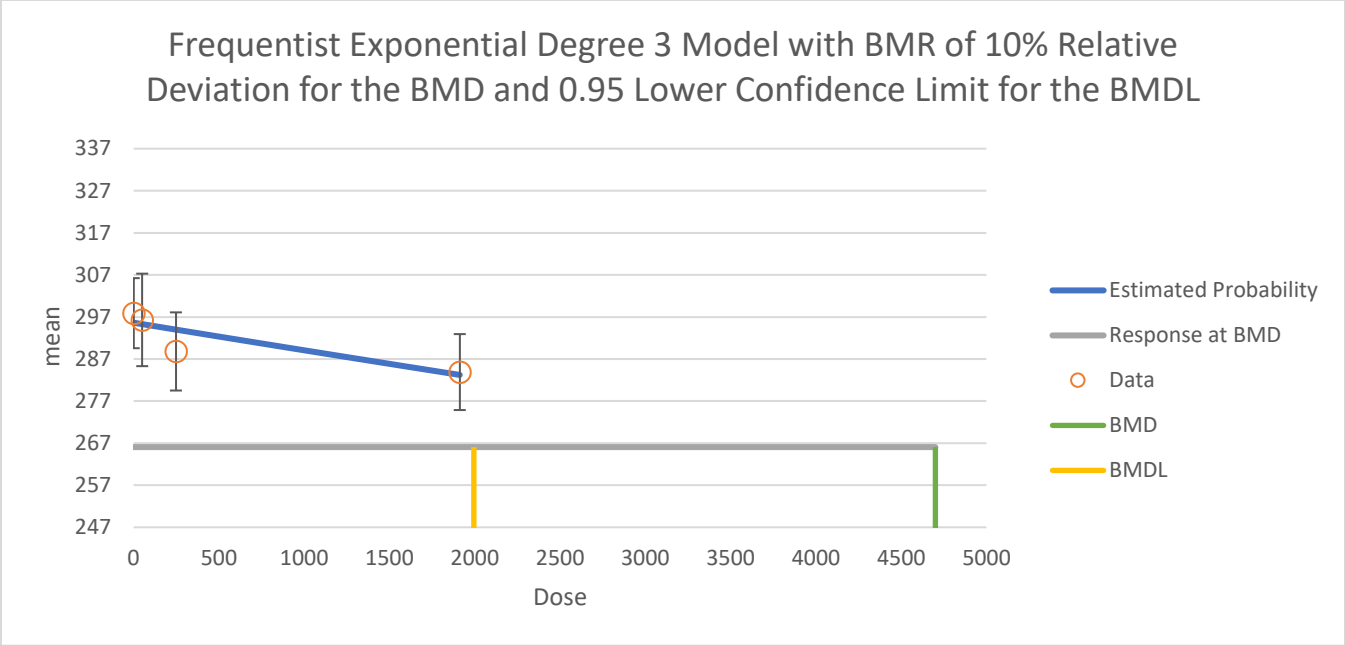

Figure 1-10. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 3, Constant Variance Model) for Decreased Maternal Body Weight on GD 20 in Pregnant Sprague-Dawley Rats Following Inhalation Exposure to 1,3-Butadiene During Gestation (GD 6-15) and BMR of 10%RD

Summary:

BMD	2321.14
BMDL	1528.14
BMDU	4674.34
AIC	864.228
Log Likelihood	429.114
P-Value	0.149362
Model DOF	2

Model Parameters:

Variable	Estimate	Bounded	Std Error	Lower CI	Upper CI
a	295.63	no	1.74774	292.205	299.056
b	2.2413e-05	no	6.73252e-06	9.21754e-06	3.56085e-05
d	1	yes	NA	NA	NA
log-alpha	5.41431	no	0.138675	5.14251	5.68611

Goodness of Fit:

Dose	Size	Observed Mean	Calculated Mean	Estimated Mean	Scaled Residual
0.7	36	297.9	297.9	295.625	0.910629
50.5	22	296.3	296.3	295.296	0.314327
248	23	288.8	288.8	293.991	-1.6613
1912	23	283.9	283.9	283.229	0.214769

Dose	Size	Observed SD	Calculated SD	Estimated SD
0.7	36	15.7	15.7	14.9866
50.5	22	16.2	16.2	14.9866
248	23	14	14	14.9866
1912	23	13.6	13.6	14.9866

Likelihoods of Interest:

Model	Log Likelihood	# Params	AIC
A1	-427.212	5	864.425
A2	-426.66	8	869.321
A3	-427.212	5	864.425
fitted	-429.114	3	864.228
reduced	-434.491	2	872.981

Tests of Interest:

Name	Loglikelihood Ratio	Test DOF	P-Value
Test 1	15.6603	6	0.0156979
Test 2	1.10409	3	0.776087
Test 3	1.10409	3	0.776087
Test 4	3.80276	2	0.149362

Figure 1-11. Details Regarding the Selected Model (Exponential 3, Constant Variance Model) for Decreased Maternal Body Weight on GD 20 in Pregnant Sprague-Dawley Rats Following Inhalation Exposure to 1,3-Butadiene During Gestation (GD 6-15)

1.1.2 Developmental Effects

1.1.2.1 Fetal Body Weight Effects

EPA identified fetal body weight endpoints in a gestational inhalation exposure study in CD-1 mice for BMD modeling (Battelle PNL, 1987). The study did not specify how the means for fetal body weight were derived; however, based on calculations using the individual male fetal weight, it appears that the values were derived using the means of litter averages for each test group. Data were modeled for mean fetal body weight in male mice/litter (treating the means as litter averages), mean fetal body weight for male fetuses (not averaged by litter), and mean fetal body weight for male and female fetuses combined (not averaged by litter). In addition, nested modeling was conducted on the fetal weight data for male fetuses using a dichotomized approach to determine the number of male fetuses with weights below the 5th and 10th percentiles of the control male fetal weights.

Modeled results for mean fetal body weight in male fetuses/litter and nested model results for the number of male fetuses with body weight below the 5th and 10th percentiles of control male fetal weight are presented here.

Modeled results are not presented for mean fetal body weight of male fetuses or mean fetal body weight of male and female fetuses (combined) because neither the constant nor nonconstant variance models provided adequate fit to the variance data, even with the highest concentration dropped from the data sets.

1.1.2.1.1 Fetal Body Weight in Male Fetuses/Litter from Female CD-1 Mice Exposed via Inhalation on GD 6 to 15 (Battelle PNL, 1987)

Mean fetal body weight per litter was significantly decreased in male fetuses from Pregnant CD-1 mice exposed to 1,3-butadiene by inhalation on GD 6 to 15 (six hours per day) (Battelle PNL, 1987). The data appear to be the means of litter averages and were modeled as such. First, the exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day rather than six hours per day. Then, continuous models were fit to the dose-response data.

A BMR of one SD was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). BMRs of five percent and 10 percent RD were also selected because EPA considers these BMRs to be biologically relevant for fetal body weight change in a developmental study. The concentrations and response data used for the modeling are presented in Table 1-11.

Table 1-11. Decreased Mean Fetal Body Weight in Male Fetuses/Litter and Associated Concentrations Selected for Dose-Response Modeling for 1,3-Butadiene from a Gestational Inhalation Exposure Study (GD 6-15)

Adjusted Concentration (ppm)	Number of Litters	Mean (g)	SD (g)
0	18	1.38	0.13
10	19	1.31	0.09
49.95	21	1.13	0.09
250	20	1.06	0.09

The BMD modeling results for decreased mean fetal body weight in male fetuses/litter are summarized in Table 1-12. Both the constant and nonconstant variance models provide adequate fit to the variance data; however, with either variance model applied, none of the models provided adequate fit to the means (test 4 p-value < 0.1). The full data set is not suitable for BMD modeling. With the highest concentration dropped from the data set, the constant variance model provided an adequate fit to the variance data. With the constant variance model applied, the Exponential 3, Polynomial 2-degree, Power, and Linear models provided adequate fit to the means (test 4 p-value > 0.1). The goodness-of-fit test for the means (test 4) could not be calculated for the Exponential 5 and Hill models because the models were saturated (degree of freedom = 0). BMDLs of the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Exponential 3).

Table 1-12. Summary of BMD Modeling Results for Decreased Mean Fetal Body Weight in Male Fetuses/Litter Following Exposure to 1,3-Butadiene During Gestation (GD 6-15)[a]

Model	Goodness of Fit (Means)		BMD 1SD (ppm)	BMDL 1SD (ppm)	BMD 5%RD (ppm)	BMDL 5%RD (ppm)	BMD 10%RD (ppm)	BMDL 10%RD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC							
Full Data set (Constant Variance Model)									For the full data set, both the constant and nonconstant variance models provide adequate fit to the variance data; however, with either variance model applied, none of the models provided adequate fit to the means (test 4 p-value < 0.1). The full data set is not suitable for BMD modeling. With the highest concentration dropped from the data set, the constant variance model provided an adequate fit to the variance data. With the constant variance model applied, the Exponential 3, Polynomial 2-degree, Power, and Linear models provided adequate fit to the means (test 4 p-value > 0.1). BMDLs of the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Exponential 3).
Exponential 3	<0.0001	−101.6	106	82.7	55.5	45.2	114	92.8	
Exponential 5	NA	−131.0	14.2	8.28	9.86	5.68	20.8	13.1	
Hill	NA	−131.0	13.4	7.39	9.88	6.44	19.0	12.3	
Polynomial Degree 3	<0.0001	−100.1	118	94.0	62.4	51.8	125	104	
Polynomial Degree 2	<0.0001	−100.1	118	94.0	62.3	51.8	125	104	
Power	<0.0001	−100.1	118	94.0	62.4	51.8	125	104	
Linear	<0.0001	−100.1	118	94.0	62.4	51.8	125	104	
Highest Concentration Dropped (Constant Variance Model)									
Exponential 3	**0.5980**	**−94.73**	**19.6**	**15.3**	**13.1**	**10.7**	**26.8**	**22.1**	
Exponential 5	NA	−93.01	15.1	7.59	9.84	4.92	21.9	10.0	
Hill	NA	−91.01	14.0	7.41	9.88	4.65	19.4	10.9	
Polynomial Degree 2	0.5125	−94.58	21.0	16.7	14.1	11.9	28.3	23.7	
Power	0.5125	−94.58	21.0	16.7	14.1	11.9	28.2	23.7	
Linear	0.5125	−94.58	21.0	16.7	14.1	11.9	28.2	23.7	

[a] Selected model in bold.

Plots of the Exponential 3 model fit to the data set (with highest concentration dropped from the data set) using BMRs of one SD, five percent RD, and 10 percent RD are shown in Figure 1-12, Figure 1-13, and Figure 1-14, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown below in Figure 1-15. (BMD and BMDL shown are for BMR of one SD; the rest is applicable to all BMRs).

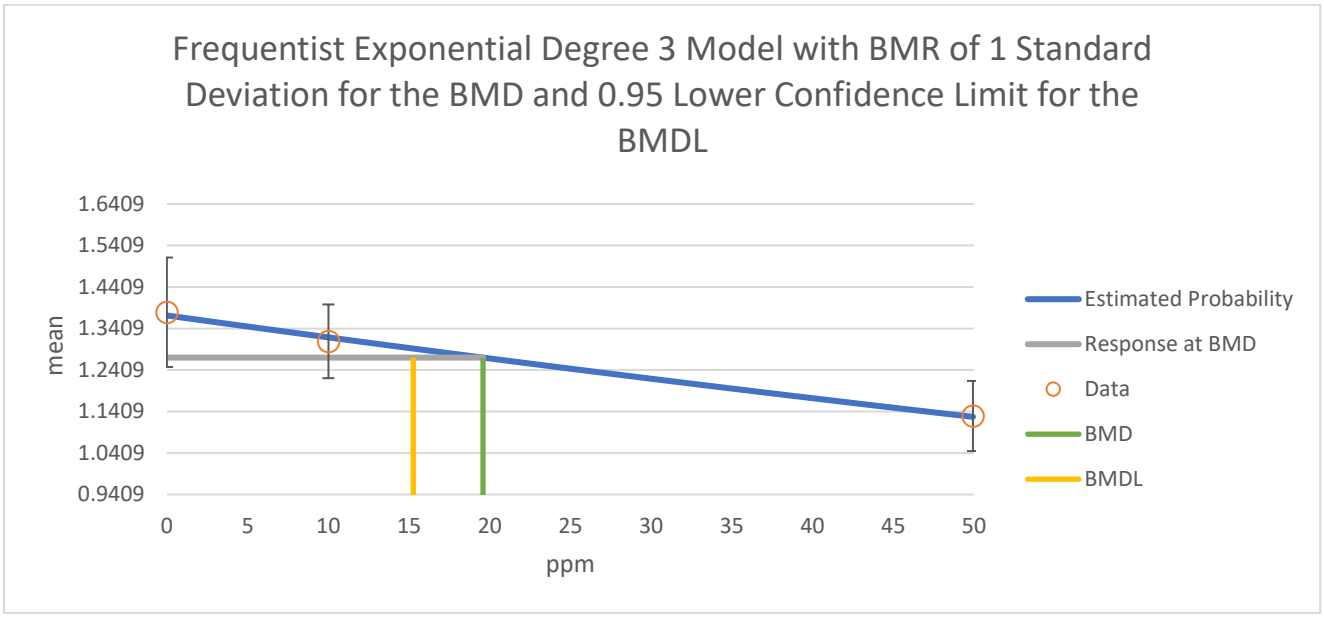

Figure 1-12. Plot of Response by Concentration with Fitted Curve for the Selected Model (Exponential 3, Constant Variance Model) for Decreased Mean Fetal Body Weight in Male Fetuses/Litter Following Exposure to 1,3-Butadiene During Gestation (GD 6-15) and BMR of 1SD (Highest Concentration Dropped)

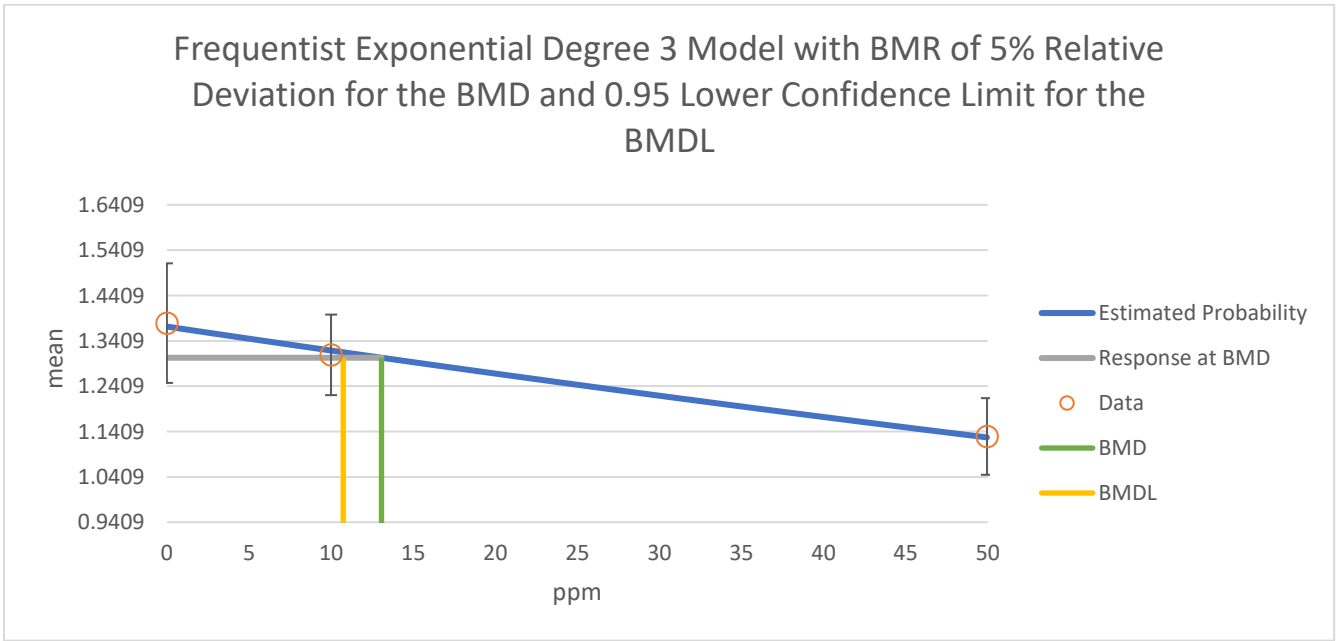

Figure 1-13. Plot of Response by Concentration with Fitted Curve for the Selected Model (Exponential 3, Constant Variance Model) for Decreased Mean Fetal Body Weight in Male Fetuses/Litter Following Exposure to 1,3-Butadiene During Gestation (GD 6-15) and BMR of 5%RD (Highest Concentration Dropped)

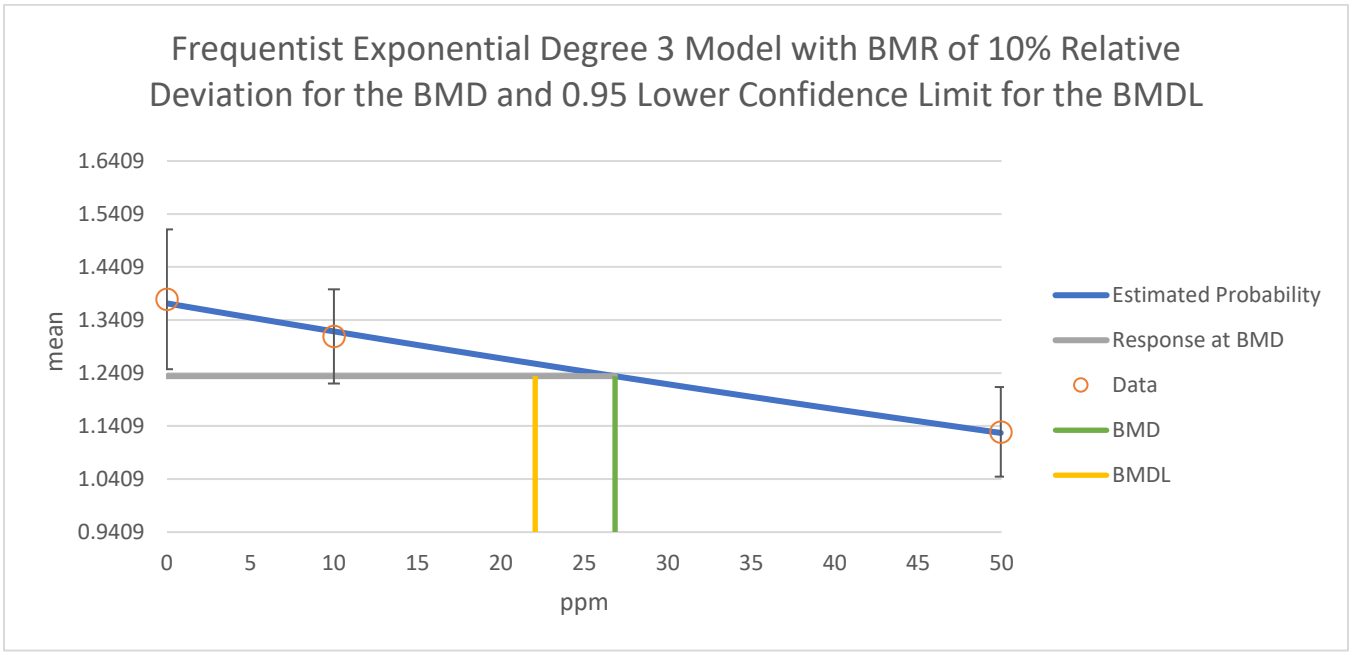

Figure 1-14. Plot of Response by Concentration with Fitted Curve for the Selected Model (Exponential 3, Constant Variance Model) for Decreased Mean Fetal Body Weight in Male Fetuses/Litter Following Exposure to 1,3-Butadiene During Gestation (GD 6-15) and BMR of 10%RD (Highest Concentration Dropped)

Summary:

BMD	19.5849
BMDL	15.2621
BMDU	33.0268
AIC	-94.7342
Log Likelihood	-50.3671
P-Value	0.59796
Model DOF	1

Model Parameters:

Variable	Estimate	Bounded	Std Error	Lower CI	Upper CI
a	1.3723	no	0.0189609	1.33514	1.40946
b	0.00392496	no	0.000505941	0.00293334	0.00491659
d	1	yes	NA	NA	NA
log-alpha	-4.57467	no	0.185695	-4.93863	-4.21072

Goodness of Fit:

Dose	Size	Observed Mean	Calculated Mean	Estimated Mean	Scaled Residual
0	18	1.38	1.38	1.3723	0.32165
10	19	1.31	1.31	1.31948	-0.407106
49.95	21	1.13	1.13	1.12799	0.0906856

Dose	Size	Observed SD	Calculated SD	Estimated SD
0	18	0.13	0.13	0.101536
10	19	0.09	0.09	0.101536
49.95	21	0.09	0.09	0.101536

Likelihoods of Interest:

Model	Log Likelihood	# Params	AIC
A1	50.5062	4	-93.0123
A2	52.2837	6	-92.5675
A3	50.5062	4	-93.0123
fitted	50.3671	3	-94.7342
reduced	28.8857	2	-53.7715

Tests of Interest:

Name	Loglikelihood Ratio	Test DOF	P-Value
Test 1	46.796	4	1.68165e-09
Test 2	3.55513	2	0.169049
Test 3	3.55513	2	0.169049
Test 4	0.278084	1	0.59796

Figure 1-15. Details Regarding the Selected Model (Exponential 3, Constant Variance Model) for Decreased Mean Fetal Body Weight in Male Fetuses/Litter Following Exposure to 1,3-Butadiene During Gestation (GD 6-15) (Highest Concentration Dropped)

1.1.2.1.2 Nested Modeling of Male Fetuses with Fetal Weight Below the 5th and 10th Percentiles of Control Male Fetal Weights Following Gestational Inhalation Exposure to Female CD-1 Mice on GD 6 to 15 (Battelle PNL, 1987)

Mean fetal body weight per litter was significantly decreased in male fetuses from Pregnant CD-1 mice exposed to 1,3-butadiene by inhalation on GD 6 to 15 (six hours per day) (Battelle PNL, 1987). Nested modeling was conducted to consider the within-dam grouping of fetal weight observations as well as litter size. To apply this model, the individual male fetal weights were converted to dichotomous data using as cutoff values the 5th and 10th percentiles of the control male fetal weight distribution (1.1405 g and 1.1925 g, respectively). All individual male fetal weights were binned by litter to determine the number of male fetuses in each litter with body weights below each percentile cutoff. Total litter size (number of live male and female fetuses) was used as the litter specific covariate using the default "Overall Mean" option (averaged across all dose groups). The exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day rather than six hours per day. Then, the Nested Logistic model forms were fit to the dichotomized data for each of the cutoff percentiles.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). A BMR of five percent ER was also selected because EPA considers that BMR to be biologically relevant for changes of fetal body weights in a developmental study. The concentrations and response data used for the nested modeling are presented in Table 1-13.

Table 1-13. Incidence of Male Fetuses with Body Weights Below the 5th or 10th Percentiles of Control Male Fetal Body Weights Following Gestational Exposure (GD 6-15) and Associated Concentrations Selected for Nested Dose-Response Modeling for 1,3-Butadiene

Duration Adjusted Concentration (ppm)	Number of Live Male Fetuses [a]	Number of Male Fetuses with Body Weight Below 5th Percentile of Control	Number of Male Fetuses with Body Weight Below 10th Percentile of Control	Litter Specific Covariate (litter size)[b]
0	6	0	0	9
0	6	0	0	10
0	2	0	0	3
0	5	1	1	13
0	7	3	5	12
0	5	0	0	13
0	8	0	0	15
0	7	0	0	13
0	4	1	3	13
0	6	0	0	13
0	11	0	0	12
0	6	0	0	13
0	3	0	0	9
0	8	0	1	13

Duration Adjusted Concentration (ppm)	Number of Live Male Fetuses [a]	Number of Male Fetuses with Body Weight Below 5th Percentile of Control	Number of Male Fetuses with Body Weight Below 10th Percentile of Control	Litter Specific Covariate (litter size)[b]
0	6	0	0	9
0	3	0	0	13
0	7	0	0	14
0	6	1	1	14
10.0	6	0	0	11
10.0	3	0	1	11
10.0	3	0	0	13
10.0	8	0	0	14
10.0	8	0	0	13
10.0	11	5	9	15
10.0	6	0	0	13
10.0	6	0	0	12
10.0	8	0	1	16
10.0	6	0	1	11
10.0	6	0	0	12
10.0	3	1	1	6
10.0	7	0	0	13
10.0	7	0	0	11
10.0	4	1	1	10
10.0	8	0	0	15
10.0	7	0	0	14
10.0	3	1	2	14
10.0	7	0	1	13
49.95	7	3	6	13
49.95	8	1	7	12
49.95	7	1	3	12
49.95	4	4	4	13
49.95	6	6	6	14
49.95	9	4	9	15
49.95	5	3	5	11
49.95	7	2	7	14
49.95	6	6	6	11

Duration Adjusted Concentration (ppm)	Number of Live Male Fetuses [a]	Number of Male Fetuses with Body Weight Below 5th Percentile of Control	Number of Male Fetuses with Body Weight Below 10th Percentile of Control	Litter Specific Covariate (litter size)[b]
49.95	6	1	3	12
49.95	7	5	6	11
49.95	8	6	8	11
49.95	5	5	5	13
49.95	6	1	3	14
49.95	8	1	5	12
49.95	7	0	2	12
49.95	7	7	7	15
49.95	8	2	3	16
49.95	7	6	6	15
49.95	9	1	3	11
250	4	4	4	9
250	5	5	5	14
250	5	5	5	11
250	7	7	7	12
250	6	5	6	14
250	9	9	9	14
250	7	6	7	15
250	7	5	5	12
250	9	7	9	16
250	8[c]	8	8	14
250	9	8	9	14
250	7	7	7	11
250	4	3	3	10
250	7	5	6	9
250	5	4	4	12
250	3	1	3	8
250	6	0	0	10
250	9	3	6	13
250	2	2	2	11
250	6	6	6	15

Duration Adjusted Concentration (ppm)	Number of Live Male Fetuses [a]	Number of Male Fetuses with Body Weight Below 5th Percentile of Control	Number of Male Fetuses with Body Weight Below 10th Percentile of Control	Litter Specific Covariate (litter size)[b]

[a] In the 49.95 ppm group, Dam # 382 had only two female fetuses and no male fetuses; this litter was excluded from the analysis.
[b] Total litter size (# of live male and female fetuses) was used as litter-specific covariate.
[c] Dam # 317 had 10 male fetuses; however, two male fetuses did not have weight measurements; used N = 8.

The nested BMD modeling results for increased number of fetuses with body weights below the 5th and 10th percentiles of control male fetal body weights are summarized in Table 1-14. For both data sets, the model forms applying the intralitter correlation (ilc+) provided adequate fit to the data (chi-square p-value > 0.1) both with and without the litter-specific covariate (lsc) applied. Model forms without the intralitter correlation (ilc-) did not provide adequate fits. Between the Nested Logistic (lsc+ilc+) and Nested Logistic (lsc-ilc+), the Nested Logistic (lsc-ilc+) had the lower AIC; therefore, this model form is selected for both data sets.

Table 1-14. BMD Modeling Results for Incidence of Male Fetuses with Body Weights Below the 5th or 10th Percentiles of Control Male Fetal Body Weights Following Gestational Exposure (GD 6-15)[a]

Model	Goodness of Fit		BMD 5%ER (ppm)	BMDL 5%ER (ppm)	BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Basis for Model Selection
	p-value	AIC					
Below 5th Percentile							The model forms applying the intralitter correlation (ilc +) provided adequate fit to the data (chi-square p_value > 0.1) both with and without the litter-specific covariate (lsc) applied. Model forms without the intralitter correlation (ilc-) did not provide adequate fits. Between the Nested Logistic (lsc+ilc+) and Nested Logistic (lsc-ilc+), the Nested Logistic (lsc-ilc+) had the lower AIC; therefore, this model form is selected.
Nested Logistic (lsc+ilc+)	0.5943	376.8	6.88	2.64	12.6	5.57	
Nested Logistic (lsc+ilc-)	<0.0001	428.3	8.37	5.11	14.8	9.99	
Nested Logistic (lsc-ilc+)	**0.5047**	**374.3**	**5.49**	**2.52**	**10.4**	**5.32**	
Nested Logistic (lsc-ilc-)	<0.0001	431.7	6.75	4.03	12.3	8.21	
Below 10th Percentile							
Nested Logistic (lsc+ilc+)	0.3817	353.2	4.62	1.29	7.89	2.72	
Nested Logistic (lsc+ilc-)	<0.0001	423.9	5.13	3.11	8.54	5.69	
Nested Logistic (lsc-ilc+)	**0.2073**	**351.8**	**3.41**	**1.20**	**6.09**	**2.53**	
Nested Logistic (lsc-ilc-)	<0.0001	430.3	3.90	2.32	6.77	4.45	

[a] Selected model in bold.

Plots of the Nested Logistic (lsc-ilc+) model for male fetuses with weights below the 5th percentile of control male fetal weight with BMRs of five percent ER and 10 percent ER are shown in Figure 1-16

and Figure 1-17, respectively. Plots of the Nested Logistic (lsc-ilc+) model for male fetuses with weights below the 10th percentile of control male fetal weight with BMRs of five percent ER and 10 percent ER are shown in Figure 1-18 and Figure 1-19, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown below in Figure 1-20 and Figure 1-21 for fetuses with weight below the 5th percentile and 10th percentile, respectively (BMD and BMDL shown are for BMR of five percent ER; the rest is applicable to both BMRs).

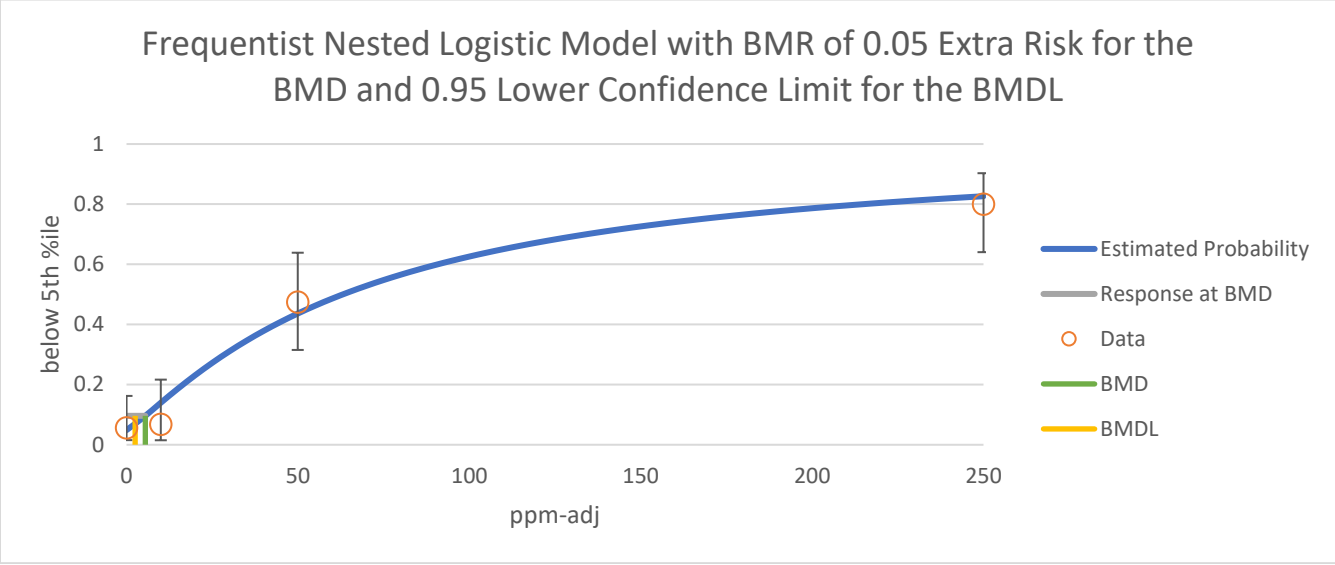

Figure 1-16. Plot of Response by Concentration with Fitted Curve for the Selected Model (Nested Logistic (lsc-ilc+)) for Fetuses with Body Weights Below the 5th Percentile of Control Male Fetal Body Weights Following Gestational Exposure (GD 6-15) and BMR of 5% ER

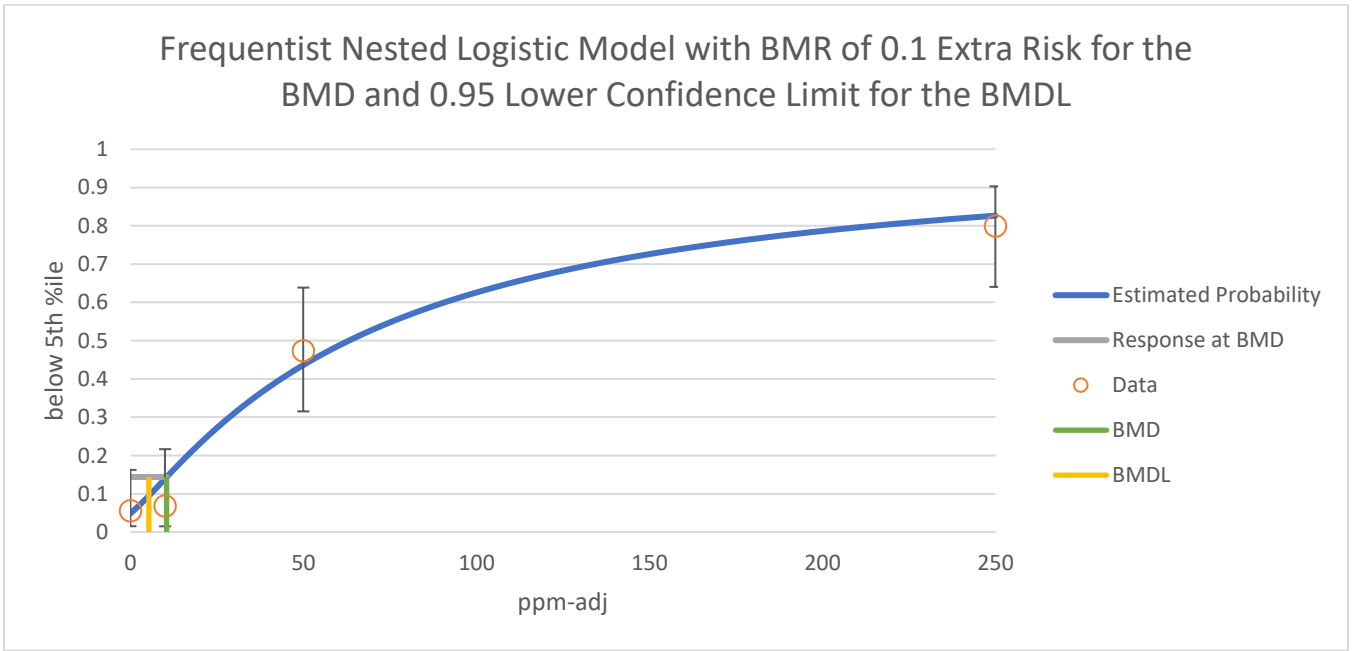

Figure 1-17. Plot of Response by Concentration with Fitted Curve for the Selected Model (Nested Logistic (lsc-ilc+)) for Fetuses with Body Weights Below the 5th Percentile of Control Male Fetal Body Weights Following Gestational Exposure (GD 6-15) and BMR of 10% ER

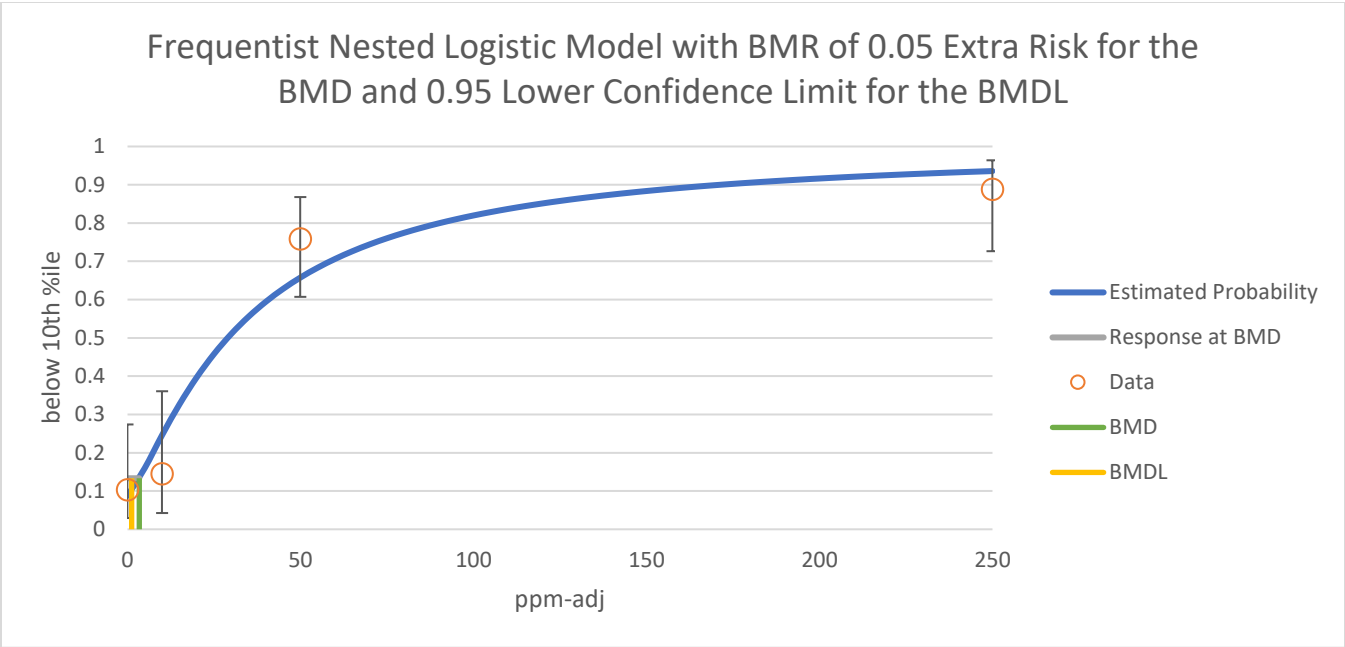

Figure 1-18. Plot of Response by Concentration with Fitted Curve for the Selected Model (Nested Logistic (lsc-ilc+)) for Fetuses with Body Weights Below the 10th Percentile of Control Male Fetal Body Weights Following Gestational Exposure (GD 6-15) and BMR of 5% ER

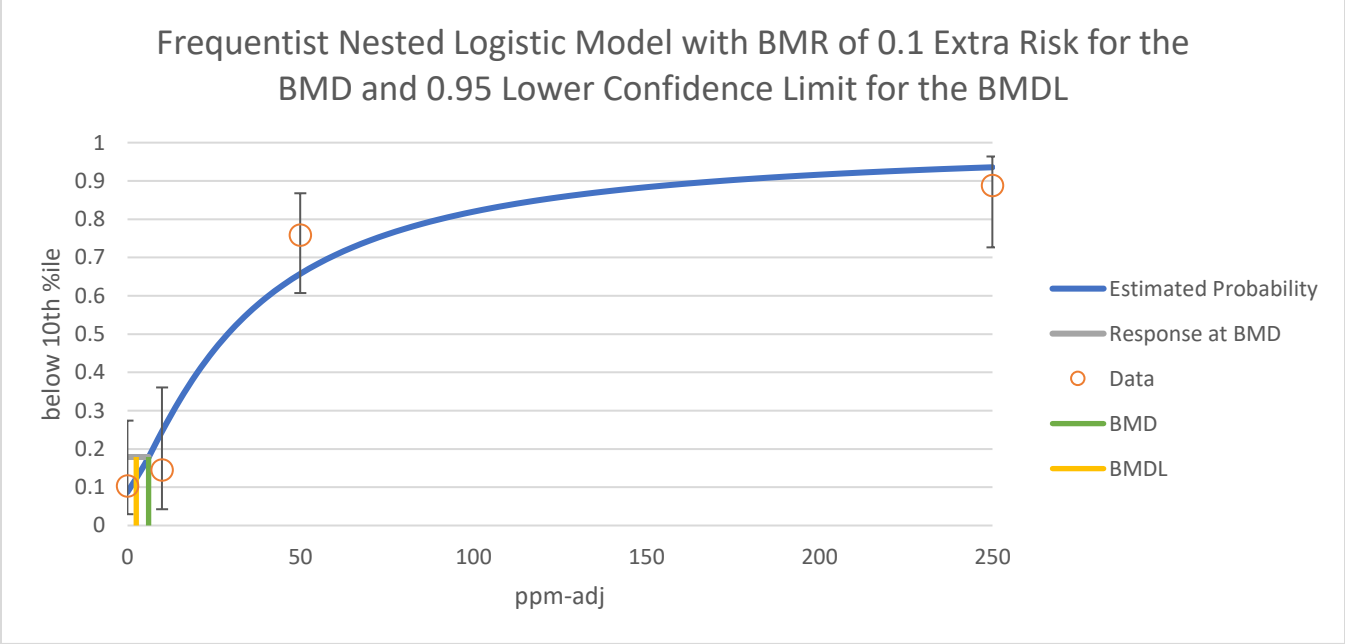

Figure 1-19. Plot of Response by Concentration with Fitted Curve for the Selected Model (Nested Logistic (lsc-ilc+)) for Fetuses with Body Weights Below the 10th Percentile of Control Male Fetal Body Weights Following Gestational Exposure (GD 6-15) and BMR of 10% ER

Model Results

Benchmark Dose	
BMD	5.491115997
BMDL	2.51906695
BMDU	-
AIC	374.266808
P-value	0.504666667
D.O.F.	70
Chi^2	74.81920925

Model Parameters	
# of Parameters	9
Variable	Estimate
alpha	0.048692423
beta	-4.9268329
theta1	0
theta2	0
rho	1.163969961
phi1	0.134619409
phi2	0.455588015
phi3	0.394841059

Bootstrap Results	
# Iterations	1000
Bootstrap Seed	1721756778
Log-likelihood	-180.133404
Observed Chi-square	74.81920925
Combined P-value	0.504666667

Bootstrap Runs

Run	Bootstrap Chi-square Percentiles				
	P-Value	50th	90th	95th	99th
1	0.503	74.91545422	104.927532	116.5308	134.89495
2	0.512	75.43176498	103.844308	113.0436	135.73198
3	0.499	74.80132605	103.764785	113.1185	131.27892
Combined	0.504666667	75.06880652	104.227062	114.7986	135.05061

Scaled Residuals

Minimum scaled residual for dose group nearest the BMD	-0.54512
Minimum ABS(scaled residual) for dose group nearest the BMD	0.545124
Average Scaled residual for dose group nearest the BMD	-0.54512
Average ABS(scaled residual) for dose group nearest the BMD	0.545124
Maximum scaled residual for dose group nearest the BMD	-0.54512
Maximum ABS(scaled residual) for dose group nearest the BMD	0.545124

0	10	0.048692423	6	0.292155	0	-0.428435325
0	12	0.048692423	11	0.535617	0	-0.489874223
0	12	0.048692423	7	0.340847	3	3.473265545
0	13	0.048692423	7	0.340847	0	-0.445198895
0	13	0.048692423	6	0.292155	0	-0.428435325
0	13	0.048692423	8	0.389539	0	-0.459148365

0	13	0.048692423	5	0.243462	0	-0.407858597
0	13	0.048692423	4	0.19477	1	1.578837101
0	13	0.048692423	6	0.292155	0	-0.428435325
0	13	0.048692423	3	0.146077	0	-0.347823697
0	13	0.048692423	5	0.243462	1	1.267386034
0	14	0.048692423	6	0.292155	1	1.038032839
0	14	0.048692423	7	0.340847	0	-0.445198895
0	15	0.048692423	8	0.389539	0	-0.459148365
10	6	0.139670818	3	0.419012	1	0.69995591
10	10	0.139670818	4	0.558683	1	0.413768806
10	11	0.139670818	6	0.838025	0	-0.545124413
10	11	0.139670818	3	0.419012	0	-0.504813306
10	11	0.139670818	6	0.838025	0	-0.545124413
10	11	0.139670818	7	0.977696	0	-0.551708684
10	12	0.139670818	6	0.838025	0	-0.545124413
10	12	0.139670818	6	0.838025	0	-0.545124413
10	13	0.139670818	8	1.117367	0	-0.556806513
10	13	0.139670818	6	0.838025	0	-0.545124413
10	13	0.139670818	3	0.419012	0	-0.504813306
10	13	0.139670818	7	0.977696	0	-0.551708684
10	13	0.139670818	7	0.977696	0	-0.551708684
10	14	0.139670818	8	1.117367	0	-0.556806513
10	14	0.139670818	3	0.419012	1	0.69995591
10	14	0.139670818	7	0.977696	0	-0.551708684
10	15	0.139670818	11	1.536379	5	1.278122328
10	15	0.139670818	8	1.117367	0	-0.556806513
10	16	0.139670818	8	1.117367	0	-0.556806513
49.95	11	0.43630197	9	3.926718	1	-0.964633757
49.95	11	0.43630197	8	3.490416	6	0.922192587
49.95	11	0.43630197	7	3.054114	5	0.807975294
49.95	11	0.43630197	6	2.617812	6	1.614432253
49.95	11	0.43630197	5	2.18151	3	0.459573811
49.95	12	0.43630197	7	3.054114	0	-1.268136071
49.95	12	0.43630197	8	3.490416	1	-0.915148781
49.95	12	0.43630197	6	2.617812	1	-0.772236034
49.95	12	0.43630197	7	3.054114	1	-0.852913798
49.95	12	0.43630197	8	3.490416	1	-0.915148781
49.95	13	0.43630197	5	2.18151	5	1.582553266
49.95	13	0.43630197	4	1.745208	4	1.538088548
49.95	13	0.43630197	7	3.054114	3	-0.022469252
49.95	14	0.43630197	6	2.617812	1	-0.772236034
49.95	14	0.43630197	7	3.054114	2	-0.437691525
49.95	14	0.43630197	6	2.617812	6	1.614432253
49.95	15	0.43630197	7	3.054114	6	1.223197567
49.95	15	0.43630197	7	3.054114	7	1.63841984
49.95	15	0.43630197	9	3.926718	4	0.024153524
49.95	16	0.43630197	8	3.490416	2	-0.547680507
250	8	0.826454627	3	2.479364	1	-1.808840496
250	9	0.826454627	4	3.305819	4	0.677158668
250	9	0.826454627	7	5.785182	5	-0.480147187
250	10	0.826454627	6	4.958728	0	-3.460319583
250	10	0.826454627	4	3.305819	3	-0.298319183
250	11	0.826454627	5	4.132273	5	0.705569357

250	11	0.826454627	2	1.652909	2	0.57341942
250	11	0.826454627	7	5.785182	7	0.742873583
250	12	0.826454627	7	5.785182	7	0.742873583
250	12	0.826454627	5	4.132273	4	-0.107554435
250	12	0.826454627	7	5.785182	5	-0.480147187
250	13	0.826454627	9	7.438092	3	-2.177512745
250	14	0.826454627	6	4.958728	5	0.028800759
250	14	0.826454627	5	4.132273	5	0.705569357
250	14	0.826454627	9	7.438092	9	0.766337339
250	14	0.826454627	9	7.438092	8	0.275695659
250	14	0.826454627	8	6.611637	8	0.75580179
250	15	0.826454627	6	4.958728	6	0.726624828
250	15	0.826454627	7	5.785182	6	0.131363198
250	16	0.826454627	9	7.438092	7	-0.214946022

Figure 1-20. Details Regarding the Selected Model (Nested Logistic (lsc-ilc+)) for Fetuses with Body Weights Below the 5th Percentile of Control Male Fetal Body Weights Following Gestational Exposure (GD 6-15)

Model Results

Benchmark Dose	
BMD	3.407232314
BMDL	1.196923217
BMDU	-
AIC	351.7876667
P-value	0.207333333
D.O.F.	70
Chi^2	93.50122328

Model Parameters	
# of Parameters	9
Variable	Estimate
alpha	0.087708923
beta	-4.521029256
theta1	0
theta2	0
rho	1.286067266
phi1	0.352036656
phi2	0.431041678
phi3	0.374843742

Bootstrap Results	
# Iterations	1000
Bootstrap Seed	1721759031
Log-likelihood	-168.8938333
Observed Chi-square	93.50122328
Combined P-value	0.207333333

Bootstrap Runs

Run	Bootstrap Chi-square Percentiles				
	P-Value	50th	90th	95th	99th
1	0.204	74.36774681	105.889189	118.3439	138.93205
2	0.198	74.20269028	103.016837	112.5913	132.5875
3	0.22	75.53207001	105.993802	116.4232	131.30467
Combined	0.207333333	74.93252382	105.260607	116.5713	136.94923

Scaled Residuals

Minimum scaled residual for dose group nearest the BMD	-0.48369
Minimum ABS(scaled residual) for dose group nearest the BMD	0.483687
Average Scaled residual for dose group nearest the BMD	1.419156
Average ABS(scaled residual) for dose group nearest the BMD	1.902843
Maximum scaled residual for dose group nearest the BMD	3.322
Maximum ABS(scaled residual) for dose group nearest the BMD	3.322

0	10	0.087708923	6	0.526254	0	-0.457153281
0	12	0.087708923	11	0.964798	0	-0.483687309
0	12	0.087708923	7	0.613962	5	3.321999634
0	13	0.087708923	7	0.613962	0	-0.465017243
0	13	0.087708923	6	0.526254	0	-0.457153281
0	13	0.087708923	8	0.701671	1	0.200334749
0	13	0.087708923	5	0.438545	0	-0.446785136
0	13	0.087708923	4	0.350836	3	3.265631122
0	13	0.087708923	6	0.526254	0	-0.457153281
0	13	0.087708923	3	0.263127	0	-0.41140699
0	13	0.087708923	5	0.438545	1	0.572005469
0	14	0.087708923	6	0.526254	1	0.411540696
0	14	0.087708923	7	0.613962	0	-0.465017243
0	15	0.087708923	8	0.701671	0	-0.471189001
10	6	0.246157947	3	0.738474	1	0.256866718
10	10	0.246157947	4	0.984632	1	0.011779649
10	11	0.246157947	6	1.476948	1	-0.254468473
10	11	0.246157947	3	0.738474	1	0.256866718
10	11	0.246157947	6	1.476948	0	-0.788003872
10	11	0.246157947	7	1.723106	0	-0.798353964
10	12	0.246157947	6	1.476948	0	-0.788003872
10	12	0.246157947	6	1.476948	0	-0.788003872
10	13	0.246157947	8	1.969264	0	-0.80638986
10	13	0.246157947	6	1.476948	0	-0.788003872
10	13	0.246157947	3	0.738474	0	-0.725316937
10	13	0.246157947	7	1.723106	0	-0.798353964
10	13	0.246157947	7	1.723106	1	-0.335031258
10	14	0.246157947	8	1.969264	0	-0.80638986
10	14	0.246157947	3	0.738474	2	1.239050373
10	14	0.246157947	7	1.723106	0	-0.798353964
10	15	0.246157947	11	2.707737	9	1.911168948
10	15	0.246157947	8	1.969264	0	-0.80638986
10	16	0.246157947	8	1.969264	1	-0.396901831
49.95	11	0.657459496	9	5.917135	3	-1.024667006
49.95	11	0.657459496	8	5.259676	8	1.0724523
49.95	11	0.657459496	7	4.602216	6	0.617620071
49.95	11	0.657459496	6	3.944757	6	1.042886833

49.95	11	0.657459496	5	3.287297	5	1.020917761
49.95	12	0.657459496	7	4.602216	2	-1.149806885
49.95	12	0.657459496	8	5.259676	5	-0.101626701
49.95	12	0.657459496	6	3.944757	3	-0.479395672
49.95	12	0.657459496	7	4.602216	3	-0.707950146
49.95	12	0.657459496	8	5.259676	7	0.681092633
49.95	13	0.657459496	5	3.287297	5	1.020917761
49.95	13	0.657459496	4	2.629838	4	0.990421139
49.95	13	0.657459496	7	4.602216	6	0.617620071
49.95	14	0.657459496	6	3.944757	3	-0.479395672
49.95	14	0.657459496	7	4.602216	7	1.05947681
49.95	14	0.657459496	6	3.944757	6	1.042886833
49.95	15	0.657459496	7	4.602216	6	0.617620071
49.95	15	0.657459496	7	4.602216	7	1.05947681
49.95	15	0.657459496	9	5.917135	9	1.082880658
49.95	16	0.657459496	8	5.259676	3	-0.884346034
250	8	0.935737668	3	2.807213	3	0.348329821
250	9	0.935737668	4	3.742951	4	0.366327382
250	9	0.935737668	7	6.550164	6	-0.482085018
250	10	0.935737668	6	5.614426	0	-5.641566229
250	10	0.935737668	4	3.742951	3	-1.058797456
250	11	0.935737668	5	4.678688	5	0.378564167
250	11	0.935737668	2	1.871475	2	0.319086737
250	11	0.935737668	7	6.550164	7	0.394172429
250	12	0.935737668	7	6.550164	7	0.394172429
250	12	0.935737668	5	4.678688	4	-0.799619553
250	12	0.935737668	7	6.550164	5	-1.358342466
250	13	0.935737668	9	8.421639	6	-1.690419708
250	14	0.935737668	6	5.614426	6	0.387437863
250	14	0.935737668	5	4.678688	5	0.378564167
250	14	0.935737668	9	8.421639	9	0.403723597
250	14	0.935737668	9	8.421639	9	0.403723597
250	14	0.935737668	8	7.485901	8	0.399460348
250	15	0.935737668	6	5.614426	6	0.387437863
250	15	0.935737668	7	6.550164	7	0.394172429
250	16	0.935737668	9	8.421639	9	0.403723597

Figure 1-21. Details Regarding the Selected Model (Nested Logistic (lsc-ilc+)) for Fetuses with Body Weights Below the 10th Percentile of Control Male Fetal Body Weights Following Gestational Exposure (GD 6-15)

1.1.2.2 Fetal Malformation Effects

EPA identified fetal malformation endpoints in a gestational inhalation exposure study in CD-1 mice for BMD modeling (Battelle PNL, 1987). Modeled results are presented for the number of litters with supernumerary ribs, number of fetuses with supernumerary ribs, and mean percent of supernumerary ribs per litter. In addition, nested modeling was conducted on the number of fetuses with supernumerary ribs to consider the within-dam grouping of fetal malformation observations as well as litter size.

1.1.2.2.1 Number of Litters with Supernumerary Ribs from Female CD-1 Mice Exposed via Inhalation on GD 6 to 15 (Battelle PNL, 1987)

Increased incidence of litters with supernumerary ribs was observed in fetuses from Pregnant CD-1 mice exposed to 1,3-butadiene by inhalation on GD 6 to 15 (six hours per day) (Battelle PNL, 1987). Exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day rather than six hours per day. Dichotomous models were fit to the incidence data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). A BMR of five percent ER was also selected for the developmental endpoint. The concentration and response data used for the modeling are presented in Table 1-15.

Table 1-15. Incidence of Litters with Supernumerary Ribs Following Gestation Exposure (GD 6-15) and Associated Concentrations Selected for Dose-Response Modeling for 1,3-Butadiene

Concentration (ppm)	Number of Litters	Incidence
0	18	11
10.0	19	9
49.95	21	20
250	20	20

The BMD modeling results for increased incidence of litter with supernumerary ribs are summarized in Table 1-16. All models provided adequate fit to the data (chi-square p-value > 0.1). The Weibull model was unusable because the BMDL computation failed. BMDLs of the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Multistage 3-degree).

Table 1-16. BMD Modeling Results for Litters with Supernumerary Ribs Following Exposure to 1,3-Butadiene During Gestation (GD 6-15)[a]

Model	Goodness of Fit		BMD 5%ER (ppm)	BMDL 5%ER (ppm)	BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Basis for Model Selection
	p-value	AIC					
Dichotomous Hill	0.4018	65.09	29.7	3.17	32.1	4.84	All models provided adequate fit to the data (chi-square p-value > 0.1). The Weibull model was unusable because the BMDL computation failed. BMDLs of the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was
Gamma	0.4018	65.09	23.0	1.81	25.7	3.42	
Log-Logistic	0.4018	65.09	29.7	3.17	32.1	4.84	
Multistage 3	**0.6733**	**63.18**	**14.2**	**1.38**	**18.0**	**2.84**	
Multistage 2	0.5512	63.58	7.65	1.27	11.0	2.60	
Multistage 1	0.1504	66.16	1.50	0.838	3.08	1.72	
Weibull	0.3277	65.34	10.3	1.49	14.0	0	
Logistic	0.2339	65.27	1.98	1.23	3.97	2.47	
Log-Probit	0.4018	65.09	26.8	3.46	29.0	4.92	
Probit	0.2626	65.03	2.10	1.39	4.20	2.79	

Model	Goodness of Fit		BMD 5%ER (ppm)	BMDL 5%ER (ppm)	BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Basis for Model Selection
	p-value	AIC					
Quantal Linear	0.1504	66.16	1.50	0.838	3.08	1.72	selected (Multistage 3-degree).
[a] Selected model in bold.							

Plots of the Multistage 3-degree model with a BMR of five percent ER and 10 percent ER are shown in Figure 1-22 and Figure 1-23, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 1-24 (BMD and BMDL shown are for BMR of five percent ER; the rest is applicable to both BMRs).

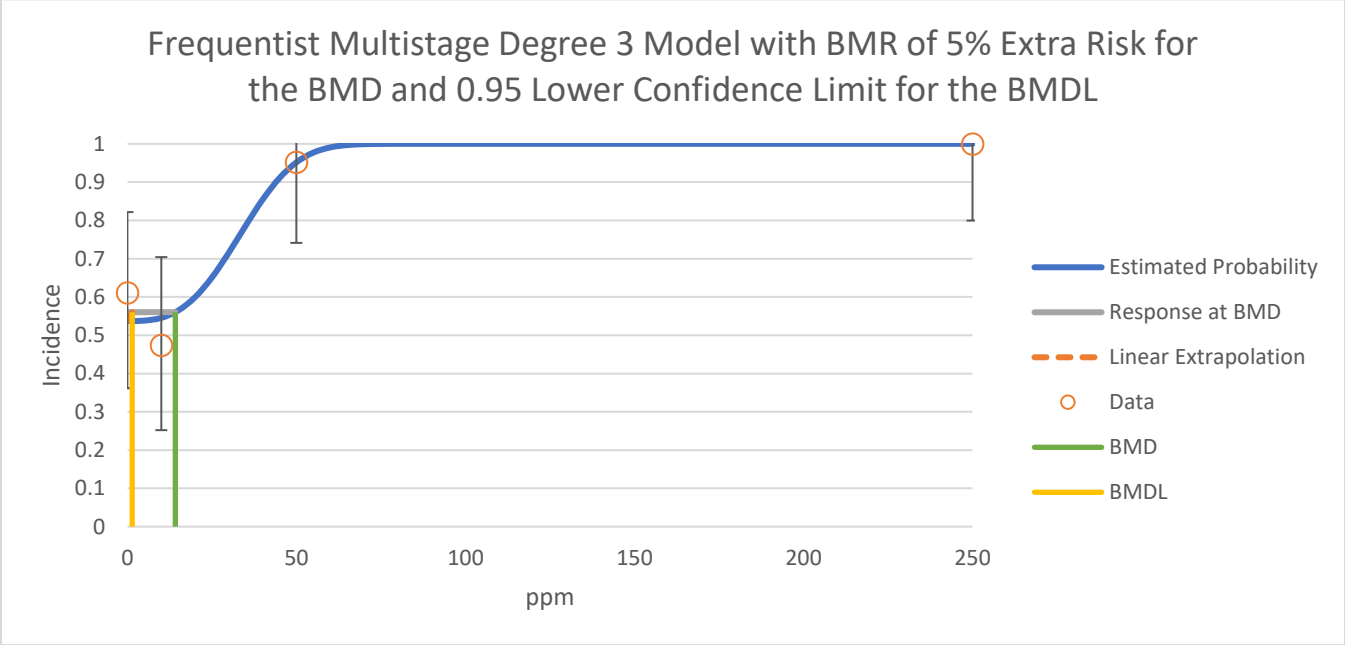

Figure 1-22. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 3-Degree) for Litters with Supernumerary Ribs Following Exposure to 1,3-Butadiene During Gestation (GD 6-15) and BMR of 5%ER

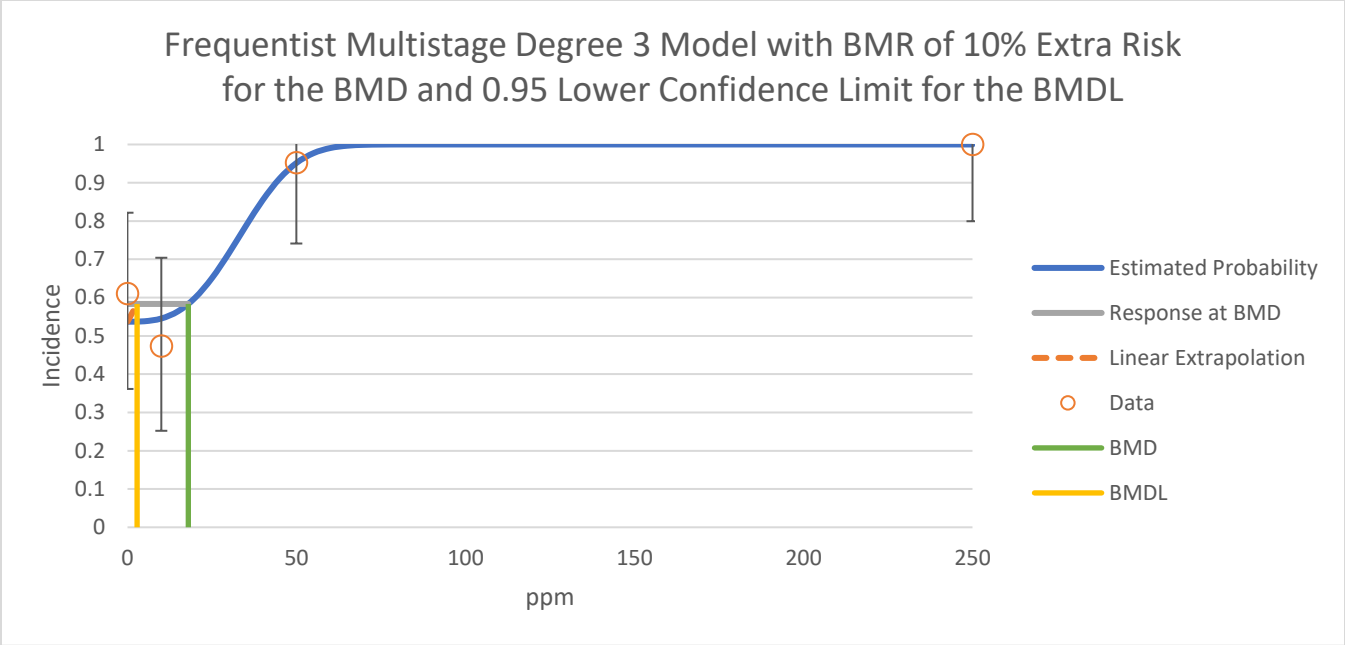

Figure 1-23. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 3-Degree) for Litters with Supernumerary Ribs Following Exposure to 1,3-Butadiene During Gestation (GD 6-15) and BMR of 10%ER

Summary:

BMD	14.1521
BMDL	1.38207
BMDU	18.6704
AIC	63.178
Log Likelihood	29.589
P-Value	0.673307
Overall DOF	2
Chi²	0.791107

Model Parameters:

Variable	Estimate	Bounded	Std Error	Lower CI	Upper CI
g	0.53713	no	0.0178271	0.502189	0.57207
b1	1.70051e-19	yes	NA	NA	NA
b2	1.55196e-19	yes	NA	NA	NA
b3	1.80967e-05	no	77.7249	-152.338	152.338

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	18	11	9.66833	0.53713	0.629491
10	19	9	10.3632	0.545431	-0.62807
49.95	21	20	19.9809	0.951472	0.0193777
250	20	20	20	1	0

Analysis of Deviance:

Model	Log Likelihood	# Params	Deviance	Test DOF	P-Value
Full model	-29.1923	4	-	-	-
Fitted model	-29.589	2	0.793489	2	0.672506
Reduced model	-42.1359	1	25.8873	3	1.00698e-05

Figure 1-24. Details Regarding the Selected Model (Multistage 1-Degree) for Litters with Supernumerary Ribs Following Exposure to 1,3-Butadiene During Gestation (GD 6-15)

1.1.2.2.2 Number of Fetuses with Supernumerary Ribs from Female CD-1 Mice Exposed via Inhalation on GD 6 to 15 (Battelle PNL, 1987)

Increased incidence of fetuses with supernumerary ribs was observed in fetuses from Pregnant CD-1 mice exposed to 1,3-butadiene by inhalation on GD 6 to 15 (six hours per day) (Battelle PNL, 1987). Exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day rather than six hours per day. Dichotomous models were fit to the incidence data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). A BMR of five percent ER was also selected for the developmental endpoint. The concentration and response data used for the modeling are presented in Table 1-17.

Table 1-17. Incidence of Fetuses with Supernumerary Ribs Following Exposure During Gestation (GD 6-15) and Associated Concentrations Selected for Dose-Response Modeling for 1,3-Butadiene

Adjusted Concentration (ppm)	Number of Fetuses	Incidence
0	211	30
10.0	237	30
49.95	259	127
250	244	198

The BMD modeling results for increased incidence of fetuses with supernumerary ribs are summarized in Table 1-18. None of the models provided an adequate fit to the data (chi-square p-value > 0.1). The full data set is not suitable for BMD modeling. With the highest concentration dropped, the Gamma and Multistage 2-degree models provided adequate fit to the data (chi-square p-value > 0.1). The goodness-of-fit test (chi-square p-value) could not be calculated for the Dichotomous Hill, Log-logistic, Weibull, and Log-probit models because the models were saturated (degree of freedom = 0). BMDLs of the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Gamma).

Table 1-18. BMD Modeling Results for Number of Fetuses with Supernumerary Ribs Following Exposure to 1,3-Butadiene During Gestation (GD 6-15)[a]

Model	Goodness of Fit		BMD 5%ER (ppm)	BMDL 5%ER (ppm)	BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Basis for Model Selection
	p-value	AIC					
Full Data set							For the whole data set, none of the models provided an adequate fit to the data (chi-square p-value > 0.1). The full data set is not suitable for BMD modeling. With the highest concentration
Dichotomous Hill	NA	956.0	38.9	10.7	41.6	16.2	
Gamma	<0.0001	972.6	7.33	6.46	15.1	13.3	
Log-Logistic	0.00209	963.6	7.16	4.67	13.1	9.30	
Multistage 3	<0.0001	972.6	7.33	6.46	15.1	13.3	
Multistage 2	<0.0001	972.6	7.33	6.46	15.1	13.3	
Multistage 1	<0.0001	972.6	7.33	6.46	15.1	13.3	

Model	Goodness of Fit		BMD 5%ER (ppm)	BMDL 5%ER (ppm)	BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Basis for Model Selection
	p-value	AIC					
Weibull	<0.0001	972.6	7.33	6.46	15.1	13.3	dropped from the data set, the Gamma and Multistage 2-degree models provided adequate fit to the data (chi-square p-value > 0.1). BMDLs of the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Gamma).
Logistic	<0.0001	1006	18.8	17.0	35.7	32.3	
Log-Probit	0.0056	961.6	8.73	5.92	14.2	10.3	
Probit	<0.0001	1005	18.4	16.8	35.1	32.2	
Quantal Linear	<0.0001	972.6	7.33	6.46	15.1	13.3	
Highest concentration dropped							
Dichotomous Hill	NA	719.8	42.8	10.7	44.7	10.8	
Gamma	**0.6285**	**715.8**	**34.7**	**10.7**	**38.2**	**16.7**	
Log-Logistic	NA	717.8	43.3	10.7	45.1	16.5	
Multistage 2	0.2884	716.7	15.5	9.43	22.2	16.4	
Multistage 1	0.0014	726.4	5.09	4.24	10.5	8.71	
Weibull	NA	717.8	43.7	10.7	45.6	17.1	
Logistic	0.0521	719.3	9.57	8.55	17.1	15.4	
Log-Probit	NA	717.8	39.4	10.6	41.9	15.6	
Probit	0.0373	719.9	8.81	7.88	16.1	14.5	
Quantal Linear	0.0014	726.4	5.09	4.24	10.5	8.71	

[a] Selected model in bold.

Plots of the Gamma model to the data set with highest concentration dropped using a BMR of five percent ER and 10 percent ER are shown in Figure 1-25 and Figure 1-26, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 1-27 (BMD and BMDL shown are for BMR of five percent ER; the rest is applicable to both BMRs).

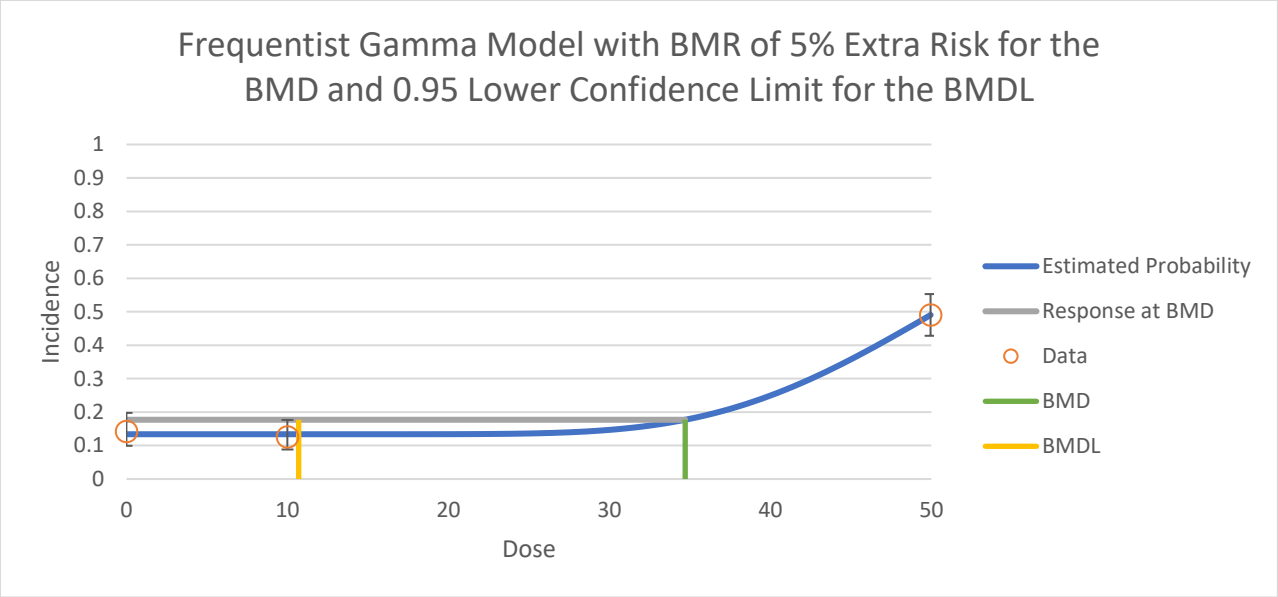

Figure 1-25. Plot of Response by Concentration with Fitted Curve for the Selected Model (Gamma) for Fetuses with Supernumerary Ribs Following Exposure to 1,3-Butadiene During Gestation (GD 6-15) and BMR of 5%ER (Highest Concentration Dropped)

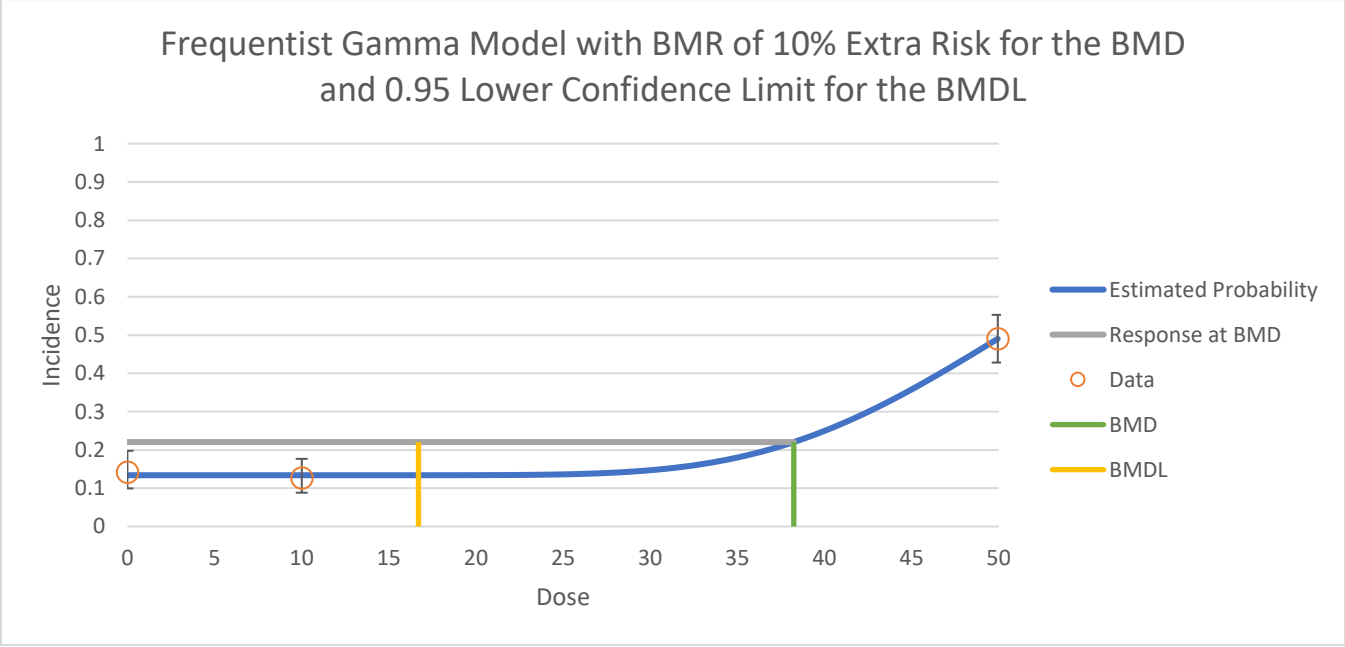

Figure 1-26. Plot of Response by Concentration with Fitted Curve for the Selected Model (Gamma) for Fetuses with Supernumerary Ribs Following Exposure to 1,3-Butadiene During Gestation (GD 6-15) and BMR of 10%ER (Highest Concentration Dropped)

Summary:

BMD	34.7028
BMDL	10.6954
BMDU	36.1116
AIC	715.787
Log Likelihood	355.893
P-Value	0.628479
Overall DOF	1
Chi²	0.234129

Model Parameters:

Variable	Estimate	Bounded	Std Error	Lower CI	Upper CI
g	0.133929	no	0.00859263	0.117087	0.15077
a	18	yes	NA	NA	NA
b	0.335255	no	0.00781121	0.319945	0.350565

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	211	30	28.2589	0.133929	0.351935
10	237	30	31.7411	0.133929	-0.33207
49.95	259	127	127	0.490347	1.07643e-07

Analysis of Deviance:

Model	Log Likelihood	# Params	Deviance	Test DOF	P-Value
Full model	-355.777	3	-	-	-
Fitted model	-355.893	2	0.233798	1	0.628722
Reduced model	-408.44	1	105.328	2	0

Figure 1-27. Details Regarding the Selected Model (Gamma) for Fetuses with Supernumerary Ribs Following Exposure to 1,3-Butadiene During Gestation (GD 6-15) (Highest Concentration Dropped)

1.1.2.2.3 Nested Modeling of Number of Fetuses with Supernumerary Ribs from Female CD-1 Mice Exposed via Inhalation on GD 6 to 15 (Battelle PNL, 1987)

The number of supernumerary ribs was significantly increased in fetuses from pregnant CD-1 mice exposed to 1,3-butadiene by inhalation on GD 6 to 15 (six hours per day) (Battelle PNL, 1987). Nested modeling was conducted to consider the within-litter grouping of supernumerary ribs observations as well as litter size. To apply this model, the individual incidences of fetuses with supernumerary ribs were binned by litter. Total litter size (number of live male and female fetuses) was used as the litter specific covariate using the default "Overall Mean" option (averaged across all dose groups). The exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day rather than six hours per day. Then, the Nested Logistic model forms were fit to the data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). A BMR of five percent ER was also selected for the developmental endpoint. The concentrations and response data used for the nested modeling are presented in Table 1-19.

Table 1-19. Incidence of Fetuses with Supernumerary Ribs Following Gestational Exposure and Associated Concentrations Selected for Nested Dose-Response Modeling for 1,3-Butadiene

Duration Adjusted Concentration (ppm)	Litter Size (Number of Live Fetuses)	Incidence	Litter Specific Covariate (Litter Size)
0	9	1	9
0	10	2	10
0	3	0	3
0	13	2	13
0	12	2	12
0	13	0	13
0	15	3	15
0	13	0	13
0	13	9	13
0	13	0	13
0	12	1	12
0	13	2	13
0	9	0	9
0	13	2	13
0	9	5	9
0	13	0	13
0	14	0	14
0	14	1	14
10.0	11	2	11
10.0	11	0	11
10.0	13	0	13
10.0	14	3	14
10.0	13	1	13
10.0	15	3	15
10.0	13	0	13
10.0	12	5	12
10.0	16	0	16
10.0	11	7	11
10.0	12	0	12
10.0	6	4	6
10.0	13	0	13
10.0	11	0	11

Duration Adjusted Concentration (ppm)	Litter Size (Number of Live Fetuses)	Incidence	Litter Specific Covariate (Litter Size)
10.0	10	1	10
10.0	15	0	15
10.0	14	4	14
10.0	14	0	14
10.0	13	0	13
49.95	13	11	13
49.95	12	2	12
49.95	12	12	12
49.95	13	6	13
49.95	14	12	14
49.95	15	7	15
49.95	11	6	11
49.95	14	1	14
49.95	11	6	11
49.95	12	8	12
49.95	11	3	11
49.95	11	4	11
49.95	13	11	13
49.95	14	5	14
49.95	12	5	12
49.95	12	7	12
49.95	15	4	15
49.95	2	0	2
49.95	16	2	16
49.95	15	5	15
49.95	11	10	11
250	9	7	9
250	14	14	14
250	11	10	11
250	12	11	12
250	14	6	14
250	14	13	14
250	15	12	15

Duration Adjusted Concentration (ppm)	Litter Size (Number of Live Fetuses)	Incidence	Litter Specific Covariate (Litter Size)
250	12	12	12
250	16	8	16
250	14	14	14
250	14	5	14
250	11	10	11
250	10	6	10
250	9	8	9
250	12	10	12
250	8	7	8
250	10	9	10
250	13	13	13
250	11	10	11
250	15	13	15

The nested BMD modeling results for increased number of fetuses per litter with supernumerary ribs are summarized in Table 1-20. The model forms applying the intralitter correlation (ilc+) provided adequate fit to the data (chi-square p-value > 0.1) both with and without the litter-specific covariate (lsc) applied. Model forms without the intralitter correlation (ilc-) did not provide adequate fits. Between the Nested Logistic (lsc+ilc+) and Nested Logistic (lsc-ilc+), the Nested Logistic (lsc-ilc+) had the lower AIC; therefore, this model form is selected.

Table 1-20. BMD Modeling Results for Incidence of Fetuses with Supernumerary Ribs Following Gestational Exposure (GD 6-15)[a]

Model	Goodness of Fit		BMD 5%ER (ppm)	BMDL 5%ER (ppm)	BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Basis for Model Selection
	p-value	AIC					
Nested Logistic (lsc+ilc+)	0.4187	861.5	6.17	2.84	11.6	5.99	The model forms applying the intralitter correlation (ilc+) provided adequate fit to the data (chi-square p-value > 0.1) both with and without the litter-specific covariate (lsc) applied. Model forms without the intralitter correlation (ilc-) did not provide adequate fits. Between the Nested
Nested Logistic (lsc+ilc-)	<0.0001	949.0	6.31	4.08	11.6	8.15	
Nested Logistic (lsc-ilc+)	**0.3887**	**858.9**	**6.31**	**2.90**	**11.9**	**6.13**	

Model	Goodness of Fit		BMD 5%ER (ppm)	BMDL 5%ER (ppm)	BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Basis for Model Selection
	p-value	AIC					
Nested Logistic (lsc-ilc-)	<0.0001	963.6	7.16	4.67	13.1	9.30	Logistic (lsc+ilc+) and Nested Logistic (lsc-ilc+), the Nested Logistic (lsc-ilc+) had the lower AIC; therefore, this model form is selected.
[a] Selected model in bold.							

Plots of the Nested Logistic (lsc-ilc+) model for fetuses with supernumerary ribs with BMRs of five percent ER and 10 percent ER are shown in Figure 1-28 and Figure 1-29, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown below in Figure 1-30 (BMD and BMDL shown are for BMR of five percent ER; the rest is applicable to both BMRs).

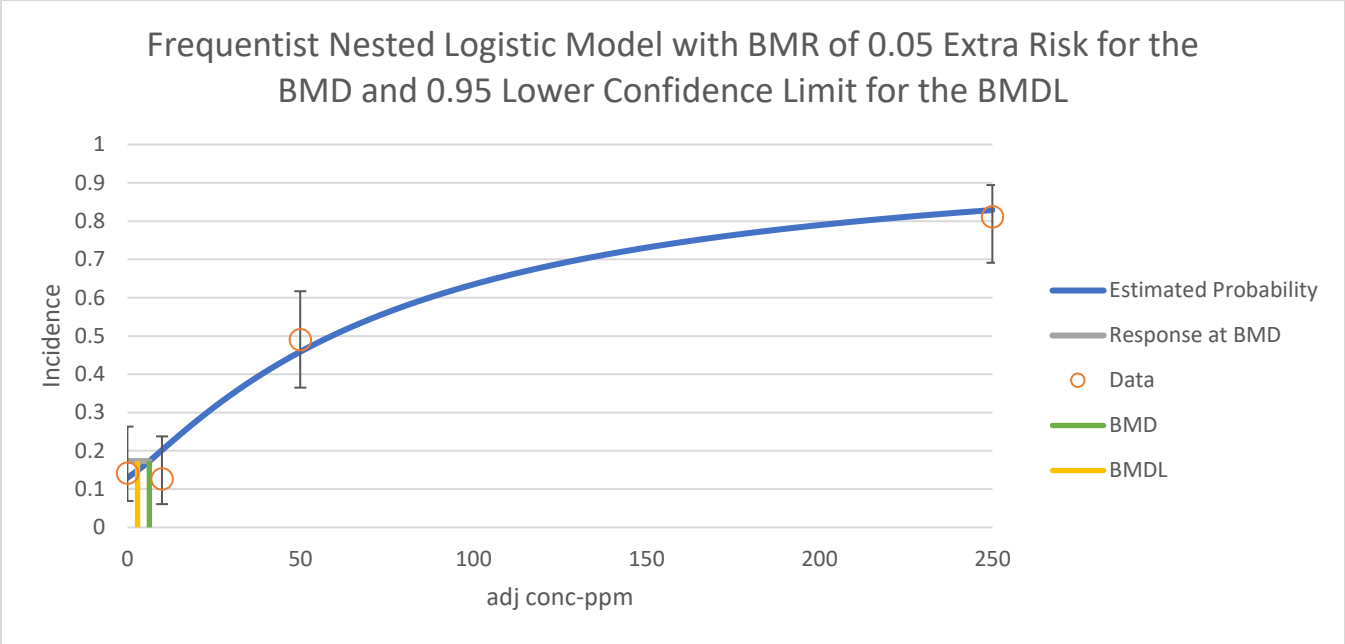

Figure 1-28. Plot of Response by Concentration with Fitted Curve for the Selected Model (Nested Logistic (lsc-ilc+)) for Fetuses with Supernumerary Ribs Following Gestational Exposure (GD 6-15) and BMR of 5% ER

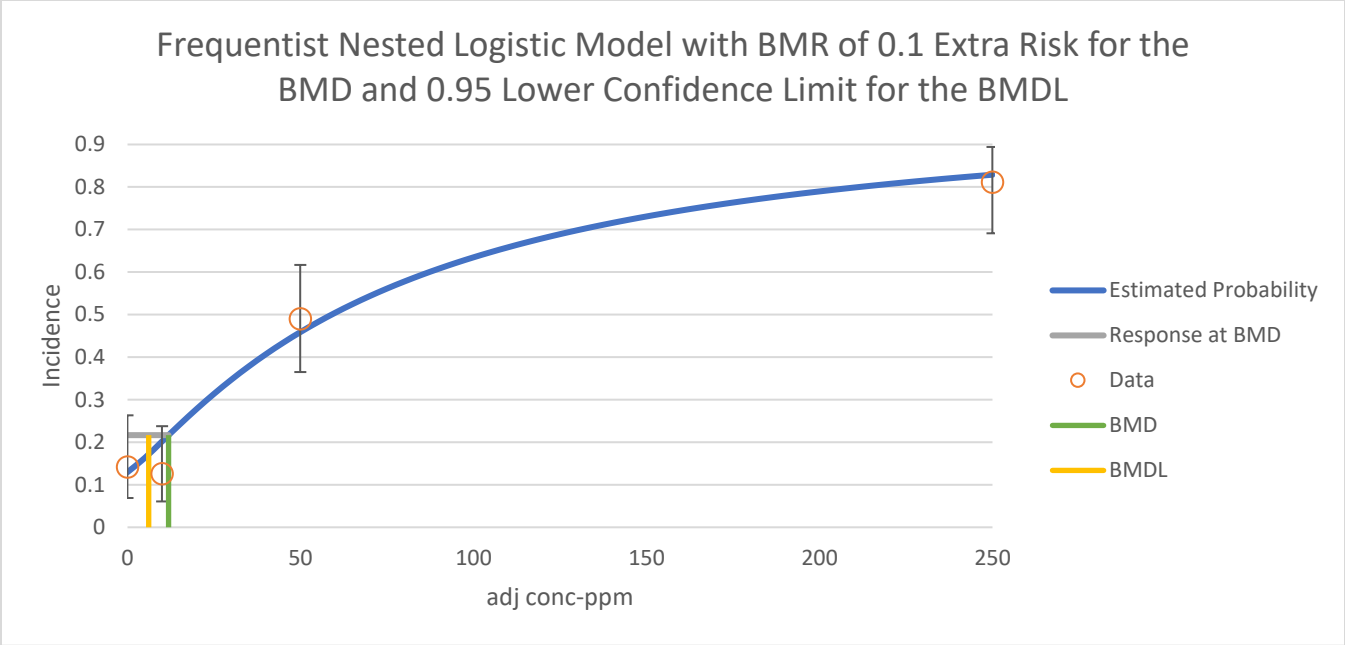

Figure 1-29. Plot of Response by Concentration with Fitted Curve for the Selected Model (Nested Logistic (lsc-ilc+)) for Fetuses with Supernumerary Ribs Following Exposure to 1,3-Butadiene During Gestation (GD 6-15) and BMR of 10 %ER

Model Results

Benchmark Dose	
BMD	6.308282812
BMDL	2.902606396
BMDU	-
AIC	858.8831481
P-value	0.388666667
D.O.F.	71
Chi^2	80.66626403

Model Parameters	
# of Parameters	9
Variable	Estimate
alpha	0.129660738
beta	-5.122839844
theta1	0
theta2	0
rho	1.182715691
phi1	0.16958108
phi2	0.389340729
phi3	0.230851103

Bootstrap Results	
# Iterations	1000
Bootstrap Seed	1721754371
Log-likelihood	-422.441574
Observed Chi-square	80.66626403
Combined P-value	0.388666667

Bootstrap Runs

Run	Bootstrap Chi-square Percentiles				
	P-Value	50th	90th	95th	99th
1	0.407	77.42882763	99.4000209	107.2851	122.03606
2	0.38	76.3752463	98.1046983	104.4778	114.36361
3	0.379	76.71092859	96.914456	102.6257	118.48856
Combined	0.388666667	76.80917063	98.1046983	105.1206	119.03275

Scaled Residuals

Minimum scaled residual for dose group nearest the BMD	-0.75848
Minimum ABS(scaled residual) for dose group nearest the BMD	0.758477
Average Scaled residual for dose group nearest the BMD	0.023471
Average ABS(scaled residual) for dose group nearest the BMD	0.781948
Maximum scaled residual for dose group nearest the BMD	0.805419
Maximum ABS(scaled residual) for dose group nearest the BMD	0.805419

0	10	0.129660738	10	1.296607	2	0.416593852
0	12	0.129660738	12	1.555929	1	-0.282220169
0	12	0.129660738	12	1.555929	2	0.225435023
0	13	0.129660738	13	1.68559	0	-0.798829729
0	13	0.129660738	13	1.68559	0	-0.798829729
0	13	0.129660738	13	1.68559	2	0.149004469
0	13	0.129660738	13	1.68559	0	-0.798829729
0	13	0.129660738	13	1.68559	2	0.149004469
0	13	0.129660738	13	1.68559	0	-0.798829729
0	13	0.129660738	13	1.68559	2	0.149004469
0	13	0.129660738	13	1.68559	9	3.466424161
0	14	0.129660738	14	1.81525	0	-0.806752229
0	14	0.129660738	14	1.81525	1	-0.36232194
0	15	0.129660738	15	1.944911	3	0.44148268
10	6	0.20207998	6	1.21248	4	1.650945851
10	10	0.20207998	10	2.0208	1	-0.378788557
10	11	0.20207998	11	2.22288	7	1.621521904
10	11	0.20207998	11	2.22288	0	-0.754523246
10	11	0.20207998	11	2.22288	2	-0.075653204
10	11	0.20207998	11	2.22288	0	-0.754523246
10	12	0.20207998	12	2.42496	5	0.805419468
10	12	0.20207998	12	2.42496	0	-0.758477391
10	13	0.20207998	13	2.62704	1	-0.471860529
10	13	0.20207998	13	2.62704	0	-0.761872209
10	13	0.20207998	13	2.62704	0	-0.761872209
10	13	0.20207998	13	2.62704	0	-0.761872209
10	13	0.20207998	13	2.62704	0	-0.761872209
10	14	0.20207998	14	2.82912	3	0.046195436
10	14	0.20207998	14	2.82912	0	-0.764818622
10	14	0.20207998	14	2.82912	4	0.316533455

10	15	0.20207998	15	3.0312	3	-0.007898738
10	15	0.20207998	15	3.0312	0	-0.767400024
10	16	0.20207998	16	3.23328	0	-0.769680322
49.95	2	0.458819605	2	0.917639	0	-1.173713754
49.95	11	0.458819605	11	5.047016	10	1.647639931
49.95	11	0.458819605	11	5.047016	4	-0.348296032
49.95	11	0.458819605	11	5.047016	3	-0.680952026
49.95	11	0.458819605	11	5.047016	6	0.317015955
49.95	11	0.458819605	11	5.047016	6	0.317015955
49.95	12	0.458819605	12	5.505835	7	0.460101184
49.95	12	0.458819605	12	5.505835	5	-0.155762878
49.95	12	0.458819605	12	5.505835	8	0.768033214
49.95	12	0.458819605	12	5.505835	12	1.999761337
49.95	12	0.458819605	12	5.505835	2	-1.07955897
49.95	13	0.458819605	13	5.964655	11	1.44338637
49.95	13	0.458819605	13	5.964655	6	0.010131717
49.95	13	0.458819605	13	5.964655	11	1.44338637
49.95	14	0.458819605	14	6.423474	5	-0.381685696
49.95	14	0.458819605	14	6.423474	1	-1.454232357
49.95	14	0.458819605	14	6.423474	12	1.49527096
49.95	15	0.458819605	15	6.882294	5	-0.474112432
49.95	15	0.458819605	15	6.882294	4	-0.725992538
49.95	15	0.458819605	15	6.882294	7	0.029647782
49.95	16	0.458819605	16	7.341114	2	-1.268462798
250	8	0.828863408	8	6.630907	7	0.24157055
250	9	0.828863408	9	7.459771	7	-0.273835684
250	9	0.828863408	9	7.459771	8	0.321756207
250	10	0.828863408	10	8.288634	6	-1.251068322
250	10	0.828863408	10	8.288634	9	0.388863985
250	11	0.828863408	11	9.117497	10	0.445913447
250	11	0.828863408	11	9.117497	10	0.445913447
250	11	0.828863408	11	9.117497	10	0.445913447
250	12	0.828863408	12	9.946361	11	0.495046413
250	12	0.828863408	12	9.946361	10	0.025202032
250	12	0.828863408	12	9.946361	12	0.964890794
250	13	0.828863408	13	10.77522	13	0.976952277
250	14	0.828863408	14	11.60409	6	-2.310154108
250	14	0.828863408	14	11.60409	14	0.987658813
250	14	0.828863408	14	11.60409	5	-2.722380723
250	14	0.828863408	14	11.60409	14	0.987658813
250	14	0.828863408	14	11.60409	13	0.575432198
250	15	0.828863408	15	12.43295	13	0.220282964
250	15	0.828863408	15	12.43295	12	-0.168189655
250	16	0.828863408	16	13.26181	8	-1.932852993

Figure 1-30. Details Regarding the Selected Model (Nested Logistic (lsc-ilc+)) for Fetuses with Supernumerary Ribs Following Exposure to 1,3-Butadiene During Gestation (GD 6-15)

1.1.2.2.4 Mean Percent (%) of Supernumerary Ribs per Litter from Female CD-1 Mice Exposed via Inhalation on GD 6 to 15 (Battelle PNL, 1987)

Mean percent of supernumerary ribs per litter was significantly increased in fetuses from Pregnant CD-1 mice exposed to 1,3-butadiene by inhalation on GD 6 to 15 (six hours per day) (Battelle PNL, 1987).

First, the exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day rather than six hours per day. Then, continuous models were fit to the dose-response data.

A BMR of one SD was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). BMRs of five percent and 10 percent RD were also selected for the developmental study. The concentrations and response data used for the modeling are presented in Table 1-21.

Table 1-21. Increased Mean Percent of Supernumerary Ribs per Litter and Associated Concentrations Selected for Dose-Response Modeling for 1,3-Butadiene from a Gestational Inhalation Exposure Study (GD 6-15)

Adjusted Concentration (ppm)	Number of Animals	Mean (%)	SD (%)
0	18	1.7	2.3
10.0	19	1.6	2.1
49.95	21	6.0	3.6
250	20	9.9	3.0

The BMD modeling results for increased mean percent of supernumerary ribs per litter are summarized in Table 1-22. Both the constant and nonconstant variance models provide adequate fit to the variance data; however, with either variance model applied, none of the models provided adequate fit to the means (test 4 p-value < 0.1). The full data set is not suitable for BMD modeling. With the highest concentration dropped from the data set, the constant variance model did not provide adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, only the Polynomial 2-degree model provided adequate fit to the means (test 4 p-value > 0.1). The goodness-of-fit test for the means (test 4) could not be calculated for the Exponential 3 and 5, Hill, and Power models because the models were saturated (degree of freedom = 0). The polynomial 2-degree model was selected for BMRs of 1SD and 10%RD. When applying a BMR of 5%RD, the Polynomial 2-degree model was considered questionable because the BMDL value was 10 times lower than the lowest non-zero dose; no model was selected for this BMR.

Table 1-22. BMD Modeling Results for Increased Mean Percent of Supernumerary Ribs per Litter Following Exposure to 1,3-Butadiene During Gestation (GD 6-15)[a]

Model	Goodness of Fit (Means)		BMD 1SD (ppm)	BMDL 1SD (ppm)	BMD 5%RD (ppm)	BMDL 5%RD (ppm)	BMD 10%RD (ppm)	BMDL 10%RD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC							
Full Data set (Nonconstant Variance Model)[b]									For the whole data set, both the constant and nonconstant variance models provide adequate fit to the variance data; however, with either variance model applied, none of the models provided adequate fit to the means (test 4 p-value < 0.1). The full data set is not suitable for BMD modeling. With the highest concentration dropped from the data set, the constant variance model did not provide adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, only the Polynomial 2-degree model provided adequate fit to the means (test 4 p-value > 0.1). The goodness-of-fit test for the means (test 4) could not be calculated for the Exponential 3 and 5, Hill, and Power models because the models were saturated (degree of freedom = 0). The polynomial 2-degree model was selected for BMRs of 1SD and 10%RD. When applying a BMR of 5%RD, the Polynomial 2-degree model was considered questionable because the BMDL
Exponential 3	-	-	-	-	-	-	-	-	
Exponential 5	NA	387.3	47.4	20.0	39.1	0.930	40.7	1.66	
Hill	NA	387.3	46.1	44.0	36.4	1.19	38.1	2.00	
Polynomial Degree 3	<0.0001	401.9	84.6	59.5	3.49	2.05	6.98	4.11	
Polynomial Degree 2	<0.0001	401.9	84.3	59.5	3.48	2.05	6.96	4.11	
Power	<0.0001	401.9	84.3	59.5	3.48	2.05	6.96	4.11	
Linear	<0.0001	401.9	84.3	59.5	3.48	2.05	6.96	4.11	
Highest Concentration Dropped (Nonconstant Variance Model)									
Exponential 3	NA	283.7	47.3	27.2	33.5	1.33	36.3	2.60	
Exponential 5	NA	285.7	25.2	11.5	20.7	0.917	21.5	1.74	
Hill	NA	285.7	46.5	11.1	34.9	1.05	37.1	1.92	
Polynomial Degree 2	**0.5202**	**282.0**	**34.5**	**22.2**	6.67 [c]	0.686 [c]	**9.43**	**1.37**	
Power	NA	283.7	48.0	22.5	40.1	0.917	41.6	1.74	

Model	Goodness of Fit (Means)		BMD 1SD (ppm)	BMDL 1SD (ppm)	BMD 5%RD (ppm)	BMDL 5%RD (ppm)	BMD 10%RD (ppm)	BMDL 10%RD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC							
Linear	0.0719	284.8	23.7	16.7	0.773	0.324	1.55	0.648	value was 10 times lower than the lowest non-zero dose; no model was selected for this BMR.

[a] Selected model in bold.
[b] Both the constant and nonconstant variance models provided adequate fit to the full data set; model results with the nonconstant variance model applied are presented.
[c] BMD and BMDL values from the Polynomial 2-degree model should not be used for the 5% BMR because the BMDL value was 10 times lower than the lowest non-zero dose.

Plots of the Polynomial 2-degree model (nonconstant variance) to the data set (with highest concentration dropped) using BMRs of one SD and 10 percent RD are shown in Figure 1-31 and Figure 1-32, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown below in Figure 1-33 (BMD and BMDL shown are for BMR of one SD; the rest is also applicable to the BMR of 10 percent RD). The plot for the BMR of five percent RD is not presented because the model did not provide an adequate fit for this BMR.

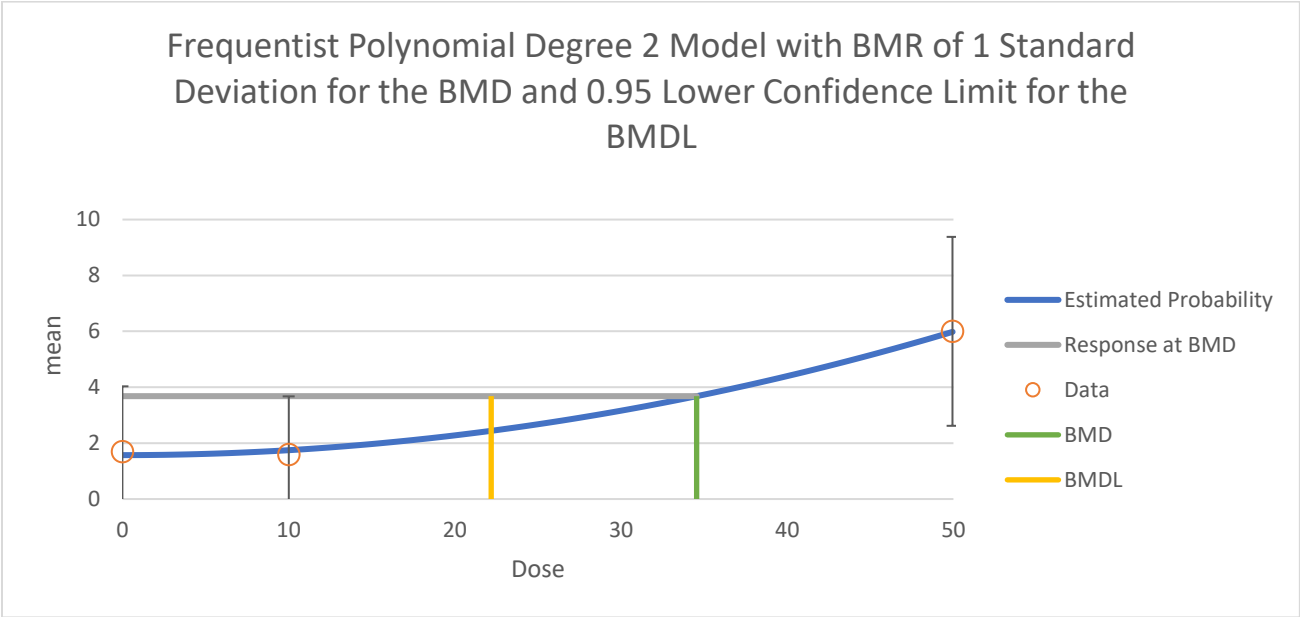

Figure 1-31. Plot of Response by Concentration with Fitted Curve for the Selected Model (Polynomial 2-Degree, Nonconstant Variance Model) for Increased Mean Percent of Supernumerary Ribs per Litter Following Exposure to 1,3-Butadiene During Gestation (GD 6-15) and BMR of 1SD (Highest Concentration Dropped)

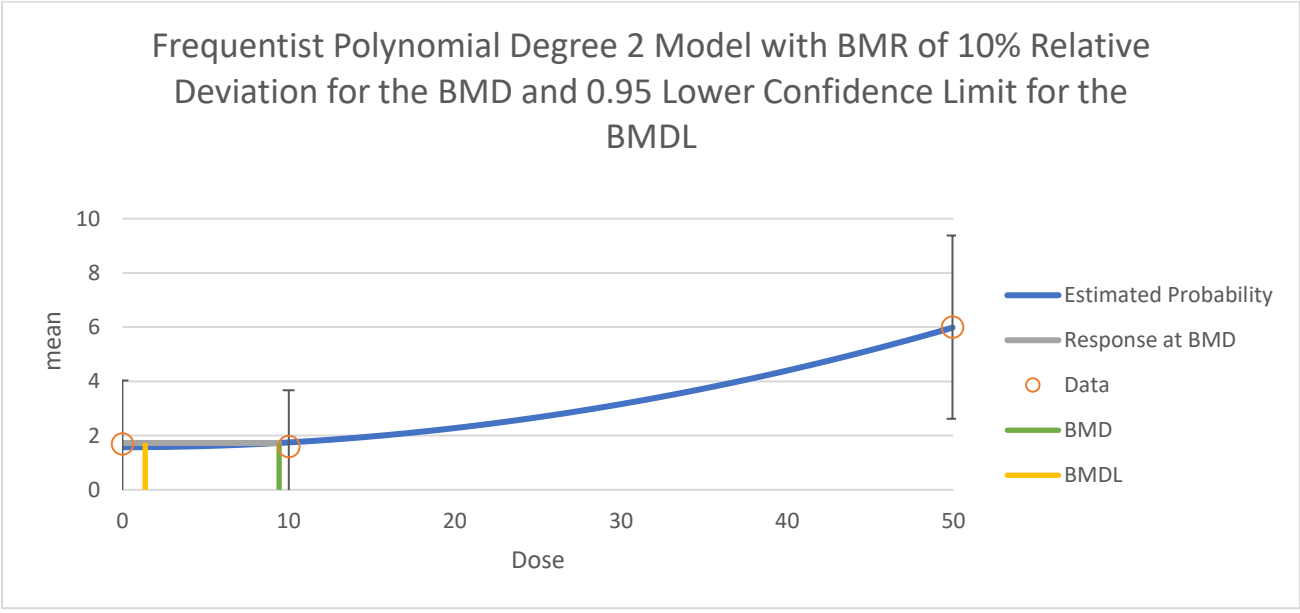

Figure 1-32. Plot of Response by Concentration with Fitted Curve for the Selected Model (Polynomial 2-Degree, Nonconstant Variance Model) for Increased Mean Percent of

Supernumerary Ribs per Litter Following Exposure to 1,3-Butadiene During Gestation (GD 6-15) and BMR of 10%RD (Highest Concentration Dropped)

Summary:

BMD	34.5479
BMDL	22.1858
BMDU	43.1026
AIC	281.961
Log Likelihood	136.981
P-Value	0.52015
Model DOF	1

Model Parameters:

Variable	Estimate	Bounded	Std Error	Lower CI	Upper CI
g	1.57063	no	0.359722	0.865585	2.27567
b1	0	yes	NA	NA	NA
b2	0.00176778	no	0.000343	0.00109551	0.00244005
rho	0.755677	no	0.334525	0.10002	1.41133
alpha	3.16503	no	4.15418	-4.97702	11.3071

Goodness of Fit:

Dose	Size	Observed Mean	Calculated Mean	Estimated Mean	Scaled Residual
0	18	1.7	1.7	1.57063	0.260138
10	19	1.6	1.6	1.74741	-0.292494
49.95	21	6	6	5.98125	0.0245741

Dose	Size	Observed SD	Calculated SD	Estimated SD
0	18	2.3	2.3	2.10995
10	19	2.1	2.1	2.19672
49.95	21	3.6	3.6	3.49696

Likelihoods of Interest:

Model	Log Likelihood	# Params	AIC
A1	-140.295	4	288.589
A2	-136.747	6	285.494
A3	-136.774	5	283.547
fitted	-136.981	4	281.961
reduced	-153.782	2	311.565

Tests of Interest:

Name	Loglikelihood Ratio	Test DOF	P-Value
Test 1	34.071	4	7.2063e-07
Test 2	7.09567	2	0.0287868
Test 3	0.0537641	1	0.816638
Test 4	0.413596	1	0.52015

Figure 1-33. Details Regarding the Selected Model (Polynomial 2-Degree, Nonconstant Variance Model) for Increased Mean Percent of Supernumerary Ribs per Litter Following Exposure to 1,3-Butadiene During Gestation (GD 6-15) (Highest Concentration Dropped)

1.2 Male Reproductive System and Resulting Developmental Toxicity

1.2.1 Dominant Lethality Effects

EPA identified dominant lethality endpoints in two 10-week inhalation dominant lethality studies in CD-1 mice for BMD modeling (Anderson et al., 1996), (Brinkworth et al., 1998). Modeled results are presented for incidence of all deaths (total early and late deaths including dead fetuses) for the Anderson et al. (1996) study and for all deaths in the Anderson et al. (1996) and Brinkworth et al. (1998) studies combined. The data are reported as the total number of deaths from each treatment group and is independent of litter.

1.2.1.1 Incidence of All Fetal Deaths following Inhalation Exposure to Male CD-1 Mice for 10 Weeks in a Dominant Lethality Study (Anderson et al., 1996)

Increased incidence of all deaths (total of early and late deaths including dead fetuses) was observed in an inhalation dominant lethality study in CD-1 mice where unexposed dams were mated with male mice exposed to 1,3-butadiene by inhalation for 10 weeks (six hours/day, five days/week) prior to mating (Anderson et al., 1996). Exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day and seven days per week. Dichotomous models were fit to the incidence data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). A BMR of five percent ER was also selected for the lethality endpoint. The concentration and response data used for the modeling are presented in Table 1-23.

Table 1-23. Incidence of All Fetal Deaths Following Inhalation Exposure in Male CD-1 Mice in a Dominant Lethality Study and Associated Concentrations Selected for Dose-Response Modeling for 1,3-Butadiene

Adjusted Concentration (ppm)	Number of Implants	Incidence (Total Deaths)
0	278	15
2.23	306	24
223.2	406	94

The BMD modeling results for increased incidence of all deaths (total of early and late deaths including dead fetuses) are summarized in Table 1-24. All models provided adequate fit to the data (chi-square p-value > 0.1) except for the Dichotomous Hill and Log-Probit models; these models were saturated (degree of freedom = 0). BMDLs of the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Log-Logistic).

Table 1-24. BMD Modeling Results for All Fetal Deaths Following Inhalation Exposure to 1,3-Butadiene in Male CD-1 Mice for 10 Weeks in a Dominant Lethality Study[a]

Model	Goodness of Fit		BMD 5%ER (ppm)	BMDL 5%ER (ppm)	BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Basis for Model Selection
	p-value	AIC					
Dichotomous Hill	NA	732.40	5.00	1.68	15.0	2.72	All models provided adequate fit to the data (chi-square p-value > 0.1) except for the Dichotomous Hill and Log-Probit models; these models were saturated (degree of freedom = 0). BMDLs of the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Log-Logistic).
Gamma	0.2725	729.61	58.5	46.4	120	95.3	
Log-Logistic	**0.2764**	**729.59**	**54.2**	**41.9**	**114**	**88.5**	
Multistage 2	0.2725	729.61	58.5	46.4	120	95.3	
Multistage 1	0.2725	729.61	58.5	46.4	120	95.3	
Weibull	0.2725	729.61	58.5	46.4	120	95.3	
Logistic	0.2541	729.71	90.2	79.5	152	134	
Log-Probit	NA	730.40	8.24	1.13	40.0	12.3	
Probit	0.2559	729.70	84.9	74.1	147	128	
Quantal Linear	0.2725	729.61	58.5	46.4	120	95.3	

[a] Selected model in bold.

Plots of the Log-Logistic model with BMRs of five percent ER and 10 percent ER are shown in Figure 1-34 and Figure 1-35, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 1-36 (BMD and BMDL shown are for BMR of five percent ER; the rest is applicable to both BMRs).

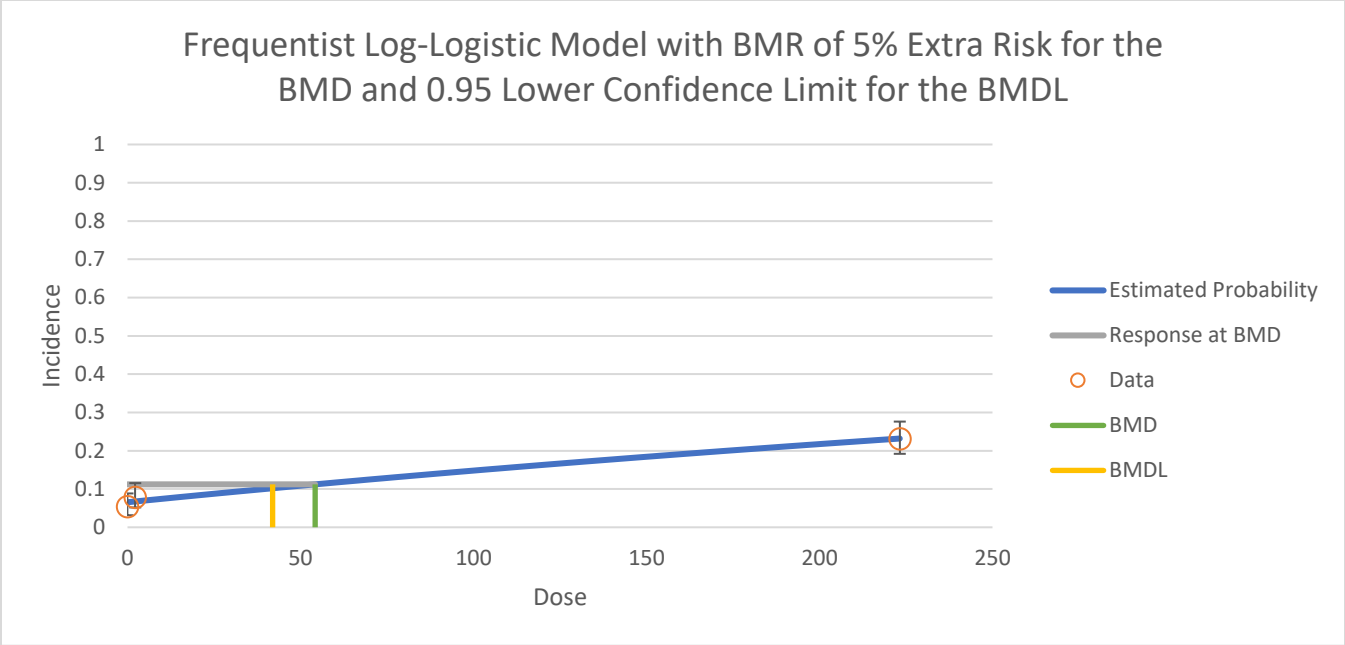

Figure 1-34. Plot of Response by Concentration with Fitted Curve for the Selected Model (Log-Logistic) for All Fetal Deaths Following Inhalation Exposure to 1,3-Butadiene in Male CD-1 Mice for 10 Weeks in a Dominant Lethality Study and BMR of 5%ER

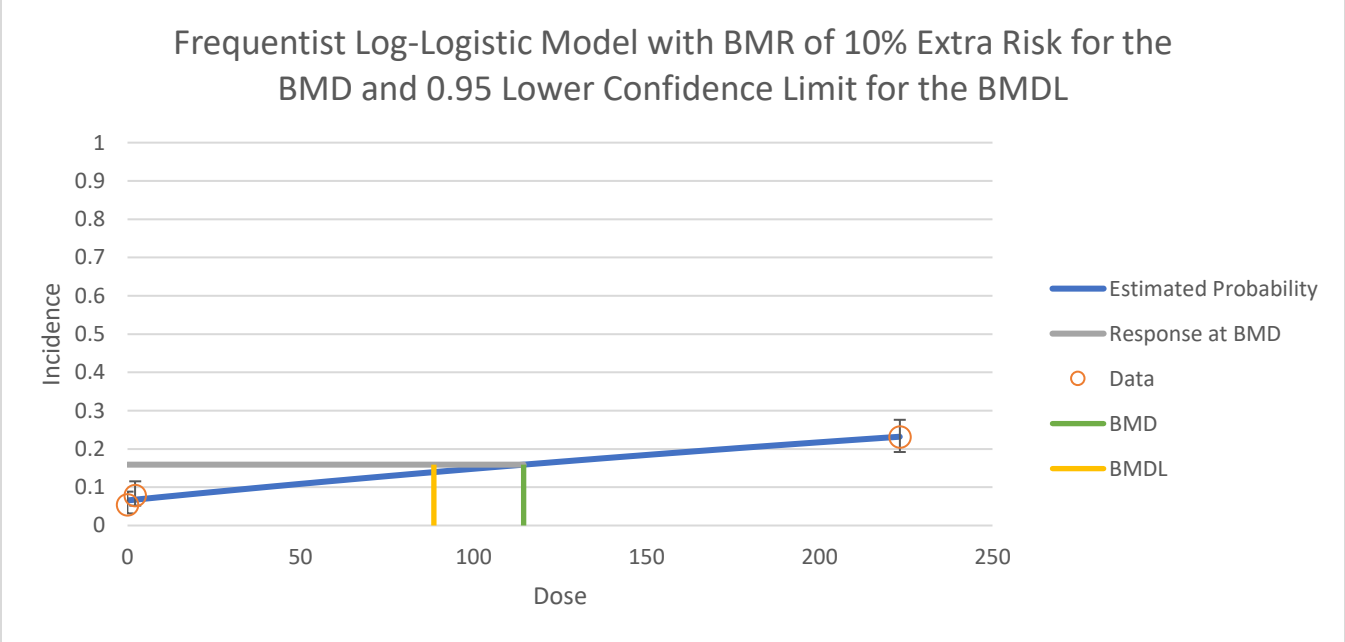

Figure 1-35. Plot of Response by Concentration with Fitted Curve for the Selected Model (Log-Logistic) for All Fetal Deaths Following Inhalation Exposure to 1,3-Butadiene in Male CD-1 Mice for 10 Weeks in a Dominant Lethality Study and BMR of 10%ER

Summary:

BMD	54.2325
BMDL	41.9389
BMDU	209.699
AIC	729.594
Log Likelihood	362.797
P-Value	0.276429
Overall DOF	1
Chi²	1.18456

Model Parameters:

Variable	Estimate	Bounded	Std Error	Lower CI	Upper CI
g	0.0654848	no	0.0106089	0.0446919	0.0862778
a	-6.93772	no	0.166598	-7.26425	-6.61119
b	1	yes	NA	NA	NA

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	278	15	18.2048	0.0654848	-0.776985
2.23	306	24	20.6559	0.0675029	0.761964
223.2	406	94	94.1393	0.23187	-0.0163842

Analysis of Deviance:

Model	Log Likelihood	# Params	Deviance	Test DOF	P-Value
Full model	-362.2	3	-	-	-
Fitted model	-362.797	2	1.19387	1	0.274551
Reduced model	-390.615	1	56.8302	2	4.56524e-13

Figure 1-36. Details Regarding the Selected Model (Log-Logistic) for All Fetal Deaths Following Inhalation Exposure to 1,3-Butadiene in Male CD-1 Mice for 10 Weeks in a Dominant Lethality Study

1.2.1.2 Combined Incidence of All Fetal Deaths following Inhalation Exposure to Male CD-1 Mice for 10 Weeks in Two Dominant Lethality Studies (Anderson et al., 1996), (Brinkworth et al., 1998)

Increased incidence of all deaths (total of early and late deaths including dead fetuses) was observed in two inhalation dominant lethality studies in CD-1 mice where unexposed dams were mated with male mice exposed to 1,3-butadiene by inhalation for 10 weeks (six hours/day, five days/week) prior to mating (Anderson et al., 1996), (Brinkworth et al., 1998). Data for the two studies were combined. Exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration 24 hours per day and seven days per week. The concentration and response data used for the modeling are presented in Table 1-25. Dichotomous models were fit to the incidence data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). A BMR of five percent ER was also selected for the lethality endpoint.

Table 1-25. Incidence of All Fetal Deaths Following Inhalation Exposure in Male CD-1 Mice in Two Dominant Lethality Studies (Combined) and Associated Concentrations Selected for Dose-Response Modeling for 1,3-Butadiene

Adjusted Concentration (ppm)	Number of Implants		Total Deaths (Total Early and Late Deaths Including Dead Fetuses)		Modeled Number of Implants	Modeled Total Deaths
	Anderson et al. (1996)	Brinkworth et al. (1998)	Anderson et al. (1996)	Brinkworth et al. (1998)	Combined	Combined
0	278	576	15	42	854	57
2.23	306	502	24	44	808	68
22.3	-	602	-	77	602	77
223.2	406	-	94	-	406	94

The BMD modeling results for increased combined incidence of all deaths (total of early and late deaths including dead fetuses) from the two studies are summarized in Table 1-26. Only the Log-Probit and Dichotomous Hill models provided adequate fit to the data (chi-square p-value > 0.1). Between these two models, the BMDLs were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Log-Probit).

Table 1-26. BMD Modeling Results for All Fetal Deaths Following Inhalation Exposure to 1,3-Butadiene in Male CD-1 Mice for 10 Weeks in Two Dominant Lethality Studies Combined[a]

Model	Goodness of Fit		BMD 5%ER (ppm)	BMDL 5%ER (ppm)	BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Basis for Model Selection
	p-value	AIC					
Dichotomous Hill	0.4608	1792	15.8	8.08	45.8	25.0	Only the Log-Probit and Dichotomous Hill models provided adequate fit to the data (chi-square p-value > 0.1). Between these two models, the BMDLs were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Log-Probit).
Gamma	0.0154	1797	59.9	47.2	123	96.9	
Log-Logistic	0.0210	1797	54.9	42.1	116	89.0	
Multistage 3	0.0154	1797	59.9	47.2	123	96.9	
Multistage 2	0.0154	1797	59.9	47.2	123	96.9	
Multistage 1	0.0154	1797	59.9	47.2	123	96.9	
Weibull	0.0154	1797	59.9	47.2	123	96.9	
Logistic	0.0034	1800	89.4	77.3	155	134	
Log-Probit	**0.9800**	**1791**	**13.0**	**4.83**	**55.0**	**30.1**	
Probit	0.0041	1800	84.8	72.5	151	129	
Quantal Linear	0.0154	1797	59.9	47.2	123	96.9	

[a] Selected model in bold.

Plots of the Log-Probit model with BMRs of five percent ER and 10 percent ER are shown in Figure 1-37 and Figure 1-38, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 1-39 (BMD and BMDL shown are for BMR of five percent ER; the rest is applicable to both BMRs).

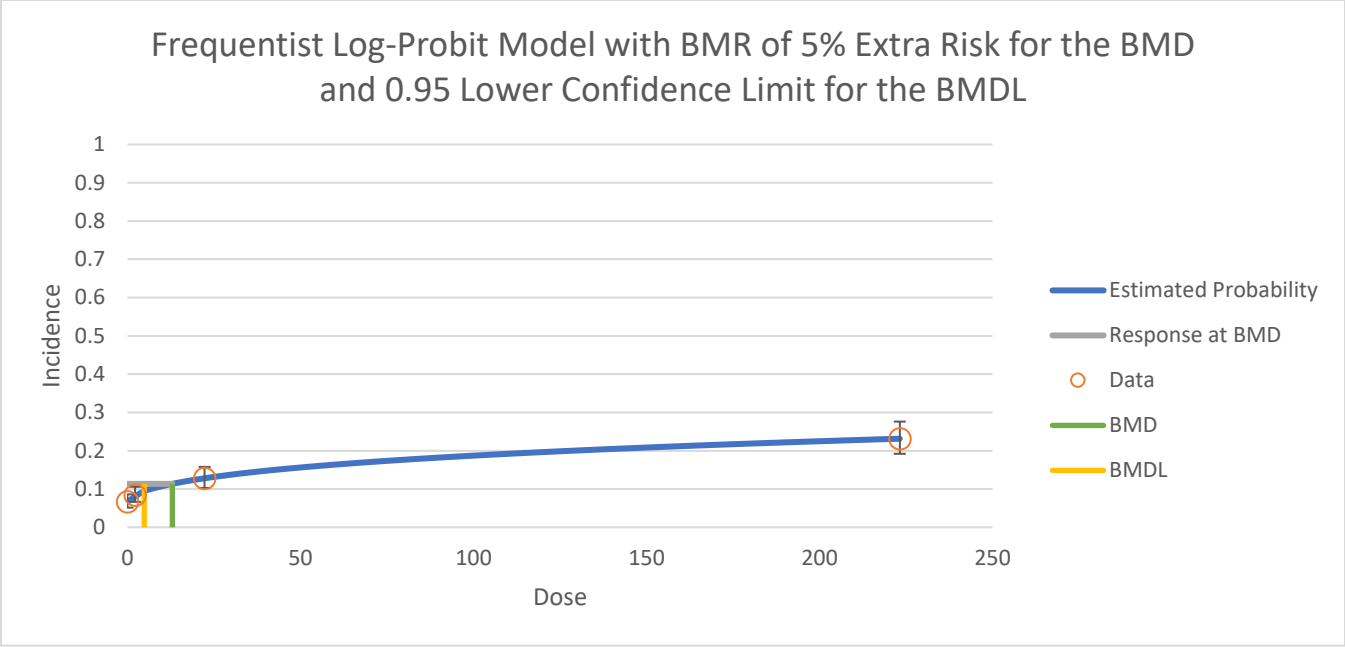

Figure 1-37. Plot of Response by Concentration with Fitted Curve for the Selected Model (Log-Probit) for All Fetal Deaths Following Inhalation Exposure to 1,3-Butadiene in Male CD-1 Mice for 10 Weeks in Two Dominant Lethality Studies Combined and BMR of 5% ER

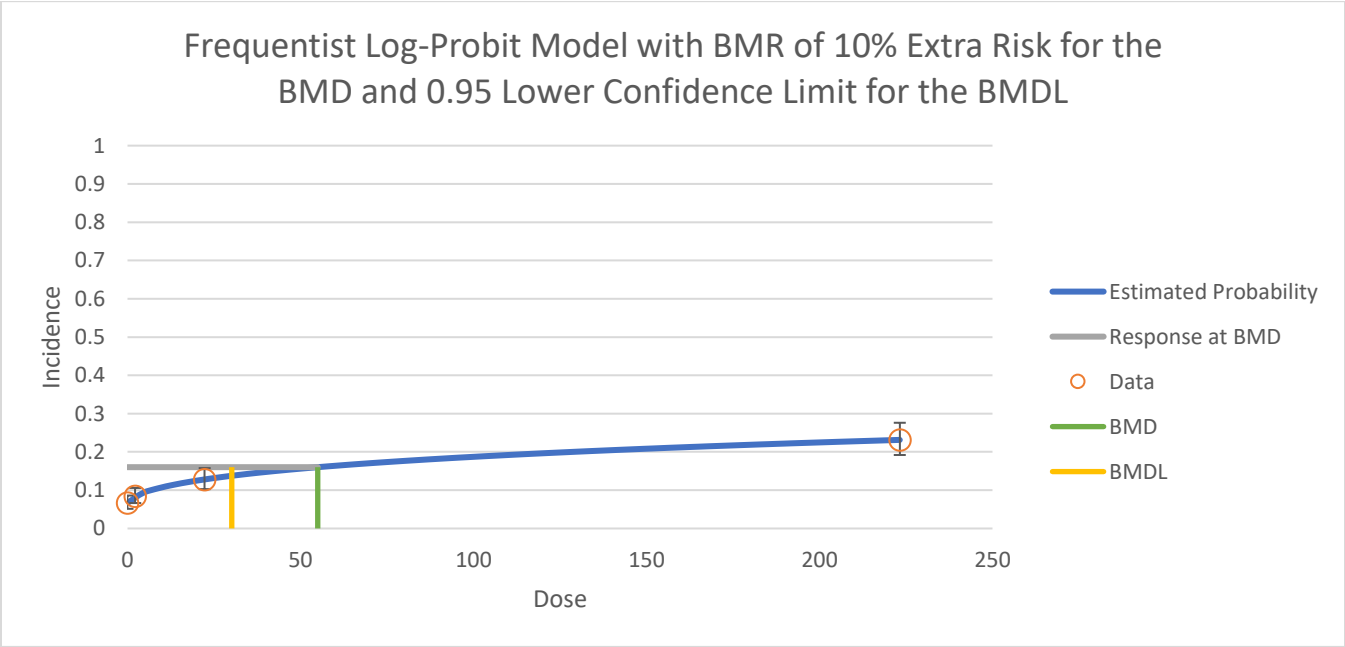

Figure 1-38. Plot of Response by Concentration with Fitted Curve for the Selected Model (Log-Probit) for All Fetal Deaths Following Inhalation Exposure to 1,3-Butadiene in Male CD-1 Mice for 10 Weeks in Two Dominant Lethality Studies Combined and BMR of 10% ER

Summary:

BMD	12.9639
BMDL	4.8302
BMDU	31.6517
AIC	1791.19
Log Likelihood	892.595
P-Value	0.979965
Overall DOF	1
Chi²	0.000630639

Model Parameters:

Variable	Estimate	Bounded	Std Error	Lower CI	Upper CI
g	0.0668027	no	0.00823921	0.0506541	0.0829512
a	-2.2891	no	0.26468	-2.80787	-1.77034
b	0.251446	no	0.0525665	0.148418	0.354475

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	854	57	57.0495	0.0668027	-0.00678103
2.23	808	68	67.8688	0.083996	0.0166409
22.3	602	77	77.1345	0.12813	-0.0164031
223.2	406	94	93.9472	0.231397	0.00621908

Analysis of Deviance:

Model	Log Likelihood	# Params	Deviance	Test DOF	P-Value
Full model	-892.595	4	-	-	-
Fitted model	-892.595	3	0.000630618	1	0.979966
Reduced model	-929.995	1	74.7988	3	4.44089e-16

Figure 1-39. Details Regarding the Selected Model (Log-Probit) for All Fetal Deaths Following Inhalation Exposure to 1,3-Butadiene in Male CD-1 Mice for 10 Weeks in Two Dominant Lethality Studies Combined

1.3 Hematological and Immune Effects

One chronic repeat-dose inhalation exposure study was identified for BMD modeling that showed significant changes in hematological endpoints consistent with anemia (NTP, 1993)

1.3.1 Erythrocyte Counts in Male B6C3F1 Mice Exposed via Inhalation for 40 Weeks (NTP, 1993)

Erythrocyte counts were significantly decreased in male B6C3F1 mice exposed to 1,3-butadiene by inhalation for 40 weeks (six hours per day, five days per week) (NTP, 1993). The measured exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day and seven days per week. Continuous models were fit to the dose-response data.

A BMR of one SD was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). A BMR of 10 percent RD was also selected. The concentration and response data used for the modeling are presented in Table 1-27.

Table 1-27. Decreased Erythrocyte Counts in Male B6C3F1 Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,3-Butadiene from an Inhalation Exposure Study

Adjusted Concentration (ppm)	Number of Animals	Mean (10^6/µL)	SD (10^6/µL)
0	10	10.38	0.28
1.11	10	10.29	0.32
3.54	10	10.40	0.41
11.0	10	9.86	0.38
35.5	10	9.60	0.44
111	10	7.55	1.20

The BMD modeling results for decreased erythrocyte count in male mice are summarized in Table 1-28. The constant variance model did not provide adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, none of the models provided adequate fit to the means (test 4 p-value < 0.1). The full data set is not suitable for BMD modeling. With the highest concentration dropped, the constant variance model provided an adequate fit to the variance data. With the constant variance model applied, all models provided adequate fit to the means (test 4 p-value > 0.1) when using the BMR of one SD. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Exponential 5). When applying a BMR of 10 percent RD, the BMD computation failed for the Exponential 5 and Hill models, and they were unusable. Among the remaining models, the BMDLs were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Exponential 3); using a BMR of 10 percent RD resulted in BMD and BMDL values being higher than the maximum modeled concentration.

Table 1-28. Summary of BMD Modeling Results for Decreased Erythrocyte Count in Male B6C3F1 Mice Following Inhalation Exposure to 1,3-Butadiene for 40 Weeks[a]

Model	Goodness of Fit (Means)		BMD 1SD (ppm)	BMDL 1SD (ppm)	BMD 10%RD (ppm)	BMDL 10%RD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC					
Full Data set (Nonconstant Variance Model)[b]							For the whole data set, the constant variance model did not provide adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, none of the models provided adequate fit to the means (test 4 p-value < 0.1). The full data set is not suitable for BMD modeling. With the highest concentration dropped from
Exponential 3	<0.0001	112.5	25.2	17.1	42.8	33.3	
Exponential 5	<0.0001	114.5	25.2	17.1	42.8	33.3	
Hill	0.0441	85.77	12.6	8.25	39.8	32.7	
Polynomial Degree 3	<0.0001	110.2	25.8	19.3	45.6	37.1	
Polynomial Degree 2	<0.0001	112.2	25.5	19.3	44.6	37.0	
Power	<0.0001	112.4	24.9	19.3	43.3	37.0	
Linear	<0.0001	110.4	23.0	19.2	41.3	36.9	

Model	Goodness of Fit (Means)		BMD 1SD (ppm)	BMDL 1SD (ppm)	BMD 10%RD (ppm)	BMDL 10%RD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC					
Highest Concentration Dropped (Constant Variance Model)							the data set, the constant variance model provided an adequate fit to the variance data. With the constant variance model applied, all models provided adequate fit to the means (test 4 p-value > 0.1) when using the BMR of 1SD. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Exponential 5). When applying a BMR of 10%RD, the BMD computation failed for the Exponential 5 and Hill models, and they were unusable. Among the remaining models, the BMDLs were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Exponential 3); using a BMR of 10%RD resulted in BMD and BMDL values being higher than the maximum modeled concentration.
Exponential 3	**0.1188**	**49.23**	16.3	12.0	**46.7**	**35.7**	
Exponential 5	**0.7587**	**45.93**	**10.7**	**8.07**	-	-	
Hill	0.4574	47.93	10.4	5.19	-	-	
Polynomial Degree 3	0.1106	49.40	16.8	12.5	46.4	35.9	
Polynomial Degree 2	0.1105	49.40	16.7	12.5	46.2	35.9	
Power	0.1106	49.40	16.8	12.5	46.4	35.9	
Linear	0.1106	49.40	16.8	12.5	46.4	35.9	

[a] Selected model in bold.
[b] Model results with nonconstant variance are presented for the full data set because the constant variance model did not provide an adequate fit to the variance data for this data set.

Plots of the Exponential 5 model with a BMR of one SD and the Exponential 3 model with a BMR of 10 percent RD fit to the data set (with highest concentration dropped from the data set) are shown in Figure 1-40 and Figure 1-41, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 1-42 for the Exponential 5 model with a BMR of one SD and Figure 1-43 for the Exponential 3 model with a BMR of 10 percent RD.

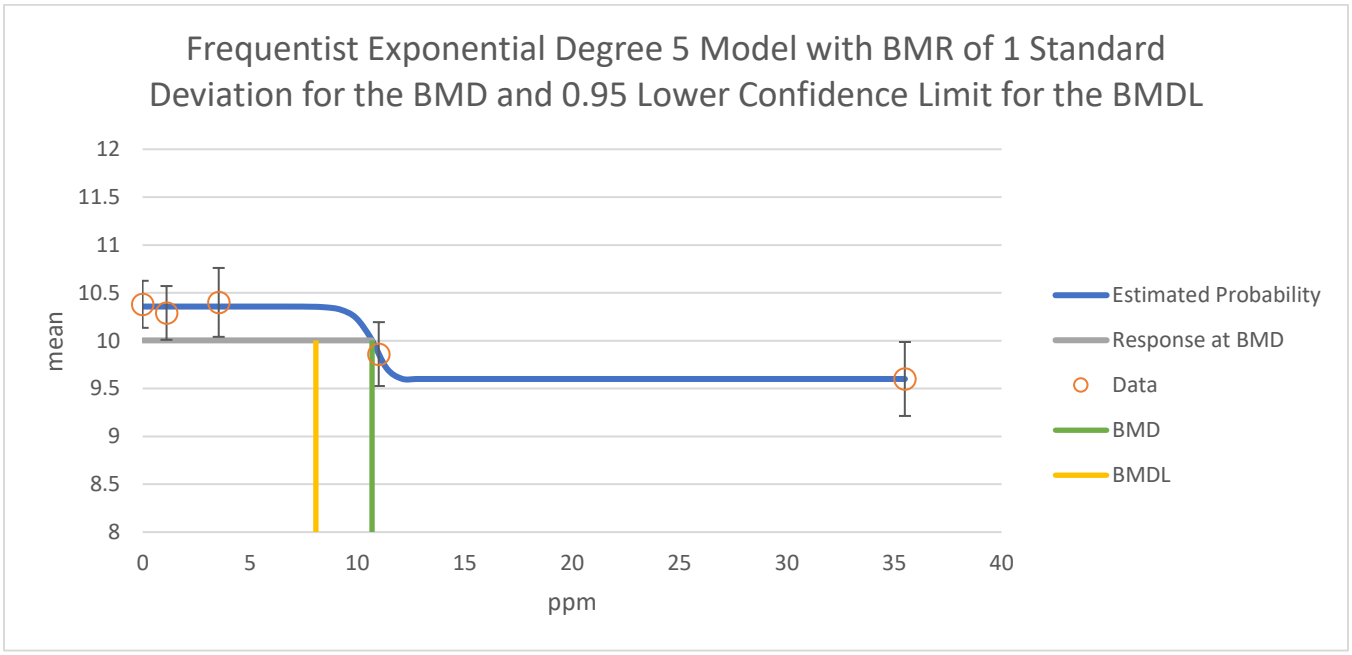

Figure 1-40. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 5, Constant Variance Model) for Decreased Erythrocyte Count in Male B6C3F1 Mice Following Inhalation Exposure to 1,3-Butadiene for 40 Weeks and BMR of 1SD (Highest Concentration Dropped)

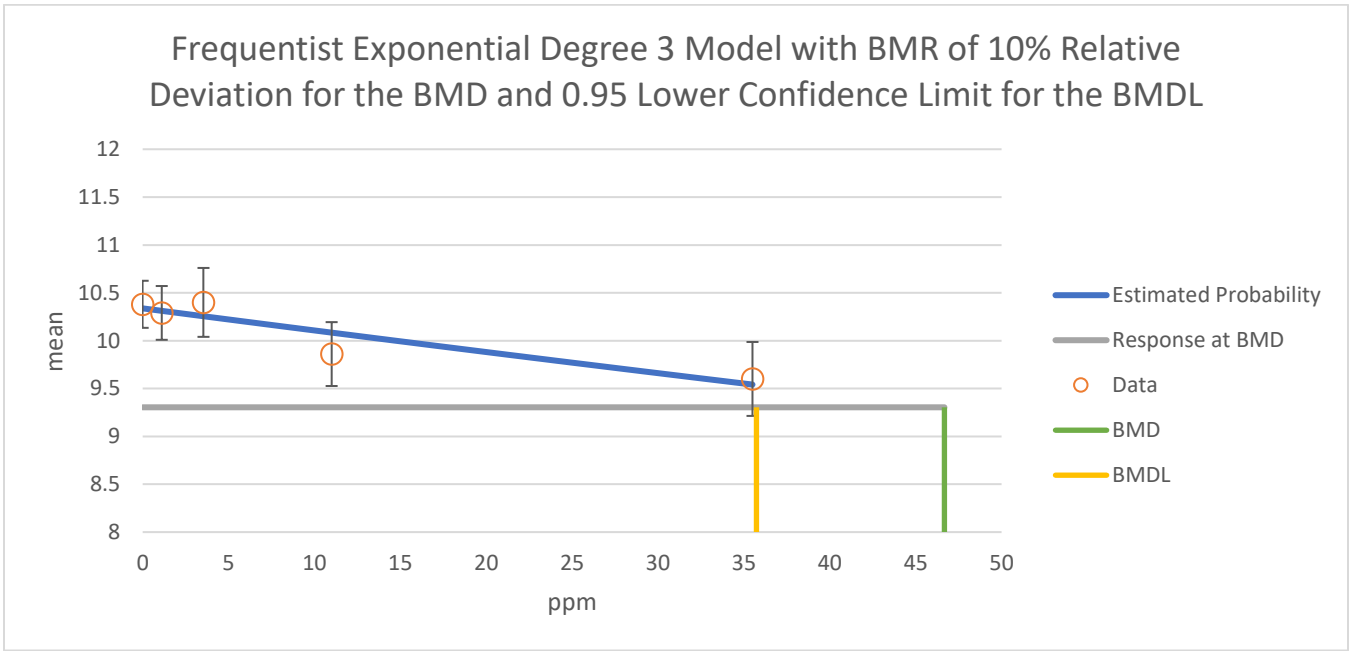

Figure 1-41. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 3, Constant Variance Model) for Decreased Erythrocyte Count in Male B6C3F1 Mice Following Inhalation Exposure to 1,3-Butadiene for 40 Weeks and BMR of 10%RD (Highest Concentration Dropped)

Summary:

BMD	10.6818
BMDL	8.92677
BMDU	11.237
AIC	45.9279
Log Likelihood	18.964
P-Value	0.758697
Model DOF	2

Model Parameters:

Variable	Estimate	Bounded	Std Error	Lower CI	Upper CI
a	10.3567	no	0.0645537	10.2301	10.4832
b	0.0912431	no	0.00247431	0.0863935	0.0960927
c	0.926939	no	0.0132099	0.901048	0.95283
d	18	yes	NA	NA	NA
log-alpha	-2.07932	no	0.2	-2.47131	-1.68733

Goodness of Fit:

Dose	Size	Observed Mean	Calculated Mean	Estimated Mean	Scaled Residual
0	10	10.38	10.38	10.3567	0.208687
1.11	10	10.29	10.29	10.3567	-0.596248
3.54	10	10.4	10.4	10.3567	0.387561
11	10	9.86	9.86	9.86	-5.94564e-08
35.5	10	9.6	9.6	9.6	-1.00321e-07

Dose	Size	Observed SD	Calculated SD	Estimated SD
0	10	0.28	0.28	0.353575
1.11	10	0.32	0.32	0.353575
3.54	10	0.41	0.41	0.353575
11	10	0.38	0.38	0.353575
35.5	10	0.44	0.44	0.353575

Likelihoods of Interest:

Model	Log Likelihood	# Params	AIC
A1	-18.6878	6	49.3756
A2	-17.3873	10	54.7746
A3	-18.6878	6	49.3756
fitted	-18.964	4	45.9279
reduced	-33.7693	2	71.5386

Tests of Interest:

Name	Loglikelihood Ratio	Test DOF	P-Value
Test 1	32.764	8	6.79184e-05
Test 2	2.60103	4	0.626641
Test 3	2.60103	4	0.626641
Test 4	0.552305	2	0.758697

Figure 1-42. Details Regarding the Selected Model (Exponential 5, Constant Variance Model) for Decreased Erythrocyte Count in Male B6C3F1 Mice Following Inhalation Exposure to 1,3-Butadiene for 40 Weeks and a BMR of 1SD (Highest Concentration Dropped)

Summary:

BMD	46.6728
BMDL	35.7296
BMDU	66.8917
AIC	49.2327
Log Likelihood	21.6163
P-Value	0.118776
Model DOF	3

Model Parameters:

Variable	Estimate	Bounded	Std Error	Lower CI	Upper CI
a	10.3375	no	0.06729	10.2057	10.4694
b	0.00225743	no	0.000411257	0.00145138	0.00306348
d	1	yes	NA	NA	NA
log-alpha	-1.97322	no	0.199999	-2.36522	-1.58123

Goodness of Fit:

Dose	Size	Observed Mean	Calculated Mean	Estimated Mean	Scaled Residual
0	10	10.38	10.38	10.3375	0.360155
1.11	10	10.29	10.29	10.3117	-0.183766
3.54	10	10.4	10.4	10.2553	1.22767
11	10	9.86	9.86	10.084	-1.89988
35.5	10	9.6	9.6	9.54143	0.496802

Dose	Size	Observed SD	Calculated SD	Estimated SD
0	10	0.28	0.28	0.372838
1.11	10	0.32	0.32	0.372838
3.54	10	0.41	0.41	0.372838
11	10	0.38	0.38	0.372838
35.5	10	0.44	0.44	0.372838

Likelihoods of Interest:

Model	Log Likelihood	# Params	AIC
A1	-18.6878	6	49.3756
A2	-17.3873	10	54.7746
A3	-18.6878	6	49.3756
fitted	-21.6163	3	49.2327
reduced	-33.7693	2	71.5386

Tests of Interest:

Name	Loglikelihood Ratio	Test DOF	P-Value
Test 1	32.764	8	6.79184e-05
Test 2	2.60103	4	0.626641
Test 3	2.60103	4	0.626641
Test 4	5.85706	3	0.118776

Figure 1-43. Details Regarding the Selected Model (Exponential 3, Constant Variance Model) for Decreased Erythrocyte Count in Male B6C3F1 Mice Following Inhalation Exposure to 1,3-Butadiene for 40 Weeks and a BMR of 10%RD (Highest Concentration Dropped)

1.3.2 Hemoglobin Concentration in Male B6C3F1 Mice Exposed via Inhalation for 40 Weeks (NTP, 1993)

Hemoglobin concentration was significantly decreased in male B6C3F1 mice exposed to 1,3-butadiene by inhalation for 40 weeks (six hours per day, five days per week) (NTP, 1993). The measured exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day and seven days per week. Continuous models were fit to the dose-response data.

A BMR of one SD was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). A BMR of 10 percent RD was also selected. The concentration and response data used for the modeling are presented in Table 1-29.

Table 1-29. Decreased Hemoglobin Concentration in Male B6C3F1 Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,3-Butadiene from an Inhalation Exposure Study

Adjusted Concentration (ppm)	Number of Animals	Mean (g/dL)	SD (g/dL)
0	10	16.5	0.3
1.11	10	16.4	0.6
3.54	10	16.7	0.6
11.0	10	15.9	0.6
35.5	10	15.6	0.9
111	10	13.5	1.9

The BMD modeling results for decreased hemoglobin concentration are summarized in Table 1-30. The constant variance model did not provide adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, none of the models provided adequate fit to the means (test 4 p-value < 0.1); dropping the highest concentration from the data set gave similar results; the full data set and the data set with the highest concentration dropped were not suitable for BMD modeling. With the two highest concentrations dropped from the data set, the constant variance model provided an adequate fit to the variance data. With the constant variance model applied, all models, except for the Exponential 5 and Hill models, provided adequate fit to the means (test 4 p-value > 0.1); the goodness-of-fit test for the means (test 4) could not be calculated for the Exponential 5 and Hill models because the models were saturated (degree of freedom = 0). The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Power). Using a BMR of 10%RD resulted in BMD and BMDL values being (slightly) higher than the maximum modeled concentration.

Table 1-30. Summary of BMD Modeling Results for Decreased Hemoglobin Concentration in Male B6C3F1 Mice Following Inhalation Exposure to 1,3-Butadiene for 40 Weeks[a]

Model	Goodness of Fit (Means)		BMD 1SD (ppm)	BMDL 1SD (ppm)	BMD 10%RD (ppm)	BMDL 10%RD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC					
Full Data set (Nonconstant Variance Model)[b]							For the full data set and the data set with the highest concentration dropped, the constant variance model did not provide adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, none of the models provided adequate fit to the means (test 4 p-value < 0.1). The full data set and the data set with the highest concentration dropped are not suitable for BMD modeling. With the two highest concentrations dropped from the data set, the constant variance model provided an adequate fit to the variance data. With the constant variance model applied, all models, except for the Exponential 5 and Hill models, provided adequate fit to the means (test 4 p-value > 0.1). The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Power).
Exponential 3	<0.0001	169.9	32.3	25.5	58.5	48.6	
Exponential 5	<0.0001	171.9	32.3	25.5	58.5	48.6	
Hill	0.0061	148.3	20.5	12.0	51.4	36.6	
Polynomial Degree 3	<0.0001	167.9	34.5	27.8	61.1	51.8	
Polynomial Degree 2	<0.0001	167.9	34.5	27.8	61.1	51.8	
Power	<0.0001	169.9	34.6	27.8	61.1	51.8	
Linear	<0.0001	167.9	34.5	27.8	61.1	51.8	
Highest Concentration Dropped (Nonconstant Variance Model)[b]							
Exponential 3	0.0500	101.3	22.8	15.6	62.0	43.6	
Exponential 5	0.0541	101.6	10.9	4.03	-	-	
Hill	0.0868	100.7	10.8	8.97	-	-	
Polynomial Degree 3	0.0229	103.3	23.1	16.1	60.8	42.1	
Polynomial Degree 2	0.0489	101.3	23.2	16.1	60.9	43.1	
Power	0.0489	101.3	23.2	16.1	60.9	43.3	
Linear	0.0489	101.3	23.2	16.1	60.9	43.3	
Two Highest Concentrations Dropped (Constant Variance Model)							
Exponential 3	0.1878	69.86	10.9	10.6	11.7	11.4	
Exponential 5	NA	71.86	10.9	10.4	11.7	11.3	
Hill	NA	71.86	10.9	4.00	11.7	11.4	
Polynomial Degree 3	0.3688	68.12	10.3	7.80	15.2	13.2	
Polynomial Degree 2	0.2768	68.70	10.1	7.31	17.9	14.4	
Power	**0.4201**	**67.86**	**10.9**	**7.95**	**11.6**	**11.3**	
Linear	0.1065	70.61	9.86	6.06	30.1	18.9	

[a] Selected model in bold.

Model	Goodness of Fit (Means)		BMD 1SD (ppm)	BMDL 1SD (ppm)	BMD 10%RD (ppm)	BMDL 10%RD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC					
[b] Model results with nonconstant variance are presented for the full data set and the data set with the highest concentration dropped because the constant variance model did not provide an adequate fit to the variance data for these data sets.							

Plots of the Power model (constant variance model with two highest concentrations dropped from the data set) with BMRs of one SD and 10 percent RD are shown in Figure 1-44 and Figure 1-45, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 1-46 (BMD and BMDL shown are for BMR of one SD; the rest is applicable to both BMRs).

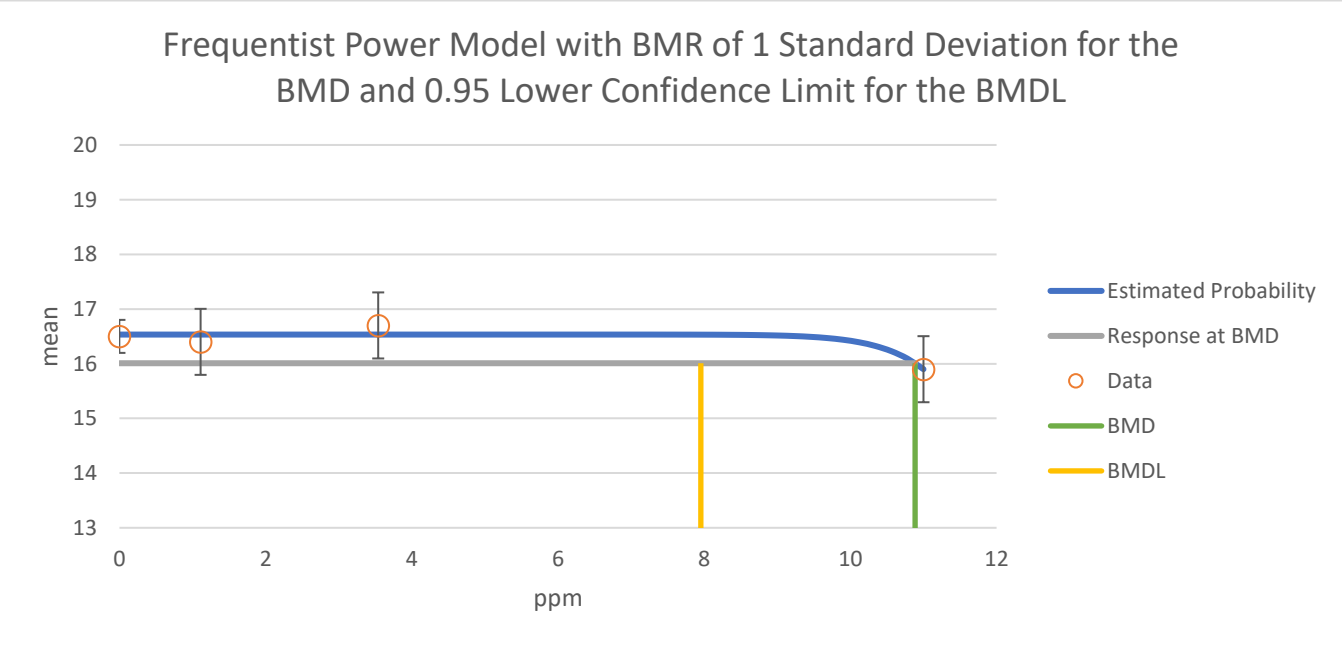

Figure 1-44. Plot of Response by Dose with Fitted Curve for the Selected Model (Power, Constant Variance Model) for Decreased Hemoglobin Concentration in Male B6C3F1 Mice Following

Inhalation Exposure to 1,3-Butadiene for 40 Weeks and BMR of 1SD (Two Highest Concentrations Dropped)

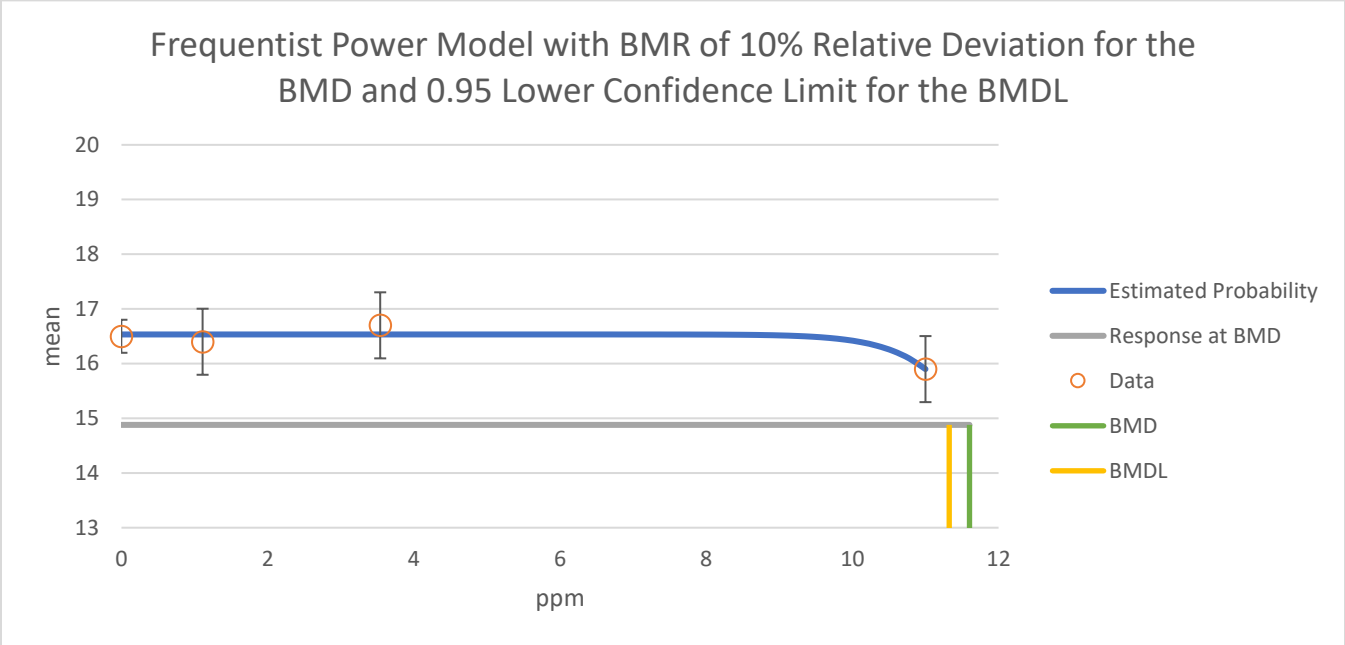

Figure 1-45. Plot of Response by Dose with Fitted Curve for the Selected Model (Power, Constant Variance Model) for Decreased Hemoglobin Concentration in Male B6C3F1 Mice Following Inhalation Exposure to 1,3-Butadiene for 40 Weeks and BMR of 10%RD (Two Highest Concentrations Dropped)

Summary:

BMD	10.8852
BMDL	7.95389
BMDU	13.8145
AIC	67.8636
Log Likelihood	30.9318
P-Value	0.420094
Model DOF	2

Model Parameters:

Variable	Estimate	Bounded	Std Error	Lower CI	Upper CI
g	16.5333	no	0.0957286	16.3457	16.721
v	-1.13911e-19	no	3.44356e-20	-1.81403e-19	-4.6418e-20
n	18	yes	NA	NA	NA
alpha	0.274917	no	0.0169001	0.241793	0.30804

Goodness of Fit:

Dose	Size	Observed Mean	Calculated Mean	Estimated Mean	Scaled Residual
0	10	16.5	16.5	16.5333	-0.201038
1.11	10	16.4	16.4	16.5333	-0.804152
3.54	10	16.7	16.7	16.5333	1.00519
11	10	15.9	15.9	15.9	-1.9556e-08

Dose	Size	Observed SD	Calculated SD	Estimated SD
0	10	0.3	0.3	0.524325
1.11	10	0.6	0.6	0.524325
3.54	10	0.6	0.6	0.524325
11	10	0.6	0.6	0.524325

Likelihoods of Interest:

Model	Log Likelihood	# Params	AIC
A1	-30.0645	5	70.129
A2	-27.2858	8	70.5717
A3	-30.0645	5	70.129
fitted	-30.9318	3	67.8636
reduced	-35.7682	2	75.5365

Tests of Interest:

Name	Loglikelihood Ratio	Test DOF	P-Value
Test 1	16.9648	6	0.00941344
Test 2	5.55737	3	0.135247
Test 3	5.55737	3	0.135247
Test 4	1.73455	2	0.420094

Figure 1-46. Details Regarding the Selected Model (Power, Constant Variance Model) for Decreased Hemoglobin Concentration in Male B6C3F1 Mice Following Inhalation Exposure to 1,3-Butadiene for 40 Weeks (Two Highest Concentration Dropped)

1.3.3 Packed Red Cell Volume in Male B6C3F1 Mice Exposed via Inhalation for 40 Weeks (NTP, 1993)

Packed red cell volume was significantly decreased in male B6C3F1 mice exposed to 1,3-butadiene by inhalation for 40 weeks (six hours per day, five days per week) (NTP, 1993). The measured exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day and seven days per week. Continuous models were fit to the dose-response data.

A BMR of one SD was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). A BMR of 10 percent RD was also selected. The concentration and response data used for the modeling are presented in Table 1-31.

Table 1-31. Decreased Packed Red Cell Volume in Male B6C3F1 Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,3-Butadiene from an Inhalation Exposure Study

Adjusted Concentration (ppm)	Number of Animals	Mean (mL/dL)	SD (mL/dL)
0	10	48.1	1.6
1.11	10	47.8	1.6
3.54	10	48.2	2.2
11.0	10	45.9	2.2
35.5	10	45.4	2.8
111	10	39.9	5.4

The BMD modeling results for decreased packed red cell volume are summarized in Table 1-32. The constant variance model did not provide adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, none of the models provided adequate fit to the means (test 4 p-value < 0.1). The full data set is not suitable for BMD modeling. With the highest concentration dropped, the constant variance model provided an adequate fit to the variance data. With the constant variance model applied, all models provided adequate fit to the means (test 4 p-value > 0.1) when using the BMR of 1SD. The BMDLs for the fit models were not sufficiently close (differed by > 3-fold); therefore, the model with the lowest BMDL was selected (Hill, which also had the lowest AIC). When applying a BMR of 10%RD, the BMD computation failed for the Hill model, and it was unusable. Among the remaining models, the BMDLs were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Exponential 3); using a BMR of 10%RD resulted in BMD and BMDL values being higher than the maximum modeled concentration.

Table 1-32. Summary of BMD Modeling Results for Decreased Packed Red Cell Volume in Male B6C3F1 Mice Following Inhalation Exposure to 1,3-Butadiene for 40 Weeks[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	BMD 10%RD (ppm)	BMDL 10%RD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC					
Full data set (Nonconstant Variance Model)[b]							For the full data set, the constant variance model did not provide adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, none of the models provided adequate fit to the means (test 4 p-value < 0.1). The full data set is not suitable for BMD modeling. With the highest concentration dropped from the data set, the constant variance model provided an adequate fit to the variance data. With the constant variance model applied, all models provided adequate fit to the means (test 4 p-value > 0.1) when using the BMR of 1SD. The
Exponential 3	0.0001	301.5	37.2	28.9	64.0	52.1	
Exponential 5	<0.0001	303.4	34.6	18.0	61.2	36.2	
Hill	0.0023	294.6	33.7	24.0	62.7	31.5	
Polynomial Degree 3	0.0001	301.5	39.5	31.3	66.5	55.2	
Polynomial Degree 2	<0.0001	305.0	38.3	29.8	65.0	52.9	
Power	0.0001	301.5	39.5	31.3	66.5	55.2	
Linear	0.0001	301.5	39.5	31.3	66.5	55.2	
Highest Concentration Dropped (Constant Variance Model)							
Exponential 3	**0.2570**	**222.2**	26.6	17.5	**62.5**	**41.9**	
Exponential 5	0.1325	224.2	26.6	17.5	62.5	41.9	
Hill[c]	**0.8993**	**220.4**	**10.8**	**3.93**	-	-	
Polynomial Degree 3	0.2485	222.3	27.9	17.9	63.4	41.5	
Polynomial Degree 2	0.2497	222.3	27.0	18.0	61.5	41.8	
Power	0.2497	222.3	27.0	18.0	61.5	41.8	

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	BMD 10%RD (ppm)	BMDL 10%RD (ppm)	Basis for Model Selection
	Test 4 p-value	AIC					
Linear	0.2497	222.3	27.0	18.0	61.5	41.8	BMDLs for the fit models were not sufficiently close (differed by > 3-fold); therefore, the model with the lowest BMDL was selected (Hill, which also had the lowest AIC). When applying a BMR of 10%RD, the BMD computation failed for the Hill model, and it was unusable. Among the remaining models, the BMDLs were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Exponential 3).

[a] Selected model in bold.
[b] Model results with nonconstant variance are presented for the full data set because the constant variance model did not provide an adequate fit to the variance data for this data set.
[c] When applying a BMR of 10%RD, the BMD computation failed for the Hill model and it was unusable; therefore, the Hill model was not the lowest AIC for this BMR.

Plots of the Hill model (constant variance model with highest concentration dropped) with a BMR of one SD and the Exponential 3 model (constant variance model with the highest concentration dropped) with a BMR of 10 percent RD are shown in Figure 1-47 and Figure 1-48, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 1-49 for the Hill model and a BMR of one SD and in Figure 1-50 for the Exponential 3 model and a BMR of 10 percent RD.

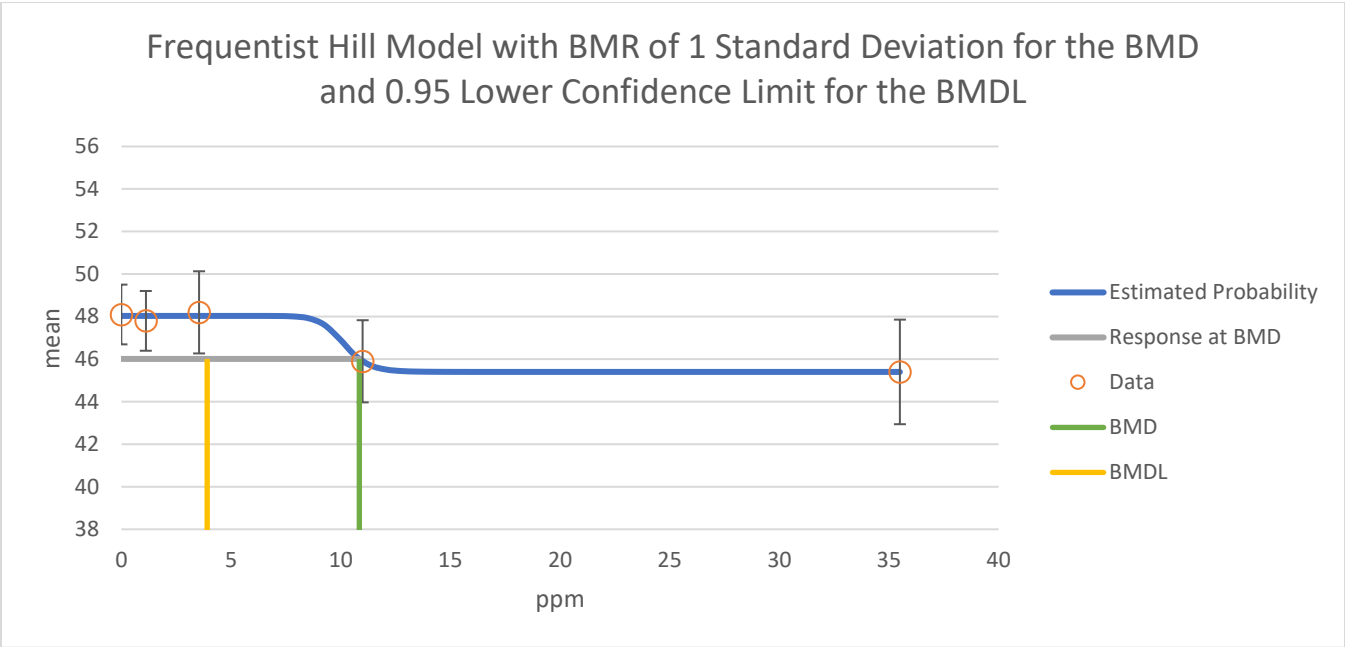

Figure 1-47. Plot of Response by Dose with Fitted Curve for the Selected Model (Hill, Constant Variance Model) for Decreased Packed Red Cell Volume in Male B6C3F1 Mice Following Inhalation Exposure to 1,3-Butadiene for 40 Weeks and BMR of 1SD (Highest Concentration Dropped)

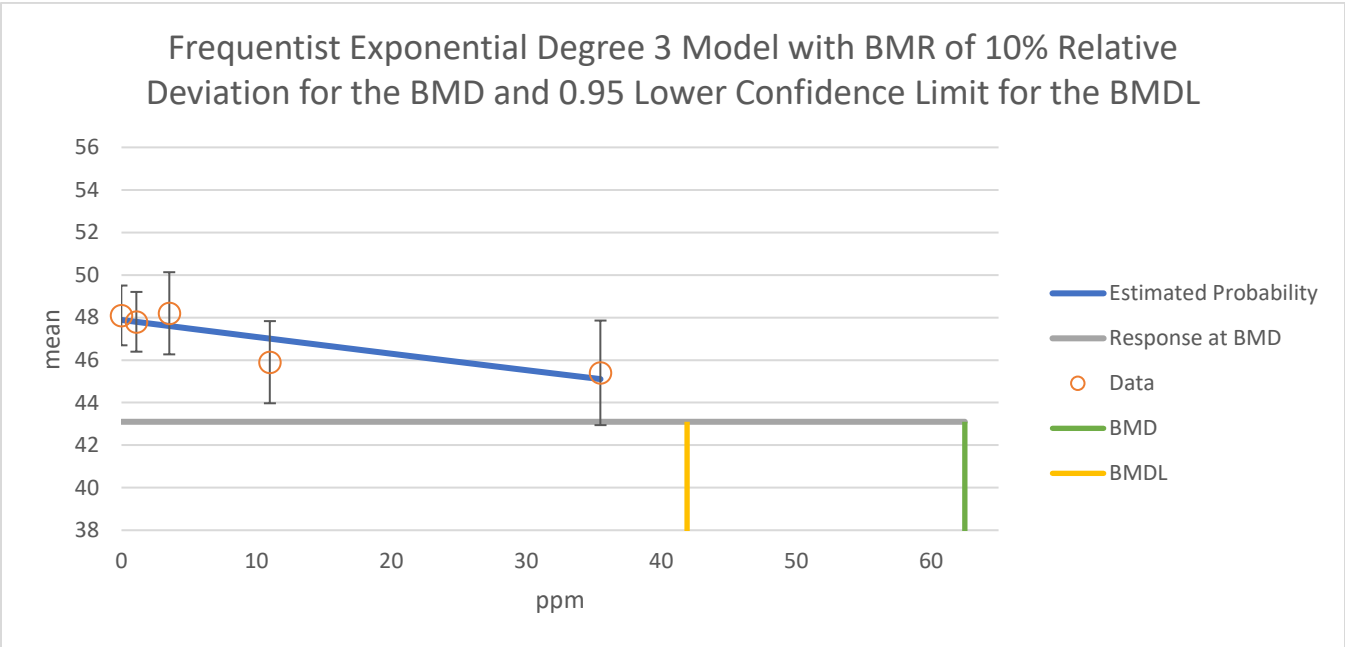

Figure 1-48. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 3, Constant Variance Model) for Decreased Packed Red Cell Volume in Male B6C3F1 Mice Following Inhalation Exposure to 1,3-Butadiene for 40 Weeks and BMR of 10%RD (Highest Concentration Dropped)

Summary:

BMD	10.8468
BMDL	3.93266
BMDU	-9999
AIC	220.352
Log Likelihood	106.176
P-Value	0.899327
Model DOF	2

Model Parameters:

Variable	Estimate	Bounded	Std Error	Lower CI	Upper CI
g	48.0333	no	0.369341	47.3094	48.7572
v	-2.63333	no	0.738642	-4.08105	-1.18562
k	10.1482	no	1.15006	7.8941	12.4022
n	18	yes	NA	NA	NA
alpha	4.09253	no	3.34972	-2.47279	10.6579

Goodness of Fit:

Dose	Size	Observed Mean	Calculated Mean	Estimated Mean	Scaled Residual
0	10	48.1	48.1	48.0333	0.104211
1.11	10	47.8	47.8	48.0333	-0.364738
3.54	10	48.2	48.2	48.0333	0.260527
11	10	45.9	45.9	45.9	-5.11461e-07
35.5	10	45.4	45.4	45.4	4.53671e-07

Dose	Size	Observed SD	Calculated SD	Estimated SD
0	10	1.6	1.6	2.023
1.11	10	1.6	1.6	2.023
3.54	10	2.2	2.2	2.023
11	10	2.2	2.2	2.023
35.5	10	2.8	2.8	2.023

Likelihoods of Interest:

Model	Log Likelihood	# Params	AIC
A1	-106.07	6	224.14
A2	-103.778	10	227.557
A3	-106.07	6	224.14
fitted	-106.176	4	220.352
reduced	-113.478	2	230.956

Tests of Interest:

Name	Loglikelihood Ratio	Test DOF	P-Value
Test 1	19.3998	8	0.0128619
Test 2	4.58319	4	0.332797
Test 3	4.58319	4	0.332797
Test 4	0.212218	2	0.899327

Figure 1-49. Details Regarding the Selected Model (Hill, Constant Variance Model) for Decreased Packed Red Cell Volume in Male B6C3F1 Mice Following Inhalation Exposure to 1,3-Butadiene for 40 Weeks and a BMR of 1SD (Highest Concentration Dropped)

Summary:

BMD	62.5002
BMDL	41.9153
BMDU	121.198
AIC	222.182
Log Likelihood	108.091
P-Value	0.256961
Model DOF	3

Model Parameters:

Variable	Estimate	Bounded	Std Error	Lower CI	Upper CI
a	47.8871	no	0.378638	47.145	48.6292
b	0.00168576	no	0.000493	0.000719499	0.00265203
d	1	yes	NA	NA	NA
log-alpha	1.48576	no	0.199997	1.09377	1.87775

Goodness of Fit:

Dose	Size	Observed Mean	Calculated Mean	Estimated Mean	Scaled Residual
0	10	48.1	48.1	47.8871	0.320251
1.11	10	47.8	47.8	47.7976	0.00360252
3.54	10	48.2	48.2	47.6022	0.899335
11	10	45.9	45.9	47.0073	-1.66588
35.5	10	45.4	45.4	45.1054	0.443191

Dose	Size	Observed SD	Calculated SD	Estimated SD
0	10	1.6	1.6	2.10198
1.11	10	1.6	1.6	2.10198
3.54	10	2.2	2.2	2.10198
11	10	2.2	2.2	2.10198
35.5	10	2.8	2.8	2.10198

Likelihoods of Interest:

Model	Log Likelihood	# Params	AIC
A1	-106.07	6	224.14
A2	-103.778	10	227.557
A3	-106.07	6	224.14
fitted	-108.091	3	222.182
reduced	-113.478	2	230.956

Tests of Interest:

Name	Loglikelihood Ratio	Test DOF	P-Value
Test 1	19.3998	8	0.0128619
Test 2	4.58319	4	0.332797
Test 3	4.58319	4	0.332797
Test 4	4.04203	3	0.256961

Figure 1-50. Details Regarding the Selected Model (Exponential 3, Constant Variance Model) for Decreased Packed Red Cell Volume in Male B6C3F1 Mice Following Inhalation Exposure to 1,3-Butadiene for 40 Weeks and a BMR of 10%RD (Highest Concentration Dropped)

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