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Pollution Prevention

Risk Evaluation for 1,1-Dichloroethane

Supplemental Information File:

Benchmark Dose Modeling Results for 1,1-Dichloroethane

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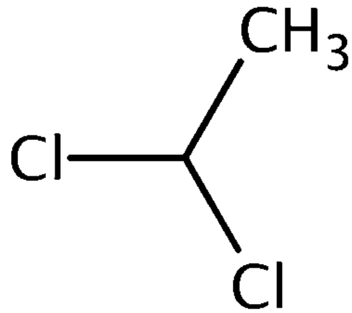

and 1,2-Dichloroethane (Analog)

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1 BENCHMARK DOSE MODELING RESULTS FOR 1,1-DICHLOROETHANE

EPA identified 16 studies and candidate points of departure (PODs) for 1,1-dichloroethane. All relevant studies were evaluated to determine whether they were suitable for POD use. Excluding studies that failed systematic review (SR), 9 studies remained. Each of these studies was considered further for potential use in POD identification for each exposure duration. Due to the small number of available studies, limited evaluations performed in many studies, and paucity of information available to identify target organs for 1,1-dichloroethane, overall no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs) were identified for each study, rather than identifying NOAELs and LOAELs by organ/system. EPA performed benchmark dose (BMD) modeling using EPA's BMD modeling software (BMDS Version 3.3) for each of the NOAELs and LOAELs that were identified during hazard identification for both non-cancer and cancer endpoints, and that received a weight-of-the-scientific-evidence judgment of at least suggestive during evidence integration. 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.*, incidences of tumors) and continuous models to fit continuous data (*e.g.*, body and organ weights), as recommended by EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The BMDs/BMDLs (benchmark doses lower 95 percent confidence limit) are provided based on a daily exposure (*i.e.*, 7 days per week) for easier comparison across all hazard endpoints and thus, doses were adjusted as needed before BMD modeling. EPA modeled endpoints that had statistically significant pairwise comparisons between individual doses and controls or significant dose-response trends. EPA also considered potential biologically significant changes from controls where possible and/or 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.

Although some of the data sets could be fit using models after dropping doses (either one, two, or three of the highest doses), EPA preferred to consider only modeling results from full data sets. When none of the models in the BMD suite provided an adequate fit to the full data sets, EPA did not present modeling results. Several additional endpoints evaluated in various 1,1-dichloroethane toxicity studies were not considered for BMD modeling because 1,1-dichloroethane was not associated with any effects or the changes were observed only at the highest dose. Studies were also not considered for BMD modeling if the LOAELs were more than 10 times greater than the most sensitive LOAEL for the health domain. For non-cancer endpoints, if BMD modeling was not possible or when data did not fit the available models, EPA used NOAELs and LOAELs during 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* 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. EPA's choice of BMRs for the 1,1-dichloroethane health endpoints are 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 extra risk or additional risk. EPA modeled the data as extra risk. EPA's *BMD Technical Guidance* defines extra risk as "a measure of the proportional increase in risk of an adverse effect adjusted for the background incidence of the same effect." Mathematically, extra risk 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]

1.1 Non-cancer Endpoints – 1,1-Dichloroethane

All non-cancer endpoints selected for modeling were based on continuous measurement data. The BMD modeling of continuous data was conducted with the EPA's BMD software (BMDS 3.3). For these data, the Exponential, Hill, Linear, Polynomial, and Power continuous models available within the software were fit employing a BMR of one SD and 10 percent RD. For inhalation data, administered concentrations were modeled in units of ppm. 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 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 Akaike's Information Criterion (AIC) was selected.

1.1.1 Inhalation Data

1.1.1.1 Maternal Body Weight in Pregnant Female Rats

Maternal body weights were significantly decreased in pregnant female rats exposed to 1,1-dichloroethane by inhalation for 10 days on gestation days (GD) 6 to 15 (Schwetz et al., 1974). First, the exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day rather than seven 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). A BMR of 10 percent RD was also selected because EPA considers a 10 percent change in body weight to be biologically significant. The concentrations and response data used for the modeling are presented in Table 1-1.

[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).

Table 1-1. Decreased Maternal Body Weight in Pregnant Female Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,1-Dichloroethane from a Gestational Inhalation Exposure Study (GD 6 to 15)

Adjusted Concentration (ppm)	Number of Animals	Mean (g)	SD (g)
0	43	317	18
1108	16	289	24
1639	19	281	24

The BMD modeling results for decreased maternal body weight in pregnant rats are summarized in Table 1-2. The constant variance model provided adequate fit to the variance data. With the constant variance model applied, all the 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 (Exponential 3) was selected. Figure 1-1 and Figure 1-2 show the Exponential 3 model for BMRs of one SD and 10 percent RD, respectively, while Figure 1-3 shows additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood.

Table 1-2. Summary of BMD Modeling Results for Decreased Maternal Body Weight in Pregnant Female Rats Following Inhalation Exposure During Gestation (GD 6 to 15) to 1,1-Dichloroethane (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	**0.6035**	**698.42**	**881**	**684**	**1388**	**1118**	Several models provided adequate fit to the means (test 4 p-values > 0.1). The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, EPA chose the Exponential 3 model, which had the lowest AIC.
Exponential 5	NA	700.15	728	12	1332	18	
Hill	NA	702.15	720	0	1335	963	
Polynomial Degree 2	0.5477	698.51	904	712	1397	1141	
Power	0.5476	698.51	905	712	1397	1141	
Linear	0.5477	698.51	904	712	1397	1141	

[a] Selected model in bold.

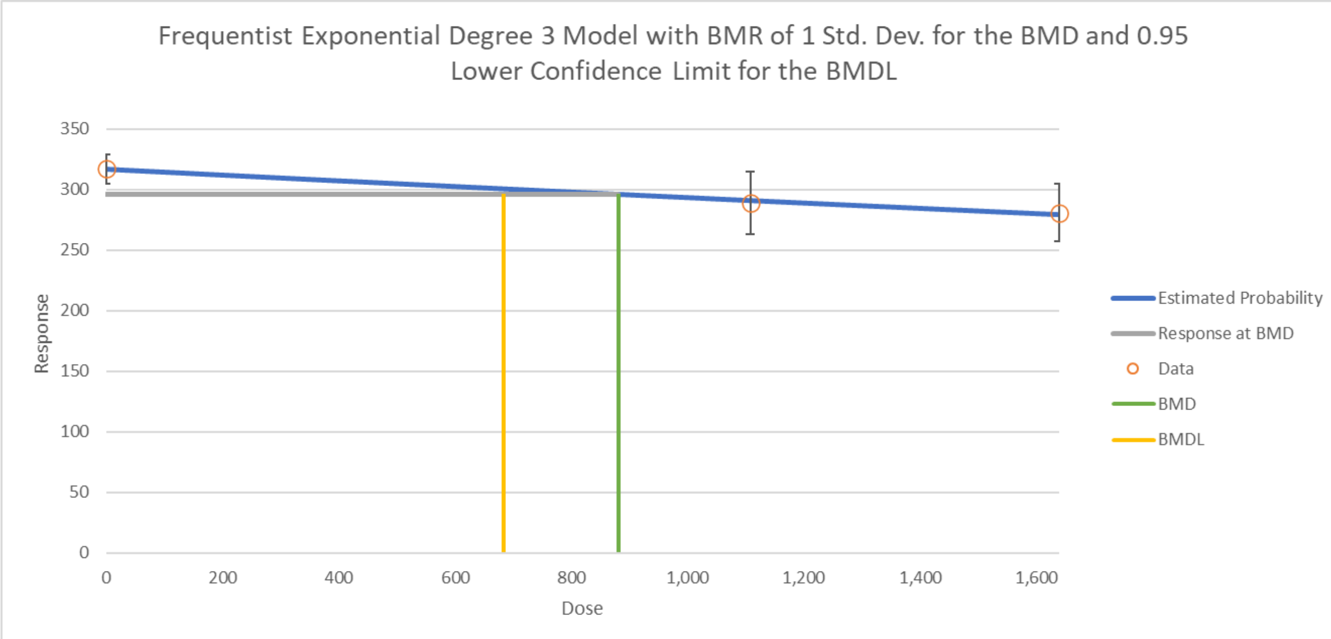

Figure 1-1. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 3) for Decreased Maternal Body Weight in Female Rats Exposed to 1,1-Dichloroethane Via Inhalation During Gestation (GD 6 to 15) and BMR of 1SD (Constant Variance Model)

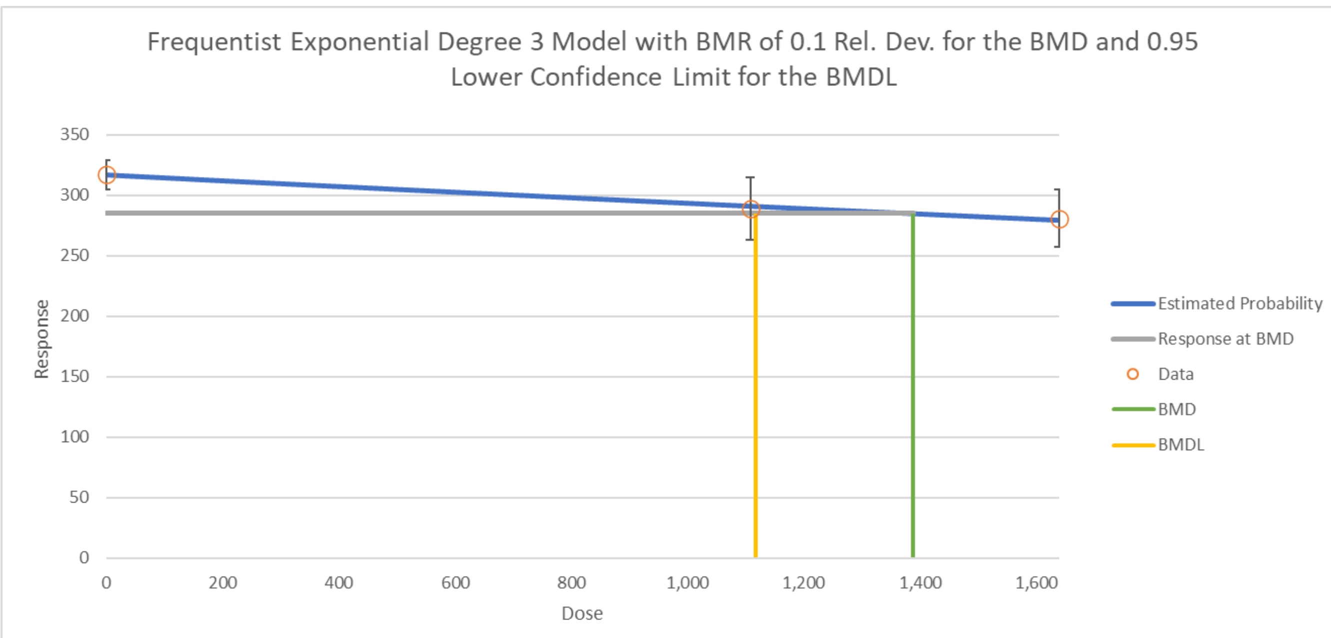

Figure 1-2. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 3) for Decreased Maternal Body Weight in Female Rats Exposed to 1,1-Dichloroethane Via Inhalation During Gestation (GD 6 to 15) and BMR of 10%RD (Constant Variance Model)

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
a	316.7552625	3.088957687	310.7010167	322.8095084
b	7.59159E-05	1.10E-05	5.44088E-05	9.7423E-05
d	Bounded	NA	NA	NA
log-alpha	6.03930729	1.60E-01	5.725462731	6.35315185

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	43	316.7552625	317	317	20.48419566	18	18	0.078345808
1107.75	16	291.2067686	289	289	20.48419566	24	24	-0.430921208
1639.166667	19	279.6924393	281	281	20.48419566	24	24	0.278240112

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-346.0753329	4	700.1506658
A2	-344.6592228	6	701.3184456
A3	-346.0753329	4	700.1506658
fitted	-346.2101901	3	698.4203803
R	-365.2701134	2	734.5402268

* Includes additive constant of -71.67721. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	41.22178125	4	<0.0001
2	2.832220217	2	0.242656089
3	2.832220217	2	0.242656089
4	0.269714495	1	0.603523356

Figure 1-3. Details Regarding the Selected Model (Exponential 3) for Decreased Maternal Body Weight in Pregnant Female Rats Following Inhalation Exposure to 1,1-Dichloroethane in a Gestational Exposure (GD 6 to 15) Toxicity Study (Constant Variance Model)

1.1.2 Oral Data

1.1.2.1 Mortality Effects

1.1.2.1.1 Mortality in Male Rats – 13 Weeks

Mortality was observed in male rats exposed by oral gavage to 1,1-dichloroethane for 13 weeks, including a significant increase at the high dose (Muralidhara et al., 2001). The incidences of mortality were 0/15, 0/15, 0/15, 1/15, and 15/15 (including animals sacrificed in extremis) at adjusted daily doses of 0, 357, 714, 1429, and 2857 mg/kg-day, respectively. The data set is problematic for BMD modeling because only one of the five data points is between 0 and 100 percent incidence. The models can easily fit this one data point; in fact, all the models with sufficient flexibility (*i.e.*, all except multistage) provide a near-perfect fit to the data set. There is insufficient information in the data set to discriminate reliably among the fits of these models. For this reason, the NOAEL/LOAEL approach is used instead for this endpoint.

1.1.2.2 Body Weight Effects

1.1.2.2.1 Body Weight in Male Rats – 10 Days

Body weights were significantly decreased in male rats exposed by oral gavage to 1,1-dichloroethane once a day for 10 consecutive days (Muralidhara et al., 2001). 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 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 1-3.

Table 1-3. Decreased Body Weight in Male Rats and Associated Doses Selected for Dose-Response Modeling for 1,1-Dichloroethane from a 10-Day Study

Dose (mg/kg-day)	Number of Animals	Mean (g)	SD (g)
0	8	341.7	5.3
1000	8	313.7	4.4
2000	8	295.0	4.4
4000	8	270.5	8.5

The BMD modeling results for decreased body weight in male rats are summarized in Table 1-4. The constant variance model provided adequate fit to the variance data. With the constant variance model applied, 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 (Hill) was selected. Figure 1-4 and Figure 1-5 show the Hill model for BMRs of one SD and 10 percent RD, respectively, while Figure 1-6 shows additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood.

Table 1-4. Summary of BMD Modeling Results for Decreased Body Weight in Male Rats Following Oral Exposure to 1,1-Dichloroethane in a 10-Day Study (Constant Variance Model)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/kg-day)	BMDL 1SD (mg/kg-day)	BMD 10%RD (mg/kg-day)	BMDL 10%RD (mg/kg-day)	Basis for Model Selection
	Test 4 p-value	AIC					
Exponential 3	0.0004	221.78	363	294	1806	1665	The Exponential 5 and Hill models provided adequate fit to the means (test 4 p-values > 0.1). The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, EPA chose the Hill model, which had the lowest AIC.
Exponential 5	0.7432	208.20	176	138	1308	1138	
Hill	**0.9110**	**208.11**	**167**	**128**	**1297**	**1167**	
Polynomial Degree 3	< 0.0001	227.02	454	359	1981	1795	
Polynomial Degree 2	< 0.0001	226.89	445	360	1953	1798	
Power	< 0.0001	226.89	443	360	1946	1800	
Linear	< 0.0001	226.89	443	360	1946	1800	

[a] Selected model in bold.

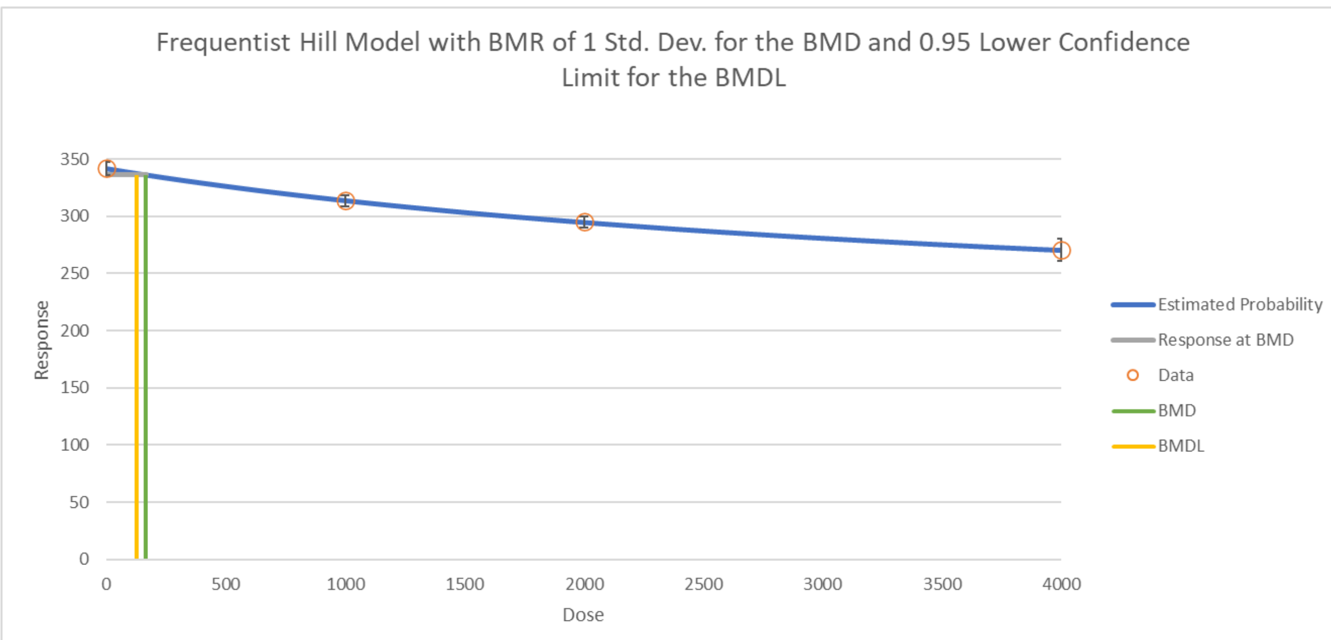

Figure 1-4. Plot of Response by Dose with Fitted Curve for the Selected Model (Hill) for Decreased Body Weight in Male Rats Exposed to 1,1-Dichloroethane Via Oral Gavage (10-Day Study) and BMR of 1SD (Constant Variance Model)

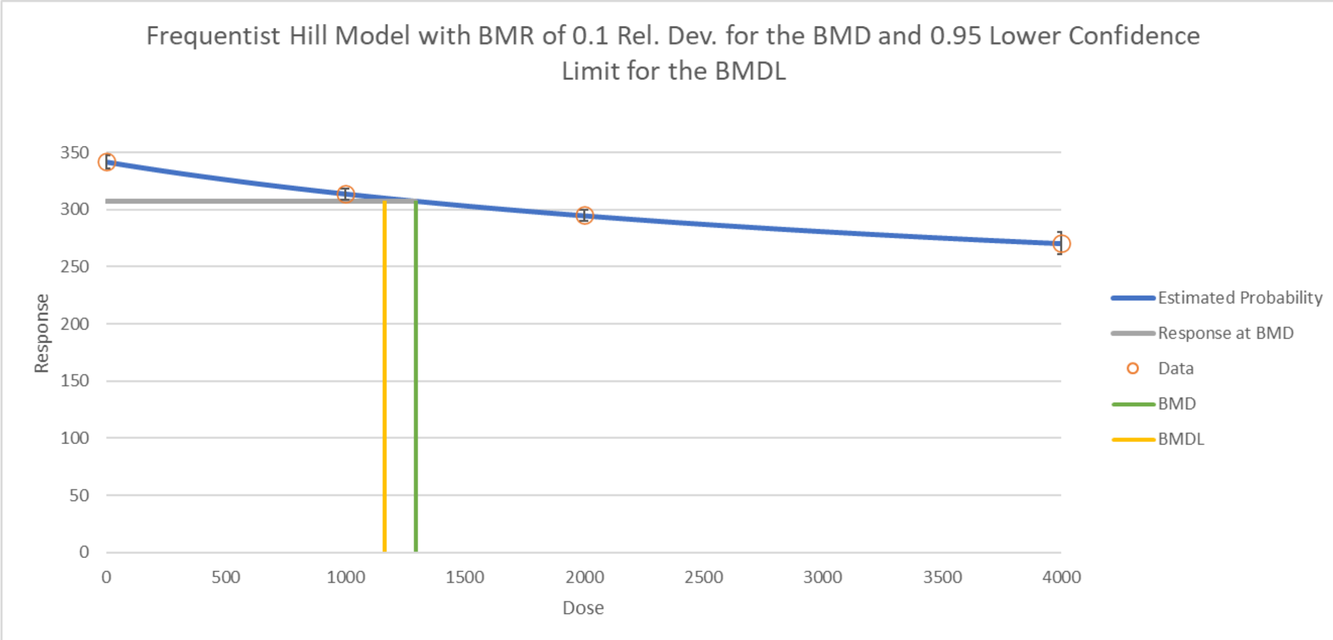

Figure 1-5. Plot of Response by Dose with Fitted Curve for the Selected Model (Hill) for Decreased Body Weight in Male Rats Exposed to 1,1-Dichloroethane Via Oral Gavage (10-Day Study) and BMR of 10%RD (Constant Variance Model)

Model Parameters				
# of Parameters	5			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	341.6643268	1.925158804	337.8910849	345.4375688
v	-147.629602	19.78805227	-186.413472	-108.8457319
k	4306.621234	1061.695823	2225.735642	6387.506827
n	Bounded	NA	NA	NA
alpha	30.43125264	231.5152221	-423.3302482	484.1927534

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	8	341.6643268	341.7	341.7	5.516452904	5.3	5.3	0.018290542
1000	8	313.8444401	313.7	313.7	5.516452904	4.4	4.4	-0.07405813
2000	8	294.8469911	295	295	5.516452904	4.4	4.4	0.078451607
4000	8	270.5742421	270.53	270.53	5.516452904	8.5	8.5	-0.022684041

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-100.0473089	5	210.0946178
A2	-97.43738731	8	210.8747746
A3	-100.0473089	5	210.0946178
fitted	-100.0535543	4	208.1071086
R	-150.4063937	2	304.8127875

* Includes additive constant of -29.40603. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	105.9380129	6	<0.0001
2	5.219843219	3	0.156389028
3	5.219843219	3	0.156389028
4	0.012490809	1	0.91101189

Figure 1-6. Details Regarding the Selected Model (Hill) for Decreased Body Weight in Male Rats Following Oral Exposure to 1,1-Dichloroethane in a 10-Day Toxicity Study

1.1.2.2.2 Body Weight in Male Rats – 13 Weeks

Body weights were significantly decreased in male rats exposed by oral gavage to 1,1-dichloroethane for 13 weeks (Muralidhara et al., 2001). First, the administered doses were duration adjusted to estimate an equivalent oral dose for animals exposed for 7 days per week rather than 5 days per week. 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). 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 1-5.

Table 1-5. Decreased Body Weight in Male Rats and Associated Doses Selected for Dose-Response Modeling for 1,1-Dichloroethane from a 13-Week Study

Adjusted Dose (mg/kg-day)	Number of Animals	Mean (g)	SD (g)
0	15	431.9	18.1
357	15	424.4	19.2
714	15	428.6	14.9
1429	14	376.3	26.7

The BMD modeling results for decreased body weight in male rats are summarized in Table 1-6. The constant variance model provided adequate fit to the variance data. With the constant variance model applied, all models except for the 2-degree Polynomial and Linear 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). Figure 1-7 and Figure 1-8 show the Power model for BMRs of one SD and 10 percent RD, respectively, while Figure 1-9 shows additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood.

Table 1-6. Summary of BMD Modeling Results for Decreased Body Weight in Male Rats Following Oral Exposure to 1,1-Dichloroethane in a 13-Week Study (Constant Variance Model)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/kg-day)	BMDL 1SD (mg/kg-day)	BMD 10%RD (mg/kg-day)	BMDL 10%RD (mg/kg-day)	Basis for Model Selection
	Test 4 p-value	AIC					
Exponential 3	0.5713	524.24	1350	884	1412	1246	Several models provided adequate fit to the means (test 4 p-values > 0.1). The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, EPA chose the Power model, which had the lowest AIC.
Exponential 5	0.29	526.24	1350	884	1412	1246	
Hill	0.29	526.24	1254	769	1367	1197	
Polynomial Degree 3	0.3144	525.43	997	789	1322	1209	
Polynomial Degree 2	0.0331	529.66	870	708	1277	1150	
Power	**0.5713**	**524.24**	**1353**	**884**	**1413**	**1248**	
Linear	0.0009	537.20	573	447	1153	943	

[a] Selected model in bold.

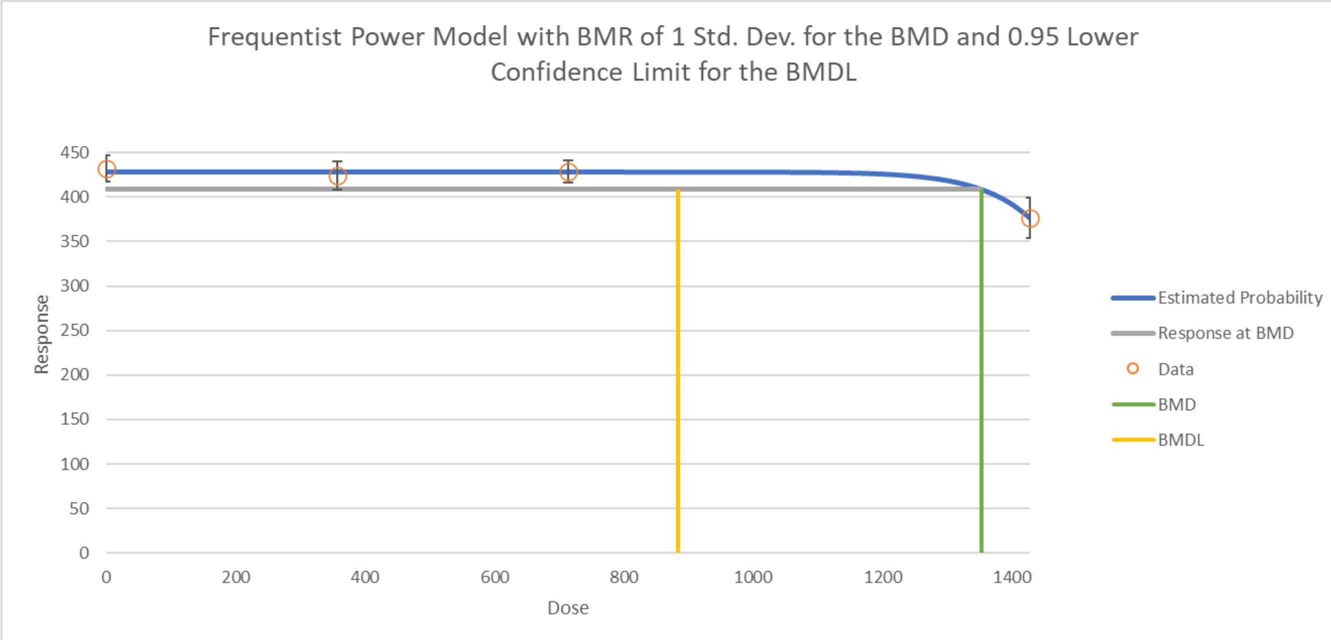

Figure 1-7. Plot of Response by Dose with Fitted Curve for the Selected Model (Power) for Decreased Body Weight in Male Rats Exposed to 1,1-Dichloroethane Via Oral Gavage (13-Week Study) and BMR of 1SD (Constant Variance Model)

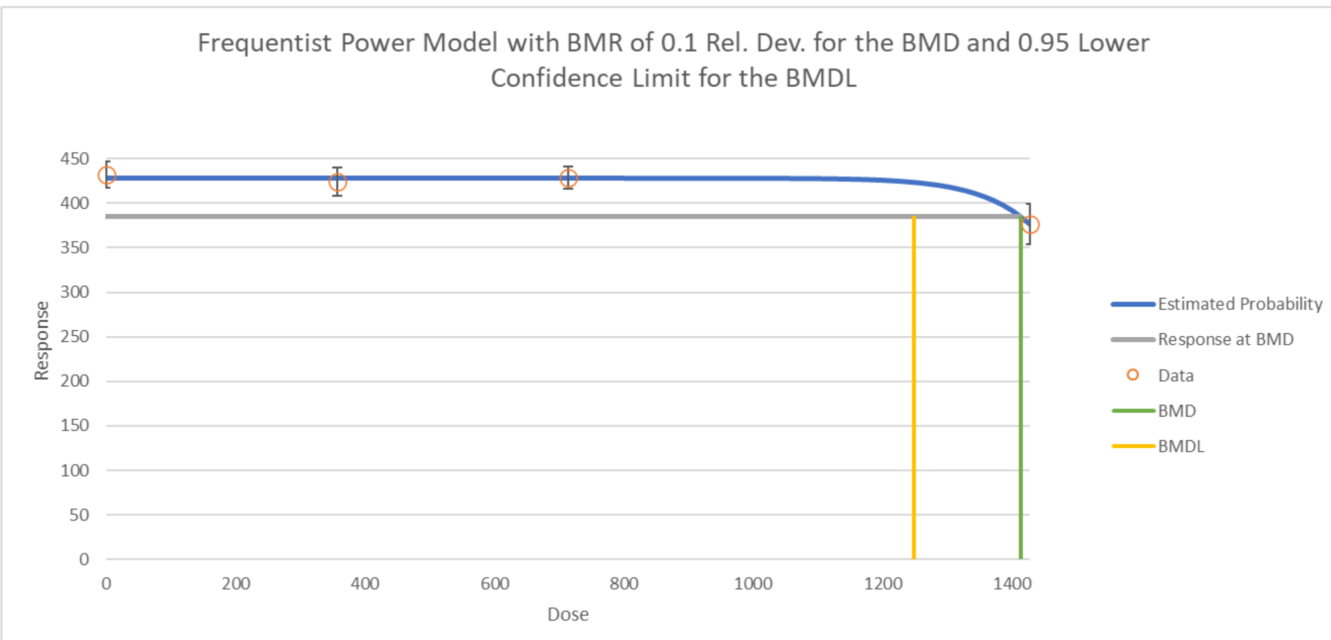

Figure 1-8. Plot of Response by Dose with Fitted Curve for the Selected Model (Power) for Decreased Body Weight in Male Rats Exposed to 1,1-Dichloroethane Via Oral Gavage (13-Week Study) and BMR of 10%RD (Constant Variance Model)

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	428.3000658	2.914141494	422.5884533	434.0116782
v	-8.46776E-56	9.74E-57	-1.03771E-55	-6.55845E-56
n	Bounded	NA	NA	NA
alpha	382.154439	2.69E+04	-52318.23724	53082.54612

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	15	428.3000658	431.9	431.9	19.54877078	18.1	18.1	0.713215452
357.142857	15	428.3000658	424.4	424.4	19.54877078	19.2	19.2	-0.772677212
714.285714	15	428.2998674	428.6	428.6	19.54877078	14.9	14.9	0.059461979
1428.57143	14	376.300001	376.3	376.3	19.54877078	26.7	26.7	-1.9727E-07

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-258.5593045	5	527.1186089
A2	-255.9143194	8	527.8286388
A3	-258.5593045	5	527.1186089
fitted	-259.1192054	3	524.2384108
R	-283.4397916	2	570.8795831

* Includes additive constant of -54.21737. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	55.0509443	6	<0.0001
2	5.289970094	3	0.151754542
3	5.289970094	3	0.151754542
4	1.119801923	2	0.571265638

Figure 1-9. Details Regarding the Selected Model (Power) for Decreased Body Weight in Male Rats Following Oral Exposure to 1,1-Dichloroethane in a 13-Week Toxicity Study

1.1.2.3 Hepatic Effects

1.1.2.3.1 Relative Liver Weight in Male Rats

Relative liver weights were significantly decreased in male rats exposed by oral gavage to 1,1-dichloroethane once a day for 10 consecutive days (Muralidhara et al., 2001). Continuous models were fit to the dose-response data. Additionally, changes in absolute liver weight (increased in female rats exposed via inhalation and decreased in male rats treated by gavage) were observed in 10-day toxicity studies; however, these changes were not consistently observed in longer-duration studies in rats, guinea pigs, rabbits, or cats, and were therefore not modeled.

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 because EPA considers a 10 percent change in relative liver weight to be biologically significant. The doses and response data used for the modeling are presented in Table 1-7.

Table 1-7. Decreased Relative Liver Weight in Male Rats and Associated Doses Selected for Dose-Response Modeling for 1,1-Dichloroethane From a 10-Day Study

Dose (mg/kg-day)	Number of Animals	Mean (g/100 g body weight)	SD (g/100 g body weight)
0	8	3.8	0.2
1000	8	3.6	0.2
2000	8	3.3	0.3
4000	8	3.4	0.3

The BMD modeling results for decreased relative liver weight are summarized in Table 1-8. The constant variance model provided adequate fit to the variance data. With the constant variance model applied, only the Hill model provided adequate fit to the means (test 4 p-value > 0.1); therefore, this model was selected. When applying the BMR of 10 percent RD, the BMD and BMDL calculation failed; therefore, this model could not be used to estimate a BMD or BMDL for this BMR. Figure 1-10 shows the Hill model for BMR of one SD while Figure 1-11 shows additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood.

Table 1-8. Summary of BMD Modeling Results for Decreased Relative Liver Weight in Male Rats Following Oral Exposure to 1,1-Dichloroethane in a 10-Day Study (Constant Variance Model)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/kg-day)	BMDL 1SD (mg/kg-day)	BMD 10%RD (mg/kg-day)	BMDL 10%RD (mg/kg-day)	Basis for Model Selection
	Test 4 p-value	AIC					
Exponential 3	0.0269	12.30	2542	1582	ND	ND	Out of the available models, only the Hill model provided adequate fit to the means (test 4 p-values > 0.1); therefore, this model was selected.
Exponential 5	NA	9.77	1053	516	ND	ND	
Hill	**0.4042**	**7.77**	**1021**	**574**	**ND**	**ND**	
Polynomial Degree 3	0.0236	12.56	2695	1711	ND	ND	
Polynomial Degree 2	0.0236	12.56	2670	1711	ND	ND	
Power	0.0236	12.56	2681	1711	ND	ND	
Linear	0.0236	12.56	2681	1711	ND	ND	

[a] Selected model in bold.

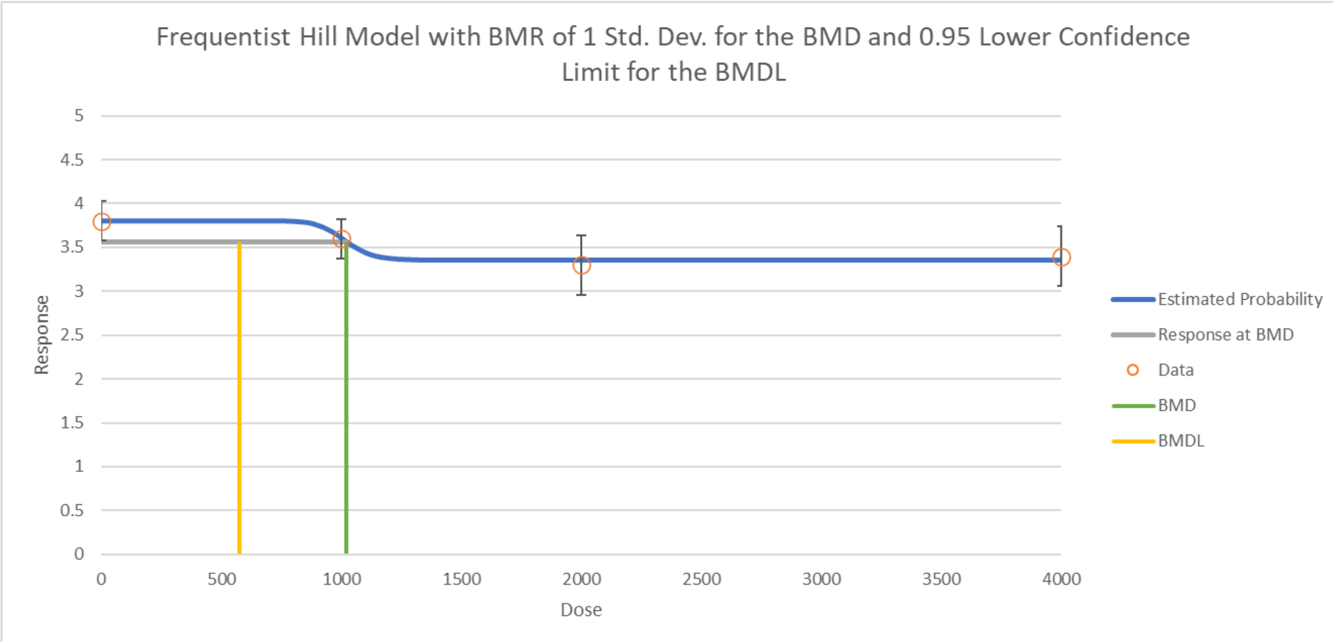

Figure 1-10. Plot of Response by Dose with Fitted Curve for the Selected Model (Hill) for Decreased Relative Liver Weight in Male Rats Exposed to 1,1-Dichloroethane Via Oral Gavage (10-Day Study) and BMR of 1SD (Constant Variance Model)

Model Parameters				
# of Parameters	5			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	3.800000406	8.52E-02	3.632935768	3.967065044
v	-0.450001072	1.04E-01	-0.654613058	-0.245389086
k	1012.473446	5.12E+01	912.1401025	1112.80679
n	Bounded	NA	NA	NA
alpha	0.058125044	8.45E-04	0.056469598	0.05978049

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	8	3.800000406	3.8	3.8	0.241091359	0.2	0.2	-4.76E-06
1000	8	3.599998789	3.6	3.6	0.241091359	0.2	0.2	1.42088E-05
2000	8	3.35000148	3.3	3.3	0.241091359	0.3	0.3	-0.586605602
4000	8	3.349999334	3.4	3.4	0.241091359	0.3	0.3	0.586596052

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	0.464357365	5	9.07128527
A2	1.745040688	8	12.50991862
A3	0.464357365	5	9.07128527
fitted	0.116502812	4	7.766994376
R	-7.532055236	2	19.06411047

* Includes additive constant of -29.40603. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	18.55419185	6	0.004986684
2	2.561366646	3	0.464302762
3	2.561366646	3	0.464302762
4	0.695709106	1	0.404229264

Figure 1-11. Details Regarding the Selected Model (Hill) for Decreased Relative Liver Weight in Male Rats Following Oral Exposure to 1,1-Dichloroethane in a 10-Day Toxicity Study

1.1.2.4 Renal Effects

1.1.2.4.1 Absolute Kidney Weight in Male Rats

Absolute kidney weights were significantly decreased in male rats exposed by oral gavage to 1,1-dichloroethane once a day for 10 consecutive days (Muralidhara et al., 2001). 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 kidney weight to be biologically significant. The doses and response data used for the modeling are presented in Table 1-9.

Table 1-9. Decreased Absolute Kidney Weight in Male Rats and Associated Doses Selected for Dose-Response Modeling for 1,1-Dichloroethane from a 10-Day Study

Dose (mg/kg-day)	Number of Animals	Mean (g)	SD (g)
0	8	2.4	0.1
1000	8	2.3	0.1
2000	8	2.0	0.2
4000	8	1.9	0.1

The BMD modeling results for decreased absolute kidney weight are summarized in Table 1-10. The constant variance model provided adequate fit to the variance data; however, with that model applied, none of the available models provided adequate fit to the means (test 4 p-value < 0.1). The nonconstant variance model also provided an adequate fit to the variance data. With the nonconstant variance model applied, only the Exponential 5 model provided adequate fit to the means (test 4 p-value > 0.1); therefore, this model was selected. Figure 1-12 and Figure 1-13 show the Exponential 5 model for BMRs of one SD and 10 percent RD, respectively, while Figure 1-14 shows additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood.

Table 1-10. Summary of BMD Modeling Results for Decreased Absolute Kidney Weight in Male Rats Following Oral Exposure to 1,1-Dichloroethane in a 10-Day Study (Nonconstant Variance Model)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/kg-day)	BMDL 1SD (mg/kg-day)	BMD 10%RD (mg/kg-day)	BMDL 10%RD (mg/kg-day)	Basis for Model Selection
	Test 4 p-value	AIC					
Exponential 3	0.0206	−29.29	947	716	1662	1363	Out of the available models, only the Exponential 5 model provided adequate fit to the means (test 4 p-values > 0.1); therefore, this model was selected.
Exponential 5	**0.143**	**−32.92**	**1089**	**724**	**1458**	**1133**	
Hill	NA	−33.06	985	739	1344	1129	
Polynomial Degree 3	0.0045	−26.25	1100	826	1815	1515	
Polynomial Degree 2	0.0047	−26.33	1078	829	1811	1518	
Power	0.0046	−26.32	1090	829	1811	1518	
Linear	0.0133	−28.33	1077	829	1811	1519	

[a] Selected model in bold.

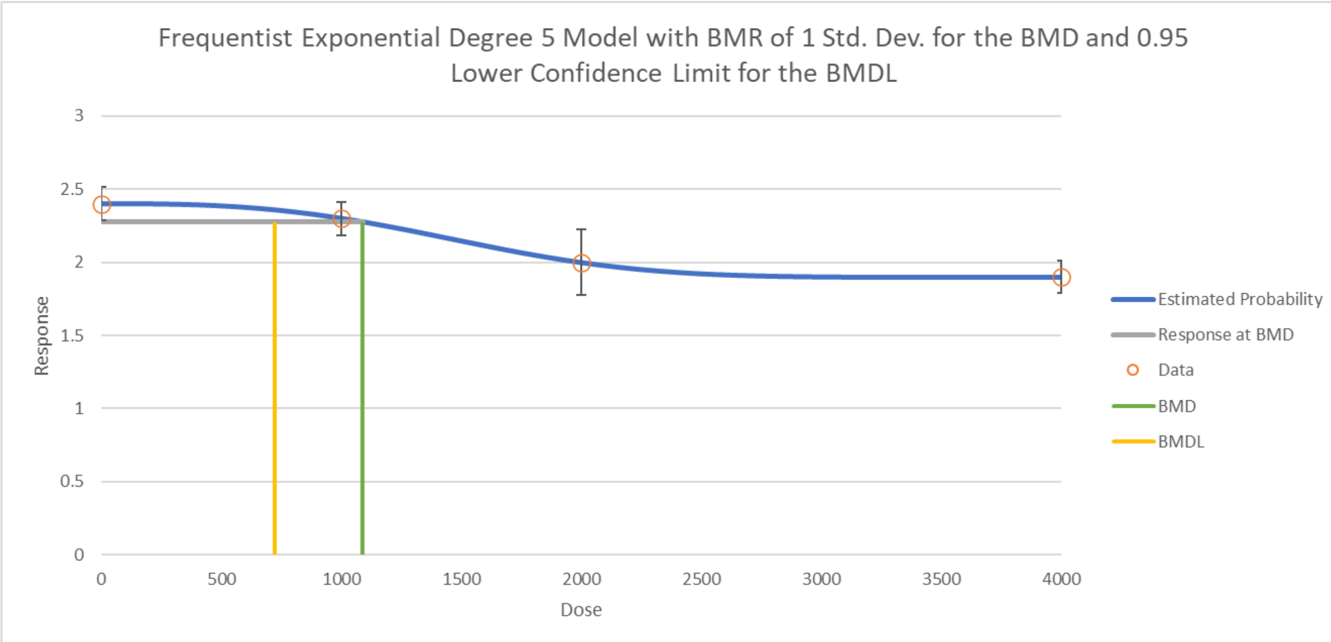

Figure 1-12. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 5) for Absolute Kidney Weight Decreases in Male Rats Exposed to 1,1-Dichloroethane Via Oral Gavage (10-Day Study) and BMR of 1SD (Nonconstant Variance Model)

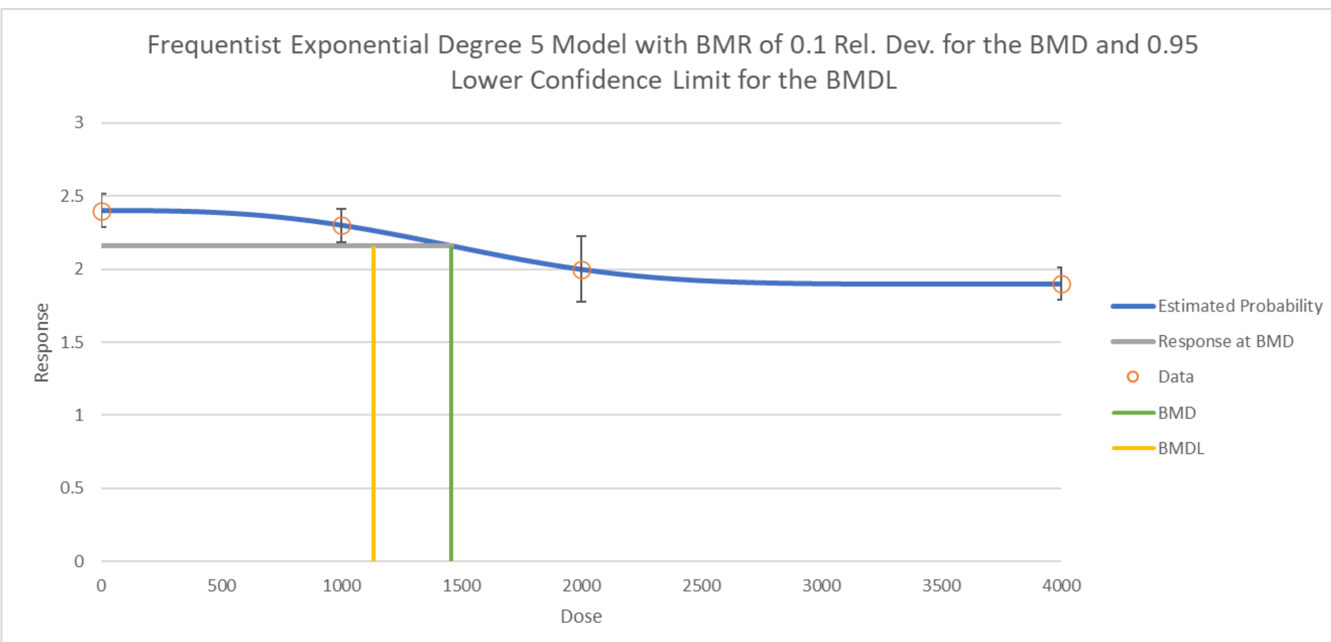

Figure 1-13. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 5) for Absolute Kidney Weight Decreases in Male Rats Exposed to 1,1-Dichloroethane Via Oral Gavage (10-Day Study) and BMR of 10%RD (Nonconstant Variance Model)

Model Parameters				
# of Parameters	6			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
a	2.4	4.37E-02	2.314251719	2.485748282
b	0.000590842	6.89E-05	0.000455747	0.000725937
c	0.791664772	2.94E-02	0.734078987	0.849250557
d	2.850495003	9.60E-01	0.969247537	4.731742469
rho	Bounded	NA	NA	NA
log-alpha	-4.179085795	2.50E-01	-4.669076531	-3.68909506

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	8	2.4	2.4	2.4	0.123743686	0.1	0.1	-1.35398E-09
1000	8	2.300000001	2.3	2.3	0.123743686	0.1	0.1	-1.67941E-08
2000	8	2.000000001	2	2	0.123743686	0.2	0.2	-1.33297E-08
4000	8	1.900000001	1.9	1.9	0.123743686	0.1	0.1	-2.36304E-08

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	21.45933959	5	-32.91867918
A2	24.86801475	8	-33.7360295
A3	22.53203157	6	-33.06406313
fitted	21.45933959	5	-32.91867918
R	0.202771157	2	3.594457686

* Includes additive constant of -29.40603. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	49.33048719	6	<0.0001
2	6.817350325	3	0.077953003
3	4.671966368	2	0.096715347
4	2.145383957	1	0.142999257

Figure 1-14. Details Regarding the Selected Model (Exponential 5) for Absolute Kidney Weight Decreases in Male Rats Following Oral Exposure to 1,1-Dichloroethane in a 10-Day Toxicity Study

2 BENCHMARK DOSE MODELING RESULTS FOR 1,2-DICHLOROETHANE

The available non-cancer and cancer data for 1,1-dichloroethane were insufficient for development of PODs (see Section 5.2.1.2 in the Risk Evaluation for 1,1-Dichloroethane (U.S. EPA, 2025). Therefore, an analysis of other chlorinated solvents was conducted to identify potential analogs for read across data (see Section 5.2.1.3 and Appendix J.2 in the Risk Evaluation for 1,1-Dichloroethane (U.S. EPA, 2025). This analysis considered structural similarities, physical and chemical properties, and toxicological similarities. Based on these various parameters, 1,2-dichloroethane was selected as a close structural analog to 1,1-dichloroethane and was used as read-across for non-cancer and cancer endpoints. EPA conducted BMD modeling on these data as described below.

EPA performed BMD modeling using EPA's BMD modeling software (BMDS Version 3.3 for continuous and cancer data and Version 3.3.2 for dichotomous non-cancer data) for the health domains that were identified during hazard identification and that received a judgment of "likely" ("evidence indicates that 1,2-dichloroethane exposure likely causes [health effect]") or "suggestive" ("evidence suggests but is not sufficient to conclude that 1,2-dichloroethane exposure causes [health effect]") during evidence integration, including cancer (various tumor types), mortality, body weight effects, respiratory tract effects, renal effects, hepatic effects, immune/hematological effects, and male reproductive effects. Although it was concluded during evidence integration that 1,2-dichloroethane exposure likely causes neurological/behavioral effects, none of the data for this domain were amenable for BMD modeling. 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.*, incidences of tumors) and continuous models to fit continuous data (*e.g.*, body and organ weights), as recommended by EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The BMDs/BMDLs are provided based on a daily exposure (*i.e.,* 7 days per week) for easier comparison across all hazard endpoints and thus, doses were adjusted as needed before BMD modeling. EPA modeled endpoints that had statistically significant pairwise comparisons 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.

Although some of the data sets could be fit using models after dropping doses (either one, two, or three of the highest doses), EPA considered only modeling results from full data sets for use in quantifying risk. 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 data sets. Endpoints were also not considered for BMD modeling if changes were observed only at the highest dose. Studies with LOAELs more than 10 times greater than the most sensitive LOAEL for the health domain were also not considered for BMD modeling. For non-cancer endpoints, if BMD modeling was not possible or when data did not fit the available models, EPA used NOAELs and LOAELs during POD selection for the risk evaluation.

EPA relied on the BMD guidance and other information to choose BMRs appropriate for each endpoint. Although the *BMD Technical Guidance* doesn't recommend default BMRs, it describes how various BMD modeling results compare with NOAEL values, and the guidance does recommend calculating 10 percent ER for quantal data and one SD for continuous data to compare modeling results across endpoints. EPA also modeled percent RD for certain continuous endpoints. EPA's choice of BMRs for the 1,2-dichloroethane 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).

2.1 Non-cancer Endpoints – 1,2-Dichloroethane

Non-cancer endpoints selected for modeling were based on both dichotomous and continuous measurement data. For dichotomous data, the Gamma, Logistic, Log-Logistic, Log-Probit, Multistage, Probit, Weibull, and Quantal Linear dichotomous models available within the software were fit using the selected BMR. For inhalation data, administered concentrations were modeled in units of mg/m^3. 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 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.

2.1.1 Inhalation Data

2.1.1.1 Acute

2.1.1.1.1 Mortality

Storer et al. (1984) provided data showing increased mortality in mice following acute inhalation exposure to 1,2-dichloroethane.

2.1.1.1.1.1 Mortality in Male B6C3F1 Mice – 4-Hour Inhalation Exposure

Increased incidence of mortality was observed in male mice exposed to 1,2-dichloroethane by inhalation for four hours (Storer et al., 1984). The measured exposure concentrations (reported in units of ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day. The concentration and response data used for the modeling are presented in Table 2-1. Dichotomous models were fit to the incidence data. EPA chose a BMR of 10 percent ER according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012) to compare with other PODs. A BMR of one percent ER was also selected based on the severity of the endpoint.

Table 2-1. Incidence of Mortality in Male Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane

Concentration (mg/m^3)	Number of Animals	Incidence
0	5	0
107	5	0
337	5	0
723.2	5	4
1313	5	5

The BMD modeling results for incidence of mortality are summarized in Table 2-2. All models provided adequate fit to the data (chi-square p-value > 0.1). Using a BMR of 10 percent ER, the BMDLs were not sufficiently close (differed by > 3-fold); therefore, the model with the lowest BMDL (Multistage 1-degree) was selected. Using a BMR of one percent ER, the Multistage 1-degree/Quantal Linear model was considered questionable because the BMD and BMDL were 10 times lower than the lowest non-zero concentration. The BMDLs of the remaining models were not sufficiently close; therefore, the BMDS recommended the model with the lowest BMDL (Multistage 2-degree).

This data set is not well suited for BMD modeling; there is a single datapoint (at 80 percent incidence) with incidence between 0 and 100 percent; there are no data to inform the shape of the curve at the region of interest, as defined by the BMR. As a result, the different models provide a broad range of BMD and BMDL estimates: an ~6-fold BMDL spread at a BMR of 10 percent and an ~ 38-fold BMDL spread at a BMR of one percent. For both BMRs, selection of the low end of the range to represent the BMDL is not among the more realistic possibilities and involves extrapolation below the range of observation to generate a BMD estimate well below the lowest tested dose. The much higher spread of BMDLs at a BMR of one percent indicates much higher uncertainty associated with modeling using this BMR, reflecting the greater distance from the lowest observable change in the study, which was only 20 percent (1/5).

Table 2-2. BMD Modeling Results for Increased Incidence of Mortality in Male Mice Following a 4-Hour Inhalation Exposure to 1,2-Dichloroethane[a]

Model	Goodness of Fit		BMD 1%ER (mg/m^3)	BMDL 1%ER (mg/m^3)	BMD 10%ER (mg/m^3)	BMDL 10%ER (mg/m^3)	Basis for Model Selection
	p-value	AIC					
Dichotomous Hill	1.000	7.004	519	130	593	263	All models provided adequate fit to the data (chi-square p-value > 0.1). With a BMR of 10 percent ER applied, the BMDLs were not sufficiently close (differed by > 3-fold); therefore, the Multistage 1-degree model, which has the lowest BMDL was selected. With a BMR of one percent ER applied, the Multistage 1-degree/Quantal Linear model was considered questionable because the BMD and BMDL were 10 times lower than the lowest non-zero concentration. The BMDLs of the remaining models were not sufficiently close; therefore, the model with the lowest BMDL (Multistage 2-degree) was selected. NOTE: This data set is not well suited for BMD modeling and the results should be interpreted with caution.
Gamma	0.9994	7.140	328	113	438	242	
Log-Logistic	1.000	7.004	519	130	593	263	
Multistage 3	0.9730	6.507	143	13.8	313	137	
Multistage 2	**0.7410**	**10.32**	**67.3**	**11.1**	218	103	
Multistage 1	**0.2538**	**15.59**	7.25	4.11	**76.0**	**43.1**	
Weibull	0.9998	7.083	350	81	491	230	
Logistic	1.000	7.005	500	57.5	590	261	
Log-Probit	1.000	9.004	553	157	604	263	
Probit	1.000	9.004	492	56.8	568	246	
Quantal Linear	0.2538	15.59	7.25	4.11	76.0	43.1	

[a] Selected model in bold.

Plots of the Multistage 1-degree and Multistage 2-degree models with BMRs of 10 percent and one Percent ER are shown in Figure 2-1 and Figure 2-2, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown below in Figure 2-3 and Figure 2-4 for the Multistage 1-degree and Multistage 2-degree models, respectively.

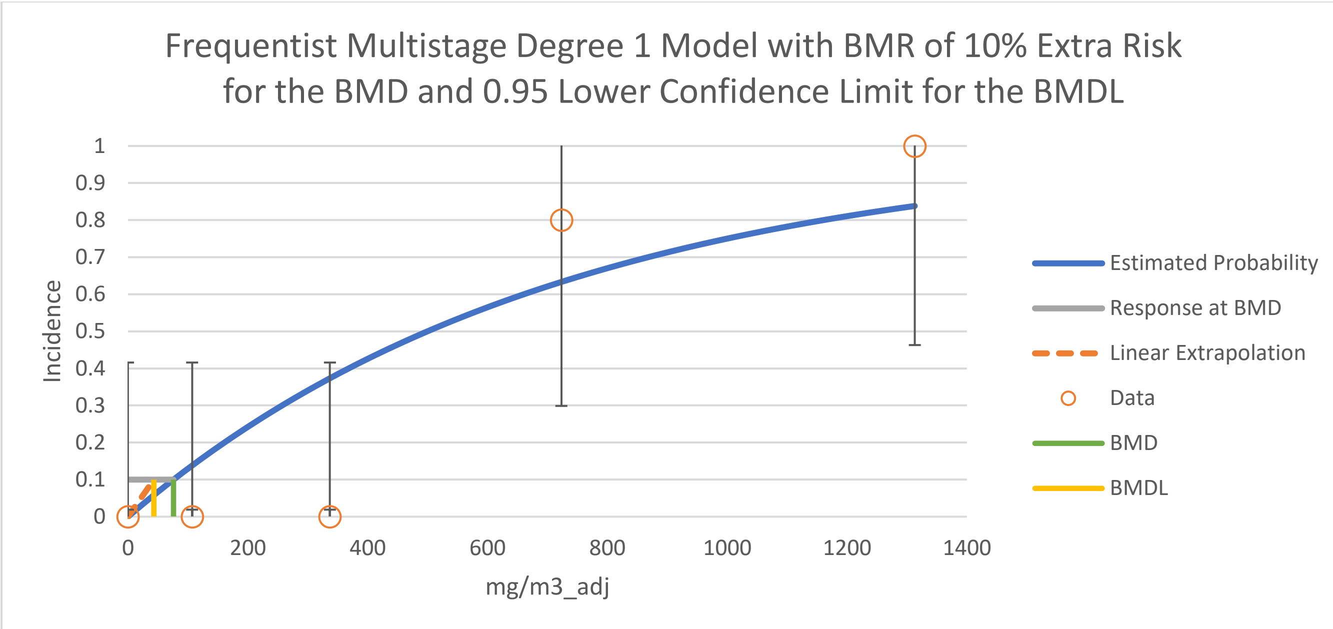

Figure 2-1. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 1-Degree) for Mortality in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for Four Hours and BMR of 10%ER

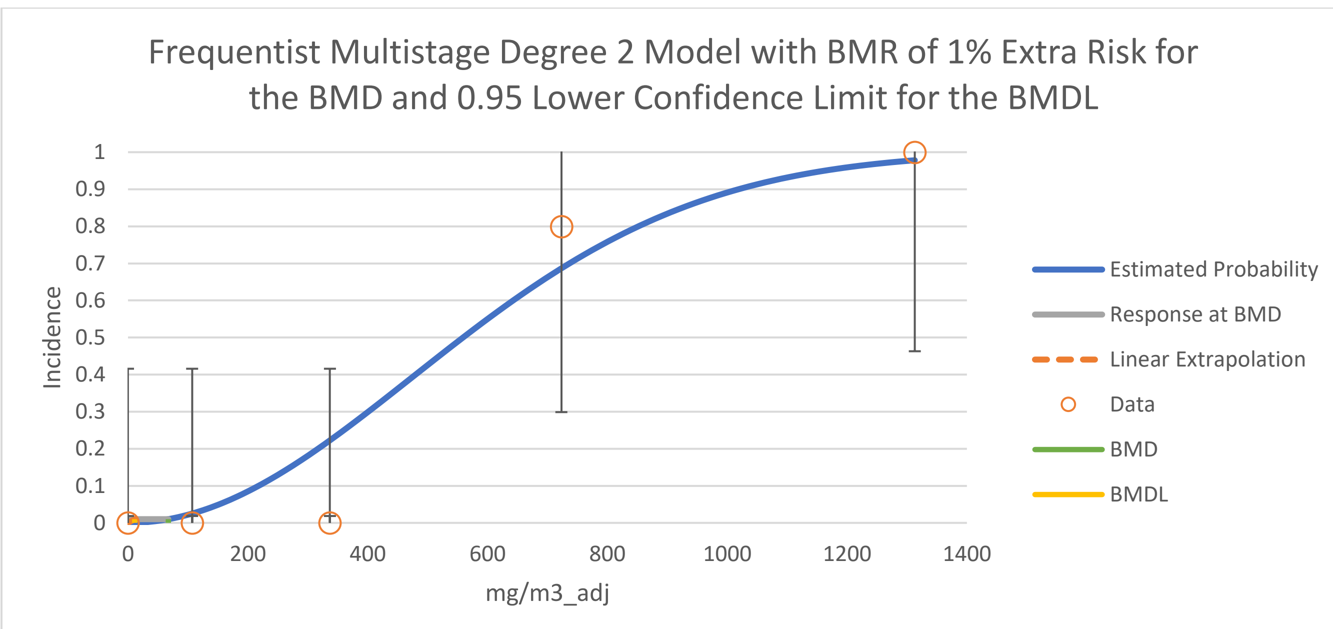

Figure 2-2. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 2-Degree) for Mortality in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for Four Hours and BMR of 1%ER

Model Results

Benchmark Dose	
BMD	75.96529122
BMDL	43.13559104
BMDU	144.8556487
AIC	15.58503443
P-value	0.253844445
D.O.F.	4
Chi^2	5.343368092
Slope Factor	0.002318271

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	0.001386956	0.664907502	-1.3018078	1.30458172

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	7.61499E-08	0	5	-0.000276
107	0.1379175	0.689587501	0	5	-0.894376
337	0.373373232	1.866866159	0	5	-1.726045
723.2	0.633239628	3.166198142	4	5	0.7737535
1313	0.838148045	4.190740227	5	5	0.9826155

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-2.502012118	5	-	-	NA
Fitted Model	-6.792517214	1	8.58101019	4	0.0724694
Reduced Model	-16.33545487	1	27.6668855	4	<0.0001

Figure 2-3. Details Regarding the Selected Model (Multistage 1-Degree) for Mortality in Male Mice Following a 4-Hour Inhalation Exposure to 1,2-Dichloroethane

Model Results

Benchmark Dose	
BMD	67.31979018
BMDL	11.12084919
BMDU	97.41764876
AIC	10.32271674
P-value	0.740950577
D.O.F.	4
Chi^2	1.971774077
Slope Factor	0.000899212

Model Parameters				
# of Parameters	3			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	Bounded	NA	NA	NA
b2	2.21766E-06	1.668562717	-3.2703206	3.27032508

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	7.61499E-08	0	5	-0.000276
107	0.025070411	0.125352057	0	5	-0.358574
337	0.22264463	1.113223149	0	5	-1.196689
723.2	0.686475475	3.432377376	4	5	0.5471752
1313	0.978141831	4.890709155	5	5	0.3342651

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-2.502012118	5	-	-	NA
Fitted Model	-4.161358368	1	3.3186925	4	0.5059761
Reduced Model	-16.33545487	1	27.6668855	4	<0.0001

Figure 2-4. Details Regarding the Selected Model (Multistage 2-Degree) for Mortality in Male Mice Following a 4-Hour Inhalation Exposure to 1,2-Dichloroethane

2.1.1.1.2 Respiratory Effects

Incidence data for degeneration with necrosis of the olfactory mucosa following a four- or eight-hour inhalation exposure and regeneration of the olfactory mucosa following a four-hour of exposure were modeled for males, females, and males and females combined (Dow Chemical, 2006).

2.1.1.1.2.1 Degeneration with Necrosis of the Olfactory Mucosa in Male F344 Rats – 4-Hour Inhalation Exposure

Increased incidence of degeneration with necrosis of the olfactory mucosa was observed in male rats exposed to 1,2-dichloroethane by inhalation for four hours (Dow Chemical, 2006). The measured exposure concentrations (reported in units of ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day. The concentration and response data used for the modeling are presented in Table 2-3. 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).

Table 2-3. Incidence of Degeneration with Necrosis of the Olfactory Mucosa in Male Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane

Concentration (mg/m^3)	Number of Animals	Incidence
0	5	0
35.3	5	0
132.5	5	3
410.0	5	5
1368.7	5	5

The BMD modeling results for increased incidence of degeneration with necrosis of the olfactory mucosa in male rats are summarized in Table 2-4. All models provided adequate fit to the data (chi-square p-value > 0.1). The BMDL computation for the Weibull model failed because the lower limit included zero. The BMDLs were not sufficiently close (differed by >3-fold). Therefore, EPA chose the model with the lowest BMDL (Multistage 1-degree model).

This data set is not well suited for BMD modeling; there is a single datapoint (at 60 percent incidence) with incidence between 0 and 100 percent; there are no data to inform the shape of the curve at the region of interest (~10 percent). As a result, the different models provide a broad range of BMD and BMDL estimates. Selection of the low end of the range to represent the BMDL is not among the more realistic possibilities and in this case involves extrapolation below the range of observation to generate a BMD estimate well below the lowest tested dose.

Table 2-4. BMD Modeling Results for Degeneration with Necrosis of the Olfactory Mucosa in Male Rats Following a 4-Hour Inhalation Exposure to 1,2-Dichloroethane[a]

Model	Goodness of Fit		BMD 10%ER (mg/m^3)	BMDL 10%ER (mg/m^3)	Basis for Model Selection
	p-value	AIC			
Dichotomous Hill	1.000	10.73	93.8	24.9	All models provided adequate fit to the data (chi-square p-value > 0.1); however, the BMDL computation for the Weibull model failed because the lower limit included zero. Of the models with adequate and viable fits, the BMDLs were not sufficiently close (differed by > 3-fold); therefore, EPA chose the model with the lowest BMDL. NOTE: This data set is not well suited for BMD modeling and the results should be interpreted with caution.
Gamma	0.9999	10.74	77.1	17.4	
Log-Logistic	1.000	10.73	93.8	24.9	
Multistage 3	0.9999	6.900	65.1	13.7	
Multistage 2	0.9876	9.349	47.3	12.6	
Multistage 1	**0.7953**	**11.76**	**16.1**	**8.33**	
Weibull	0.9560	11.30	50.2	0	
Logistic	0.9999	10.74	97.0	36.3	
Log-Probit	1.000	10.73	103	24.5	
Probit	0.7909	12.33	55.2	27.5	
Quantal Linear	0.7953	11.76	16.1	8.33	

[a] Selected model in bold.

A plot of the Multistage 1-degree model with a BMR of 10 percent ER is shown in Figure 2-5. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-6.

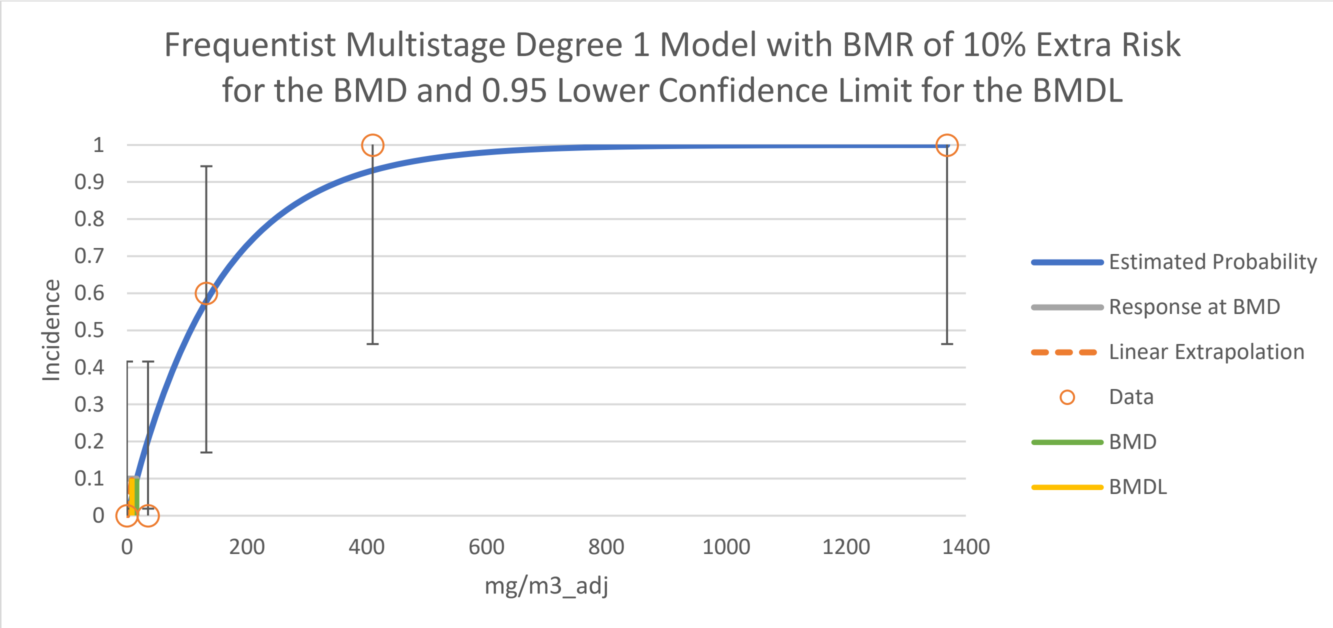

Figure 2-5. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 1-Degree) for Degeneration with Necrosis of the Olfactory Mucosa in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 4 Hours and BMR of 10%ER

Model Results

Benchmark Dose	
BMD	16.14009333
BMDL	8.334284842
BMDU	32.92192881
AIC	11.757832
P-value	0.795259973
D.O.F.	4
Chi^2	1.674965599
Slope Factor	0.01199863

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	0.006527875	3.737480823	-7.3188	7.33185574

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	7.61499E-08	0	5	-0.000276
35.3	0.205811145	1.029055727	0	5	-1.014424
132.5	0.578924623	2.894623116	3	5	0.0619369
410	0.931191546	4.655957729	5	5	0.1594437
1368.7	0.999868263	4.999341314	5	5	0.0002946

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-3.365058335	5	-	-	NA
Fitted Model	-4.878915999	1	3.02771533	4	0.5531981
Reduced Model	-17.30867418	1	27.8872317	4	<0.0001

Figure 2-6. Details Regarding the Selected Model (Multistage 1-Degree) for Degeneration with Necrosis of the Olfactory Mucosa in Male Rats Following a 4-Hour Inhalation Exposure to 1,2-Dichloroethane

2.1.1.1.2.2 Degeneration with Necrosis of the Olfactory Mucosa in Female F344 Rats – 4-Hour Inhalation Exposure

Increased incidence of degeneration with necrosis of the olfactory mucosa was observed in female rats exposed to 1,2-dichloroethane by inhalation for four hours (Dow Chemical, 2006). The measured exposure concentrations (reported in units of ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day. The concentration and response data used for the modeling are presented in Table 2-5. 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).

Table 2-5. Incidence of Degeneration with Necrosis of the Olfactory Mucosa in Female Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane

Adjusted Concentration (mg/m^3)	Number of Animals	Incidence
0	5	0
35.3	5	0
132.5	5	4
410.0	5	5
1368.7	5	5

The BMD modeling results for increased incidence of degeneration with necrosis of the olfactory mucosa in female rats are summarized in Table 2-6. All models provided adequate fit to the data (chi-square p-value > 0.1). The BMDL computation for the Weibull model failed because the lower limit included zero. The BMDLs were not sufficiently close (differed by > 3-fold). Therefore, EPA chose the model with the lowest BMDL (Multistage 1-degree model).

Table 2-6. BMD Modeling Results for Degeneration with Necrosis of the Olfactory Mucosa in Female Rats Following a 4-Hour Inhalation Exposure to 1,2-Dichloroethane[a]

Model	Goodness of Fit		BMD 10%ER (mg/m^3)	BMDL 10%ER (mg/m^3)	Basis for Model Selection
	p-value	AIC			
Dichotomous Hill	1.000	9.008	80.1	22.5	All models provided adequate fit to the data (chi-square p-value > 0.1); however, the BMDL computation for the Weibull model failed because the lower limit included zero. Of the viable models, the BMDLs were not sufficiently close (differed by > 3-fold); therefore, EPA chose the model with the lowest BMDL. NOTE: This data set is not well suited for BMD modeling and the results should be interpreted with caution.
Gamma	0.9975	9.087	60.3	17.5	
Log-Logistic	1.000	9.008	80.1	22.5	
Multistage 3	0.9995	5.301	54.2	12.7	
Multistage 2	0.9645	8.058	36.7	10.2	
Multistage 1	**0.6890**	**10.70**	**12.2**	**6.20**	
Weibull	0.8634	10.24	35.9	0	
Logistic	0.9994	9.039	83.8	30.2	
Log-Probit	1.000	9.004	98.0	22.7	
Probit	0.5357	12.24	41.4	21.1	
Quantal Linear	0.6890	10.70	12.2	6.20	

[a] Selected model in bold.

This data set is not well suited for BMD modeling; there is a single datapoint (at 80 percent incidence) with incidence between 0 and 100 percent; there are no data to inform the shape of the curve at the region of interest (~ 10 percent). As a result, the different models provide a broad range of BMD and BMDL estimates. Selection of the low end of the range to represent the BMDL is not among the more realistic possibilities and in this case involves extrapolation below the range of observation to generate a BMD estimate well below the lowest tested dose.

A plot of the Multistage 1-degree model with a BMR of 10 percent ER is shown in Figure 2-7. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-8.

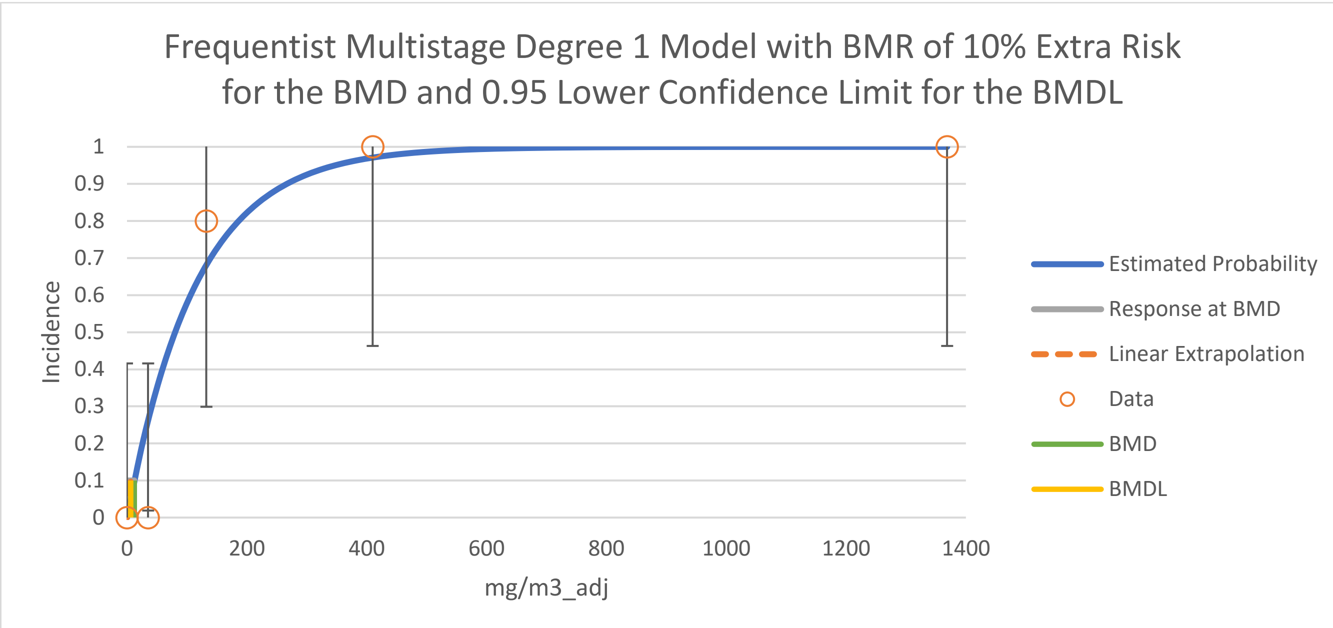

Figure 2-7. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 1-Degree) for Degeneration with Necrosis of the Olfactory Mucosa in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation for Four Hours and BMR of 10%ER

Model Results

Benchmark Dose	
BMD	12.20199573
BMDL	6.197861053
BMDU	25.08064423
AIC	10.69847938
P-value	0.689023139
D.O.F.	4
Chi^2	2.254728302
Slope Factor	0.016134599

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	0.008634695	5.028308495	-9.8466689	9.86393833

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	7.61499E-08	0	5	-0.000276
35.3	0.262732682	1.313663408	0	5	-1.334841
132.5	0.68148862	3.407443098	4	5	0.5687917
410	0.970993197	4.854965983	5	5	0.3864798
1368.7	0.999992632	4.999963158	5	5	0.0060698

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-2.502012118	5	-	-	NA
Fitted Model	-4.349239691	1	3.69445515	4	0.4489329
Reduced Model	-17.14824501	1	29.2924658	4	<0.0001

Figure 2-8. Details Regarding the Selected Model (Multistage 1-Degree) for Degeneration with Necrosis of the Olfactory Mucosa in Female Rats Following a 4-Hour Inhalation Exposure to 1,2-Dichloroethane

2.1.1.1.2.3 Degeneration with Necrosis of the Olfactory Mucosa in Male and Female F344 Rats (Combined) – 4-Hour Inhalation Exposure

Increased incidence of degeneration with necrosis of the olfactory mucosa was observed in male and female rats (combined) exposed to 1,2-dichloroethane by inhalation for four hours (Dow Chemical, 2006). The measured exposure concentrations (reported in units of ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day. The concentration and response data used for the modeling are presented in Table 2-7. 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).

Table 2-7. Incidence of Degeneration with Necrosis of the Olfactory Mucosa in Male and Female Rats (Combined) and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane

Concentration (mg/m^3)	Number of Animals	Incidence
0	10	0
35.3	10	0
132.5	10	7
410.0	10	10
1368.7	10	10

The BMD modeling results for increased incidence of degeneration with necrosis of the olfactory mucosa in male and female rats (combined) are summarized in Table 2-8. All models provided adequate fit to the data (chi-square p-value > 0.1). The BMDL computation for the Weibull model failed because the lower limit included zero. The BMDLs were not sufficiently close (differed by > 3-fold). Therefore, EPA chose the model with the lowest BMDL (Multistage 1-degree model).

This data set is not well suited for BMD modeling; there is a single datapoint (at 70 percent incidence) with incidence between 0 and 100 percent; there are no data to inform the shape of the curve at the region of interest (~ 10 percent). As a result, the different models provide a broad range of BMD and BMDL estimates. Selection of the low end of the range to represent the BMDL is not among the more realistic possibilities and in this case involves extrapolation below the range of observation to generate a BMD estimate well below the lowest tested dose.

Table 2-8. BMD Modeling Results for Degeneration with Necrosis of the Olfactory Mucosa in Male and Female Rats (Combined) Following a 4-Hour Inhalation Exposure to 1,2-Dichloroethane[a]

Model	Goodness of Fit		BMD 10%ER (mg/m^3)	BMDL 10%ER (mg/m^3)	Basis for Model Selection
	p-value	AIC			
Dichotomous Hill	1.000	16.22	87.6	34.9	All models provided adequate fit to the data (chi-square p-value > 0.1); however, the BMDL computation for the Weibull model failed because the lower limit included zero. Of the viable models, The BMDLs were not sufficiently close (differed by > 3-fold); therefore, EPA chose the model with the lowest BMDL. NOTE: This data set is not well suited for BMD modeling and the results should be interpreted with caution.
Gamma	0.9987	16.27	68.9	30.9	
Log-Logistic	1.000	16.22	87.6	34.9	
Multistage 3	0.9988	12.66	59.5	24.6	
Multistage 2	0.9280	15.82	41.8	18.8	
Multistage 1	**0.4440**	**20.68**	**14.1**	**8.76**	
Weibull	0.8079	17.90	42.7	0	
Logistic	0.9992	16.26	91.0	44.7	
Log-Probit	1.000	16.22	95.1	33.7	
Probit	0.3831	20.81	47.8	29.2	
Quantal Linear	0.4440	20.68	14.1	8.76	

[a] Selected model in bold.

A plot of the Multistage 1-degree model with a BMR of 10 percent ER is shown in Figure 2-9. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-10.

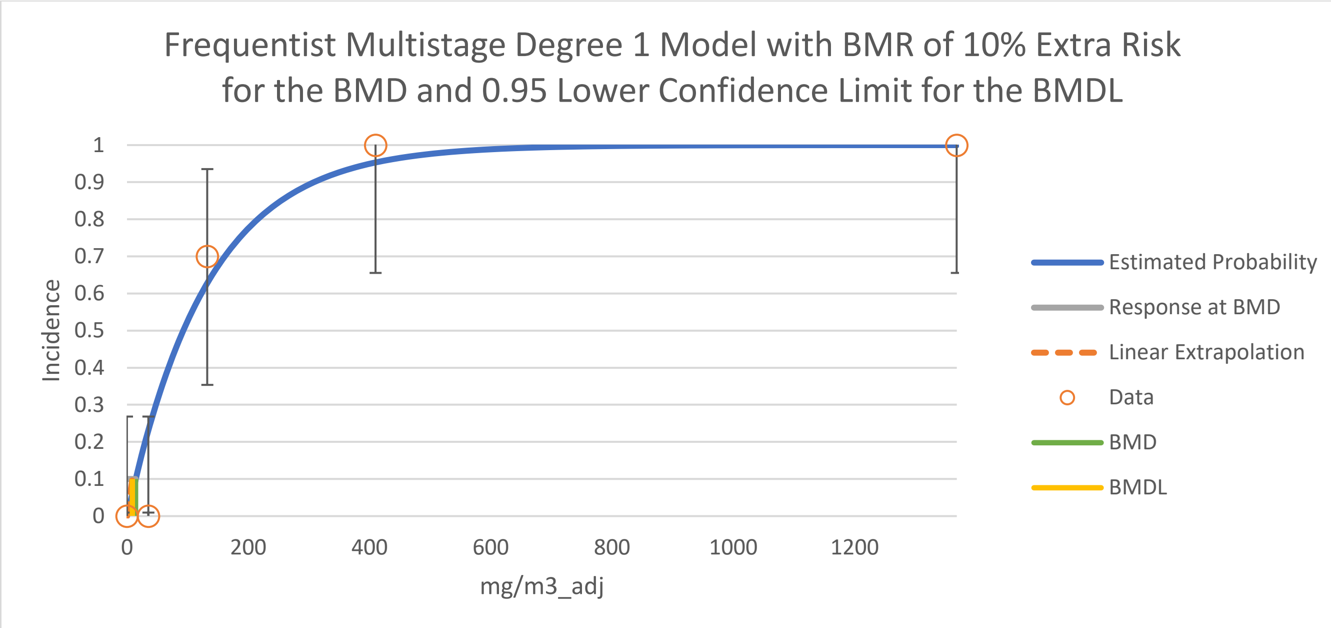

Figure 2-9. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 1-Degree) for Degeneration with Necrosis of the Olfactory Mucosa in Male and Female Rats (Combined) Exposed to 1,2-Dichloroethane Via Inhalation for 4 Hours and BMR of 10%ER

Model Results

Benchmark Dose	
BMD	14.10695256
BMDL	8.757017138
BMDU	23.27887944
AIC	20.67643472
P-value	0.444048554
D.O.F.	4
Chi^2	3.72812481
Slope Factor	0.011419414

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	0.007468694	3.038026138	-5.9469532	5.96189056

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	1.523E-07	0	10	-0.00039
35.3	0.231753727	2.317537268	0	10	-1.736853
132.5	0.628275403	6.282754027	7	10	0.4693345
410	0.953213694	9.532136945	10	10	0.7005905
1368.7	0.999963653	9.999636531	10	10	0.0190652

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-6.108643021	5	-	-	NA
Fitted Model	-9.338217359	1	6.45914868	4	0.1673826
Reduced Model	-34.49718792	1	56.7770898	4	<0.0001

Figure 2-10. Details Regarding the Selected Model (Multistage 1-Degree) for Degeneration with Necrosis of the Olfactory Mucosa in Male and Female Rats (Combined) Following a 4-Hour Inhalation Exposure to 1,2-Dichloroethane

2.1.1.1.2.4 Degeneration with Necrosis of the Olfactory Mucosa in Male F344 Rats – 8-Hour Inhalation Exposure

Increased incidence of degeneration with necrosis of the olfactory mucosa was observed in male rats exposed to 1,2-dichloroethane by inhalation for eight hours (Dow Chemical, 2006). The measured exposure concentrations (reported in units of ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day. The concentration and response data used for the modeling are presented in Table 2-9. 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).

Table 2-9. Incidence of Degeneration with Necrosis of the Olfactory Mucosa in Male Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane

Adjusted Concentration (mg/m^3)	Number of Animals	Incidence
0	5	0
71.3	5	0
145.0	5	1
210.2	5	4

The BMD modeling results for increased incidence of degeneration with necrosis of the olfactory mucosa in male rats are summarized in Table 2-10. All models provided adequate fit to the data (chi-square p-value > 0.1). The BMDLs were not sufficiently close (differed by > 3-fold). Therefore, EPA chose the model with the lowest BMDL (Multistage 1-degree model).

This data set is not well suited for BMD modeling; there is a single datapoint (at 20 percent incidence) with incidence between 0 and 80 percent. As a result, the different models provide a broad range of BMD and BMDL estimates. Selection of the low end of the range to represent the BMDL is not among the more realistic possibilities and, in this case, involves extrapolation below the range of observation to generate a BMD estimate well below the lowest tested dose.

Table 2-10. BMD Modeling Results for Degeneration with Necrosis of the Olfactory Mucosa in Male Rats Following an 8-Hour Inhalation Exposure to 1,2-Dichloroethane[a]

Model	Goodness of Fit		BMD 10%ER (mg/m^3)	BMDL 10%ER (mg/m^3)	Basis for Model Selection
	p-value	AIC			
Dichotomous Hill	1.000	14.01	138	70.1	All models provided adequate fit to the data (chi-square p-value > 0.1). The BMDLs were not sufficiently close (differed by > 3-fold); therefore, EPA chose the model with the lowest BMDL. NOTE: This data set is not well suited for BMD modeling and the results should be interpreted with caution.
Gamma	0.9992	12.03	127	67.7	
Log-Logistic	0.9969	14.02	131	69.9	
Multistage 3	0.9325	11.13	94.3	37.2	
Multistage 2	0.5937	14.54	70.9	26.8	
Multistage 1	**0.2777**	**17.03**	**33.5**	**17.1**	
Weibull	0.9989	12.05	128	63.8	
Logistic	0.9729	14.10	130	71.5	
Log-Probit	0.9999	14.01	132	71.7	
Probit	0.9926	14.03	130	68.3	
Quantal Linear	0.2777	17.03	33.5	17.1	

[a] Selected model in bold.

A plot of the Multistage 1-degree model with a BMR of 10 percent ER is shown in Figure 2-11. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-12.

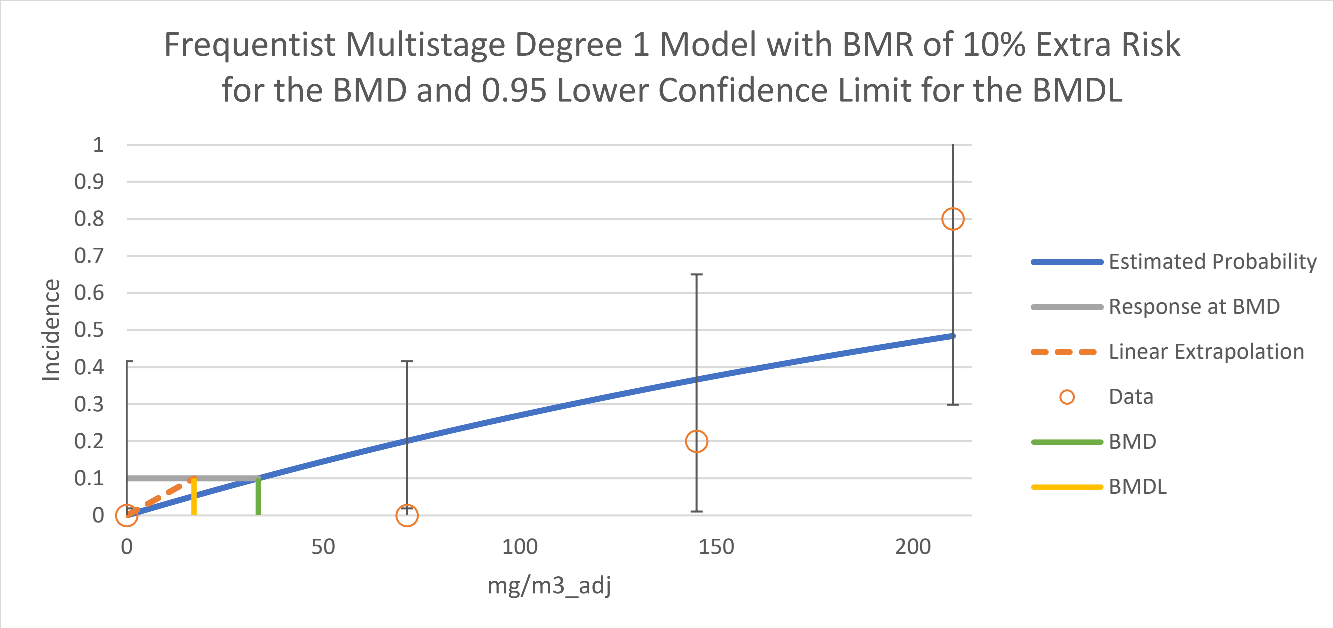

Figure 2-11. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 1-Degree) for Degeneration with Necrosis of the Olfactory Mucosa in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 8 Hours and BMR of 10%ER

Model Results

Benchmark Dose	
BMD	33.46390531
BMDL	17.11048878
BMDU	78.84479045
AIC	17.03210085
P-value	0.277708981
D.O.F.	3
Chi^2	3.853633558
Slope Factor	0.005844368

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	0.003148482	0.300815071	-0.5864382	0.59273519

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	7.61499E-08	0	5	-0.000276
71.3	0.20107387	1.005369348	0	5	-1.121785
145	0.366521946	1.832609729	1	5	-0.772753
210.2	0.484083813	2.420419067	4	5	1.4135365

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-5.004024235	4	-	-	NA
Fitted Model	-7.516050426	1	5.02405238	3	0.1700444
Reduced Model	-11.24670289	1	12.4853573	3	0.0585611

Figure 2-12. Details Regarding the Selected Model (Multistage 1-Degree) for Degeneration with Necrosis of the Olfactory Mucosa in Male Rats Following an 8-Hour Inhalation Exposure to 1,2-Dichloroethane

2.1.1.1.2.5 Degeneration with Necrosis of the Olfactory Mucosa in Female F344 Rats – 8-Hour Inhalation Exposure

Increased incidence of degeneration with necrosis of the olfactory mucosa was observed in female rats exposed to 1,2-dichloroethane by inhalation for eight hours (Dow Chemical, 2006). The measured exposure concentrations (reported in units of ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day. The concentration and response data used for the modeling are presented in Table 2-11. 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).

Table 2-11. Incidence of Degeneration with Necrosis of the Olfactory Mucosa in Female Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane

Adjusted Concentration (mg/m^3)	Number of Animals	Incidence
0	5	0
71.3	5	0
145.0	5	3
210.2	5	5

The BMD modeling results for increased incidence of degeneration with necrosis of the olfactory mucosa in male rats are summarized in Table 2-12. All models provided adequate fit to the data (chi-square p-value > 0.1). The BMDL computation for the Weibull model failed because the lower limit included zero. The BMDLs were not sufficiently close (differed by > 3-fold). Therefore, EPA chose the model with the lowest BMDL (Multistage 1-degree model).

This data set is not well suited for BMD modeling; there is a single datapoint (at 60 percent incidence) with incidence between 0 and 100 percent; there are no data to inform the shape of the curve at the region of interest (~ 10 percent). As a result, the different models provide a broad range of BMD and BMDL estimates. Selection of the low end of the range to represent the BMDL is not among the more realistic possibilities and in this case involves extrapolation below the range of observation to generate a BMD estimate well below the lowest tested dose.

Table 2-12. BMD Modeling Results for Degeneration with Necrosis of the Olfactory Mucosa in Female Rats Following an 8-Hour Inhalation Exposure to 1,2-Dichloroethane[a]

Model	Goodness of Fit		BMD 10%ER (mg/m^3)	BMDL 10%ER (mg/m^3)	Basis for Model Selection
	p-value	AIC			
Dichotomous Hill	0.9999	8.738	125	64.6	All models provided adequate fit to the data (chi-square p-value > 0.1); however, the BMDL computation for the Weibull model failed because the lower limit included zero. Of the viable models, the BMDLs were not sufficiently close (differed by > 3-fold); therefore, EPA chose the model with the lowest BMDL. NOTE: This data set is not well suited for BMD modeling and the results should be interpreted with caution.
Gamma	0.9835	9.036	97.6	57.9	
Log-Logistic	0.9999	8.738	125	64.7	
Multistage 3	0.9249	8.426	68.9	26.1	
Multistage 2	0.5547	12.47	47.1	18.6	
Multistage 1	**0.1987**	**16.31**	**16.3**	**9.20**	
Weibull	0.9997	10.73	122	0	
Logistic	1.000	8.733	124	58.8	
Log-Probit	1.000	10.73	132	64.5	
Probit	1.000	10.73	126	55.0	
Quantal Linear	0.1987	16.31	16.3	9.20	

[a] Selected model in bold.

A plot of the Multistage 1-degree model with a BMR of 10 percent ER is shown in Figure 2-13. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-14.

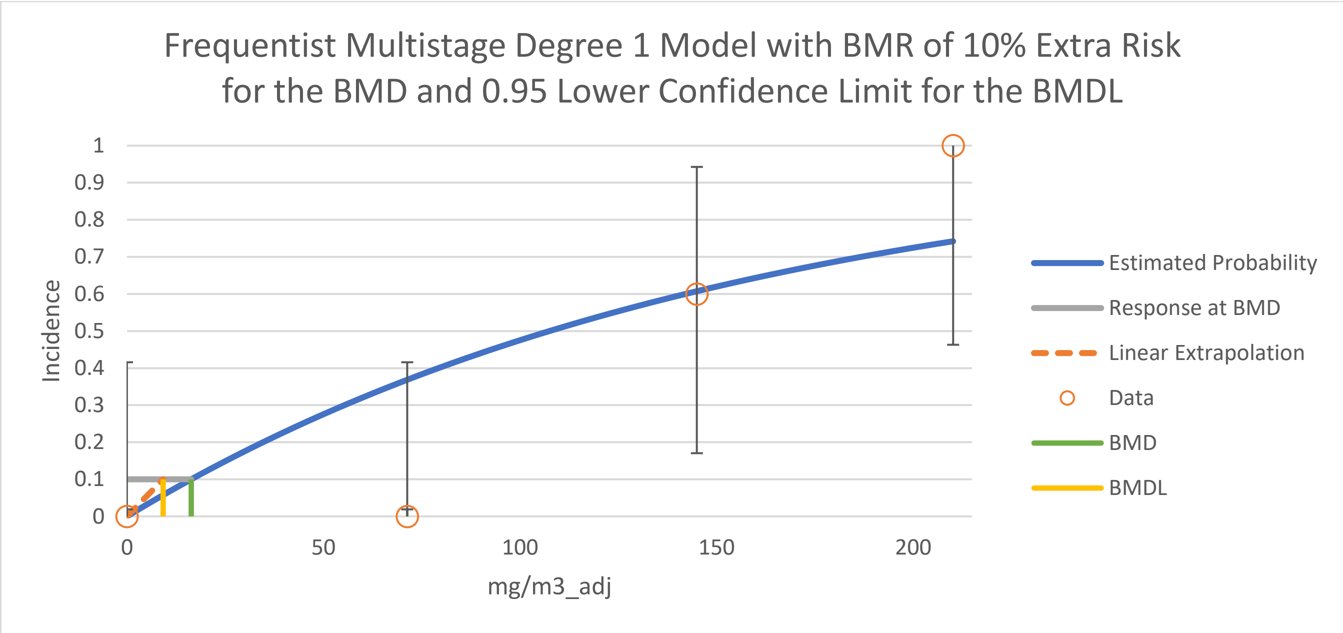

Figure 2-13. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 1-Degree) for Degeneration with Necrosis of the Olfactory Mucosa in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation for 8 Hours and BMR of 10%ER

Model Results	

Benchmark Dose	
BMD	16.34257648
BMDL	9.199716086
BMDU	32.02480499
AIC	16.31075155
P-value	0.198741114
D.O.F.	3
Chi^2	4.656587683
Slope Factor	0.010869901

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	0.006446995	0.508897083	-0.990973	1.00386696

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	7.61499E-08	0	5	-0.000276
71.3	0.368508494	1.842542471	0	5	-1.708146
145	0.607341244	3.03670622	3	5	-0.033615
210.2	0.742093574	3.710467871	5	5	1.3182165

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-3.365058335	4	-	-	NA
Fitted Model	-7.155375774	1	7.58063488	3	0.0555224
Reduced Model	-13.46023334	1	20.19035	3	0.000155

Figure 2-14. Details Regarding the Selected Model (Multistage 1-Degree) for Degeneration with Necrosis of the Olfactory Mucosa in Female Rats Following an 8-Hour Inhalation Exposure to 1,2-Dichloroethane

2.1.1.1.2.6 Degeneration with Necrosis of the Olfactory Mucosa in Male and Female F344 Rats (Combined) – 8-Hour Inhalation Exposure

Increased incidence of degeneration with necrosis of the olfactory mucosa was observed in male and female rats (combined) exposed to 1,2-dichloroethane by inhalation for eight hours (Dow Chemical, 2006). The measured exposure concentrations (reported in units of ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day. The concentration and response data used for the modeling are presented in Table 2-13. 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).

Table 2-13. Incidence of Degeneration with Necrosis of the Olfactory Mucosa in Male and Female Rats (combined) and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane

Adjusted Concentration (mg/m^3)	Number of Animals	Incidence
0	10	0
71.3	10	0
145.0	10	4
210.2	10	9

The BMD modeling results for increased incidence of degeneration with necrosis of the olfactory mucosa in male rats are summarized in Table 2-14. All models provided adequate fit to the data (chi-square p-value > 0.1) except for the Multistage 1-degree/Quantal Linear model. The BMDLs of the fit models were sufficiently close (differed by < 3-fold). Therefore, EPA chose the model with the lowest AIC (Multistage 3-degree model).

Table 2-14. BMD Modeling Results for Degeneration with Necrosis of the Olfactory Mucosa in Male and Female Rats (Combined) Following an 8-Hour Inhalation Exposure to 1,2-Dichloroethane[a]

Model	Goodness of Fit		BMD 10%ER (mg/m^3)	BMDL 10%ER (mg/m^3)	Basis for Model Selection
	p-value	AIC			
Dichotomous Hill	1.000	23.96	131	78.1	All models provided adequate fit to the data (chi-square p-value > 0.1) except for the Multistage 1-degree/Quantal Linear model. The BMDLs of the fit models were sufficiently close (differed by < 3-fold); therefore, EPA chose the model with the lowest AIC.
Gamma	0.9847	24.01	112	75.2	
Log-Logistic	0.9779	24.04	114	77.5	
Multistage 3	**0.8911**	**21.80**	**81.4**	**48.9**	
Multistage 2	0.3612	26.88	57.8	34.3	
Multistage 1	0.0570	32.87	23.1	14.8	
Weibull	0.9664	22.40	106	68.2	
Logistic	0.8515	24.46	110	72.6	
Log-Probit	0.9965	23.97	114	77.8	
Probit	0.9049	24.26	110	70.5	
Quantal Linear	0.0570	32.87	23.1	14.8	

[a] Selected model in bold.

A plot of the Multistage 3-degree model with a BMR of 10 percent ER is shown in Figure 2-15. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-16.

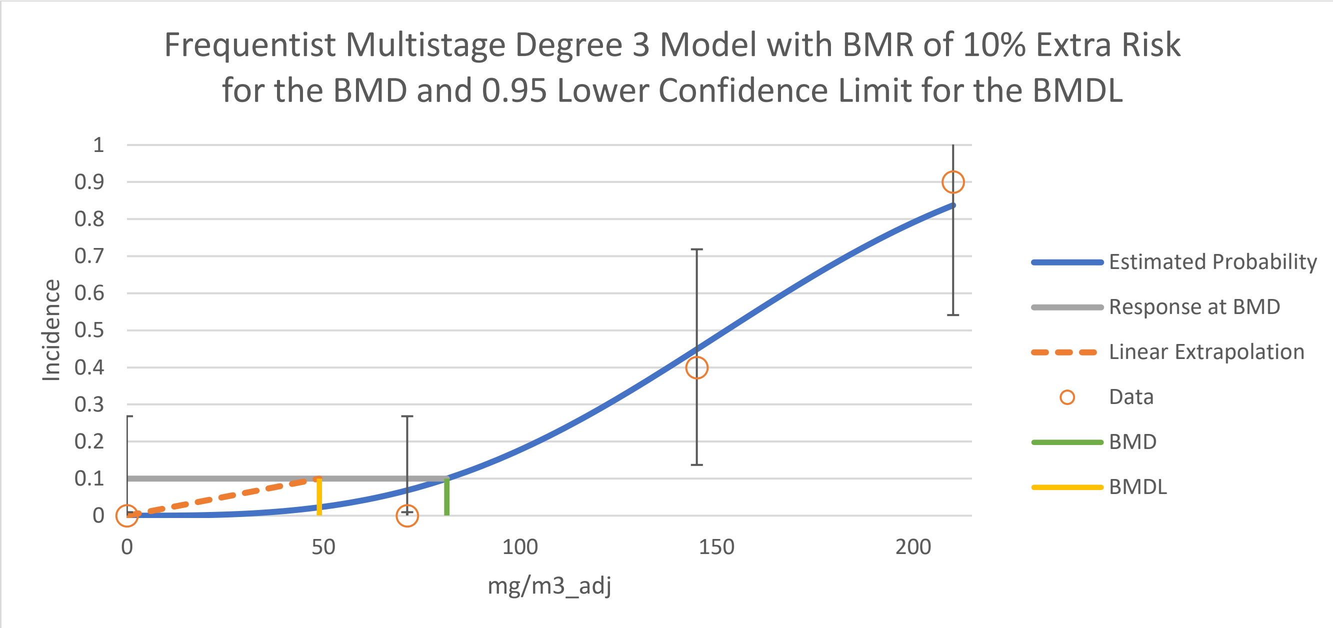

Figure 2-15. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 3-Degree) for Degeneration with Necrosis of the Olfactory Mucosa in Male and Female Rats (Combined) Exposed to 1,2-Dichloroethane Via Inhalation for 8 Hours and BMR of 10%ER

Model Results

Benchmark Dose	
BMD	81.37548237
BMDL	48.94695881
BMDU	97.14021529
AIC	21.80354181
P-value	0.891072257
D.O.F.	4
Chi^2	1.120086799
Slope Factor	0.002043028

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	Bounded	NA	NA	NA
b2	Bounded	NA	NA	NA
b3	Bounded	NA	NA	NA

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	1.523E-07	0	10	-0.00039
71.3	0.068417522	0.68417522	0	10	-0.856985
145	0.449030218	4.490302179	4	10	-0.311718
210.2	0.837310844	8.373108437	9	10	0.5371181

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-9.980946404	4	-	-	NA
Fitted Model	-10.90177091	0	1.84164901	4	0.7648543
Reduced Model	-25.22324114	1	30.4845895	3	<0.0001

Figure 2-16. Details Regarding the Selected Model (Multistage 3-Degree) for Degeneration with Necrosis of the Olfactory Mucosa in Male and Female Rats (Combined) Following an 8-Hour Inhalation Exposure to 1,2-Dichloroethane

2.1.1.1.2.7 Regeneration of the Olfactory Mucosa in Male F344 Rats – 4-Hour Inhalation Exposure

Increased incidence of regeneration of the olfactory mucosa was observed in male rats exposed to 1,2-dichloroethane by inhalation for four hours (Dow Chemical, 2006). The measured exposure concentrations (reported in units of ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day. The concentration and response data used for the modeling are presented in Table 2-15. 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).

Table 2-15. Incidence of Regeneration of the Olfactory Mucosa in Male Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane

Adjusted Concentration (mg/m^3)	Number of Animals	Incidence
0	5	0
132.5	5	4
410.0	5	5
1368.7	5	5

The BMD modeling results for increased incidence of regeneration of the olfactory mucosa in male rats are summarized in Table 2-16. All models provided adequate fit to the data (chi-square p-value > 0.1). The BMDL computations failed for the Dichotomous Hill and Log-Probit models because the lower limit included zero. The Gamma, Log-Logistic, Multistage 3-, 2-, and 1-degree, Weibull, and Quantal Linear models were questionable because the BMDL values were 10 times lower than the lowest non-zero concentration. The BMDLs of the remaining viable models (Logistic and Probit) were sufficiently close (differed by < 3-fold). Therefore, EPA chose the model with the lower AIC (Logistic).

This data set is not well suited for BMD modeling. There is a single datapoint (at 80 percent incidence) with incidence between 0 and 100 percent; there are no data to inform the shape of the curve at the region of interest (~ 10 percent). As a result, the different models provide a broad range of BMD and BMDL estimates, all of which in this case involve extrapolation below the range of observation to generate BMD estimates well below the lowest tested dose.

Table 2-16. BMD Modeling Results for Regeneration of the Olfactory Mucosa in Male Rats Following a 4-Hour Inhalation Exposure to 1,2-Dichloroethane[a]

Model	Goodness of Fit		BMD 10%ER (mg/m^3)	BMDL 10%ER (mg/m^3)	Basis for Model Selection
	p-value	AIC			
Dichotomous Hill	0.9998	9.005	80.07	0	All models provided adequate fit to the data (chi-square p-value > 0.1); however, the BMDL computations failed for the Dichotomous Hill and Log-Probit models because the lower limit included zero. The Gamma, Log-Logistic, Multistage 3-, 2-, and 1-degree, Weibull, and Quantal Linear models were questionable because the BMDL values were 10 times lower than the lowest non-zero concentration. The BMDLs of the remaining viable models (Logistic and Probit) were sufficiently close (differed by < 3-fold); therefore, EPA chose the model with the lower AIC. NOTE: This data set is not well suited for BMD modeling and the results should be interpreted with caution.
Gamma	1.000	9.004	58.72	3.712	
Log-Logistic	0.9998	9.005	80.07	0.3723	
Multistage 3	1.000	7.004	17.27	3.712	
Multistage 2	1.000	7.004	33.90	3.712	
Multistage 1	0.9983	7.065	8.302	3.679	
Weibull	1.000	9.004	28.36	3.712	
Logistic	**0.9994**	**9.007**	**83.51**	**16.06**	
Log-Probit	1.000	9.004	81.52	0	
Probit	0.6397	10.43	30.47	14.20	
Quantal Linear	0.9983	7.065	8.302	3.679	

[a] Selected model in bold.

A plot of the Logistic model with a BMR of 10 percent ER is shown in Figure 2-17. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-18.

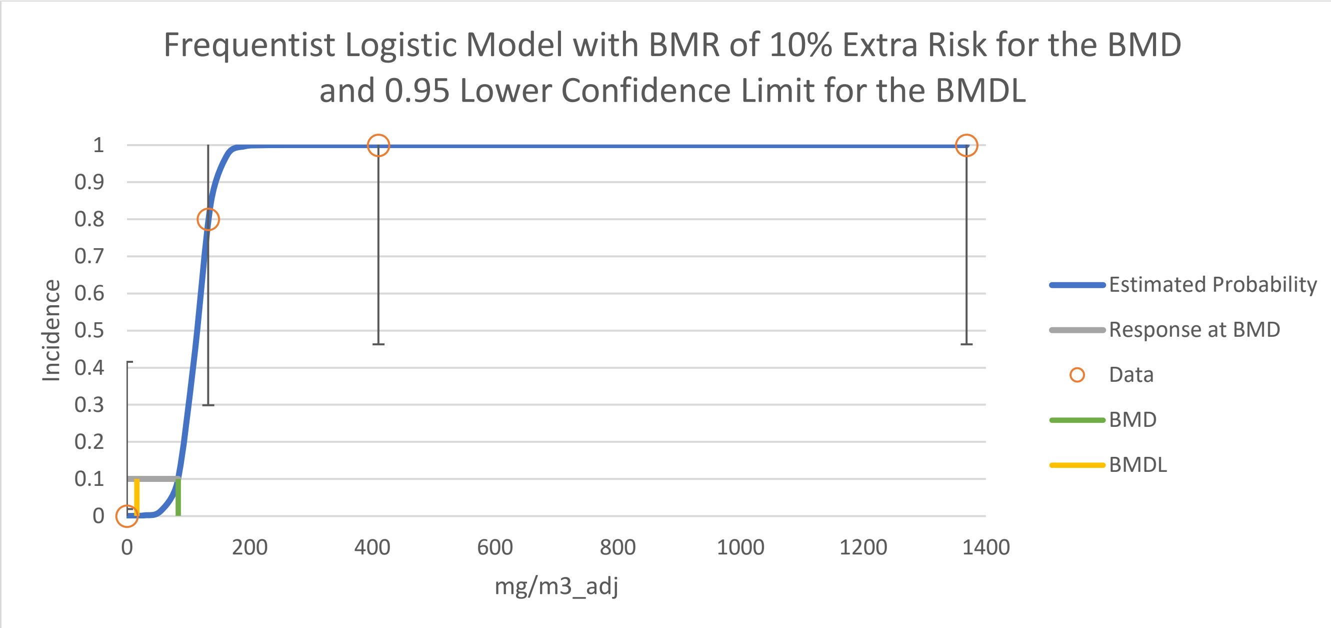

Figure 2-17. Plot of Response by Concentration with Fitted Curve for the Selected Model (Logistic) for Regeneration of the Olfactory Mucosa in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 4 Hours and BMR of 10%ER

Model Results

Benchmark Dose	
BMD	83.50781438
BMDL	16.05730006
BMDU	105.6670162
AIC	9.006521039
P-value	0.999376363
D.O.F.	2
Chi^2	0.001247664

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
a	-8.295982925	1.11664204	-10.484561	-6.1074047
b	0.07306203	3.16E-07	0.07306141	0.07306265

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.000249455	0.001247275	0	5	-0.035321
132.5	0.799750546	3.998752732	4	5	0.0013938
410	1	4.999999998	5	5	4.428E-05
1368.7	1	5	5	5	0

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-2.502012118	4	-	-	NA
Fitted Model	-2.503260519	2	0.0024968	2	0.9987524
Reduced Model	-12.21728604	1	19.4305478	3	0.0002227

Figure 2-18. Details Regarding the Selected Model (Logistic) for Regeneration of the Olfactory Mucosa in Male Rats Following a 4-Hour Inhalation Exposure to 1,2-Dichloroethane

2.1.1.1.2.8 Regeneration of the Olfactory Mucosa in Female F344 Rats – 4-Hour Inhalation Exposure

Increased incidence of regeneration of the olfactory mucosa was observed in female rats exposed to 1,2-dichloroethane by inhalation for four hours (Dow Chemical, 2006). The measured exposure concentrations (reported in units of ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day. The concentration and response data used for the modeling are presented in Table 2-17. 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).

Table 2-17. Incidence of Regeneration of the Olfactory Mucosa in Female Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane

Adjusted Concentration (mg/m^3)	Number of Animals	Incidence
0	5	0
132.5	5	4
410.0	5	5
1368.7	5	5

The BMD modeling results for increased incidence of regeneration of the olfactory mucosa in female rats are summarized in Table 2-18. All models provided adequate fit to the data (chi-square p-value > 0.1). The BMDL computations failed for the Dichotomous Hill and Log-Probit models because the lower limit included zero. The Gamma, Log-Logistic, Multistage 3-, 2-, and 1-degree, Weibull, and Quantal Linear models were considered questionable because the BMDL values were 10 times lower than the lowest non-zero concentration. The BMDLs of the remaining models (Logistic and Probit) were sufficiently close (differed by < 3-fold). Therefore, EPA chose the model with the lower AIC (Logistic).

This data set is not well suited for BMD modeling; there is a single datapoint (at 80 percent incidence) with incidence between 0 and 100 percent; there are no data to inform the shape of the curve at the region of interest (~ 10 percent). As a result, the different models provide a broad range of BMD and BMDL estimates, all of which in this case involve extrapolation below the range of observation to generate BMD estimates well below the lowest tested dose.

Table 2-18. BMD Modeling Results for Regeneration of the Olfactory Mucosa in Female Rats Following a 4-Hour Inhalation Exposure to 1,2-Dichloroethane*[a]*

Model	Goodness of Fit		BMD 10%ER (mg/m^3)	BMDL 10%ER (mg/m^3)	Basis for Model Selection
	p-value	AIC			
Dichotomous Hill	0.9998	9.005	80.07	0	All models provided adequate fit to the data (chi-square p-value > 0.1); however, the BMDL computations failed for the Dichotomous Hill and Log-Probit models because the lower limit included zero. The Gamma, Log-Logistic, Multistage 3-, 2-, and 1-degree, Weibull, and Quantal Linear models were considered questionable because the BMDL values were 10 times lower than the lowest non-zero concentration. The BMDLs of the remaining viable models (Logistic and Probit) were sufficiently
Gamma	1.000	9.004	58.72	3.712	
Log-Logistic	0.9998	9.005	80.07	0.3723	
Multistage 3	1.000	7.004	17.27	3.712	
Multistage 2	1.000	7.004	33.90	3.712	
Multistage 1	0.9983	7.065	8.302	3.679	
Weibull	1.000	9.004	28.36	3.712	
Logistic	**0.9994**	**9.007**	**83.51**	**16.06**	
Log-Probit	1.000	9.004	81.52	0	
Probit	0.6397	10.43	30.47	14.20	
Quantal Linear	0.9983	7.065	8.302	3.679	

Model	Goodness of Fit		BMD 10%ER (mg/m^3)	BMDL 10%ER (mg/m^3)	Basis for Model Selection
	p-value	AIC			
					close (differed by < 3-fold); therefore, EPA chose the model with the lower AIC. NOTE: This data set is not well suited for BMD modeling and the results should be interpreted with caution.
[a] Selected model in bold.					

A plot of the Logistic model with a BMR of 10 percent ER is shown in Figure 2-19. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-20.

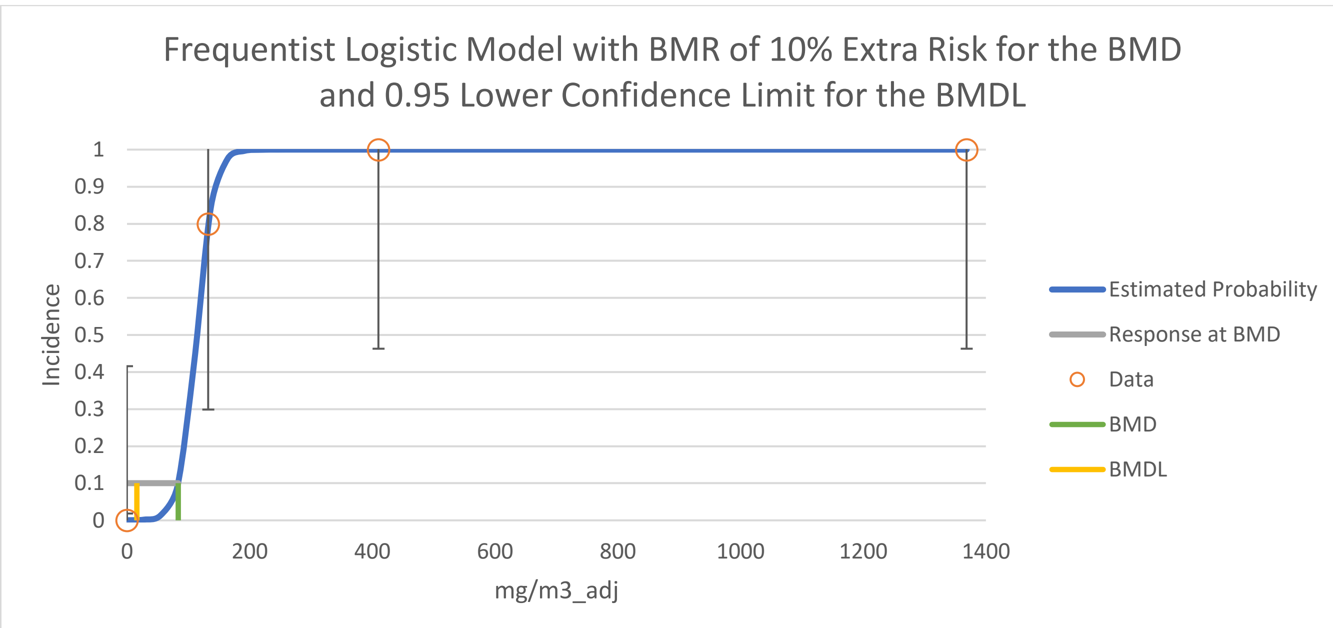

Figure 2-19. Plot of Response by Concentration with Fitted Curve for the Selected Model (Logistic) for Regeneration of the Olfactory Mucosa in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation for 4 Hours and BMR of 10%ER

Model Results

Benchmark Dose	
BMD	83.50781438
BMDL	16.05730006
BMDU	105.6670162
AIC	9.006521039
P-value	0.99937543
D.O.F.	2
Chi^2	0.00124953

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
a	-8.295982925	1.11664204	-10.484561	-6.1074047
b	0.07306203	3.16E-07	0.07306141	0.07306265

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.000249455	0.001247275	0	5	-0.035321
132.5	0.799750546	3.998752732	4	5	0.0013938
410	1	4.999999998	5	5	4.428E-05
1368.7	1	5	5	5	0

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-2.502012118	4	-	-	NA
Fitted Model	-2.503260519	2	0.0024968	2	0.9987524
Reduced Model	-12.21728604	1	19.428051	3	0.000223

Figure 2-20. Details Regarding the Selected Model (Logistic) for Regeneration of the Olfactory Mucosa in Female Rats Following a 4-Hour Inhalation Exposure to 1,2-Dichloroethane

2.1.1.1.2.9 Regeneration of the Olfactory Mucosa in Male and Female F344 Rats (Combined) – 4-Hour Inhalation Exposure

Increased incidence of regeneration of the olfactory mucosa was observed in male and female rats (combined) exposed to 1,2-dichloroethane by inhalation for four hours (Dow Chemical, 2006). The measured exposure concentrations (reported in units of ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day. The concentration and response data used for the modeling are presented in Table 2-19. 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).

Table 2-19. Incidence of Regeneration of the Olfactory Mucosa in Male and Female Rats (Combined) and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane

Adjusted Concentration (mg/m^3)	Number of Animals	Incidence
0	10	0
132.5	10	8
410.0	10	10
1368.7	10	10

The BMD modeling results for increased incidence of regeneration of the olfactory mucosa in male rats are summarized in Table 2-20. All models provided adequate fit to the data (chi-square p-value > 0.1). The Dichotomous Hill, Gamma, Log-Logistic, Multistage 3-, 2-, and 1-degree, Weibull, Log-Probit, and Quantal Linear models were considered questionable because the BMDL values were 10 times lower than the lowest non-zero concentration. The BMDLs of the remaining models (Logistic and Probit) were sufficiently close (differed by < 3-fold). Therefore, EPA chose the model with the lower AIC (Logistic).

This data set is not well suited for BMD modeling; there is a single datapoint (at 80 percent incidence) with incidence between 0 and 100 percent; there are no data to inform the shape of the curve at the region of interest (~ 10 percent). As a result, the different models provide a broad range of BMD and BMDL estimates, all of which in this case involve extrapolation below the range of observation to generate BMD estimates well below the lowest tested dose.

Table 2-20. BMD Modeling Results for Regeneration of the Olfactory Mucosa in Male and Female Rats (Combined) Following a 4-Hour Inhalation Exposure to 1,2-Dichloroethane[a]

Model	Goodness of Fit		BMD 10%ER (mg/m^3)	BMDL 10%ER (mg/m^3)	Basis for Model Selection
	p-value	AIC			
Dichotomous Hill	0.9996	14.01	80.07	0.9633	All models provided adequate fit to the data (chi-square p-value > 0.1); however, the Dichotomous Hill, Gamma, Log-Logistic, Multistage 3-, 2-, and 1-degree, Weibull, Log-Probit, and Quantal Linear models were considered questionable because the BMDL values were 10 times lower than the lowest non-zero concentration. The BMDLs of the remaining viable models (Logistic and Probit) were sufficiently close (differed by < 3-fold); therefore, EPA chose the model with the lower AIC.
Gamma	1.000	14.01	58.72	4.706	
Log-Logistic	0.9996	14.01	80.07	0.9651	
Multistage 3	1.000	12.01	17.27	4.706	
Multistage 2	1.000	12.01	33.90	4.706	
Multistage 1	0.9954	12.13	8.302	4.645	
Weibull	1.000	14.01	28.36	4.706	
Logistic	**0.9988**	**14.01**	**83.51**	**23.18**	
Log-Probit	1.000	14.01	81.52	0.005232	
Probit	0.4092	16.86	30.47	17.47	
Quantal Linear	0.995	12.13	8.302	4.645	

Model	Goodness of Fit		BMD 10%ER (mg/m³)	BMDL 10%ER (mg/m³)	Basis for Model Selection
	p-value	AIC			
					NOTE: This data set is not well suited for BMD modeling and the results should be interpreted with caution.
[a] Selected model in bold.					

A plot of the Logistic model with a BMR of 10 percent ER is shown in Figure 2-21. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-22.

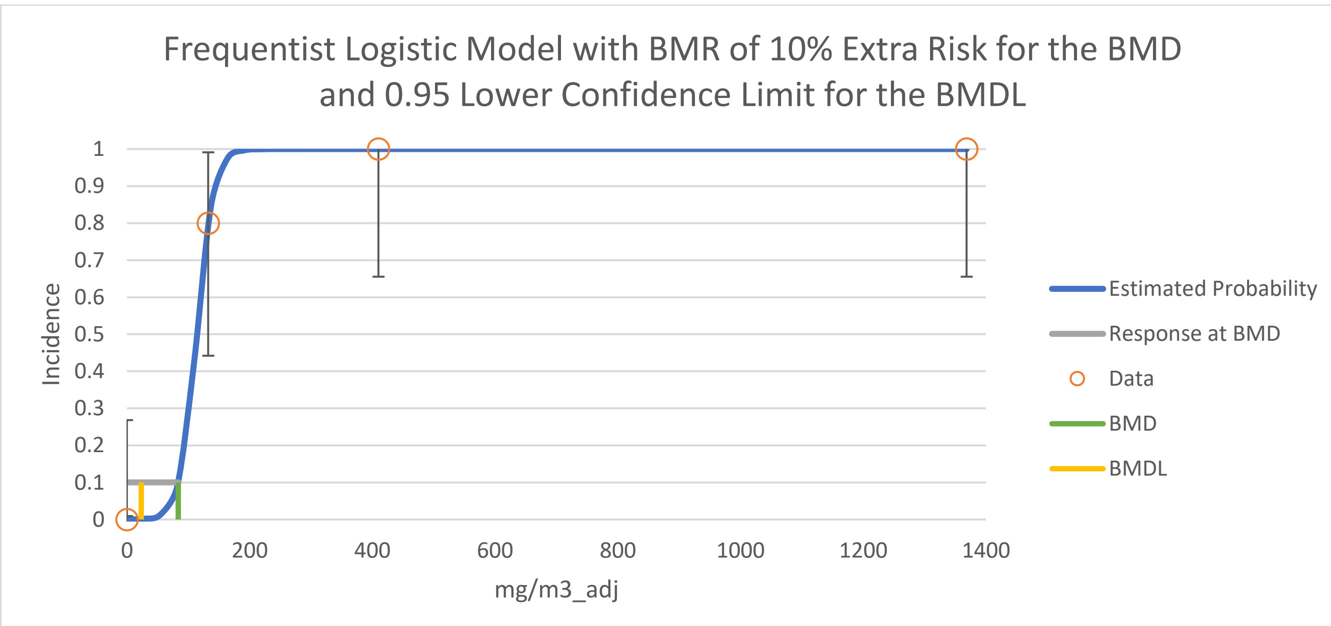

Figure 2-21. Plot of Response by Concentration with Fitted Curve for the Selected Model (Logistic) for Regeneration of the Olfactory Mucosa in Male and Female Rats (Combined) Exposed to 1,2-Dichloroethane Via Inhalation for 4 Hours and BMR of 10%ER

Model Results

Benchmark Dose	
BMD	83.50781438
BMDL	23.18348326
BMDU	99.55849153
AIC	14.01304208
P-value	0.99875125
D.O.F.	2
Chi^2	0.002499061

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
a	-8.295982925	0.789585159	-9.8435414	-6.7484244
b	0.07306203	3.16E-07	0.07306141	0.07306265

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.000249455	0.002494549	0	10	-0.049952
132.5	0.799750546	7.997505465	8	10	0.0019712
410	1	9.999999996	10	10	6.262E-05
1368.7	1	10	10	10	0

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-5.004024235	4	-	-	NA
Fitted Model	-5.006521039	2	0.00499361	2	0.9975063
Reduced Model	-24.43457208	1	38.8561021	3	<0.0001

Figure 2-22. Details Regarding the Selected Model (Logistic) for Regeneration of the Olfactory Mucosa in Male and Female Rats (Combined) Following a 4-Hour Inhalation Exposure to 1,2-Dichloroethane

2.1.1.1.3 Hepatic Effects

Only one hepatic endpoint was identified for acute-duration inhalation exposure. EPA modeled serum L-iditol dehydrogenase levels in male mice exposed to 1,2-dichloroethane by inhalation for four hours (Storer et al., 1984). The modeling results are not presented because neither the constant nor nonconstant variance models provided adequate fit to the variance data.

2.1.1.1.4 Renal Effects

For acute inhalation exposure, EPA selected two renal endpoints for quantitative dose-response analysis with BMDS, including relative kidney weights and blood urea nitrogen (BUN) levels in serum following four-hour inhalation exposure in male mice (Storer et al., 1984). For both data sets, only data for the control and two lowest concentrations (0, 107, and 337 mg/m^3) were modeled; high mortality (four of five and five of five) precluded collection of relevant data at the two highest tested concentrations (723.2

and 1313 mg/m^3, respectively). EPA did not present the BMD modeling results for increased BUN in male mice because no model resulted in an adequate fit.

2.1.1.1.4.1 Relative Kidney Weight (Kidney Weight/100 g Body Weight) in Male B6C3F1 Mice – 4-Hour Inhalation Exposure

Relative kidney weight was significantly increased in male mice exposed to 1,2-dichloroethane by inhalation for four hours (Storer et al., 1984). The measured exposure concentrations (reported in units of ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day. The concentration and response data used for the modeling are presented in Table 2-21. 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 because EPA considers a 10 percent change in relative kidney weight to be biologically significant.

Table 2-21. Increased Relative Kidney Weight in Male Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from an Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Mean (Kidney Weight/100 g Body Weight)	SD (Kidney Weight/100 g Body Weight)
0	5	1.53	0.07
107	5	1.53	0.08
337	5	1.71	0.09

The BMD modeling results for increased relative kidney weight in male mice are summarized in Table 2-22. The constant variance model provided an adequate fit to the variance data. With the constant variance model applied, only the Polynomial 2-degree and Linear models provided adequate fit to the means. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC (Polynomial 2-degree model) was selected.

Table 2-22. Summary of BMD Modeling Results for Increased Relative Kidney Weight in Male Mice Following Inhalation Exposure to 1,2-Dichloroethane (Constant Variance)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	BMD 10%RD (mg/m^3)	BMDL 10%RD (mg/m^3)	Basis for Model Selection
	Test 4 p-value	AIC					
Exponential 3	NA	−28.40	319	107	334	213	Only the Polynomial 2-degree and Linear models provided adequate fit to the means (test 4 p-value > 0.1). The BMDLs were sufficiently close (differed by < 3-fold); therefore, EPA chose the model with the lowest AIC.
Exponential 5	NA	−26.40	205	160	221	113	
Hill	NA	−26.40	299	106	330	318	
Polynomial Degree 2	**0.6765**	**−30.22**	**209**	**102**	**303**	**207**	
Power	NA	−28.40	319	105	334	211	
Linear	0.1691	−28.50	134	88.5	262	180	

[a] Selected model in bold.

Plots of the Polynomial 2-degree model with BMRs of one SD and 10 percent RD are shown in Figure 2-23 and Figure 2-24, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-25 (BMD and BMDL shown are for BMR of one SD; the rest is applicable to both BMRs).

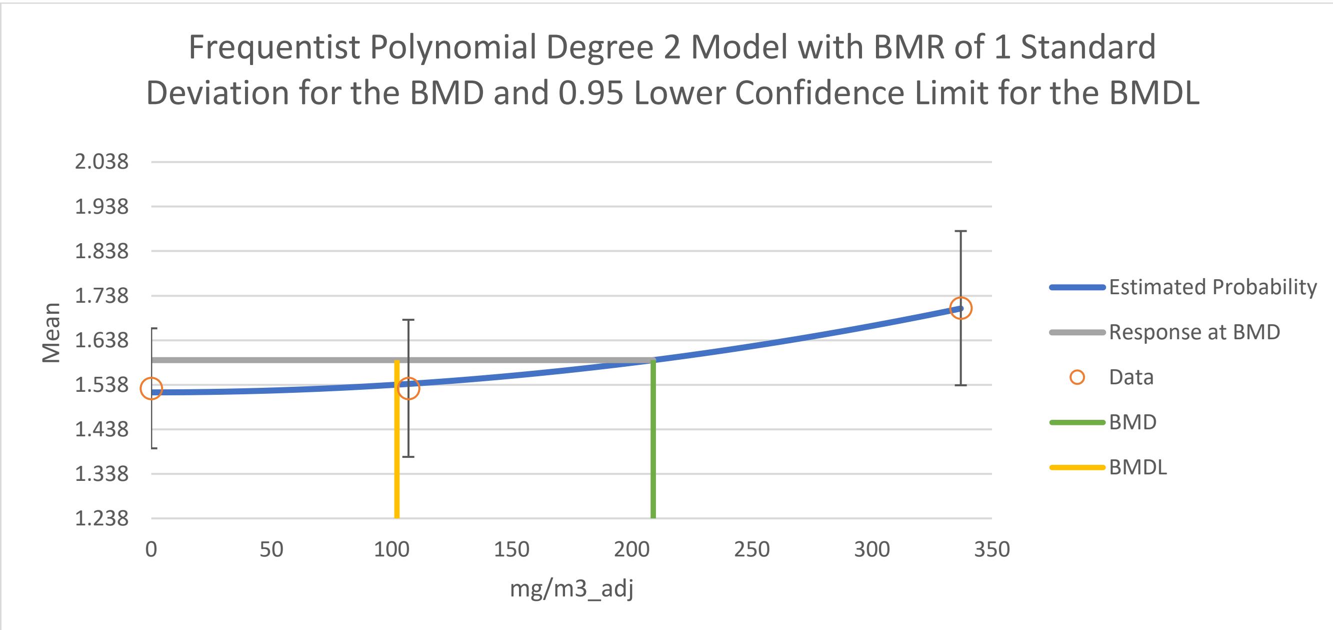

Figure 2-23. Plot of Response by Dose with Fitted Curve for the Selected Model (Polynomial 2-Degree) for Increased Relative Kidney Weight in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 4 Hours and BMR of 1SD (Constant Variance)

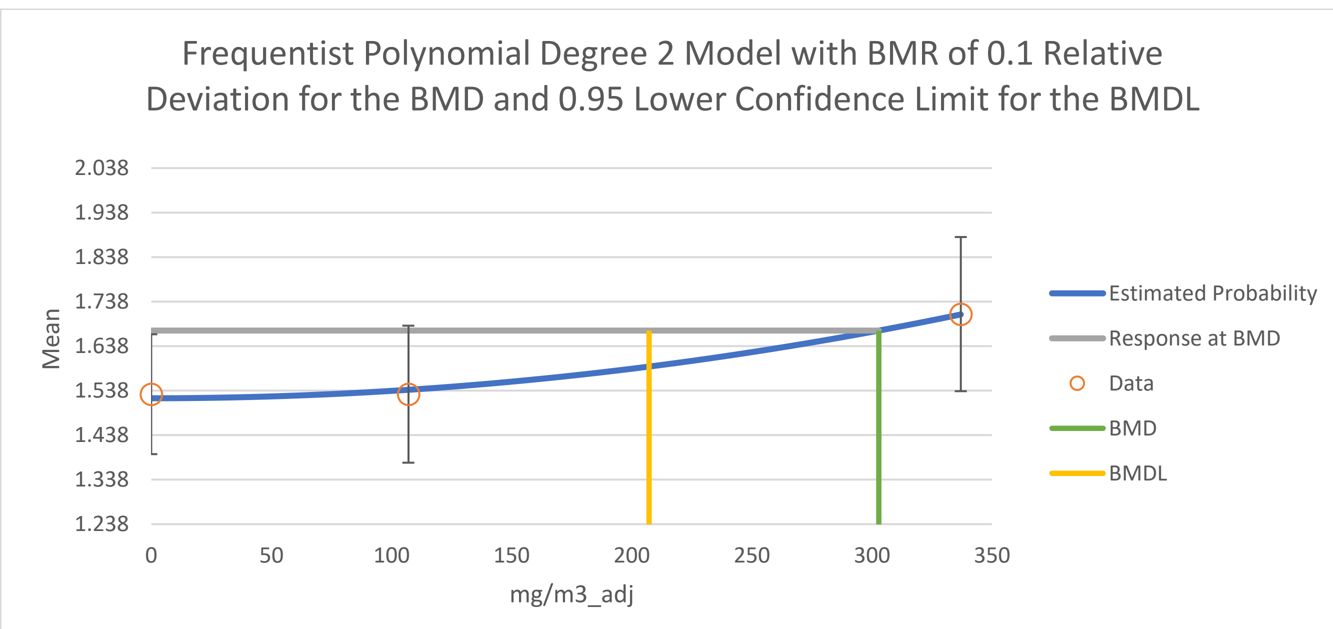

Figure 2-24. Plot of Response by Dose with Fitted Curve for the Selected Model (Polynomial 2-Degree) for Increased Relative Kidney Weight in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 4 Hours and BMR of 10%RD (Constant Variance)

Model Results

Benchmark Dose	
BMD	208.9772425
BMDL	102.2542989
BMDU	285.9155546
AIC	-30.22136297
Test 4 P-value	0.676535642
D.O.F.	1

Model Parameters

# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	1.520909738	2.41E-02	1.47361189	1.56820759
beta	Bounded	NA	NA	NA
beta2	1.65792E-06	3.66E-07	9.4021E-07	2.3756E-06
alpha	0.005242334	1.00E-05	0.00522265	0.00526202

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	5	1.520909738	1.53	1.53	0.07240397	0.07	0.07	0.280736593
107	5	1.539891291	1.53	1.53	0.07240397	0.08	0.08	-0.305474959
337	5	1.709198317	1.71	1.71	0.07240397	0.09	0.09	0.024758571

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	18.1977074	4	-28.395415
A2	18.35417009	6	-24.70834
A3	18.1977074	4	-28.395415
fitted	18.11068148	3	-30.221363
R	11.65750945	2	-19.315019

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test d.f.	p-value
1	13.39332127	4	0.0095056
2	0.312925375	2	0.85516343
3	0.312925375	2	0.85516343
4	0.174051828	1	0.67653564

Figure 2-25. Details Regarding the Selected Model (Polynomial 2-Degree) for Increased Relative Kidney Weight in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 4 Hours

2.1.1.2 Short-term/Intermediate

2.1.1.2.1 Mortality

Two short-term/intermediate-duration inhalation studies were identified that showed potentially treatment-related incidence of mortality in exposed animals (Igwe et al., 1986; Rao et al., 1980). Though neither data set showed a statistically significant increase, these data were modeled.

2.1.1.2.1.1 Mortality in Male Rats – 30-Day Inhalation Exposure

There was mortality in male rats exposed to 1,2-dichloroethane by inhalation for 30 days (seven hours per day, 5 days per week) (Igwe et al., 1986). The measured exposure concentrations (reported in units of ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day and 7 days per week. The concentration and response data used for the modeling are presented in Table 2-23. Dichotomous models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). BMRs of one and five percent ER were also selected due to severity of the endpoint.

Table 2-23. Incidence of Mortality in Male Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from an Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Incidence
0	30	0
129	12	0
256	12	1
383	12	2

The BMD modeling results for incidence of mortality are summarized in Table 2-24. All models provided adequate fit to the data (chi-square p-value > 0.1). The Dichotomous Hill and Log-Probit models were considered questionable/unusable at all attempted BMRs because the BMD/BMDL ratio was > 20 and the BMDL was > 10 times lower than the lowest non-zero concentration or the BMDL computation failed. At a BMR of 10 percent ER or five percent ER, the BMDLs of the remaining fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Multistage 3-degree). At a BMR of one percent ER, there is much greater uncertainty because the BMR is well below anything observable in the data. As a result, there is greater spread in the BMDLs (> 3-fold) and additional models provided questionable results (Multistage 1-degree and Quantal Linear models) due to BMDL > 10 times lower than the lowest non-zero concentration. Because the BMDLs of remaining viable models differed by > 3-fold, the BMDS recommended the model with the lowest BMDL (Log-Logistic); however, the Multistage 3-degree model was a viable alternative and was selected to be consistent with model selection at 10 percent ER and five percent ER. There was little difference in BMD/BMDL values between the Multistage 3-degree and Log-Logistic models.

Table 2-24. Summary of BMD Modeling Results for Incidence of Mortality in Male Rats Following Inhalation Exposure to 1,2-Dichloroethane[a]

Model	Goodness of Fit (Means)		BMD 1%ER (mg/m^3)	BMDL 1%ER (mg/m^3)	BMD 5%ER (mg/m^3)	BMDL 5%ER (mg/m^3)	BMD 10%ER (mg/m^3)	BMDL 10%ER (mg/m^3)	Basis for Model Selection
	p-value	AIC							
Dichotomous Hill	1.000	21.70	220	0.0383	244	0.0428	262	1.42	All models provided adequate fit to the data (chi-square p-value > 0.1). The Dichotomous Hill and Log-Probit models were considered questionable/unusable, however, at all attempted BMRs because the BMD/BMDL ratio was > 20 and the BMDL was > 10 times lower than the lowest non-zero concentration or the BMDL computation failed. At BMR = 10 percent ER or five percent ER, the BMDLs of the fit models were sufficiently close (differed by < 3-fold); therefore, EPA chose the model with the lowest AIC (Multistage 3-degree). At BMR = one percent ER, additional models provided questionable results (Multistage 1-degree and Quantal Linear models) due to BMDL > 10 times lower than the lowest non-zero concentration. The BMDLs of remaining viable models differed by > 3-fold and the BMDS recommended the model with the lowest BMDL (Log-Logistic); however, the Multistage 3-degree model was a viable alternative and was selected to be consistent with model selection at 10 percent ER and five percent ER.
Gamma	0.9055	31.97	145	14.9	239	75.8	304	156	
Log-Logistic	0.8976	22.00	138	13.7	238	71.2	305	150	
Multistage 3	**0.9929**	**18.02**	**141**	**14.7**	**243**	**75.1**	**308**	**154**	
Multistage 2	0.9676	20.19	92.7	14.3	209	73.1	300	150	
Multistage 1	0.8614	20.95	29.1	12.8	149	65.4	305	134	
Weibull	0.9727	20.02	136	14.7	239	75.1	307	154	
Logistic	0.7460	22.41	143	52.2	265	170	325	243	
Log-Probit	0.9254	21.91	151	0	236	0	300	0.0316	
Probit	0.8109	22.21	143	47.7	255	158	316	230	
Quantal Linear	0.8614	20.95	29.1	12.8	149	65.4	305	134	

[a] Selected model in bold.

Plots of the Multistage 3-degree model with BMRs of 10 percent, five percent, and one percent ER are shown in Figure 2-26, Figure 2-27, and Figure 2-28, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-29 (BMD and BMDL shown are for BMR of 10 percent ER; the rest is applicable to all BMRs).

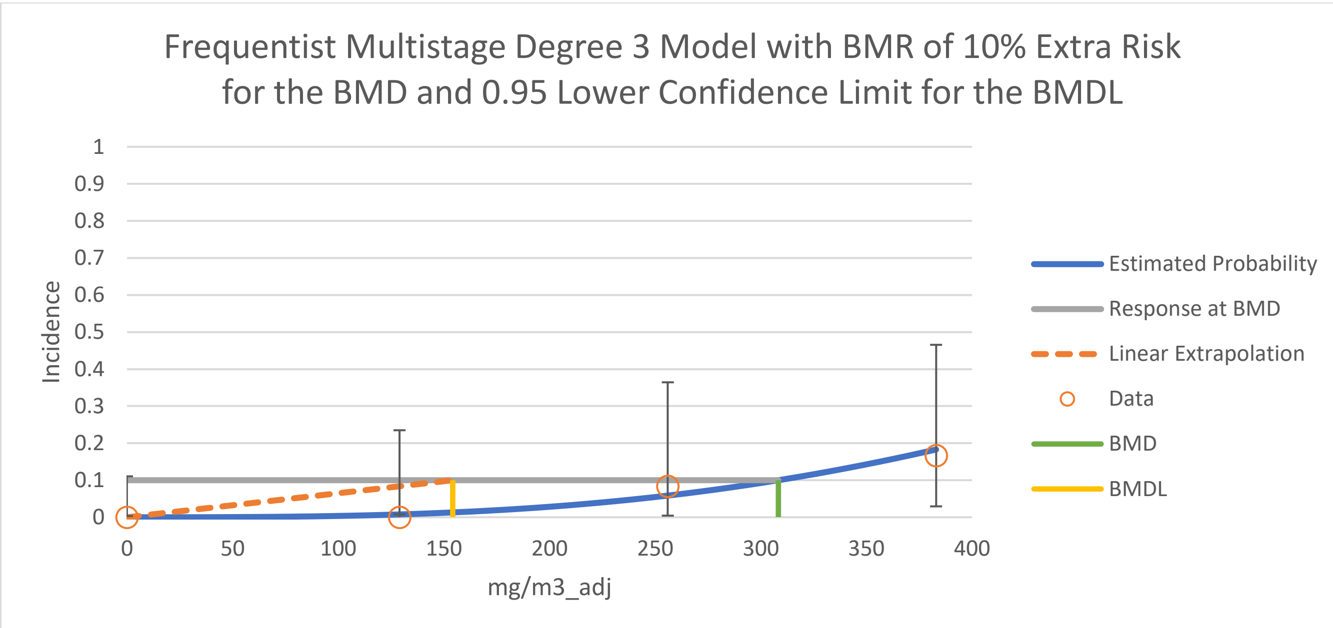

Figure 2-26. Plot of Response by Dose with Fitted Curve for the Selected Model (Multistage 3-Degree) for Mortality in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 30 Days (Seven Hours per Day, 5 days per Week) and BMR of 10%ER

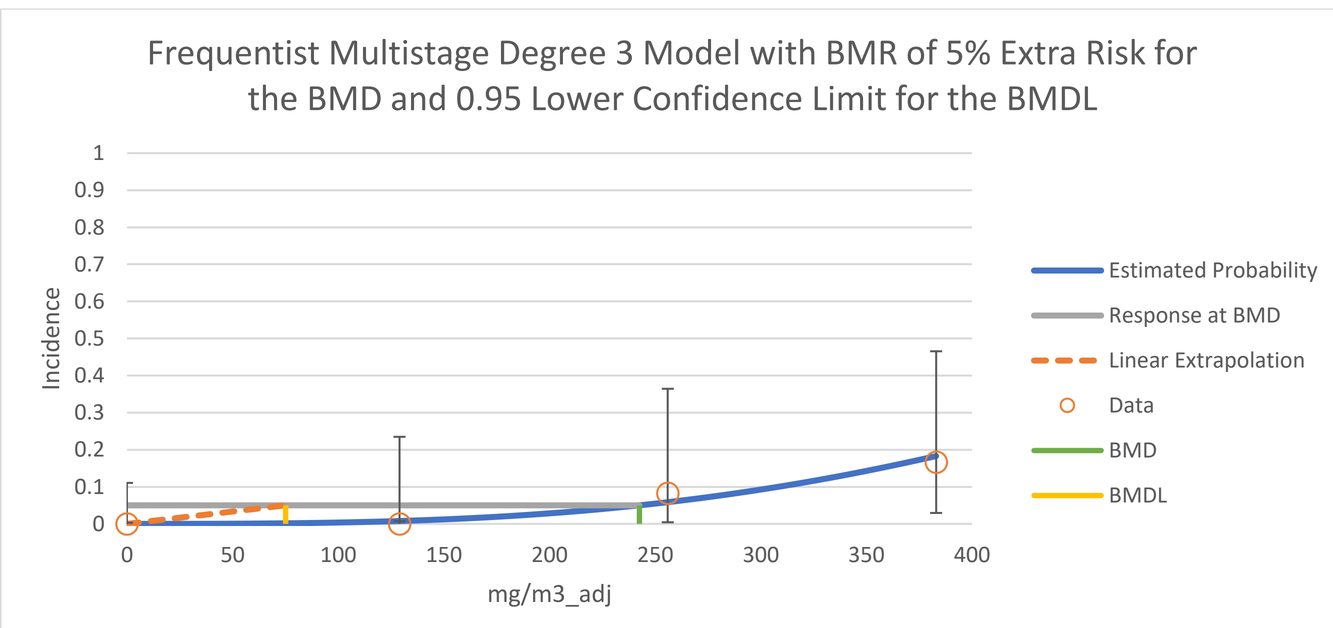

Figure 2-27. Plot of Response by Dose with Fitted Curve for the Selected Model (Multistage 3-Degree) for Mortality in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 30 Days (Seven Hours per Day, 5 days per Week) and BMR of 5%ER

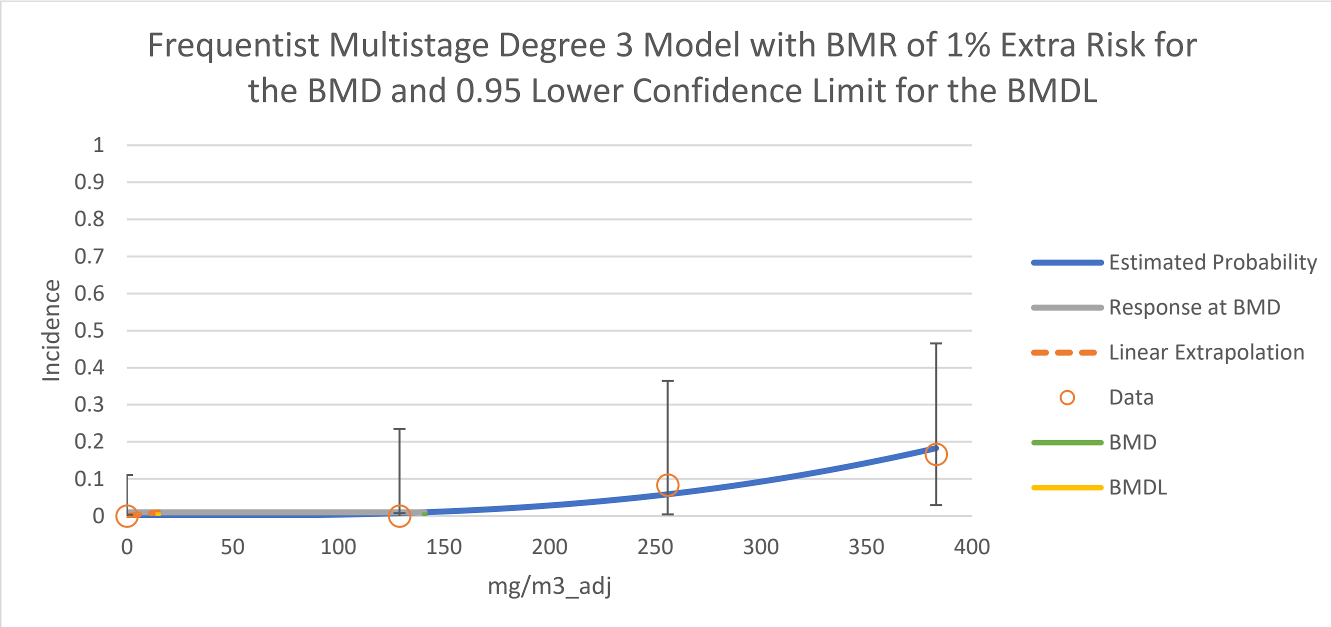

Figure 2-28. Plot of Response by Dose with Fitted Curve for the Selected Model (Multistage 3-Degree) for Mortality in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 30 Days (7n Hours per Day, 5 Days per Week) and BMR of 1%ER

Model Results

Benchmark Dose	
BMD	308.342534
BMDL	154.1950362
BMDU	738.5150207
AIC	18.0236136
P-value	0.992913128
D.O.F.	4
Chi^2	0.248106117
Slope Factor	0.000648529

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	Bounded	NA	NA	NA
b2	Bounded	NA	NA	NA
b3	Bounded	NA	NA	NA

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	4.56899E-07	0	30	-0.000676
129	0.007685521	0.092226257	0	12	-0.304862
256	0.058515379	0.702184543	1	12	0.3662815
383	0.18283766	2.194051923	2	12	-0.144924

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-8.848766303	4	-	-	NA
Fitted Model	-9.011806799	0	0.32608099	4	0.9880689
Reduced Model	-12.20388835	1	6.71024408	3	0.0817297

Figure 2-29. Details Regarding the Selected Model (Multistage 3-Degree) for Mortality in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 30 Days

2.1.1.2.1.2 Mortality in Female Rabbits – Inhalation Exposure on GD 6 to 18

There was mortality in female rabbits exposed to exposed to 1,2-dichloroethane by inhalation on GD 6 to 18 (seven hours per day) (Rao et al., 1980). The measured exposure concentrations (reported in units of ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day. The concentration and response data used for the modeling are presented in Table 2-25. Dichotomous models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). BMRs of one and five percent ER were also selected due to severity of the endpoint.

Table 2-25. Incidence of Mortality in Female Rabbits and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from an Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Incidence
0	20	0
118	21	4
353	19	3

The BMD modeling results for incidence of mortality are summarized in Table 2-26. All models provided adequate fit to the data (chi-square p-value > 0.1) except for the Logistic, Log-Probit, and Probit models. The Dichotomous Hill model was unusable because the BMDL computation failed (lower limit included zero). With BMRs of 10 percent or five percent ER applied, the BMDLs of the viable models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC (Log-Logistic) was selected. With a BMR of one percent ER applied, all models were considered questionable because the BMDLs (and in some cases the BMDs) were 10 times lower than the lowest non-zero concentration; no model was selected for the one percent ER BMR.

Table 2-26. Summary of BMD Modeling Results for Incidence of Mortality in Female Rabbits Following Inhalation Exposure to 1,2-Dichloroethane Using BMR of 10%ER or 5%ER[a]

Model	Goodness of Fit (Means)		BMD 5%ER (mg/m^3)	BMDL 5%ER (mg/m^3)	BMD 10%ER (mg/m^3)	BMDL 10%ER (mg/m^3)	Basis for Model Selection
	p-value	AIC					
Dichotomous Hill	0.7865	41.10	2.15E−06	0	7.17E−06	0	All models provided adequate fit to the data (chi-square p-value > 0.1) except for the Logistic, Log-Probit, and Probit models. The Dichotomous Hill model was unusable because the BMDL computation failed (lower limit included zero). The BMDLs of the fit models were sufficiently close (differed by < 3-fold); therefore, EPA chose the model with the lowest AIC.
Gamma	0.1759	41.94	65.9	34.8	135	71.6	
Log-Logistic	**0.2591**	**41.51**	**54.3**	**28.1**	**115**	**59.4**	
Multistage 2	0.1963	41.90	61.5	34.9	126	71.8	
Multistage 1	0.1963	41.90	61.5	34.9	126	71.8	
Weibull	0.1963	41.90	61.5	34.9	126	71.8	
Logistic	0.0537	45.64	170	97.6	286	167	
Log-Probit	–	–	–	–	–	–	
Probit	0.0542	45.54	157	89.4	271	156	
Quantal Linear	0.1963	41.90	61.5	34.9	126	71.8	

[a] Selected model in bold.

Plots of the Log-Logistic model with BMRs of 10 percent and five percent ER are shown in Figure 2-30 and Figure 2-31, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-32 (BMD and BMDL shown are for BMR of 10 percent ER; the rest is applicable to all BMRs).

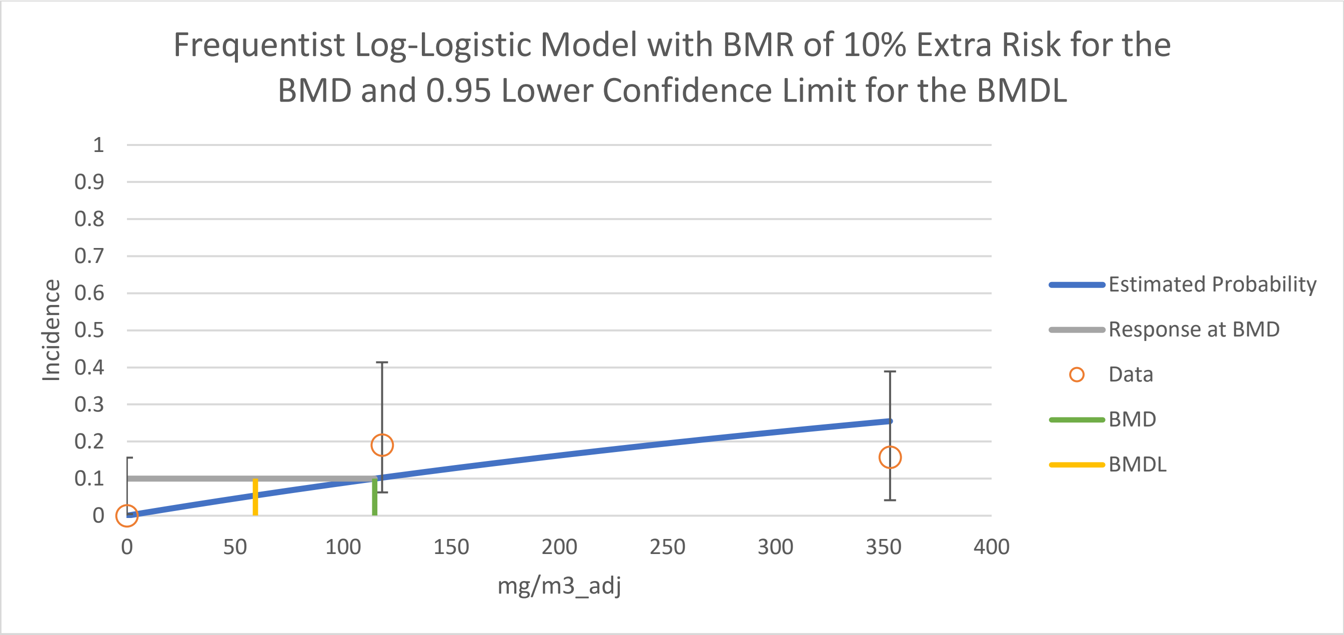

Figure 2-30. Plot of Response by Dose with Fitted Curve for the Selected Model (Log-Logistic) for Mortality in Female Rabbits Exposed to 1,2-Dichloroethane Via Inhalation on GD 6 to 18 (7 Hours per Day) and BMR of 10%ER

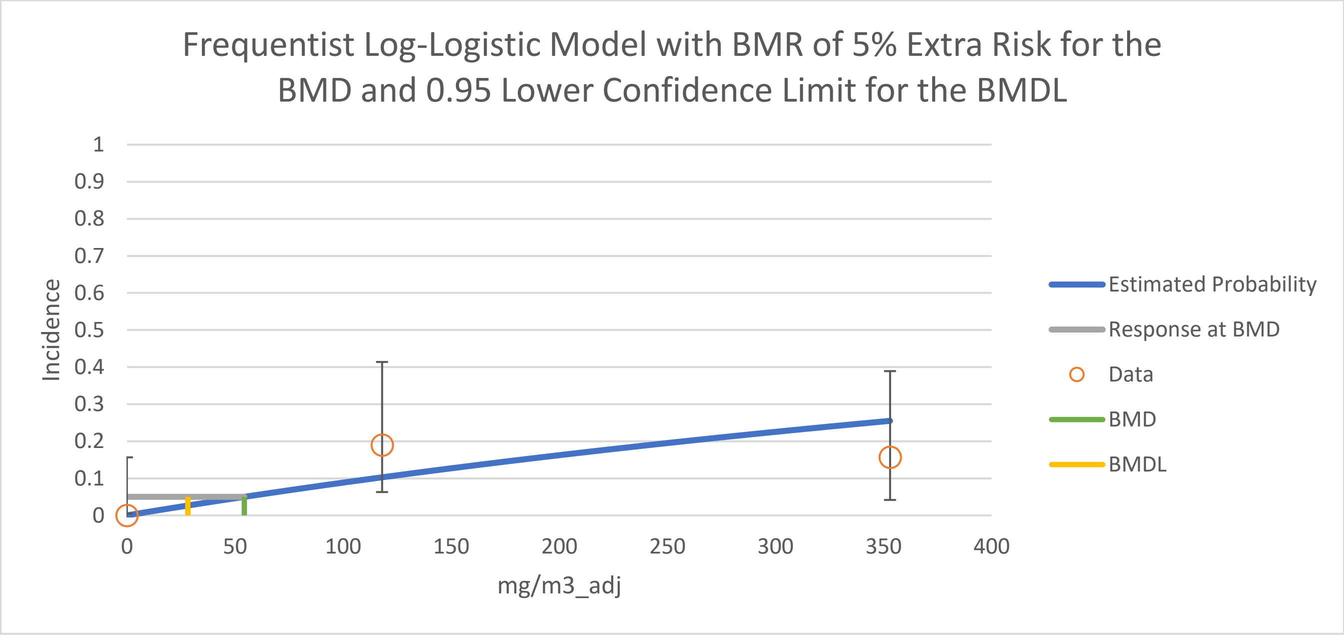

Figure 2-31. Plot of Response by Dose with Fitted Curve for the Selected Model (Log-Logistic) for Mortality in Female Rabbits Exposed to 1,2-Dichloroethane Via Inhalation on GD 6 to 18 (7 Hours per Day) and BMR of 5%ER

Model Results

Benchmark Dose	
BMD	114.6125356
BMDL	59.4154249
BMDU	760.5776692
AIC	41.51198247
P-value	0.259131334
D.O.F.	2
Chi^2	2.700840529

Model Parameters				
# of Parameters	3			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
a	-6.938781761	0.424700555	-7.7711796	-6.106384
b	Bounded	NA	NA	NA

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	3.046E-07	0	20	-0.000552
118	0.102652196	2.155696122	4	21	1.3260451
353	0.254963342	4.844303497	3	19	-0.970796

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-18.51225108	3	-	-	NA
Fitted Model	-19.75599124	1	2.48748031	2	0.2883039
Reduced Model	-21.61383127	1	6.20316038	2	0.0449781

Figure 2-32. Details Regarding the Selected Model (Log-Logistic) for Mortality in Female Rabbits Exposed to 1,2-Dichloroethane Via Inhalation on GD 6 to 18 (7 Hours per Day)

2.1.1.2.2 Body Weight effects

Two short-term/intermediate-duration inhalation studies were identified for BMD modeling that showed significant changes in body weight (Zeng et al., 2018) or body weight gain (Igwe et al., 1986).

2.1.1.2.2.1 Body Weight in Male Mice – 28-Day Inhalation Exposure

Body weight was significantly decreased at week 4 in male mice exposed to 1,2-dichloroethane by inhalation for 28 days (6 hours per day, 7 days per week) (Zeng et al., 2018). The measured exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week. The concentration and response data used for the modeling are presented in Table 2-27. 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 because EPA considers a 10 percent change in body weight to be biologically significant.

Table 2-27. Decreased Body Weight of Male Mice at Week 4 and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane in a 28-Day Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Mean (g)	SD (g)
0.068	10	39.85	0.83
90.895	10	38.80	1.08
182.78	10	35.68	0.94

The BMD modeling results for decreased body weight are summarized in Table 2-28. The constant variance model provided adequate fit to the variance data, but with this model applied, none of the available models provided adequate fit to the means (all except for the Linear model were saturated, with degree of freedom = 0). The nonconstant variance model also provided adequate fit to the variance data. With the nonconstant variance model applied, the Exponential 3, Polynomial 2-degree, and Linear models provided adequate fit to the means. The BMDLs for the fit models were sufficiently close (< 3-fold); therefore, the model with the lowest AIC (Exponential 3) was selected. The Exponential 3 and the Polynomial 2-degree model had identical goodness-of-fit statistics; BMDS recommended the Exponential 3 model.

Table 2-28. Summary of BMD Modeling Results for Decreased Body Weight in Male Mice at Week 4 Following a 28-Day Inhalation Exposure to 1,2-Dichloroethane (Nonconstant Variance)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	BMD 10%RD (mg/m^3)	BMDL 10%RD (mg/m^3)	Basis for Model Selection
	Test 4 p-value	AIC					
Exponential 3	**0.9116**	**87.24**	**84.480**	**57.281**	**178.52**	**162.78**	BMDLs for the fit models (Exponential 3, Polynomial 2-degree, and Linear models) were sufficiently close (< 3-fold); therefore, EPA chose the model with the lowest AIC.
Exponential 5	NA	89.24	84.489	57.313	178.51	98.30	
Hill	NA	91.23	87.838	55.459	161.06	111.21	
Polynomial Degree 2	0.9116	87.24	84.336	53.975	178.64	163.92	
Power	NA	89.24	84.437	56.727	178.64	163.15	
Linear	0.0237	92.72	44.945	35.028	175.95	148.16	

[a] Selected model in bold.

Plots of the Exponential 3 model with BMRs of one SD and 10 percent RD are shown in Figure 2-33 and Figure 2-34, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-35 (BMD and BMDL shown are for BMR of one SD; the rest is applicable to both BMRs).

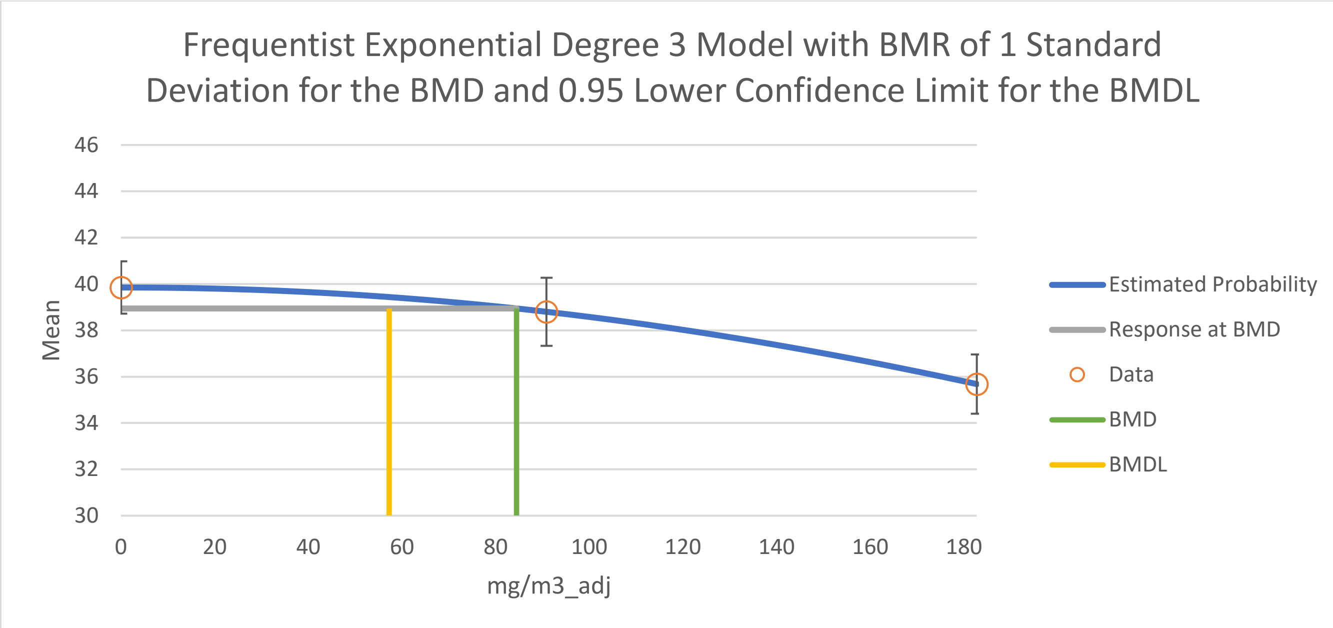

Figure 2-33. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 3) for Decreased Body Weight in Male Mice at Week 4 Following a 28-Day Inhalation Exposure to 1,2-Dichloroethane and a BMR of 1SD (Nonconstant Variance)

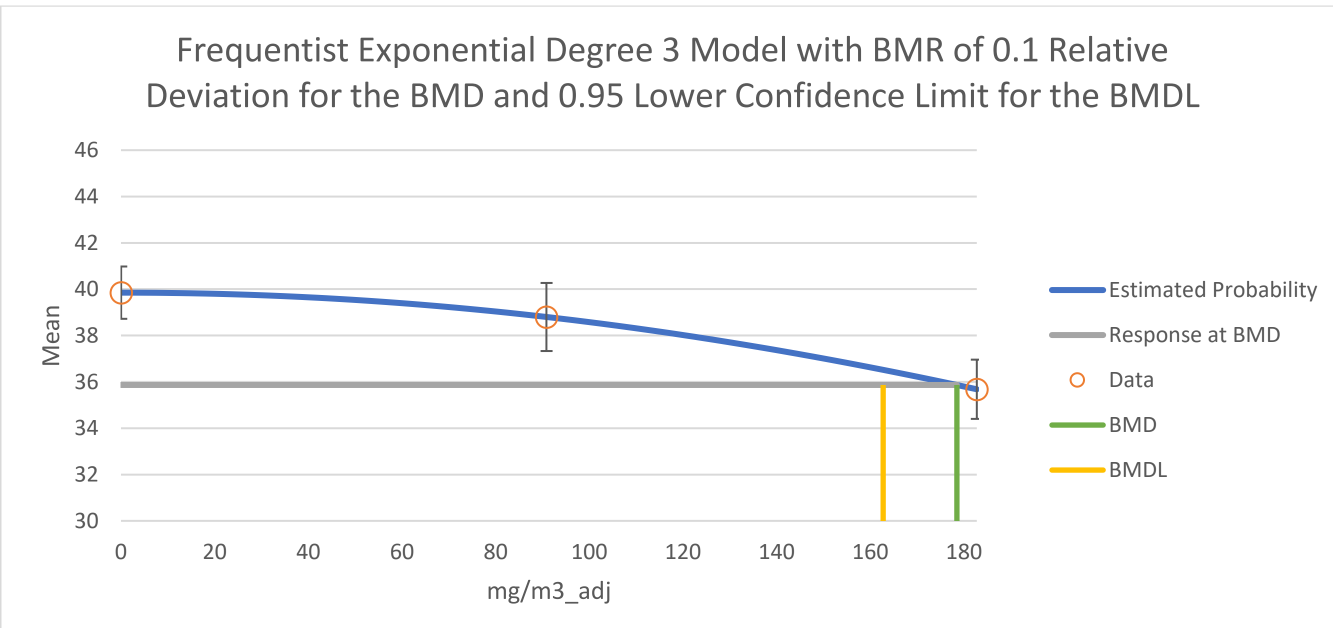

Figure 2-34. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 3) for Decreased Body Weight in Male Mice at Week 4 Following a 28-Day Inhalation Exposure to 1,2-Dichloroethane and a BMR of 10%RD (Nonconstant Variance)

Model Results

Benchmark Dose	
BMD	84.4797913
BMDL	57.28149371
BMDU	122.8881893
AIC	87.24381926
Test 4 P-value	0.911550593
D.O.F.	1

Model Parameters				
# of Parameters	5			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
a	39.85000044	0.286645626	39.2881853	40.4118156
b	0.001852231	4.83E-04	0.0009047	0.00279976
d	2.0335034	5.03E-01	1.04725263	3.01975417
rho	Bounded	NA	NA	NA
log-alpha	-0.19641642	2.58E-01	-0.7023586	0.3095258

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0.068	10	39.84999997	39.85	39.85	0.90646015	0.83	0.83	9.10707E-08
90.895	10	38.80000002	38.8	38.8	0.90646015	1.08	1.08	-7.0194E-08
182.78	10	35.68000002	35.68	35.68	0.90646015	0.94	0.94	-5.25043E-08

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-39.62190963	4	87.2438193
A2	-39.27530885	6	90.5506177
A3	-39.61573992	5	89.2314798
fitted	-39.62190963	4	87.2438193
R	-63.20374602	2	130.407492

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	47.85687434	4	<0.0001
2	0.693201554	2	0.70708756
3	0.680862138	1	0.40929001
4	0.012339415	1	0.91155059

Figure 2-35. Details Regarding the Selected Model (Exponential 3) for Decreased Body Weight in Male Mice at Week 4 Exposed to 1,2-Dichloroethane Via Inhalation for 28 Days

2.1.1.2.2.2 Body Weight Gain in Male Rats – 30-Day Inhalation Exposure

Body weight gain was significantly decreased in male rats exposed to exposed to 1,2-dichloroethane by inhalation for 30 days (seven hours per day, 5 days per week) (Igwe et al., 1986). The measured exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day and 7 days per week. The concentration and response data used for the modeling are presented in Table 2-29. 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.

Table 2-29. Decreased Body Weight Gain of Male Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 30-Day Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Mean (g)	SD (g)
0	30	190	37
129	12	194	20
256	11	170	32
383	10	147	24

The BMD modeling results for decreased body weight gain are summarized in Table 2-30. The constant variance model provided an adequate fit to the variance data. With the constant variance model applied, all models, except for the Hill model, 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 (Polynomial 2-degree) was selected.

Table 2-30. Summary of BMD Modeling Results for Decreased Body Weight Gain of Male Rats Following Inhalation Exposure to 1,2-Dichloroethane for 30 Days (Constant Variance)[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					
Exponential 3	0.4178	619.1	322	244	262	168	All models, except for the Hill model, provided adequate fit to the means (test 4 p-value > 0.1). The BMDLs for the fit models were < 3-fold different; therefore, EPA chose the model with the lowest AIC.
Exponential 5	0.7034	618.5	265	243	254	177	
Hill	NA	620.5	269	239	253	228	
Polynomial Degree 3	0.6343	617.3	336	246	282	164	
Polynomial Degree 2	**0.6688**	**617.2**	**317**	**248**	**250**	**166**	
Power	0.3992	619.1	325	305	264	168	
Linear	0.1894	619.7	306	209	188	134	

[a] Selected model in bold.

Plots of the Polynomial 2-degree model with BMRs of one SD and 10 percent RD are shown in Figure 2-36 and Figure 2-37, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-38 (BMD and BMDL shown are for BMR of one SD; the rest is applicable to both BMRs).

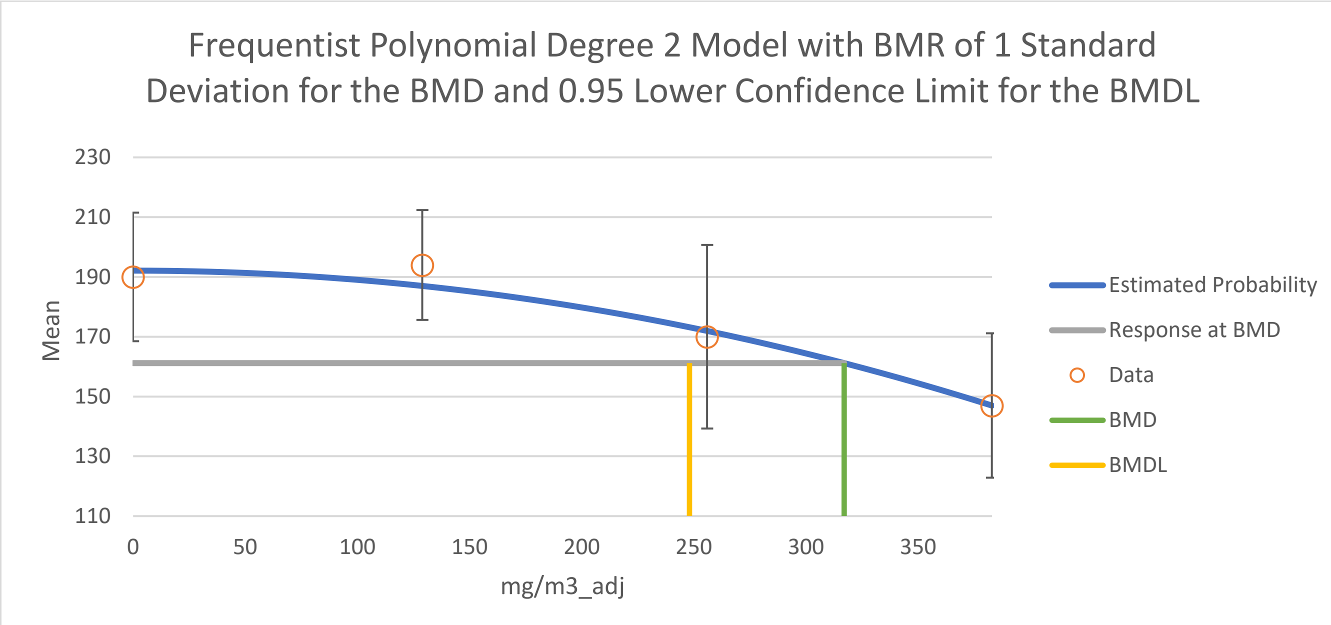

Figure 2-36. Plot of Response by Dose with Fitted Curve for the Selected Model (Polynomial 2-Degree) for Body Weight Gain in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 30 Days and BMR of 1SD (Constant Variance)

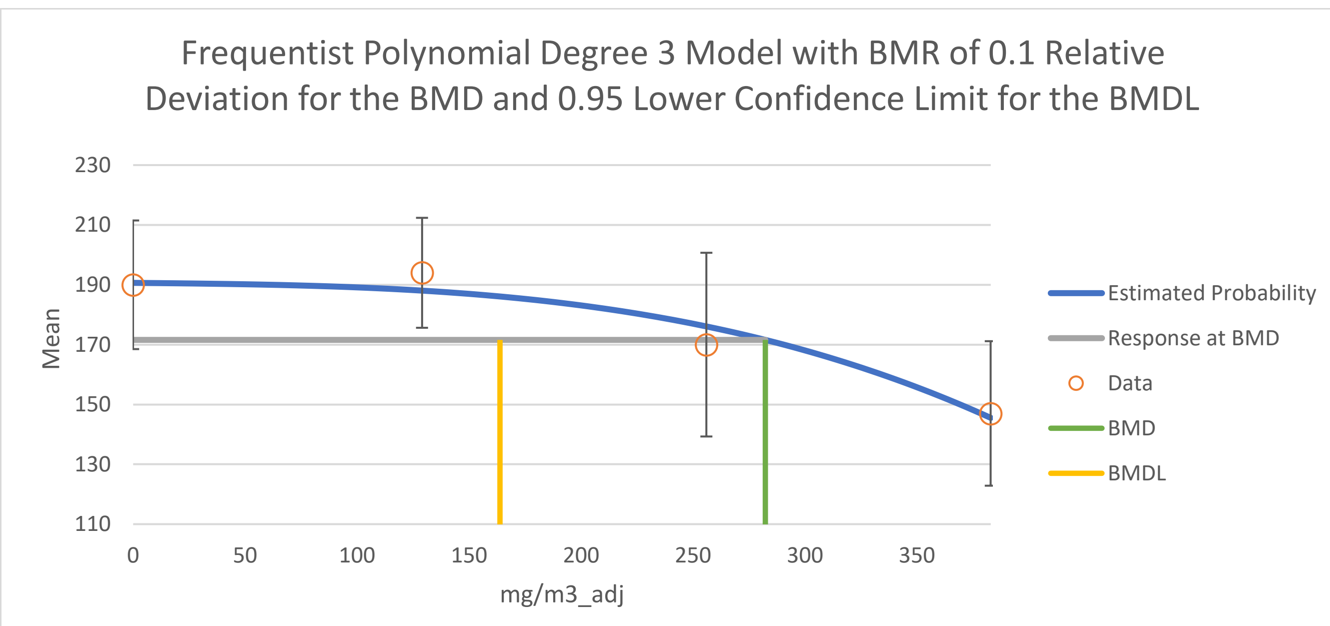

Figure 2-37. Plot of Response by Dose with Fitted Curve for the Selected Model (Polynomial 2-Degree) for Body Weight Gain in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 30 Days and BMR of 10%RD (Constant Variance)

Model Results

Benchmark Dose	
BMD	317.080575
BMDL	248.0936048
BMDU	417.0049545
AIC	617.2047371
Test 4 P-value	0.668842162
D.O.F.	2

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	192.1048183	4.79868076	182.699577	201.51006
beta	Bounded	NA	NA	NA
beta2	-0.000307689	7.39E-05	-0.0004525	-0.0001629
alpha	956.9809221	1.63E+05	-318857.33	320771.297

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	30	192.1048183	190	190	30.9351082	37	37	-0.37266928
129	12	186.984561	194	194	30.9351082	20	20	0.785586185
256	11	171.9400936	170	170	30.9351082	32	32	-0.208001943
383	10	146.9701855	147	147	30.9351082	24	24	0.003047727

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-305.2001614	5	620.400323
A2	-301.4914854	8	618.982971
A3	-305.2001614	5	620.400323
fitted	-305.6023685	3	617.204737
R	-313.2489895	2	630.497979

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	23.51500828	6	0.00064112
2	7.417351949	3	0.0597205
3	7.417351949	3	0.0597205
4	0.804414355	2	0.66884216

Figure 2-38. Details Regarding the Selected Model (Polynomial 2-Degree) for Body Weight Gain in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 30 Days

2.1.1.2.3 Hepatic Effects:

EPA modeled both absolute and relative liver weight changes in male mice in a 28-day inhalation study (Zeng et al., 2018). Absolute liver weight in male mice, though not statistically significant, was increased by > 10 percent at both concentrations tested. Relative liver weight in male mice was increased by > 10 percent at both tested concentrations and reached statistical significance at the highest concentration. EPA also modeled statistically significant increases in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in the male mice.

Modeled results for relative liver weight and serum liver enzyme levels from the Zeng et al. (2018) studies are presented. Results for absolute liver weight changes in male mice are not presented because neither the constant nor the nonconstant variance models provided adequate fit to the variance data.

EPA also modeled statistically significant metabolic changes in the liver, including increased liver concentrations of glycogen, triglycerides, and free fatty acids in male mice (Zeng et al., 2018). These results are not shown because, for each of these data sets, none of the models provided adequate fits to the data either assuming constant or nonconstant variance.

2.1.1.2.3.1 Relative Liver Weight in Male Mice – 28-Day Inhalation Exposure

Relative liver weight was significantly increased in male mice exposed to 1,2-dichloroethane by inhalation for 28 days (6 hours per day, 7 days per week) (Zeng et al., 2018). The measured exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week. The concentration and response data used for the modeling are presented in Table 2-31. 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 because EPA considers a 10 percent change in relative liver weight to be biologically significant.

Table 2-31. Relative Liver Weight in Male Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 28-Day Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Mean (Liver/Body Weight Ratio)	SD (Liver/Body Weight Ratio)
0.068	10	4.38	0.30
90.895	10	5.14	0.46
182.78	10	5.59	0.46

The BMD modeling results for increased relative liver weight are summarized in Table 2-32. 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. The Power model converged on the Linear model and these had the lowest AIC; the Linear model was selected as the more parsimonious choice.

Table 2-32. Summary of BMD Modeling Results for Increased Relative Liver Weight in Male Mice Following Inhalation Exposure to 1,2-Dichloroethane for 28 Days (Constant Variance)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	BMD 10%RD (mg/m^3)	BMDL 10%RD (mg/m^3)	Basis for Model Selection
	Test 4 p-value	AIC					
Exponential 3	0.2069	36.60	66.637	51.379	73.314	58.420	All models, except for the Exponential 5 and Hill models, provided adequate fit to the means (test 4 p-value > 0.1). Among the fit models, BMDLs differed by < 3-fold; the Linear model was selected based on the lowest AIC.
Exponential 5	NA	37.00	40.867	20.758	46.314	22.869	
Hill	NA	39.00	56.026	15.337	59.981	16.927	
Polynomial Degree 2	0.3012	36.0735	60.246	45.510	66.752	51.726	
Power	0.3013	36.0730	60.345	45.508	66.968	51.720	
Linear	**0.3013**	**36.0730**	**60.345**	**45.508**	**66.968**	**51.720**	

[a] Selected model in bold.

Plots of the Linear model with BMRs of one SD and 10 percent RD are shown in Figure 2-39 and Figure 2-40, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-41 (BMD and BMDL shown are for BMR of one SD; the rest is applicable to both BMRs).

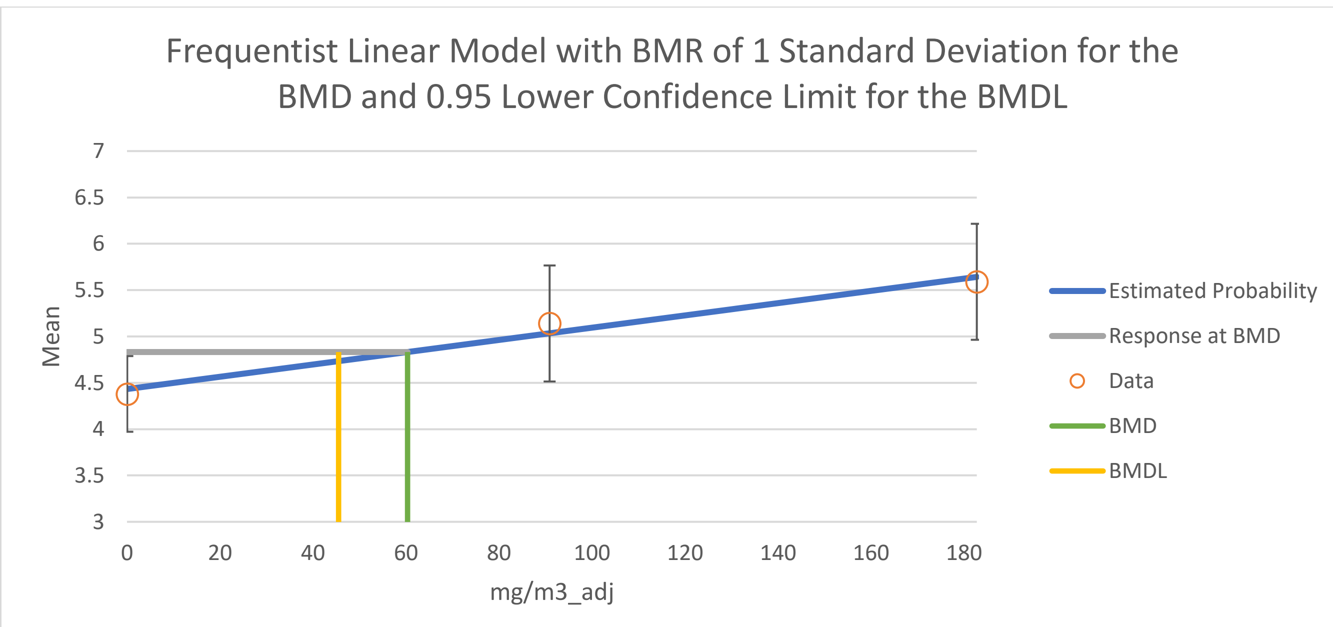

Figure 2-39. Plot of Response by Dose with Fitted Curve for the Selected Model (Linear) for Increased Relative Liver Weight in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 28 Days and BMR of 1SD (Constant Variance)

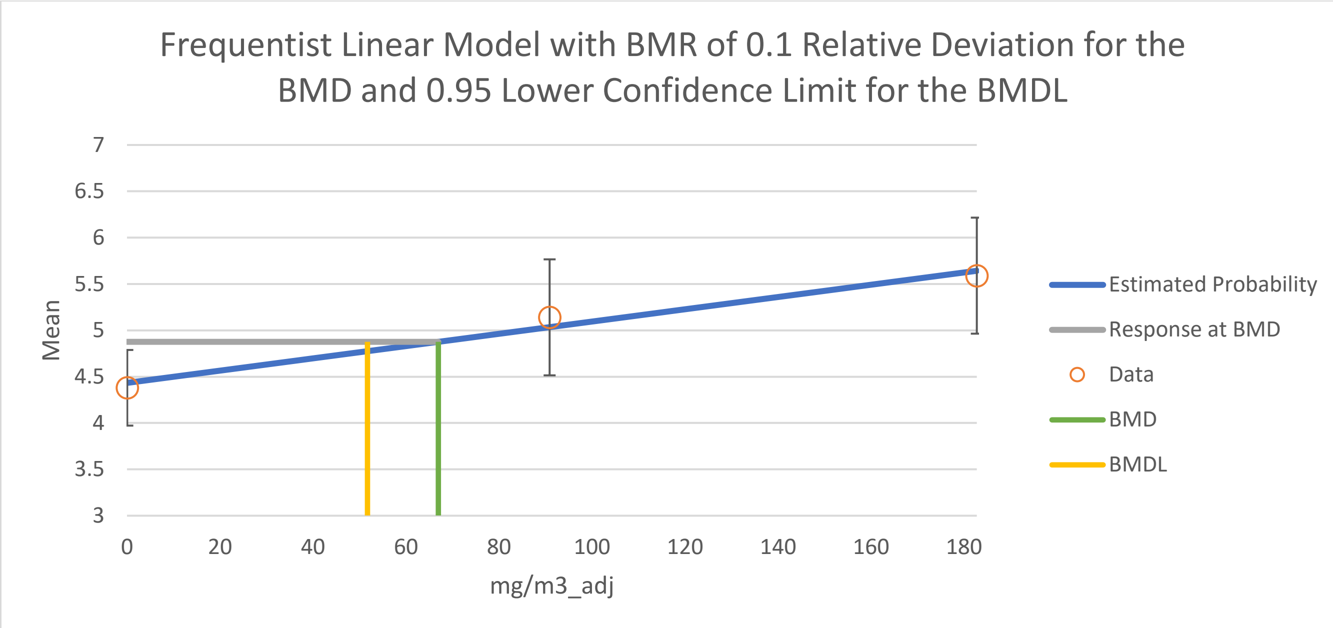

Figure 2-40. Plot of Response by Dose with Fitted Curve for the Selected Model (Linear) for Increased Relative Liver Weight in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 28 Days and BMR of 10%RD (Constant Variance)

Model Results

Benchmark Dose	
BMD	60.34484029
BMDL	45.50823313
BMDU	88.69790107
AIC	36.07303736
Test 4 P-value	0.301262139
D.O.F.	1

Model Parameters				
# of Parameters	3			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	4.432689666	0.115222371	4.20685797	4.65852137
beta	0.006619095	9.78E-04	0.00470294	0.00853525
alpha	0.15954289	6.57E-03	0.14666168	0.1724241

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0.068	10	4.433139765	4.38	4.38	0.3994282	0.3	0.3	-0.420708124
90.895	10	5.034332331	5.14	5.14	0.3994282	0.46	0.46	0.836572145
182.78	10	5.6425279	5.59	5.59	0.3994282	0.46	0.46	-0.415863983

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-14.50221924	4	37.0044385
A2	-13.41744443	6	38.8348889
A3	-14.50221924	4	37.0044385
fitted	-15.03651868	3	36.0730374
R	-28.94761589	2	61.8952318

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	31.06034292	4	<0.0001
2	2.169549619	2	0.33797789
3	2.169549619	2	0.33797789
4	1.068598887	1	0.30126214

Figure 2-41. Details Regarding the Selected Model (Linear) for Relative Liver Weight Increases in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 28 Days

2.1.1.2.3.2 Serum ALT in Male Mice – 28-Day Inhalation Exposure

Serum ALT levels were significantly increased in male mice exposed to 1,2-dichloroethane by inhalation for 28 days (6 hours per day, 7 days per week) (Zeng et al., 2018). The measured exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week. The concentration and response data used for the modeling are presented in Table 2-33. 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).

Table 2-33. Serum ALT in Male Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 28-Day Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Mean (U/L)	SD (U/L)
0.068	10	34.80	2.78
90.895	10	50.40	8.06
182.78	10	65.20	7.45

The BMD modeling results for increased serum ALT are summarized in Table 2-34. 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, the Polynomial 2-degree, Power, and Linear models provided adequate fit to the means (test 4 p-value > 0.1). The BMDLs for the fit models were sufficiently close (< 3-fold); therefore, the model with the lowest AIC (Linear Model) was selected.

Table 2-34. Summary of BMD Modeling Results for Increased Serum ALT in Male Mice Following Inhalation Exposure to 1,2-Dichloroethane for 28 Days (Nonconstant Variance)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	Basis for Model Selection
	Test 4 p-value	AIC			
Exponential 3	0.0657	198.7	27.148	18.025	The Polynomial 2-degree, Power, and Linear models provided adequate fit to the means (test 4 p-value > 0.1). The BMDLs for the fit models differed by < 3-fold; therefore, EPA chose the model with the lowest AIC.
Exponential 5	NA	199.3	18.907	7.8091	
Hill	NA	199.3	31.175	7.0150	
Polynomial Degree 2	0.4543	195.8730	18.715	12.621	
Power	0.4535	195.8752	18.607	12.620	
Linear	**0.4543**	**195.8729**	**18.705**	**12.620**	

[a] Selected model in bold.

A plot of the Linear model with a BMR of one SD is shown in Figure 2-42. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-43.

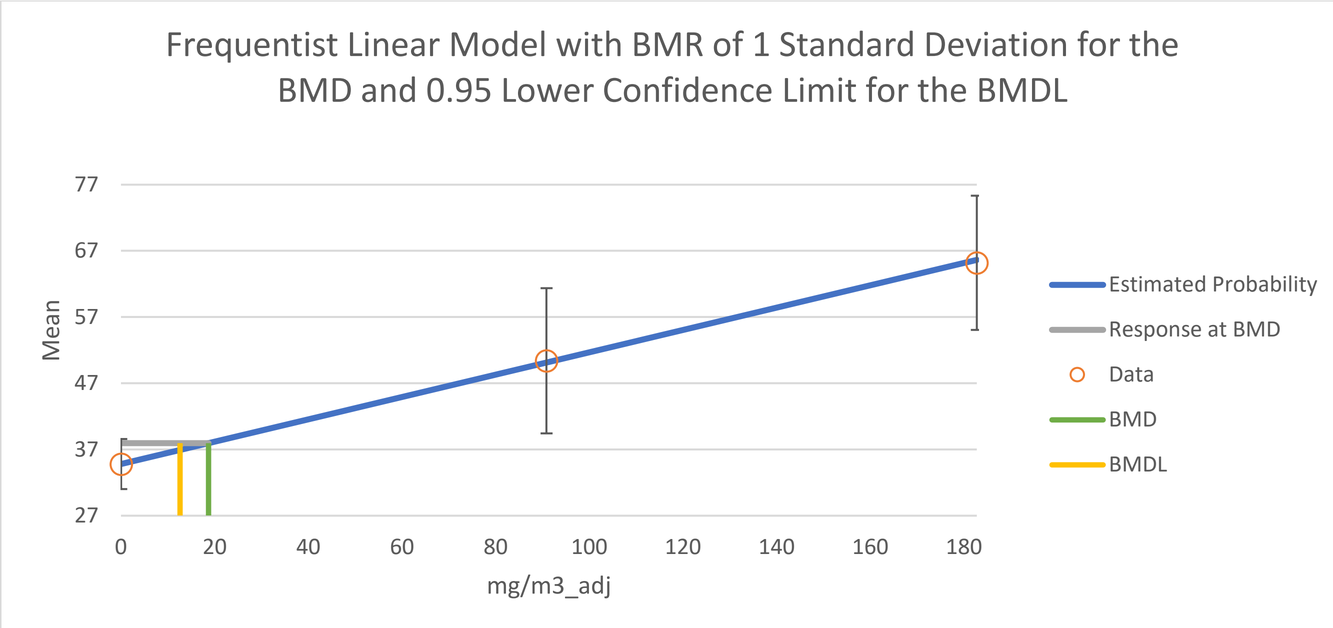

Figure 2-42. Plot of Response by Dose with Fitted Curve for the Selected Model (Linear) for Increased Serum ALT in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 28 Days and BMR of 1SD (Nonconstant Variance)

Model Results

Benchmark Dose	
BMD	18.70544198
BMDL	12.62045044
BMDU	30.11786611
AIC	195.8729428
Test 4 P-value	0.454349562
D.O.F.	1

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	34.80093952	0.977490421	32.8850935	36.7167856
beta	0.16873094	0.014569002	0.14017622	0.19728566
rho	3.377393896	1.243700214	0.93978625	5.81500154
alpha	6.19107E-05	1.85E-08	6.1874E-05	6.1947E-05

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0.068	10	34.81241322	34.8	34.8	3.15794416	2.78	2.78	-0.012430257
90.895	10	50.13773829	50.4	50.4	5.84717017	8.06	8.06	0.141836875
182.78	10	65.64158069	65.2	65.2	9.21610491	7.45	7.45	-0.151517454

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-97.31179356	4	202.623587
A2	-92.16353343	6	196.327067
A3	-93.65658221	5	197.313164
fitted	-93.93647138	4	195.872943
R	-121.4712012	2	246.942402

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	58.61533564	4	<0.0001
2	10.29652026	2	0.0058095
3	2.986097556	1	0.08398233
4	0.559778352	1	0.45434956

Figure 2-43. Details Regarding the Selected Model (Linear) for Increased Serum ALT in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 28 Days

2.1.1.2.3.3 Serum AST in Male Mice – 28-Day Inhalation Exposure

Serum AST levels were significantly increased in male mice exposed to 1,2-dichloroethane by inhalation for 28 days (6 hours per day, 7 days per week) (Zeng et al., 2018). The measured exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week. The concentration and response data used for the modeling are presented in Table 2-35. 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).

Table 2-35. Serum AST in Male Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 28-Day Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Mean (U/L)	SD (U/L)
0.068	10	137.30	9.09
90.895	10	182.30	8.82
182.78	10	231.80	18.09

The BMD modeling results for increased serum AST are summarized in Table 2-36. 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, the Exponential 3 and Linear models provided adequate fit to the means (test 4 p-value > 0.1). The BMDLs for the fit models were sufficiently close (< 3-fold); therefore, the model with the lowest AIC (Linear model) was selected.

Table 2-36. Summary of BMD Modeling Results for Increased Serum AST in Male Mice Following Inhalation Exposure to 1,2-Dichloroethane for 28 Days (Nonconstant Variance)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	Basis for Model Selection
	Test 4 p-value	AIC			
Exponential 3	0.3721	238.3	19.271	14.286	The Exponential 3 and Linear models provided adequate fit to the means (test 4 p-value > 0.1). The BMDLs for the fit models differed by < 3-fold; therefore, EPA chose the model with the lowest AIC.
Exponential 5	NA	241.5	34.809	11.861	
Hill	NA	241.5	28.918	11.976	
Polynomial Degree 2	NA	239.5	16.812	11.559	
Power	NA	239.5	18.264	11.562	
Linear	**0.5631**	**237.8**	**15.370**	**11.360**	

[a] Selected model in bold.

A plot of the Linear model with a BMR of one SD is shown in Figure 2-44. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-45.

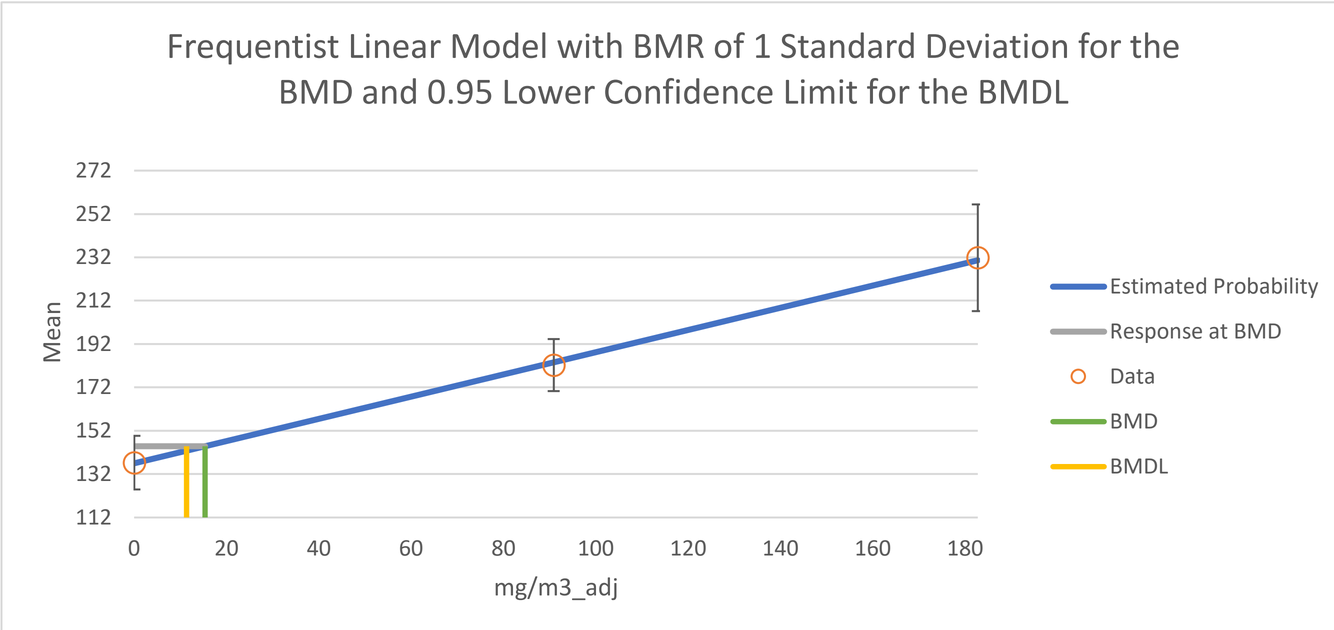

Figure 2-44. Plot of Response by Dose with Fitted Curve for the Selected Model (Linear) for Increased Serum AST in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 28 Days and BMR of 1SD (Nonconstant Variance)

Model Results

Benchmark Dose	
BMD	15.37039918
BMDL	11.35979052
BMDU	22.23350808
AIC	237.8188306
Test 4 P-value	0.563122068
D.O.F.	1

Model Parameters

# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	136.9827797	2.397347299	132.284065	141.681494
beta	0.512404641	2.81E-02	0.45735724	0.56745205
rho	2.562173101	1.12E+00	0.37562471	4.7487215
alpha	0.000208012	2.51E-07	0.00020752	0.0002085

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0.068	10	137.0176232	137.3	137.3	7.87843043	9.09	9.09	0.113341577
90.895	10	183.5577996	182.3	182.3	11.4586407	8.82	8.82	-0.347118969
182.78	10	230.6401001	231.8	231.8	15.3521135	18.09	18.09	0.238919918

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-117.3531051	4	242.70621
A2	-113.783309	6	239.566618
A3	-114.7422517	5	239.484503
fitted	-114.9094153	4	237.818831
R	-153.5664702	2	311.13294

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	79.56632236	4	<0.0001
2	7.139592092	2	0.0281616
3	1.917885267	1	0.16608997
4	0.334327285	1	0.56312207

Figure 2-45. Details Regarding the Selected Model (Linear) for Increased Serum AST in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 28 Days

2.1.1.2.4 Reproductive Effects

Reproductive endpoints from a short-term/intermediate inhalation study were identified for BMD modeling (Zhang et al., 2017). EPA did not present the BMD modeling results for abnormalities in the sperm head, abnormalities in sperm body, or total sperm abnormalities because there were no adequately fit models with either the constant or nonconstant variance models. Although the Hill model provided adequate fit to data for abnormalities in sperm tail (with nonconstant variance applied), the results are not presented because the BMD/BMDL ratio was greater than 10 and the BMDL was more than three times lower than the lowest dose tested.

2.1.1.2.4.1 Sperm Concentration in Male Mice – 4-Week Inhalation Exposure

Sperm concentration was significantly decreased in male mice exposed to 1,2-dichloroethane by inhalation for four weeks (6 hours per day, 7 days per week) (Zhang et al., 2017). The measured exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week. The concentration and response data used for the modeling are presented in Table 2-37. 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 five percent RD was also selected because EPA considers a five percent change in sperm concentration to be biologically relevant. In some strains of rats and mice, production of normal sperm can be reduced by up to 90% or more without compromising fertility (Working, 1988; Robaire et al., 1984; Meistrich et al., 1982; Aafjes et al., 1980). However, less severe reductions can cause reduced fertility in human males who appear to function closer to the threshold for the number of normal sperm needed to ensure full reproductive competence. This difference between test species and humans suggests that results from a test species may not fully represent toxicity in humans due to chemical exposure.

Table 2-37. Sperm Concentration in Male Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 4-Week Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Mean (M/g)	SD (M/g)
0.075	10	4.65	0.52
25.675	10	4.36	0.40
89.010	10	3.89	0.47
176.75	10	3.30	0.57

The BMD modeling results for decreased sperm concentration are summarized in Table 2-38. The constant variance model provided 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). The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC (Exponential 3) was selected.

Table 2-38. Summary of BMD Modeling Results for Decreased Sperm Concentration in Male Mice Following Inhalation Exposure to 1,2-Dichloroethane for 4 Weeks (Constant Variance)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	BMD 5%RD (mg/m^3)	BMDL 5%RD (mg/m^3)	Basis for Model Selection
	Test 4 p-value	AIC					
Exponential 3	**0.9453**	**59.00**	**55.847**	**41.335**	**26.735**	**21.240**	All models provided adequate fit to the means (test 4 p-value > 0.1). The BMDLs for the fit models were < 3-fold different; therefore, EPA chose the model with the lowest AIC.
Exponential 5	0.7855	60.96	51.913	26.379	24.578	12.196	
Hill	0.7929	60.95	51.506	23.774	24.276	10.475	
Polynomial Degree 3	0.8432	59.23	64.002	48.238	31.202	25.351	
Polynomial Degree 2	0.8484	59.21	62.561	48.259	30.564	25.353	
Power	0.8494	59.21	62.986	48.252	30.748	25.351	
Linear	0.8494	59.21	62.986	48.252	30.748	25.351	

[a] Selected model in bold.

Plots of the Exponential 3 model with a BMR of one SD and five percent RD are shown in Figure 2-46 and Figure 2-47, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-48. (BMD and BMDL shown are for BMR of one SD; the rest is applicable to both BMRs).

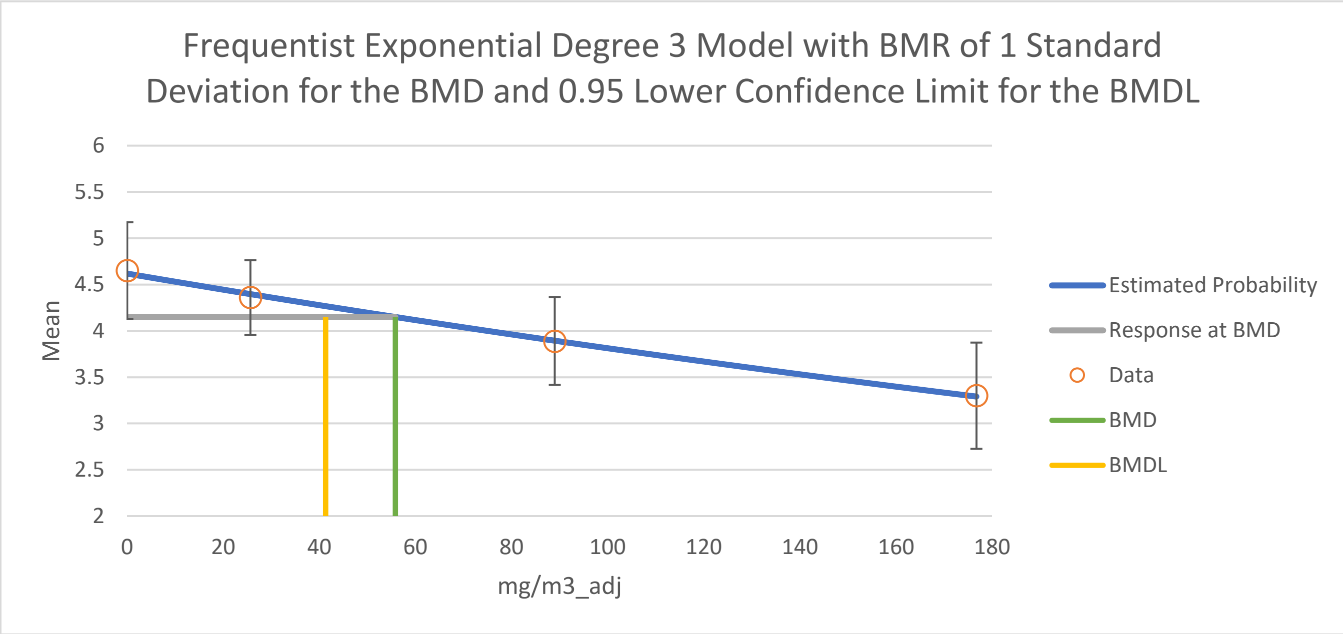

Figure 2-46. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 3) for Decreased Sperm Concentration in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 4 Weeks and BMR of 1SD (Constant Variance)

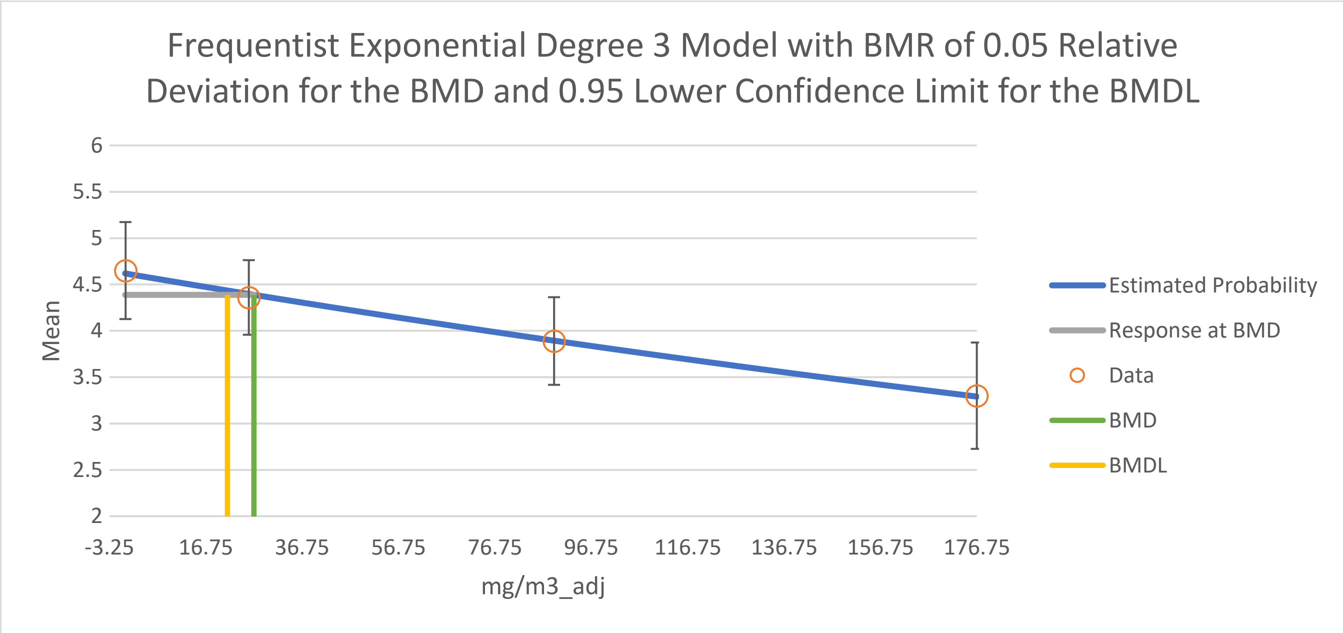

Figure 2-47. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 3) for Decreased Sperm Concentration in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 4 Weeks and BMR of 5%RD (Constant Variance)

Model Results

Benchmark Dose	
BMD	55.84663409
BMDL	41.33515229
BMDU	100.8093304
AIC	58.99784667
Test 4 P-value	0.945316531
D.O.F.	2

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
a	4.618972239	0.113350836	4.39680868	4.8411358
b	0.001918616	2.92E-04	0.00134608	0.00249115
d	Bounded	NA	NA	NA
log-alpha	-1.512930902	2.24E-01	-1.9511885	-1.0746734

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0.075	10	4.618307635	4.65	4.65	0.46932234	0.52	0.52	0.213542059
25.675	10	4.396952797	4.36	4.36	0.46932234	0.4	0.4	-0.248986667
89.01	10	3.893841526	3.89	3.89	0.46932234	0.47	0.47	-0.025884069
176.75	10	3.29055696	3.3	3.3	0.46932234	0.57	0.57	0.063626873

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-26.44268788	5	62.8853758
A2	-25.776744	8	67.553488
A3	-26.44268788	5	62.8853758
fitted	-26.49892334	3	58.9978467
R	-42.10709522	2	88.2141904

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	32.66070244	6	<0.0001
2	1.331887768	3	0.7215753
3	1.331887768	3	0.7215753
4	0.112470908	2	0.94531653

Figure 2-48. Details Regarding the Selected Model (Exponential 3) for Decreased Sperm Concentration in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 4 Weeks

2.1.1.2.4.2 Diameter of Seminiferous Tubules in Male Mice – 4-Week Inhalation Exposure

The diameter of seminiferous tubules was significantly decreased in male mice exposed to 1,2-dichloroethane by inhalation for four weeks (6 hours per day, 7 days per week) (Zhang et al., 2017). The measured exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week. The concentration and response data used for the modeling are presented in Table 2-39. 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).

Table 2-39. Diameter of Seminiferous Tubules in Male Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 4-Week Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Mean (µm)	SD (µm)
0.075	5	249	29.3
25.675	5	236	28.2
89.010	5	180	19.2
176.75	5	100	11.3

The BMD modeling results for decreased diameter of seminiferous tubules are summarized in Table 2-40. The constant variance model provided adequate fit to the variance data. With the constant variance model applied, the Exponential 3, Power, and Linear 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 (Linear) was selected.

Table 2-40. Summary of BMD Modeling Results for Decreased Diameter of Seminiferous Tubules in Male Mice Following Inhalation Exposure to 1,2-Dichloroethane for 4 Weeks (Constant Variance)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	Basis for Model Selection
	Test 4 p-value	AIC			
Exponential 3	0.9424	186.0	37.039	20.640	The Exponential 3, Power, and Linear models provided adequate fit to the means (test 4 p-value > 0.1). BMDLs differed by < 3-fold; therefore, EPA chose the model with the lowest AIC.
Exponential 5	NA	188.0	37.039	20.640	
Hill	NA	189.0	81.915	16.819	
Polynomial Degree 3	NA	188.3	28.539	19.113	
Polynomial Degree 2	0.0353	190.5	64.600	63.257	
Power	0.7415	186.1	31.371	19.242	
Linear	**0.7447**	**184.6**	**24.471**	**18.815**	

[a] Selected model in bold.

A plot of the Linear model with a BMR of one SD is shown in Figure 2-49. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-50.

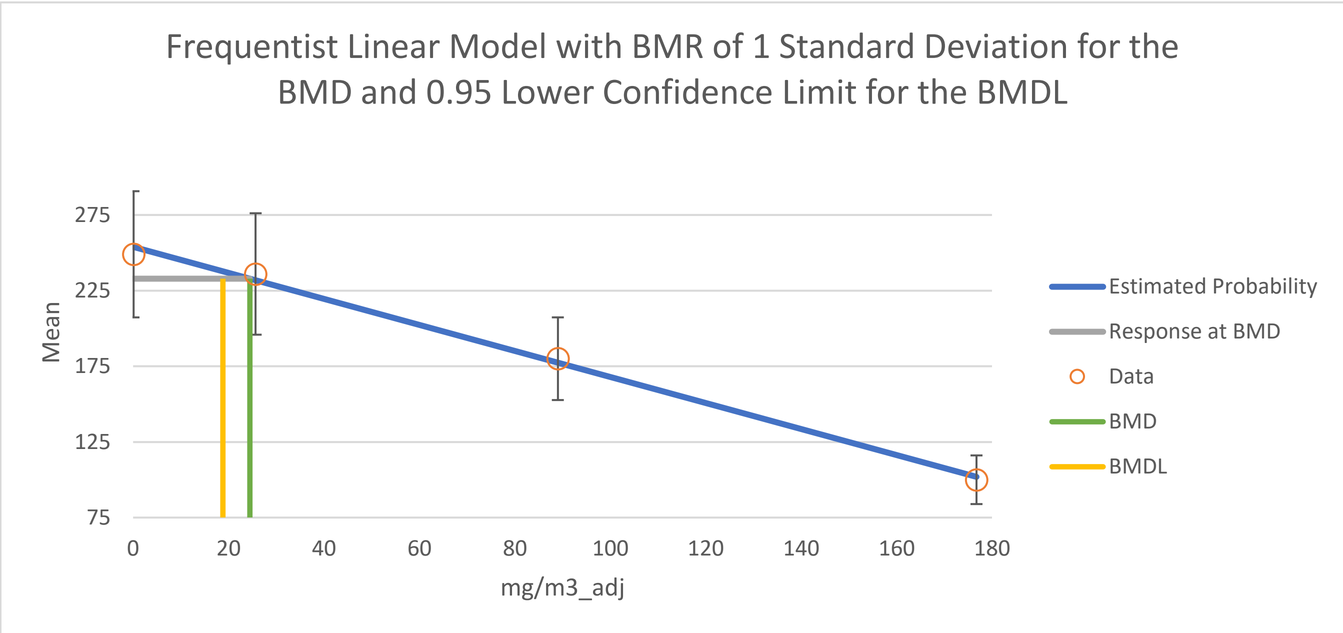

Figure 2-49. Plot of Response by Dose with Fitted Curve for the Selected Model (Linear) for Decreased Diameter of Seminiferous Tubules in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 4 Weeks and BMR of 1SD (Constant Variance)

Model Results

Benchmark Dose	
BMD	24.47144499
BMDL	18.81509191
BMDU	34.10427505
AIC	184.6234089
Test 4 P-value	0.744678566
D.O.F.	2

Model Parameters				
# of Parameters	3			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	253.9223097	6.889545669	240.419048	267.425571
beta	-0.85996788	6.90E-02	-0.9953008	-0.724635
alpha	442.8775746	6.20E+04	-121124.09	122009.843

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0.075	5	253.8578122	249	249	21.0446567	29.3	29.3	-0.51615944
25.675	5	231.8426344	236	236	21.0446567	28.2	28.2	0.441734553
89.01	5	177.3765688	180	180	21.0446567	19.2	19.2	0.278748693
176.75	5	101.922987	100	100	21.0446567	11.3	11.3	-0.20432406

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-89.01690182	5	188.033804
A2	-86.63044764	8	189.260895
A3	-89.01690182	5	188.033804
fitted	-89.31170443	3	184.623409
R	-111.0087441	2	226.017488

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	48.75659293	6	<0.0001
2	4.772908345	3	0.18920143
3	4.772908345	3	0.18920143
4	0.589605219	2	0.74467857

Figure 2-50. Details Regarding the Selected Model (Linear) for Decreased Diameter of Seminiferous Tubules in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 4 Weeks

2.1.1.2.4.3 Height of Germinal Epithelium in Male Mice – 4-Week Inhalation Exposure

The height of germinal epithelium was significantly decreased in male mice exposed to 1,2-dichloroethane by inhalation for four weeks (6 hours per day, 7 days per week) (Zhang et al., 2017). The measured exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week. The concentration and response data used for the modeling are presented in Table 2-41. 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).

Table 2-41. Height of Germinal Epithelium in Male Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 4-Week Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Mean (µm)	SD (µm)
0.075	5	100	8.2
25.675	5	90	9.4
89.010	5	52	8.2
176.75	5	30	5.9

The BMD modeling results for decreased height of germinal epithelium are summarized in Table 2-42. 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); therefore, this model was selected.

Table 2-42. Summary of BMD Modeling Results for Decreased Height of Germinal Epithelium in Male Mice Following Inhalation Exposure to 1,2-Dichloroethane for 4 Weeks (Constant Variance)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	Basis for Model Selection
	Test 4 p-value	AIC			
Exponential 3	**0.1184**	**146.0**	**13.975**	**8.6304**	Only the Exponential 3 model provided adequate fit to the means (test 4 p-value > 0.1); therefore, this model was selected.
Exponential 5	NA	145.6	20.581	10.711	
Hill	NA	145.6	20.977	11.178	
Polynomial Degree 3	< 0.0001	168.0	71.926	70.452	
Polynomial Degree 2	0.0022	152.9	22.452	17.037	
Power	0.0010	150.8	22.172	17.118	
Linear	0.0010	150.8	22.172	17.118	

[a] Selected model in bold.

A plot of the Exponential 3 model with a BMR of one SD is shown in Figure 2-51. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-52.

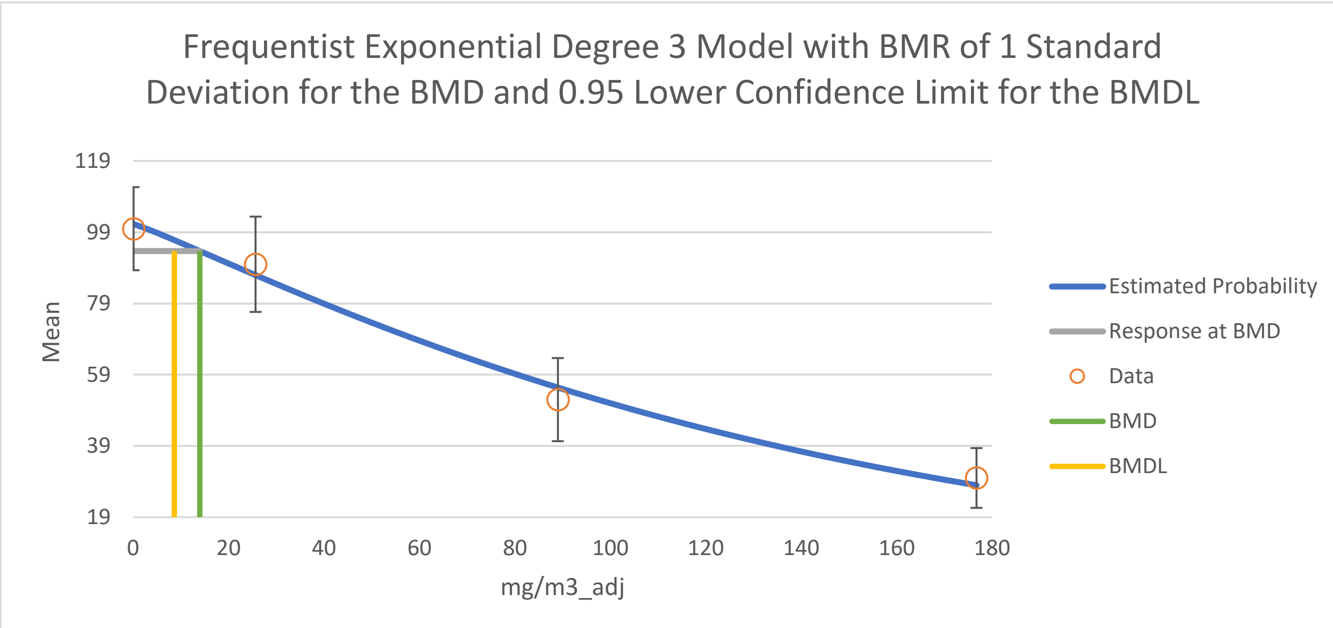

Figure 2-51. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 3) for Decreased Height of Germinal Epithelium in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 4 Weeks and BMR of 1SD (Constant Variance)

Model Results

Benchmark Dose	
BMD	13.97510463
BMDL	8.630430863
BMDU	25.05659301
AIC	146.0395411
Test 4 P-value	0.118373042
D.O.F.	1

Model Parameters

# of Parameters: 4

Variable	Estimate	Std Error	Lower Conf	Upper Conf
a	101.3424129	3.217463633	95.0363	107.648526
b	0.007113595	5.18E-04	0.00609928	0.00812791
d	1.103577087	1.41E-01	0.82721977	1.3799344
log-alpha	4.064099969	3.16E-01	3.44430945	4.68389048

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0.075	5	101.3176446	100	100	7.62971113	8.2	8.2	-0.386167039
25.675	5	86.95185553	90	90	7.62971113	9.4	9.4	0.893331102
89.01	5	55.40096565	52	52	7.62971113	8.2	8.2	-0.996733724
176.75	5	27.96627608	30	30	7.62971113	5.9	5.9	0.596031076

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-67.80041229	5	145.600825
A2	-67.26698689	8	150.533974
A3	-67.80041229	5	145.600825
fitted	-69.01977056	4	146.039541
R	-95.87257757	2	195.745155

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	57.21118136	6	<0.0001
2	1.066850786	3	0.78508185
3	1.066850786	3	0.78508185
4	2.438716552	1	0.11837304

Figure 2-52. Details Regarding the Selected Model (Exponential 3) for Decreased Height of Germinal Epithelium in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 4 Weeks

2.1.1.2.4.4 Number of Apoptotic Cells in the Testis in Male Mice – 4-Week Inhalation Exposure

The number of apoptotic cells in the testis was significantly increased in male mice exposed to 1,2-dichloroethane by inhalation for four weeks (6 hours per day, 7 days per week) (Zhang et al., 2017). The measured exposure concentrations were duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week. The concentration and response data used for the modeling are presented in Table 2-43. 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).

Table 2-43. Number of Apoptotic Cells in Male Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 4-Week Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Mean	SD
0.075	5	169	108
25.675	5	207	160
89.010	5	273	198
176.75	5	400	216

The BMD modeling results for increased number of apoptotic cells are summarized in Table 2-44. 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 (Linear) was selected.

Table 2-44. Summary of BMD Modeling Results for Increased Number of Apoptotic Cells in Male Mice Following Inhalation Exposure to 1,2-Dichloroethane for 4 Weeks (Constant Variance)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	Basis for Model Selection
	Test 4 p-value	AIC			
Exponential 3	0.9847	265.019	137.37	98.972	All models, except for the Exponential 5 and Hill models, provided adequate fit to the means (test 4 p-value > 0.1). BMDLs differed by < 3-fold; therefore, EPA chose the model with the lowest AIC.
Exponential 5	NA	269.009	127.39	87.083	
Hill	NA	269.016	127.36	23.227	
Polynomial Degree 3	0.9605	265.068	112.45	71.178	
Polynomial Degree 2	0.9054	267.002	128.54	71.734	
Power	0.8850	267.009	127.39	71.487	
Linear	**0.9852**	**265.018**	**122.18**	**71.431**	

[a] Selected model in bold.

A plot of the Linear model with a BMR of one SD is shown in Figure 2-53. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-54.

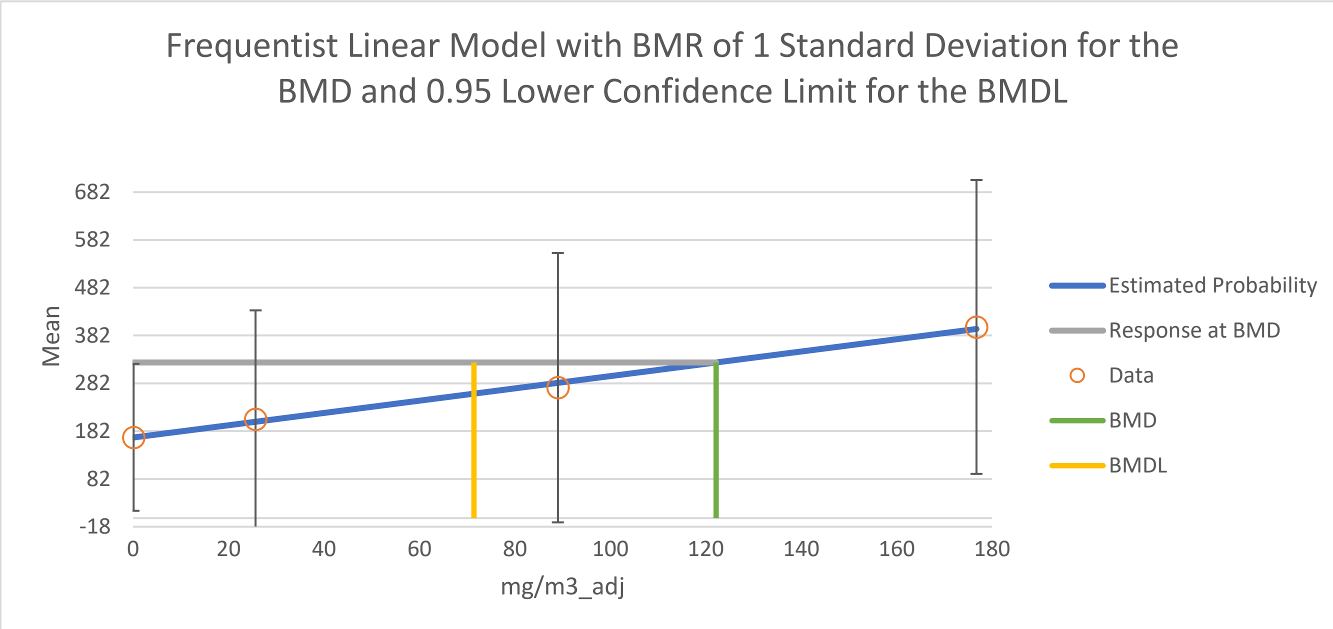

Figure 2-53. Plot of Response by Dose with Fitted Curve for the Selected Model (Linear) for Increased Number of Apoptotic Cells in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 4 Weeks and BMR of 1SD (Constant Variance)

Model Results

Benchmark Dose	
BMD	122.1802163
BMDL	71.4305637
BMDU	417.429177
AIC	265.0175897
Test 4 P-value	0.985180162
D.O.F.	2

Model Parameters				
# of Parameters	3			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	168.5794306	51.40667943	67.8241895	269.334672
beta	1.285315329	0.515232602	0.27547798	2.29515268
alpha	24661.59453	192327488.6	-376930292	376979615

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0.075	5	168.6758292	169	169	157.040105	108	108	0.004615814
25.675	5	201.5799016	207	207	157.040105	160	160	0.077175881
89.01	5	282.985348	273	273	157.040105	198	198	-0.142179712
176.75	5	395.7589149	400	400	157.040105	216	216	0.060388106

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-129.4938641	5	268.987728
A2	-128.2515876	8	272.503175
A3	-129.4938641	5	268.987728
fitted	-129.5087949	3	265.01759
R	-132.2176673	2	268.435335

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	7.9321595	6	0.24311574
2	2.484553103	3	0.47808915
3	2.484553103	3	0.47808915
4	0.029861498	2	0.98518016

Figure 2-54. Details Regarding the Selected Model (Linear) for Increased Number of Apoptotic Cells in Male Mice Exposed to 1,2-Dichloroethane Via Inhalation for 4 Weeks

2.1.1.3 Chronic

2.1.1.3.1 Hepatic Effects

EPA identified hepatic endpoints in a chronic inhalation study for BMD modeling (IRFMN, 1978). Modeling results are presented for increased serum lactate dehydrogenase (LDH) levels in female rats. Modeled results are not presented for serum LDH levels in male rats or serum ALT or cholesterol levels in male or female rats because neither the constant nor nonconstant variance models provided adequate fit to the variance data or because none of the models provided adequate fits to the means (test 4 p-value < 0.1) assuming either constant or nonconstant variance.

2.1.1.3.1.1 LDH Levels in Female Sprague-Dawley Rats – 12-Month Inhalation Exposure

Serum LDH levels were significantly increased in female rats exposed to 1,2-dichloroethane by inhalation for 12 months (seven hours per day, 5 days per week) (IRFMN, 1978). The exposure concentrations (reported in ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day and 7 days per week. The concentration and response data used for the modeling are presented in Table 2-45. 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).

Table 2-45. Increased LDH Levels in Female Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 12-Month Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Mean (mU/mL)	SD (mU/mL)
0	8	617.50	47.12
4	8	682.50	78.15
8.3	8	700.00	81.40
42	8	770.00	51.28
126	8	705.00	91.81

The BMD modeling results for increased serum LDH levels in female rats are summarized in Table 2-46. The constant variance model provided an adequate fit to the variance data. With the constant variance model applied, only the Exponential 5 model provided adequate fit to the means (test 4 p-value > 0.1); therefore, this model was selected.

Table 2-46. Summary of BMD Modeling Results for Increased LDH Levels in Female Rats Following Inhalation Exposure to 1,2-Dichloroethane for 12 Months (Constant Variance)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	Basis for Model Selection
	Test 4 p-value	AIC			
Exponential 3	0.0019	471.3	210	100	Only the Exponential 5 model provided adequate fit to the means (test 4 p-value > 0.1); therefore, this model was selected.
Exponential 5	**0.1563**	**462.2**	**5.5**	**1.7**	
Hill	0.0007	472.8	210	210	
Polynomial Degree 3	0.0020	471.2	210	96	
Polynomial Degree 2	0.0020	471.2	210	96	
Power	0.0020	471.2	210	96	
Linear	0.0020	471.2	210	96	

[a] Selected model in bold.

A plot of the Exponential 5 model with a BMR of one SD is shown in Figure 2-55. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-56.

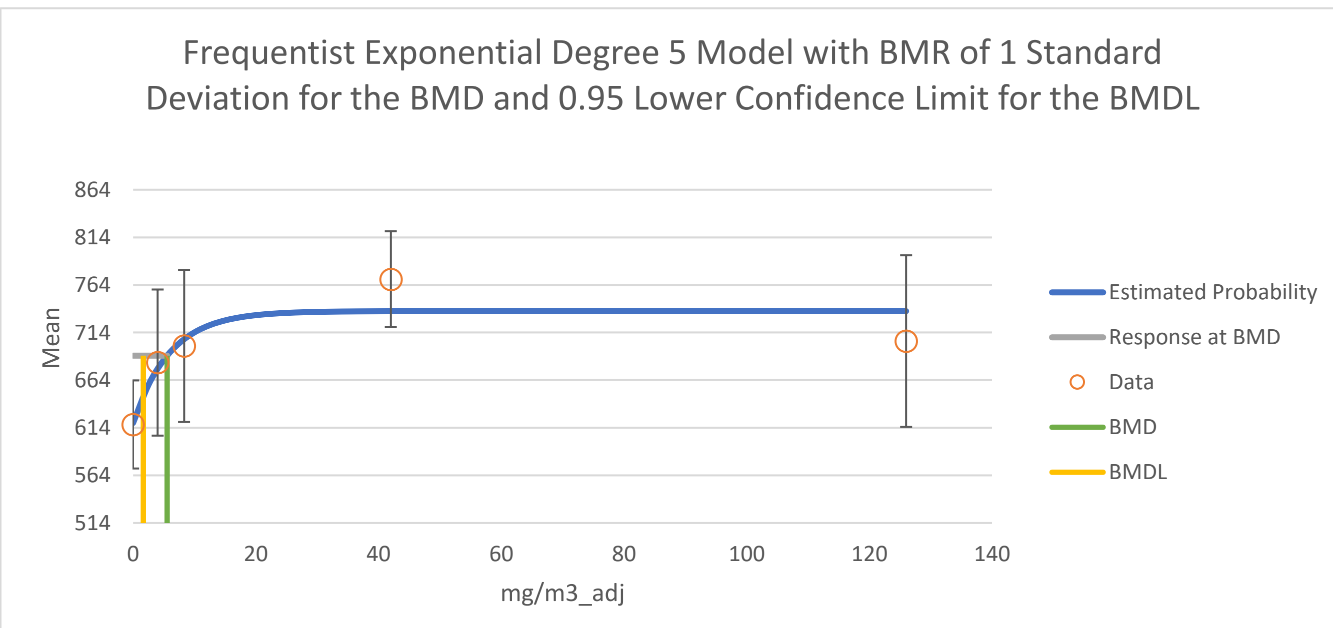

Figure 2-55. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 5) for Increased LDH Levels in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation for 12 Months and BMR of 1SD (Constant Variance)

Model Results

Benchmark Dose	
BMD	5.542740664
BMDL	1.66153532
BMDU	Infinity
AIC	462.1616961
Test 4 P-value	0.156276737
D.O.F.	2

Model Parameters

# of Parameters: 5

Variable	Estimate	Std Error	Lower Conf	Upper Conf
a	619.0800415	24.60242104	570.860182	667.299901
b	0.166171746	9.54E-02	-0.0207616	0.35310507
c	1.18966716	4.58E-02	1.09996	1.27937432
d	Bounded	NA	NA	NA
log-alpha	8.516165337	2.24E-01	8.07790512	8.95442556

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	8	619.0800415	617.5	617.5	70.6743473	47.12	47.12	-0.063234151
4	8	676.094728	682.5	682.5	70.6743473	78.15	78.15	0.256342587
8.3	8	706.9361662	700	700	70.6743473	81.4	81.4	-0.277589271
42	8	736.3898734	770	770	70.6743473	51.28	51.28	1.345096167
126	8	736.4991947	705	705	70.6743473	91.81	91.81	-1.260615487

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-225.2247211	6	462.449442
A2	-222.6287127	10	465.257425
A3	-225.2247211	6	462.449442
fitted	-227.080848	4	462.161696
R	-233.6433119	2	471.286624

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	22.0291984	8	0.00486206
2	5.192016838	4	0.26815665
3	5.192016838	4	0.26815665
4	3.712253773	2	0.15627674

Figure 2-56. Details Regarding the Selected Model (Exponential 5) for Increased LDH Levels in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation for 12 Months

2.1.1.3.2 Renal Effects

EPA identified renal endpoints in a chronic inhalation study for BMD modeling (IRFMN, 1978). Modeled results are presented for BUN and serum potassium levels in male and female rats and serum calcium levels in male rats. Modeled results are not presented for serum calcium in female rats or serum uric acid in male or female rats (IRFMN, 1978) because neither the constant nor nonconstant variance models provided adequate fit to the variance data or because none of the models provided adequate fits to the means (test 4 p-value < 0.1) assuming either constant or nonconstant variance.

2.1.1.3.2.1 Blood Urea Nitrogen (BUN) Levels in Male Sprague-Dawley Rats – 12-Month Inhalation Exposure

Serum BUN levels were significantly increased in male rats exposed to 1,2-dichloroethane by inhalation for 12 months (seven hours per day, 5 days per week) (IRFMN, 1978). The exposure concentrations (reported in ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day and 7 days per week. The concentration and response data used for the modeling are presented in Table 2-47. 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).

Table 2-47. BUN Levels in Male Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 12-Month Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Mean (mg%)	SD (mg%)
0	8	10.29	0.82
4	8	11.00	1.50
8.3	8	10.25	1.27
42	8	10.63	1.41
126	8	15.50	2.06

The BMD modeling results for increased serum BUN levels in male rats are summarized in Table 2-48. The constant variance model provided an adequate fit to the variance data. With the constant variance model applied, all models, except for the Linear model, 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 (Polynomial 3-degree) was selected.

Table 2-48. Summary of BMD Modeling Results for Increased BUN Levels in Male Rats Following Inhalation Exposure to 1,2-Dichloroethane for 12 Months (Constant Variance)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	Basis for Model Selection
	Test 4 p-value	AIC			
Exponential 3	0.4759	148.3	89	50	All models, except for the Linear model, provided adequate fit to the means (test 4 p-value > 0.1). BMDLs for the fit models differed by < 3-fold; therefore, EPA chose the model with the lowest AIC.
Exponential 5	0.2232	150.3	52	43	
Hill	0.2232	150.3	68	43	
Polynomial Degree 3	**0.6821**	**146.4**	**82**	**50**	
Polynomial Degree 2	0.5522	147.0	67	47	
Power	0.4760	148.3	87	50	
Linear	0.0473	152.8	38	30	

[a] Selected model in bold.

A plot of the Polynomial 3-degree model with a BMR of one SD is shown in Figure 2-57. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-58.

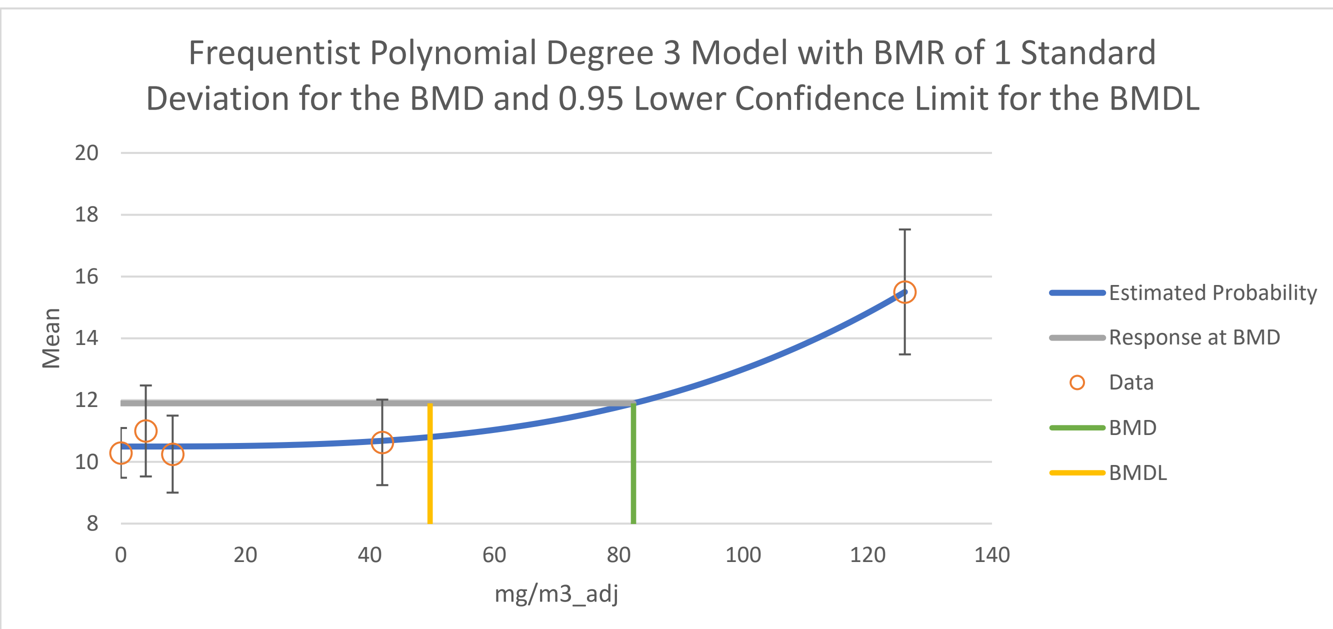

Figure 2-57. Plot of Response by Dose with Fitted Curve for the Selected Model (Polynomial 3-Degree) for Increased BUN Levels in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 12 Months and BMR of 1SD (Constant Variance)

Model Results

Benchmark Dose	
BMD	82.38167775
BMDL	49.68477751
BMDU	90.9704127
AIC	146.3563545
Test 4 P-value	0.682130008
D.O.F.	3

Model Parameters				
# of Parameters	5			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	10.49575203	0.249598752	10.0065475	10.9849566
beta	Bounded	NA	NA	NA
beta2	Bounded	NA	NA	NA
beta3	2.5017E-06	2.79E-07	1.9552E-06	3.0482E-06
alpha	1.956385162	8.56E-01	0.27882579	3.63394453

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	8	10.49575203	10.29	10.29	1.39870839	0.82	0.82	-0.416065723
4	8	10.49591214	11	11	1.39870839	1.5	1.5	1.019351707
8.3	8	10.49718247	10.25	10.25	1.39870839	1.27	1.27	-0.499845144
42	8	10.681098	10.63	10.63	1.39870839	1.41	1.41	-0.10332888
126	8	15.50009328	15.5	15.5	1.39870839	2.06	2.06	-0.000188621

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-69.42787324	6	150.855746
A2	-66.18552753	10	152.371055
A3	-69.42787324	6	150.855746
fitted	-70.17817725	3	146.356355
R	-92.22187689	2	188.443754

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	52.07269871	8	<0.0001
2	6.484691423	4	0.16575751
3	6.484691423	4	0.16575751
4	1.500608017	3	0.68213001

Figure 2-58. Details Regarding the Selected Model (Polynomial 3-Degree) for Increased BUN Levels in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 12 Months

2.1.1.3.2.2 Blood Urea Nitrogen (BUN) in Female Sprague-Dawley Rats – 12-Month Inhalation Exposure

Serum BUN levels were significantly increased in female rats exposed to 1,2-dichloroethane by inhalation for 12 months (seven hours per day, 5 days per week) (IRFMN, 1978). The exposure concentrations (reported in ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day and 7 days per week. The concentration and response data used for the modeling are presented in Table 2-49. 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).

Table 2-49. BUN Levels in Female Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 12-Month Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Mean (mg%)	SD (mg%)
0	8	10.50	0.93
4	8	10.88	0.99
8.3	8	10.75	1.50
42	8	10.72	2.04
126	8	15.25	2.38

The BMD modeling results for increased serum BUN levels in female rats are summarized in Table 2-50. The constant variance model did not provide adequate fit to the variance data. With the nonconstant variance model applied, all models provided an 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 (Polynomial 2-degree) was selected.

Table 2-50. Summary of BMD Modeling Results for Increased BUN Levels in Female Rats Following Inhalation Exposure to 1,2-Dichloroethane for 12 Months (Nonconstant Variance)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	Basis for Model Selection
	Test 4 p-value	AIC			
Exponential 3	0.7765	155.2	74	32	All models provided an adequate fit to the means (test 4 p-value > 0.1). BMDLs differed by < 3-fold; therefore, EPA chose the model with the lowest AIC.
Exponential 5	0.4750	157.2	73	64	
Hill	0.4748	157.2	73	24	
Polynomial Degree 3	0.8080	155.1	76	29	
Polynomial Degree 2	**0.9064**	**153.2**	**67**	**29**	
Power	0.7748	155.2	73	29	
Linear	0.5460	154.8	38	25	

[a] Selected model in bold.

A plot of the Polynomial 2-degree model with a BMR of one SD is shown in Figure 2-59. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-60.

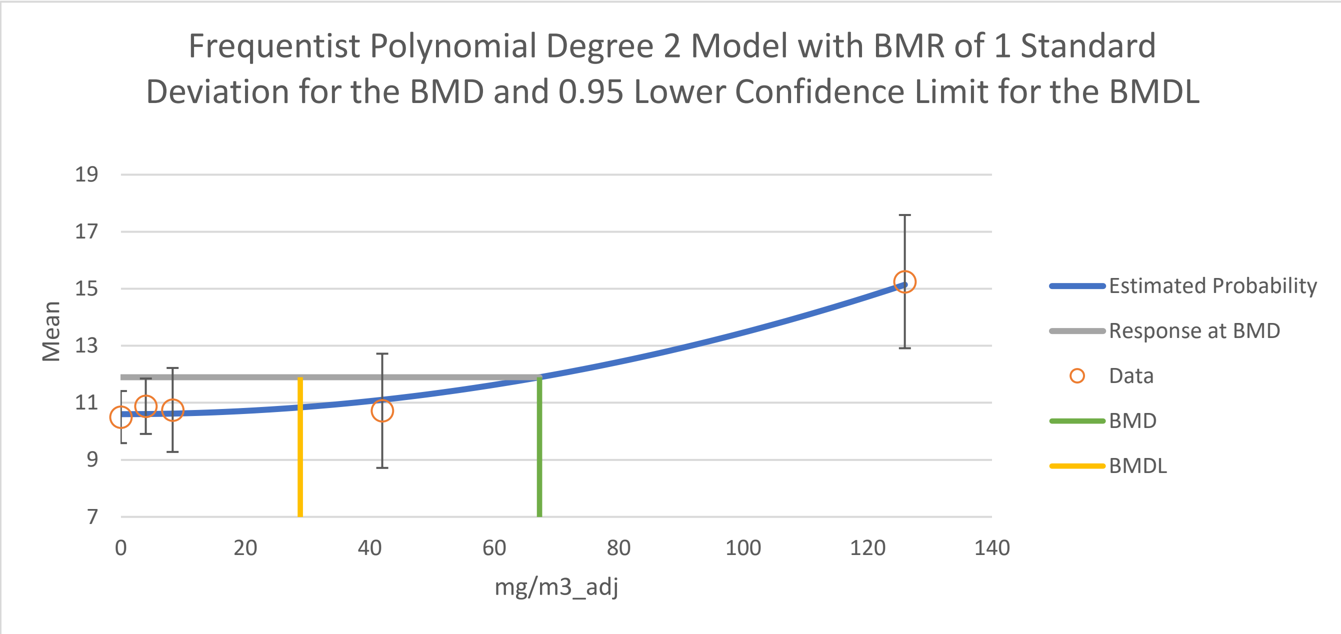

Figure 2-59. Plot of Response by Dose with Fitted Curve for the Selected Model (Polynomial 2-Degree) for Increased BUN Levels in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation for 12 Months and BMR of 1SD (Nonconstant Variance)

Model Results

Benchmark Dose	
BMD	67.27795923
BMDL	28.82214651
BMDU	84.94460652
AIC	153.2223286
Test 4 P-value	0.906394034
D.O.F.	3

Model Parameters				
# of Parameters	5			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	10.60180857	0.240171167	10.1310817	11.0725354
beta	Bounded	NA	NA	NA
beta2	0.00028596	5.57E-05	0.00017677	0.00039515
rho	3.413973354	1.87E+00	-0.2537519	7.08169862
alpha	0.000529032	1.28E-06	0.00052652	0.00053154

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	8	10.60180857	10.5	10.5	1.29434746	0.93	0.93	-0.222473594
4	8	10.60638393	10.88	10.88	1.29530112	0.99	0.99	0.597469648
8.3	8	10.62150836	10.75	10.75	1.29845562	1.5	1.5	0.279893469
42	8	11.10624197	10.72	10.72	1.40123221	2.04	2.04	-0.779640423
126	8	15.14170917	15.25	15.25	2.37839389	2.38	2.38	0.128781329

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-74.56612506	6	161.13225
A2	-69.31006848	10	158.620137
A3	-72.33309109	7	158.666182
fitted	-72.61116432	4	153.222329
R	-91.72530575	2	187.450612

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	44.83047455	8	<0.0001
2	10.51211316	4	0.03263054
3	6.046045235	3	0.10939139
4	0.556146456	3	0.90639403

Figure 2-60. Details Regarding the Selected Model (Polynomial 2-Degree) for Increased BUN Levels in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation for 12 Months

2.1.1.3.2.3 Calcium Levels in Male Sprague-Dawley Rats – 12-Month Inhalation Exposure

Serum calcium levels were significantly decreased in male rats exposed to 1,2-dichloroethane by inhalation for 12 months (seven hours per day, 5 days per week) (IRFMN, 1978). The exposure concentrations (reported in ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day and 7 days per week. The concentration and response data used for the modeling are presented in Table 2-51. 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 because EPA considers a 10 percent change in serum calcium levels to be biologically relevant.

Table 2-51. Serum Calcium Levels in Male Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 12-Month Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Mean (mg%)	SD (mg%)
0	8	9.98	0.37
4	8	9.63	0.31
8.3	8	9.48	0.31
42	8	8.95	0.14
126	8	8.73	0.37

The BMD modeling results for decreased serum calcium levels in male rats are summarized in Table 2-52. The constant variance model provided an adequate fit to the variance data. With the constant variance model applied, 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 (Hill model) was selected.

Table 2-52. Summary of BMD Modeling Results for Decreased Serum Calcium Levels in Male Rats Following Inhalation Exposure to 1,2-Dichloroethane for 12 Months (Constant Variance)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	BMD 10%RD (mg/m^3)	BMDL 10%RD (mg/m^3)	Basis for Model Selection
	Test 4 p-value	AIC					
Exponential 3	0.0004	39.30	42	32	110	91	The Exponential 5 and Hill models provided adequate fit to the means (test 4 p-value > 0.1). BMDLs for the fit models differed by < 3-fold; therefore, EPA chose the model with the lowest AIC.
Exponential 5	0.5273	24.18	5.2	2.6	34	16	
Hill	**0.9146**	**23.08**	**3.8**	**2.0**	**38**	**18**	
Polynomial Degree 3	0.0003	39.91	44	34	120	94	
Polynomial Degree 2	0.0003	39.91	44	34	120	94	
Power	0.0003	39.91	44	34	120	94	
Linear	0.0003	39.91	44	34	120	94	

[a] Selected model in bold.

Plots of the Hill model with BMRs of one SD and 10 percent RD are shown in Figure 2-61 and Figure 2-62, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-63 (BMD and BMDL shown are for BMR of one SD; the rest is applicable to both BMRs).

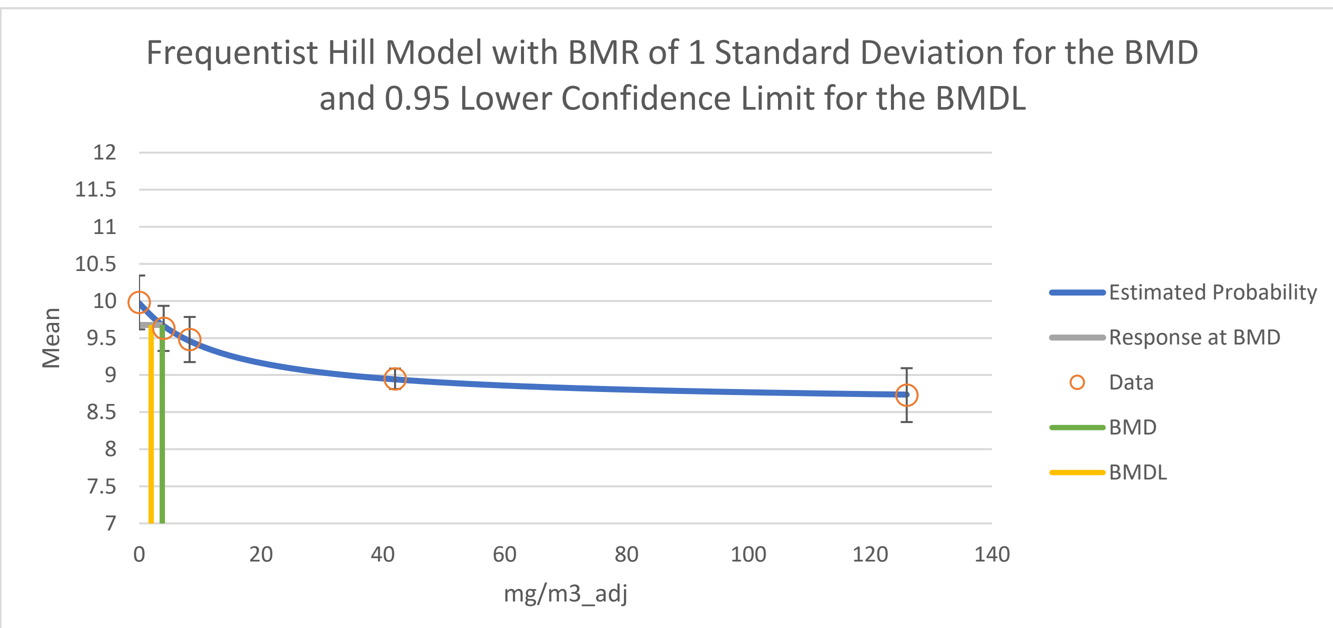

Figure 2-61. Plot of Response by Dose with Fitted Curve for the Selected Model (Hill) for Decreased Serum Calcium Levels in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 12 Months and BMR of 1SD (Constant Variance)

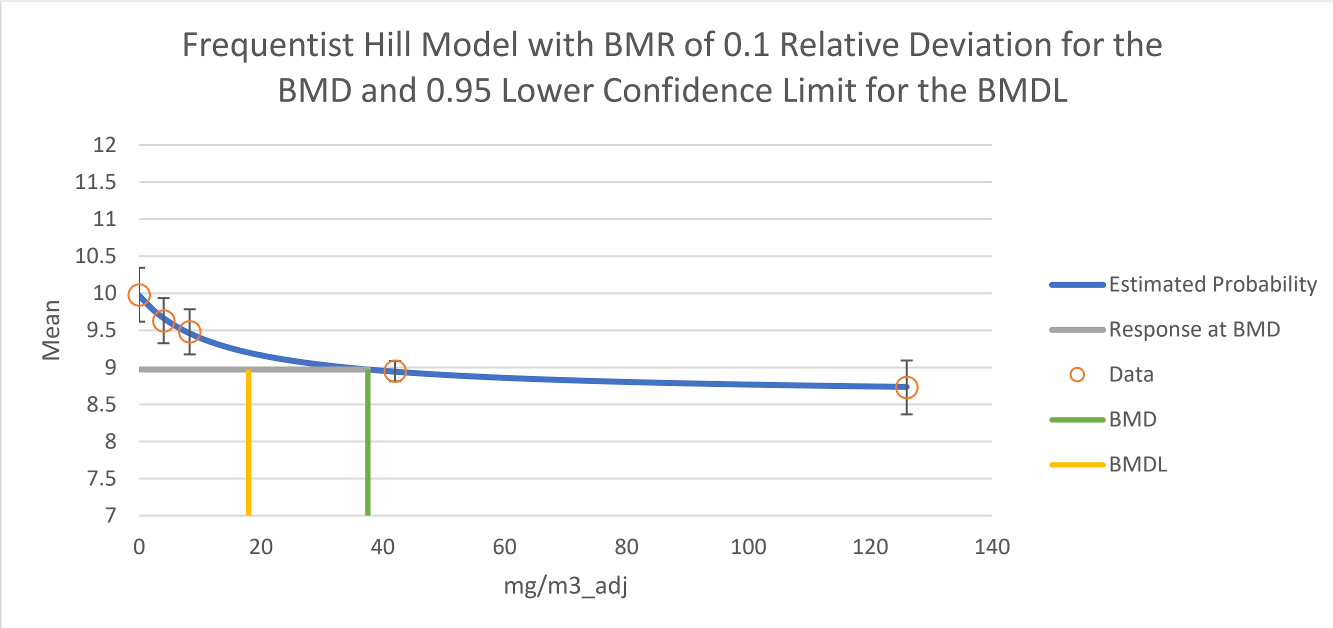

Figure 2-62. Plot of Response by Dose with Fitted Curve for the Selected Model (Hill) for Decreased Serum Calcium Levels in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 12 Months and BMR of 10%RD (Constant Variance)

Model Results

Benchmark Dose	
BMD	3.793853645
BMDL	1.973102694
BMDU	9.002210197
AIC	23.07602981
Test 4 P-value	0.916438367
D.O.F.	2

Model Parameters				
# of Parameters	5			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	9.968378751	9.97E-02	9.77293889	10.1638186
v	-1.367698827	1.45E-01	-1.6527488	-1.0826488
k	13.96705849	6.12E+00	1.9724673	25.9616497
n	Bounded	NA	NA	NA
alpha	0.08535158	1.63E-03	0.0821589	0.08854426

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	8	9.968378751	9.98	9.98	0.29214993	0.37	0.37	0.112510234
4	8	9.663888435	9.63	9.63	0.29214993	0.31	0.31	-0.328088289
8.3	8	9.458571842	9.48	9.48	0.29214993	0.31	0.31	0.207455072
42	8	8.942000873	8.95	8.95	0.29214993	0.14	0.14	0.077442935
126	8	8.737160105	8.73	8.73	0.29214993	0.37	0.37	-0.069320011

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-7.450754442	6	26.9015089
A2	-3.711046548	10	27.4220931
A3	-7.450754442	6	26.9015089
fitted	-7.538014904	4	23.0760298
R	-32.1569544	2	68.3139088

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	56.89181569	8	<0.0001
2	7.479415788	4	0.1126204
3	7.479415788	4	0.1126204
4	0.174520924	2	0.91643837

Figure 2-63. Details Regarding the Selected Model (Hill) for Increased Serum Calcium Levels in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 12 Months

2.1.1.3.2.4 Serum Potassium Levels in Male Sprague-Dawley Rats – 12-Month Inhalation Exposure

Serum potassium levels were significantly increased in male rats exposed to 1,2-dichloroethane by inhalation for 12 months (seven hours per day, 5 days per week) (IRFMN, 1978). The exposure concentrations (reported in ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day and 7 days per week. The concentration and response data used for the modeling are presented in Table 2-53. 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 because EPA considers a 10 percent change in serum potassium levels to be biologically relevant.

Table 2-53. Serum Potassium Levels in Male Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 12-Month Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Mean (mg%)	SD (mg%)
0	8	4.91	0.57
4	8	5.34	0.48
8.3	8	6.44	0.71
42	8	6.08	0.71
126	8	6.26	0.59

The BMD modeling results for increased serum potassium levels in male rats are summarized in Table 2-54. The constant variance model provided an adequate fit to the variance data. With the constant variance model applied, 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 (Hill) was selected.

Table 2-54. Summary of BMD Modeling Results for Increased Serum Potassium Levels in Male Rats Following Inhalation Exposure to 1,2-Dichloroethane for 12 Months (Constant Variance)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	BMD 10%RD (mg/m^3)	BMDL 10%RD (mg/m^3)	Basis for Model Selection
	Test 4 p-value	AIC					
Exponential 3	-	-	-	-	-	-	The Exponential 5 and Hill models provided adequate fit to the means (test 4 p-value > 0.1). BMDLs for the fit models differed by < 3-fold; therefore, EPA chose the model with the lowest AIC.
Exponential 5	0.2176	81.23	4.1	3.0	4.0	3.8	
Hill	**0.4676**	**79.23**	**4.1**	**3.6**	**4.0**	**3.8**	
Polynomial Degree 3	< 0.0001	97.90	119	71	87	51	
Polynomial Degree 2	< 0.0001	97.90	119	71	87	51	
Power	< 0.0001	97.90	119	71	87	51	

Model	Goodness of Fit (Means)		BMD 1SD (mg/m³)	BMDL 1SD (mg/m³)	BMD 10%RD (mg/m³)	BMDL 10%RD (mg/m³)	Basis for Model Selection
	Test 4 p-value	AIC					
Linear	< 0.0001	97.90	119	71	87	51	
[a] Selected model in bold.							

Plots of the Hill model with BMRs of one SD and 10 percent RD are shown in Figure 2-64 and Figure 2-65, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-66 (BMD and BMDL shown are for BMR of one SD; the rest is applicable to both BMRs).

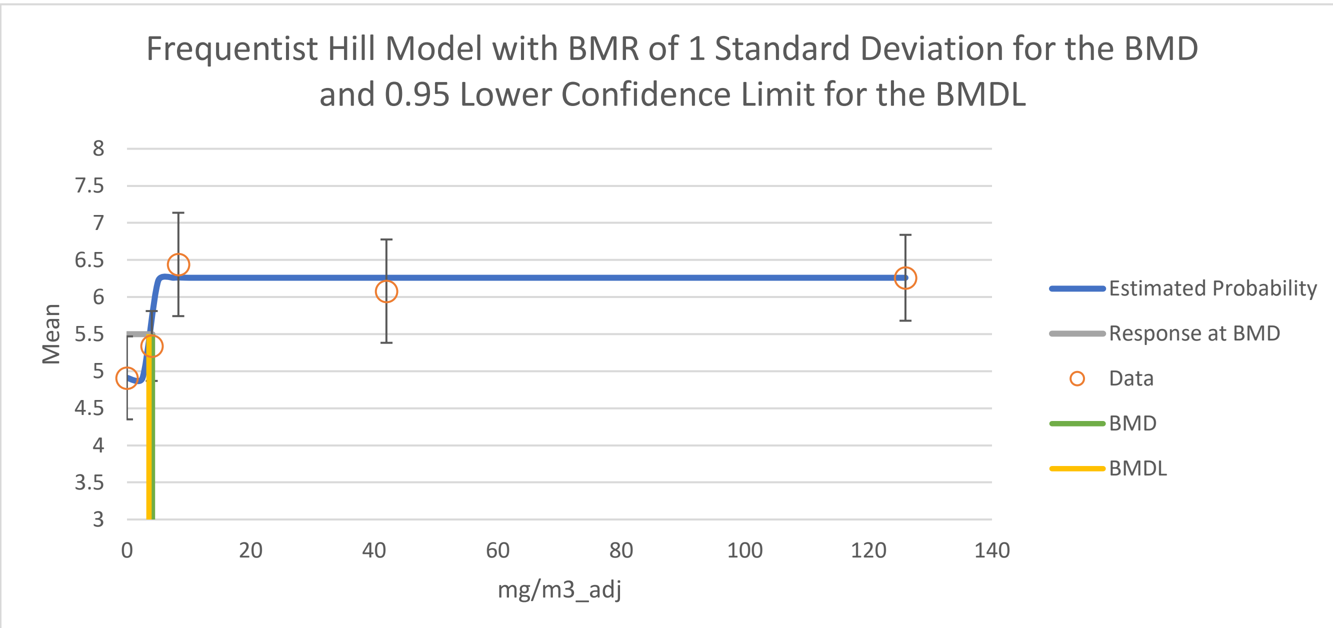

Figure 2-64. Plot of Response by Dose with Fitted Curve for the Selected Model (Hill) for Increased Serum Potassium Levels in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 12 Months and BMR of 1SD (Constant Variance)

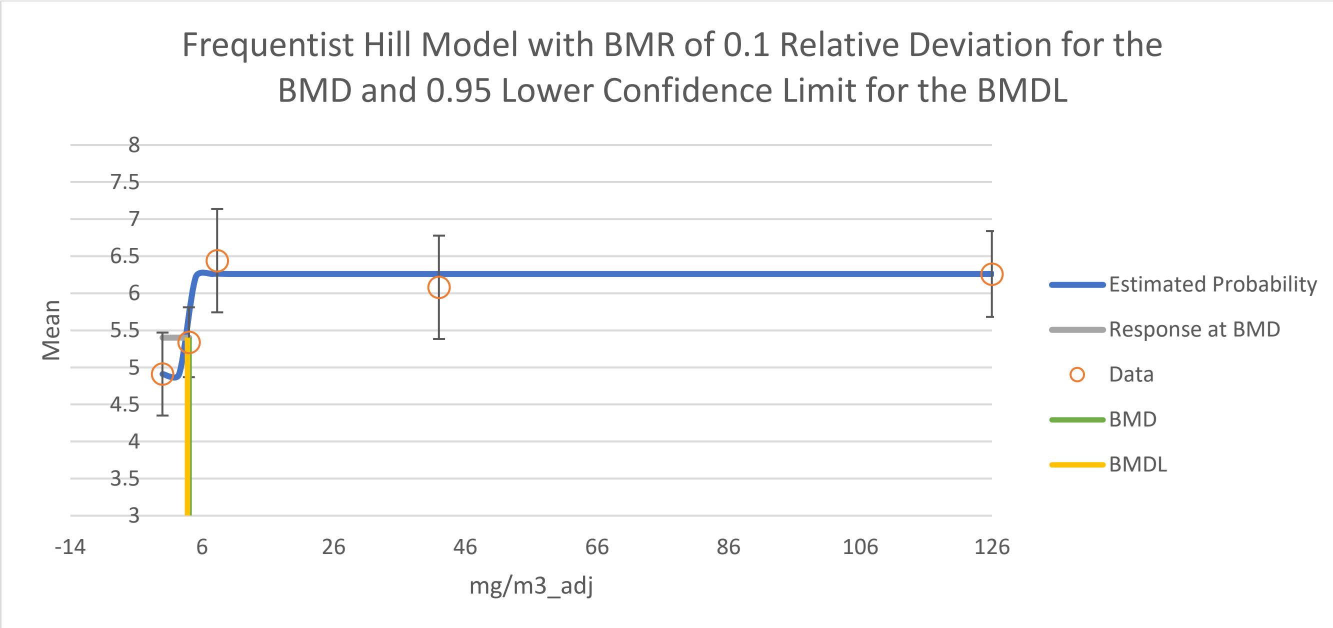

Figure 2-65. Plot of Response by Dose with Fitted Curve for the Selected Model (Hill) for Increased Serum Potassium Levels in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 12 Months and BMR of 10%RD (Constant Variance)

Model Results

Benchmark Dose	
BMD	4.113998297
BMDL	3.556136042
BMDU	6.037422863
AIC	79.23435408
Test 4 P-value	0.467568201
D.O.F.	2

Model Parameters

# of Parameters	5			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	4.909998383	0.208411252	4.50151983	5.31847693
v	1.350002887	0.240652145	0.87833335	1.82167243
k	4.172638129	0.201800737	3.77711595	4.56816031
n	Bounded	NA	NA	NA
alpha	0.347490412	0.026999944	0.29457149	0.40040933

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	8	4.909998383	4.91	4.91	0.58948317	0.57	0.57	7.76078E-06
4	8	5.340003496	5.34	5.34	0.58948317	0.48	0.48	-1.67735E-05
8.3	8	6.25999559	6.44	6.44	0.58948317	0.71	0.71	0.863687681
42	8	6.26000127	6.08	6.08	0.58948317	0.71	0.71	-0.863672616
126	8	6.26000127	6.26	6.26	0.58948317	0.59	0.59	-6.09342E-06

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-34.85696698	6	81.713934
A2	-34.01730185	10	88.0346037
A3	-34.85696698	6	81.713934
fitted	-35.61717704	4	79.2343541
R	-48.90125201	2	101.802504

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	29.76790032	8	0.0002323
2	1.679330262	4	0.79446879
3	1.679330262	4	0.79446879
4	1.520420112	2	0.4675682

Figure 2-66. Details Regarding the Selected Model (Hill) for Increased Serum Potassium Levels in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation for 12 Months

2.1.1.3.2.5 Serum Potassium Levels in Female Sprague-Dawley Rats – 12-Month Inhalation Exposure

Serum potassium levels were significantly increased in female rats exposed to 1,2-dichloroethane by inhalation for 12 months (seven hours per day, 5 days per week) (IRFMN, 1978). The exposure concentrations (reported in ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day and 7 days per week. The concentration and response data used for the modeling are presented in Table 2-55. 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 because EPA considers a 10 percent change in serum potassium levels to be biologically relevant.

Table 2-55. Serum Potassium Levels in Female Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 12-Month Inhalation Exposure Study

Adjusted Concentration (mg/m^3)	Number of Animals	Mean (mg%)	SD (mg%)
0	8	4.97	0.76
4	8	5.61	1.10
8.3	8	6.64	0.74
42	8	6.19	0.57
126	8	6.10	0.71

The BMD modeling results for increased serum potassium levels in female rats are summarized in Table 2-56. The constant variance model provided an adequate fit to the variance data. With the constant variance model applied, the Exponential 5 and Hill models provided adequate fit to the means (test 4 p-value > 0.1). At a BMR of one SD, the BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC (Hill) was selected. At a BMR of 10 percent RD, the BMDLs for the fit models were not sufficiently close (differed by > 3-fold); therefore, BMDS recommended the model with the lowest BMDL (Exponential 5). The Hill model was selected, however, because it has a lower AIC, has an estimated BMD/BMDL ratio within 3-fold, BMDL within 3-fold of lowest non-zero concentration, and is consistent with the selection for the one SD BMR.

Table 2-56. Summary of BMD Modeling Results for Increased Serum Potassium Levels in Female Rats Following Inhalation Exposure to 1,2-Dichloroethane for 12 Months[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	BMD 10%RD (mg/m^3)	BMDL 10%RD (mg/m^3)	Basis for Model Selection
	Test 4 p-value	AIC					
Exponential 3	-	-	-	-	-	-	The Exponential 5 and Hill models provided adequate fit to the means (test 4 p-value > 0.1). At a BMR of one SD, BMDLs for the fit models differed by < 3-fold; therefore, the model with the lowest AIC was selected (Hill). At a BMR of 10 percent RD, the BMDLs for the fit models differed by > 3-fold; therefore, BMDS recommended the model with the lowest BMDL (Exponential 5). The Hill model was selected, however, because it has a lower AIC, has a BMD/BMDL ratio within 3-fold, BMDL within 3-fold of lowest non-zero concentration, and is consistent with the selection for the one SD BMR.
Exponential 5	0.1254	102.2	4.2	1.9	3.7	1.0	
Hill	**0.3091**	**100.2**	**4.1**	**3.2**	**3.9**	**3.6**	
Polynomial Degree 3	0.0007	112.8	250	100	160	63	
Polynomial Degree 2	0.0007	112.8	250	100	160	63	
Power	0.0007	112.8	250	100	150	63	
Linear	0.0007	112.8	250	100	150	63	

[a] Selected model in bold.

Plots of the Hill model with BMRs of one SD and 10 percent RD are shown in Figure 2-67 and Figure 2-68, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-69 (BMD and BMDL shown are for BMR of one SD; the rest is applicable to both BMRs).

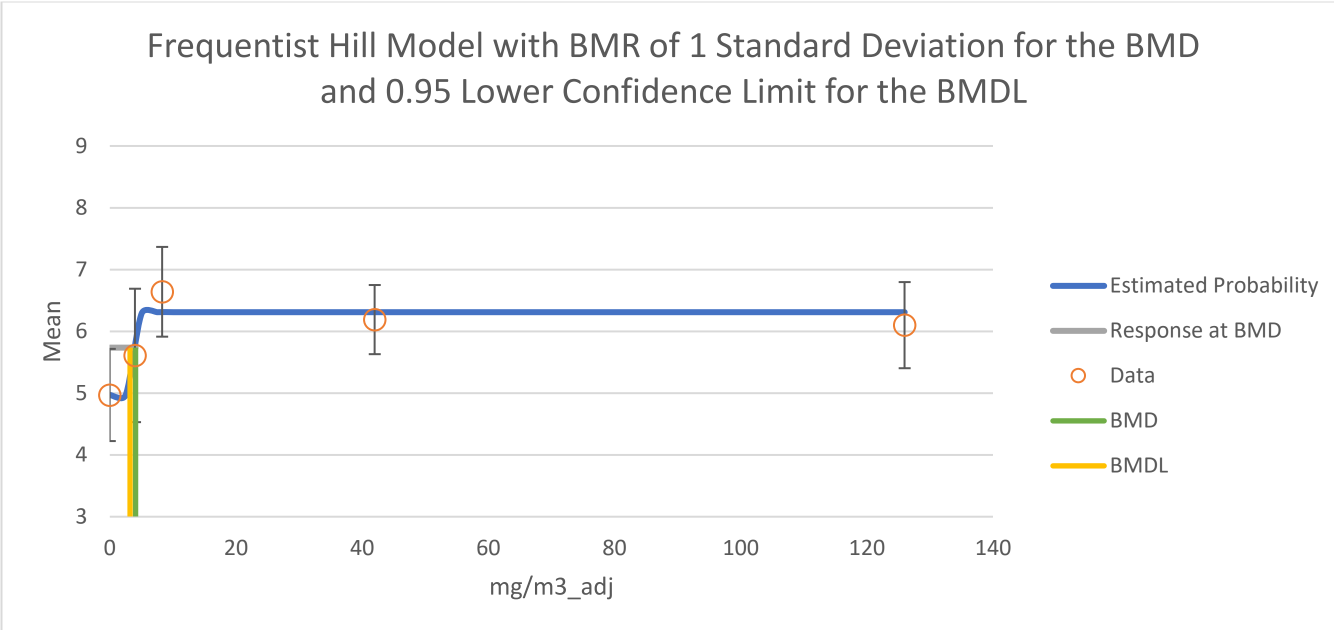

Figure 2-67. Plot of Response by Dose with Fitted Curve for the Selected Model (Hill) for Increased Serum Potassium Levels in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation for 12 Months and BMR of 1SD (Constant Variance)

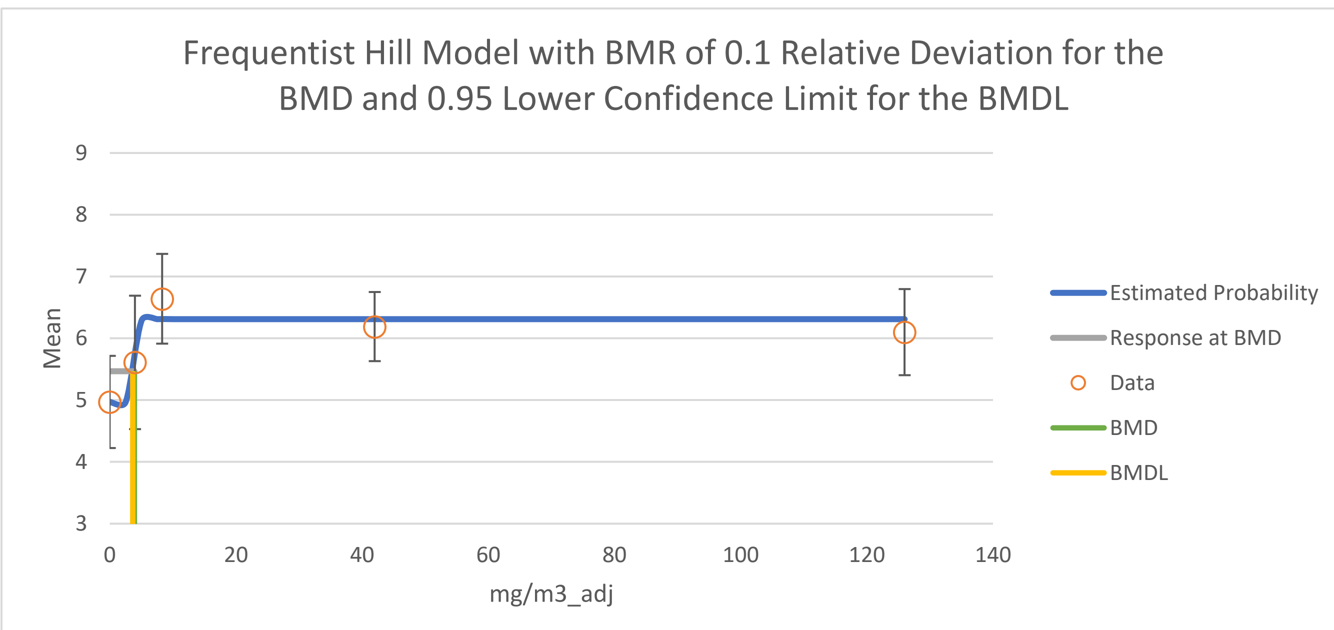

Figure 2-68. Plot of Response by Dose with Fitted Curve for the Selected Model (Hill) for Increased Serum Potassium Levels in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation for 12 Months and BMR of 10%RD (Constant Variance)

Model Results

Benchmark Dose	
BMD	4.085130438
BMDL	3.209977644
BMDU	5.384570286
AIC	100.2205383
Test 4 P-value	0.309094341
D.O.F.	2

Model Parameters				
# of Parameters	5			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	4.969999172	0.270915253	4.43901503	5.50098332
v	1.340001086	0.312822339	0.72688056	1.95312161
k	4.01996137	0.210192831	3.60799099	4.43193175
n	Bounded	NA	NA	NA
alpha	0.587215363	7.71E-02	0.43611298	0.73831774

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	8	4.969999172	4.97	4.97	0.76629979	0.76	0.76	3.05499E-06
4	8	5.610002828	5.61	5.61	0.76629979	1.1	1.1	-1.04376E-05
8.3	8	6.309997376	6.64	6.64	0.76629979	0.74	0.74	1.218045977
42	8	6.310000258	6.19	6.19	0.76629979	0.57	0.57	-0.442923242
126	8	6.310000258	6.1	6.1	0.76629979	0.71	0.71	-0.775114958

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-44.93616041	6	101.872321
A2	-43.00818559	10	106.016371
A3	-44.93616041	6	101.872321
fitted	-46.11026914	4	100.220538
R	-54.15242891	2	112.304858

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	22.28848664	8	0.00440857
2	3.855949636	4	0.42585182
3	3.855949636	4	0.42585182
4	2.348217473	2	0.30909434

Figure 2-69. Details Regarding the Selected Model (Hill) for Increased Serum Potassium Levels in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation for 12 Months

2.1.1.4 Developmental

2.1.1.4.1 Developmental Effects

Male pup weight at weaning (~21 days of age) was nonsignificantly decreased by ≥5 percent at the highest tested concentration in a one-generation reproduction study of 1,2-dichloroethane inhalation in rats when the data were limited to a very small subset of available pups (five pups from different F1b litters selected for organ weight measurements) (Rao et al., 1980). There was no decrease relative to controls in the corresponding selected F1b female pups. Overall, pup body weight data from all pups of both sexes in F1a and F1b litters recorded from birth through weaning were reported by the study authors not to show any differences from controls (data for whole group were not presented in the study).

2.1.1.4.1.1 Body Weight in Male Weanling F1b Rats

The data for body weight at weaning of the selected male F1b pups were modeled (Rao et al., 1980). The parental exposure concentrations (reported in ppm) were converted to units of mg/m^3 and duration adjusted to estimate an equivalent time-weighted average (TWA) inhalation concentration for parental animals (exposure was 6 hours per day, 5 days per week for 60 days prior to mating and then 7 days per week for 116 days, except that maternal exposure was stopped to allow for delivery and rearing of the young from GD 21 to postnatal day 4). The concentration and response data used for the modeling are presented in Table 2-57. 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 pup body weight change in a reproduction study.

Table 2-57. Body Weight of Selected F1b Male Weanling Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a One-Generation Developmental Study[a]

TWA Concentration (mg/m^3)	Number of Animals	Mean (g)	SD (g)
0	5	42	9
23	5	42	6
68	5	40	5
137	5	36	6

[a] Weanling body weight data presented are only for the small subset limited to male weanlings from F1B litters that were selected for organ weight measurements.

The BMD modeling results for body weight of selected F1b male rats at weaning are summarized in Table 2-58. The test for significant difference in responses and variances failed (test 1 p-value > 0.05), indicating that there is no clear dose-response present in the data. This means the additional modeling results presented here are suspect and should be interpreted with caution. 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 (Linear model) was selected.

Table 2-58. Summary of BMD Modeling Results for Decreased Body Weight of Selected F1b Male Weanling Rats Following Inhalation Exposure to 1,2-Dichloroethane in a One-Generation Reproduction Study (Constant Variance)[a]

Model	Goodness of Fit (Means)		BMD 1SD (mg/m^3)	BMDL 1SD (mg/m^3)	BMD 5%RD (mg/m^3)	BMDL 5%RD (mg/m^3)	BMD 10%RD (mg/m^3)	BMDL 10%RD (mg/m^3)	Basis for Model Selection
	Test 4 p-value	AIC							
Exponential 3	0.9195	136.2	130	110	69	23	110	46	All models, except for the Exponential 5 and Hill models, provided adequate fit to the means (test 4 p-value > 0.1). BMDLs for the fit models differed by < 3-fold; therefore, EPA chose the model with the lowest AIC. NOTE: This data set (small subset of the available data) is not representative of larger results in this study and BMD modeling no showed no clear dose-response present in these selected data. Although BMDs and BMDLs are presented here, they are suspect and should be interpreted with caution.
Exponential 5	NA	138.2	95	35	69	2	78	10	
Hill	NA	138.2	130	24	69	16	82	21	
Polynomial Degree 3	0.8615	136.2	130	67	70	25	110	51	
Polynomial Degree 2	0.8932	136.2	130	67	71	25	110	51	
Power	0.9144	136.2	130	67	69	25	110	51	
Linear	**0.9366**	**134.3**	**130**	**67**	**46**	**25**	**93**	**50**	

[a] Selected model in bold.

Plots of the Linear model with BMRs of one SD, five percent RD, and 10 percent RD are shown in Figure 2-70, Figure 2-71, and Figure 2-72, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-73 (BMD and BMDL shown are for BMR of one SD; the rest is applicable to all BMRs).

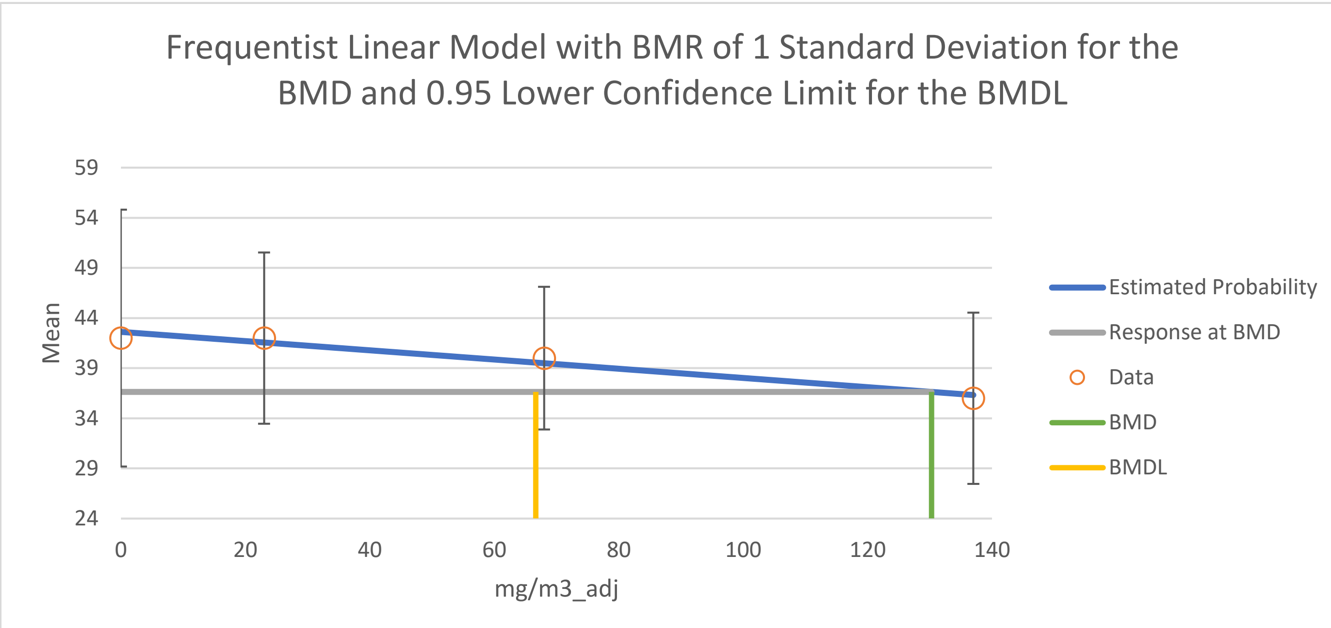

Figure 2-70. Plot of Response by Dose with Fitted Curve for the Selected Model (Linear) for Decreased Body Weight of Selected F1B Male Weanling Rats Exposed to 1,2-Dichloroethane Via Inhalation in a One-Generation Reproduction Study and BMR of 1SD (Constant Variance)

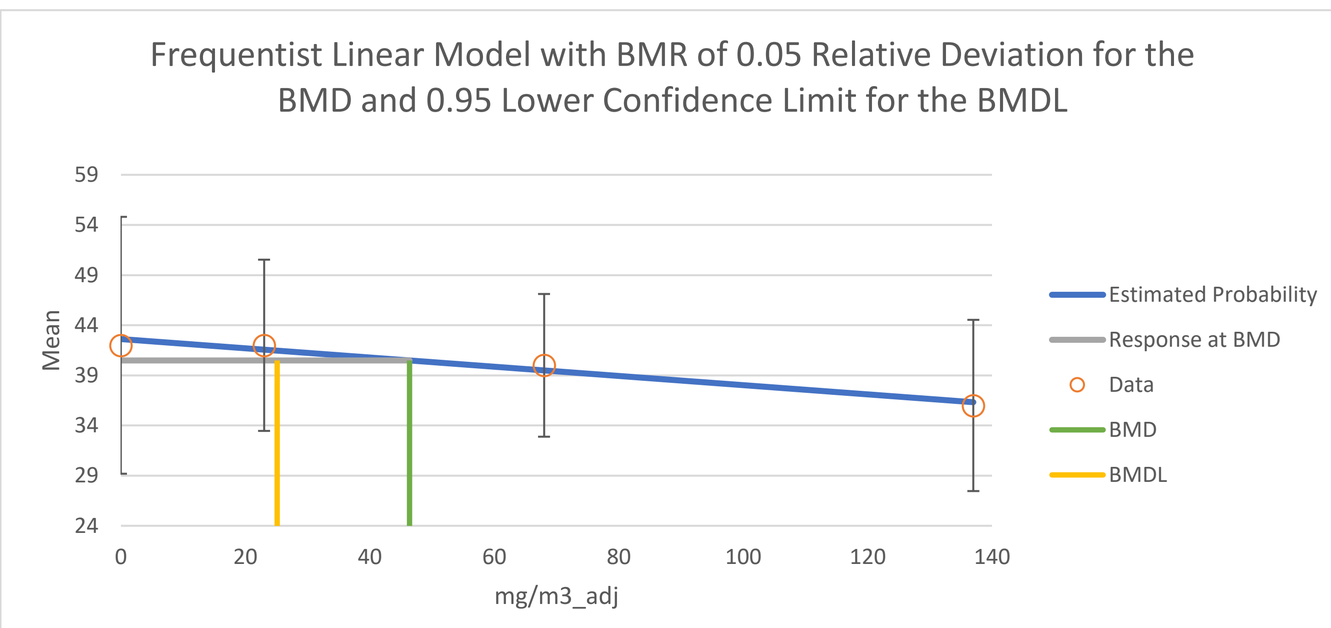

Figure 2-71. Plot of Response by Dose with Fitted Curve for the Selected Model (Linear) for Decreased Body Weight of Selected F1B Male Weanling Rats Exposed to 1,2-Dichloroethane Via Inhalation in a One-Generation Reproduction Study and BMR of 5%RD (Constant Variance)

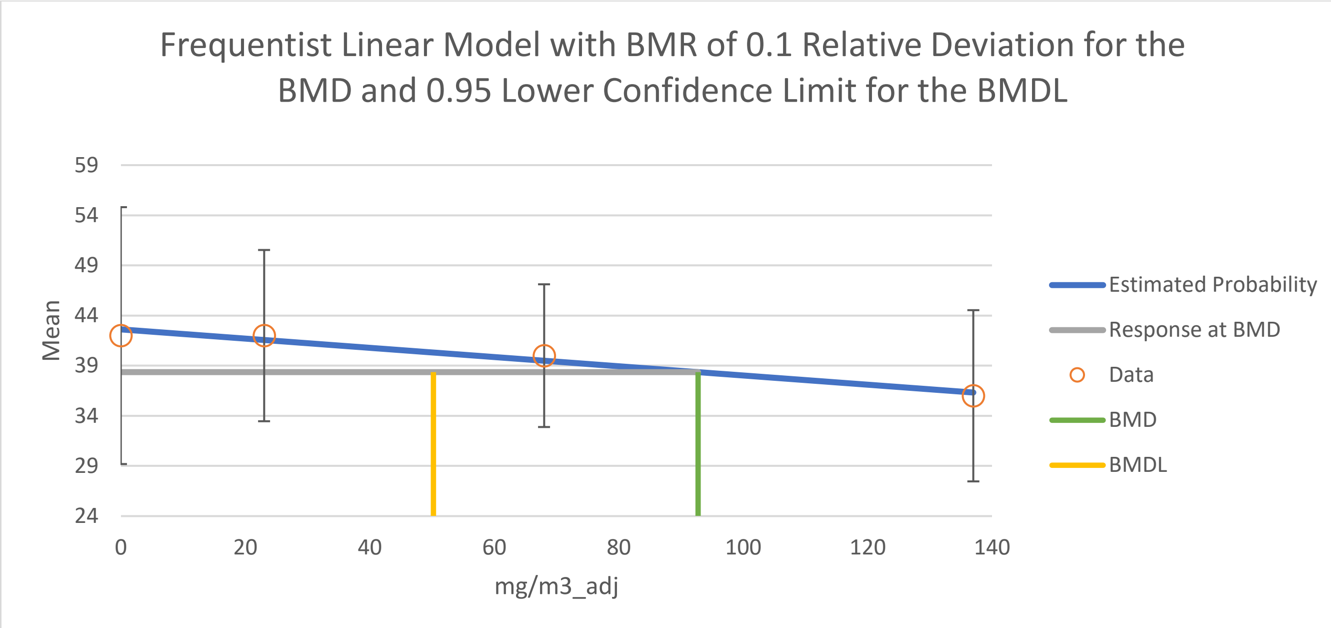

Figure 2-72. Plot of Response by Dose with Fitted Curve for the Selected Model (Linear) for Decreased Body Weight of Selected F1B Male Weanling Rats Exposed to 1,2-Dichloroethane Via Inhalation in a One-Generation Reproduction Study and BMR of 10%RD (Constant Variance)

Model Results

Benchmark Dose	
BMD	130.2879275
BMDL	66.67084085
BMDU	2727.30983
AIC	134.3353986
Test 4 P-value	0.936625044
D.O.F.	2

Model Parameters				
# of Parameters	3			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	42.61889064	1.980363222	38.73745	46.5003313
beta	-0.045945453	2.56E-02	-0.096131	0.00424011
alpha	35.83384612	4.06E+02	-760.01881	831.686503

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	5	42.61889064	42	42	5.98613783	9	9	-0.231181035
23	5	41.56214522	42	42	5.98613783	6	6	0.163556716
68	5	39.49459984	40	40	5.98613783	5	5	0.188787687
137	5	36.32436359	36	36	5.98613783	6	6	-0.121163103

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-64.10222704	5	138.204454
A2	-63.09824229	8	142.196485
A3	-64.10222704	5	138.204454
fitted	-64.16769929	3	134.335399
R	-65.65977234	2	135.319545

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	5.123060089	6	0.52812954
2	2.007969501	3	0.57075425
3	2.007969501	3	0.57075425
4	0.130944487	2	0.93662504

Figure 2-73. Details Regarding the Selected Model (Linear) for Decreased Body Weight of Selected F1B Male Weanling Rats Exposed to 1,2-Dichloroethane Via Inhalation in a One-Generation Reproduction Study

2.1.2 Oral Data

2.1.2.1 Acute

2.1.2.1.1 Mortality

Storer et al. (1984) provided data showing increased mortality in male mice following an acute oral exposure to 1,2-dichloroethane.

2.1.2.1.1.1 Mortality in Male B6C3F1 Mice – Single Oral Gavage

There was an increased incidence of mortality in male mice exposed to 1,2-dichloroethane following a single oral gavage exposure in an acute toxicity study by Storer et al. (1984). The dose and response data used for the modeling are presented in Table 2-59. Dichotomous models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to *BMD Technical Guidance* (U.S. EPA, 2012). A BMR of one percent ER was selected due to severity of the endpoint and a BMR of 20 percent ER was selected because it is near the low end of the observable range in the study.

Table 2-59. Incidence of Mortality in Male Mice and Associated Doses Selected for Dose-Response Modeling for 1,2-Dichloroethane from an Acute Oral Exposure Study

Dose (mg/kg)	Number of Animals	Incidence
0	5	0
200	5	0
300	5	0
400	5	2
500	5	4
600	5	4

The BMD modeling results for increased incidence of mortality in male rats are summarized in Table 2-60. With the BMRs of 10 and 20 percent applied, all models provided adequate fit to the data (chi-square p-value > 0.1). Despite the overall adequate fit, the Multistage 1-degree model was not considered further because this model provided poor fit in the lower portion of the dose-response curve, with scaled residuals of -1.3 and -1.6 at the two lowest doses. The BMDLs for the remaining models differed by < 3-fold and were considered sufficiently close; therefore, the model with the lowest AIC (Multistage 3-degree) was selected. Model outputs could not be generated by the BMDS using a BMR of one percent ER.

Table 2-60. Summary of BMD Modeling Results for Increased Incidence of Mortality in Male Mice Following a Single Oral Exposure to 1,2-Dichloroethane Using BMR of 10%ER or 20%ER[a]

Model	Goodness of Fit		BMD 10%ER (mg/kg)	BMDL 10%ER (mg/kg)	BMD 20%ER (mg/kg)	BMDL 20%ER (mg/kg)	Basis for Model Selection
	p-value	AIC					
Dichotomous Hill	0.9999	20.79	360	257	377	303	All models provided adequate fit to the data (chi-square p-value > 0.1). Despite the overall adequate fit, the Multistage 1-degree model was not considered further because this model provided poor fit in the lower portion of the dose-response curve, with scaled residuals of −1.3 and −1.6 at the two lowest doses. The BMDLs for the remaining models differed by less than 3-fold and were considered sufficiently close; therefore, EPA chose the model with the lowest AIC (Multistage 3-degree).
Gamma	0.8556	22.30	323	216	363	273	
Log-Logistic	0.8800	22.15	325	222	364	277	
Multistage 3	**0.9027**	**20.21**	**239**	**129**	**307**	**224**	
Multistage 2	0.5828	24.55	174	90.9	254	170	
Multistage 1	0.2148	28.84	74.6	45.6	158	96.5	
Weibull	0.8616	21.17	301	184	356	254	
Logistic	0.7493	22.94	316	199	366	275	
Log-Probit	0.8880	22.07	326	227	363	277	
Probit	0.7659	22.86	318	195	365	270	
Quantal Linear	0.2148	28.84	74.6	45.6	158	96.5	

[a] Selected model in bold.

Plots of the Multistage 3-degree model with BMRs of 10 percent ER and 20 percent ER are shown in Figure 2-74 and Figure 2-75, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-76 (BMD and BMDL shown are for BMR of 10 percent RD; the rest is applicable to both BMRs).

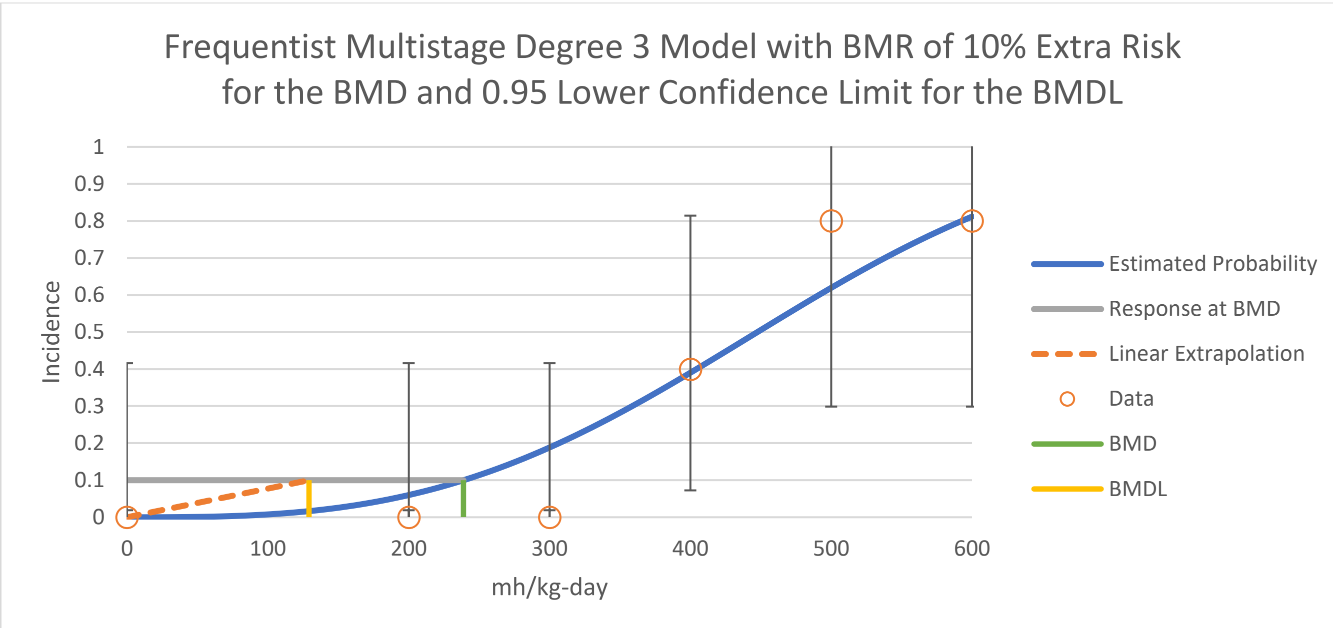

Figure 2-74. Plot of Response by Dose with Fitted Curve for the Selected Model (Multistage 3-Degree) for Incidence of Mortality in Male Mice Exposed to 1,2-Dichloroethane Via Oral Gavage in an Acute Toxicity Study and BMR of 10%ER

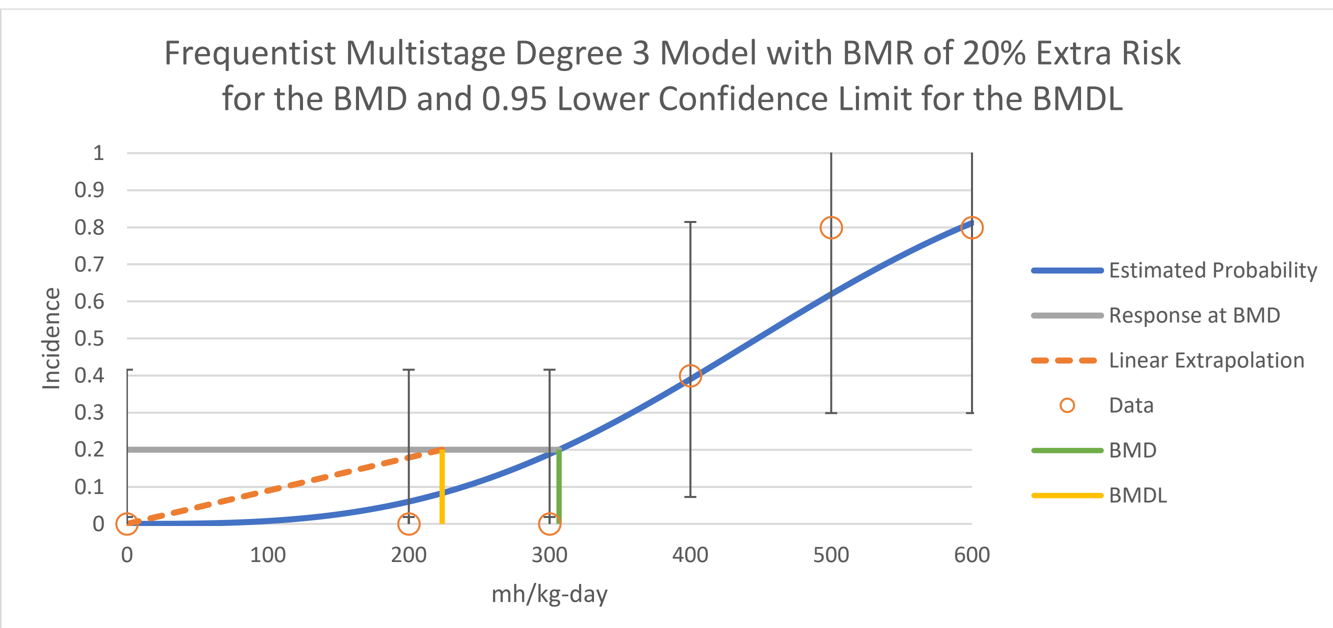

Figure 2-75. Plot of Response by Dose with Fitted Curve for the Selected Model (Multistage 3-Degree) for Incidence of Mortality in Male Mice Exposed to 1,2-Dichloroethane Via Oral Gavage in an Acute Toxicity Study and BMR of 20%ER

Model Results

Benchmark Dose	
BMD	238.9043391
BMDL	129.2249981
BMDU	291.4737157
AIC	20.20936618
P-value	0.902688778
D.O.F.	6
Chi^2	2.177325909
Slope Factor	0.000773844

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	Bounded	NA	NA	NA
b2	Bounded	NA	NA	NA
b3	Bounded	NA	NA	NA

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	7.61499E-08	0	5	-0.000276
200	0.059943491	0.299717454	0	5	-0.56465
300	0.188301704	0.941508522	0	5	-1.076998
400	0.390137775	1.950688873	2	5	0.0452101
500	0.619345703	3.096728513	4	5	0.8319579
600	0.811566932	4.057834662	4	5	-0.06614

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-8.36908257	6	-	-	NA
Fitted Model	-10.10468309	0	3.47120104	6	0.7477972
Reduced Model	-19.09542505	1	21.452685	5	0.0006651

Figure 2-76. Details Regarding the Selected Model (Multistage 3-Degree) for Increased Incidence of Mortality in Male Mice Exposed to 1,2-Dichloroethane Via Oral Gavage in an Acute Toxicity Study

2.1.2.1.2 Hepatic Effects

EPA identified hepatic endpoints in an acute oral gavage study in male mice for BMD modeling (Storer et al., 1984). Modeled results are presented for relative liver weight. Modeled results are not presented for serum ALT or LDH because neither the constant nor nonconstant variance models provided adequate fit to the variance data or because none of the models provided adequate fits to the means (test 4 p-value < 0.1) and viable results assuming either constant or nonconstant variance.

2.1.2.1.2.1 Relative Liver Weight in Male B6C3F1 Mice – Single Oral Gavage

Relative liver weights were significantly increased in male mice exposed to 1,2-dichloroethane following a single oral gavage exposure in an acute toxicity study by Storer et al. (1984). The dose and response data used for the modeling are presented in Table 2-61. 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 because EPA considers a 10 percent change in relative liver weight to be biologically significant.

Table 2-61. Relative Liver Weight in Male Mice and Associated Doses Selected for Dose-Response Modeling for 1,2-Dichloroethane from an Acute Oral Exposure Study

Dose (mg/kg)	Number of Animals	Mean (Liver Weight/100 g Body Weight)	SD (Liver Weight/100 g Body Weight)
0	5	4.26	0.14
200	5	4.21	0.27
300	5	4.47	0.20
400	3	5.10	0.58

The BMD modeling results for increased relative liver weight in male mice are summarized in Table 2-62. 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 and using a BMR of one SD, the Exponential 3, Exponential 5, and Power models provided an adequate fit to the means (test 4 p-value > 0.1). BMD computations failed for the Polynomial 2- and 3-degree and Linear models. 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 a BMR of 10 percent RD was applied, the same models plus the Polynomial 3-degree provided an adequate fit to the means (test 4 p-value > 0.1). The BMDLs among these models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Polynomial 3-degree).

Table 2-62. Summary of BMD Modeling Results for Increased Relative Liver Weight in Male Mice Following a Single Oral Exposure to 1,2-Dichloroethane (Nonconstant Variance)[a]

Model	Goodness of Fit		BMD 1SD (mg/kg)	BMDL 1SD (mg/kg)	BMD 10%RD (mg/kg)	BMDL 10%RD (mg/kg)	Basis for Model Selection
	Test 4 p-value	AIC					
Exponential 3	0.7631	7.354	290	220	345	300	Using a BMR of one SD, the Exponential 3, Exponential 5, and Power models provided an adequate fit to the means (test 4 p-value > 0.1). BMDLs for the fit models differed by < 3-fold; therefore, EPA chose the model with the lowest AIC (Exponential 5). Using a BMR of 10 percent RD, the same models plus the Polynomial 3-degree provided an adequate fit to the means (test 4 p-value > 0.1). BMDLs among these models differed by < 3-fold; therefore, the EPA chose the model with the lowest AIC (Polynomial 3-degree).
Exponential 5	**0.9858**	**7.263**	**297**	**272**	315	298	
Hill	NA	9.263	297	278	319	310	
Polynomial Degree 3	**0.6308**	**4.991**	**-**	**-**	**326**	**285**	
Polynomial Degree 2	0.0965	9.939	-	-	313	259	
Power	0.7732	7.346	290	252	345	300	
Linear	0.0073	15.10	-	-	307	209	

[a] Selected model in bold.

A Plot of the Exponential 5 model with a BMR of one SD is shown in Figure 2-77 and a plot of the Polynomial 3-degree model with a BMR of 10 percent RD is shown in Figure 2-78. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood for the Exponential 5 model with BMR of one SD are shown in Figure 2-79 and additional modeling details for the Polynomial 3-degree model with BMR of 10 percent RD are shown in Figure 2-80.

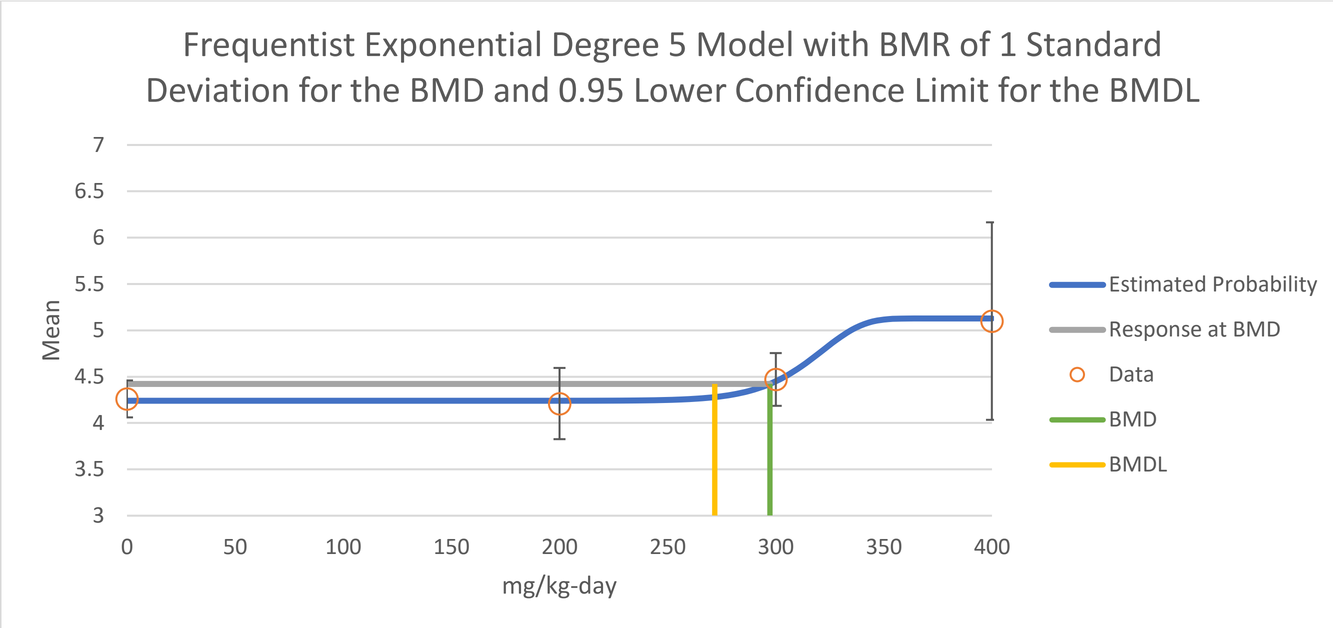

Figure 2-77. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 5) for Increased Relative Liver Weight in Male Mice Exposed to 1,2-Dichloroethane Via Oral Gavage in an Acute Toxicity Study and BMR of 1SD (Nonconstant Variance)

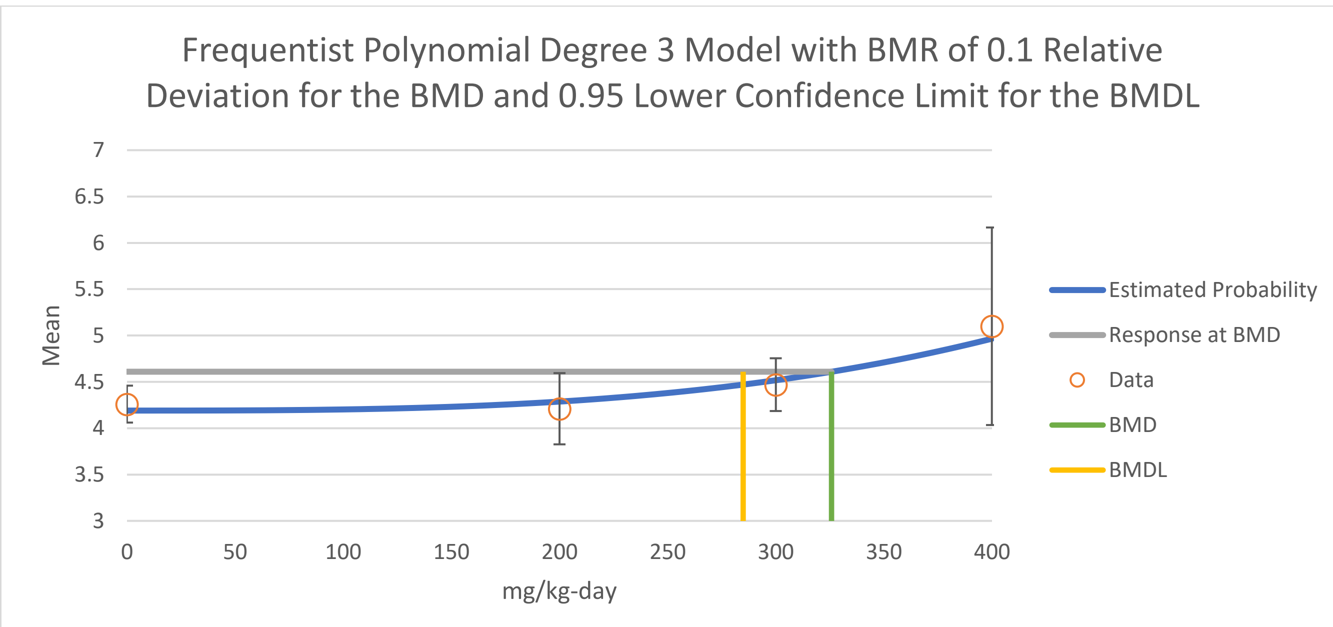

Figure 2-78. Plot of Response by Dose with Fitted Curve for the Selected Model (Polynomial 3-Degree) for Increased Relative Liver Weight in Male Mice Exposed to 1,2-Dichloroethane Via Oral Gavage in an Acute Toxicity Study and BMR of 10%RD (Nonconstant Variance)

Model Results

Benchmark Dose	
BMD	297.3046064
BMDL	271.7913769
BMDU	334.4904423
AIC	7.263445078
Test 4 P-value	0.985787525
D.O.F.	1

Model Parameters				
# of Parameters	6			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
a	4.239995767	5.76E-02	4.12701127	4.35298026
b	0.003099096	1.10E-04	0.00288322	0.00331498
c	1.209416148	5.05E-02	1.11038106	1.30845124
d	Bounded	NA	NA	NA
rho	9.32012481	5.00E+00	-0.4827733	19.123023
log-alpha	-16.87383537	7.44E+00	-31.448574	-2.2990966

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	5	4.239995767	4.26	4.26	0.18174197	0.14	0.14	0.246122706
200	5	4.240157615	4.21	4.21	0.1817743	0.27	0.27	-0.370979159
300	5	4.449696613	4.47	4.47	0.22759008	0.2	0.2	0.199480371
400	3	5.127919347	5.1	5.1	0.44082218	0.58	0.58	-0.109698943

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-1.189417326	5	12.3788347
A2	2.79948267	8	10.4010347
A3	1.368436124	6	9.26312775
fitted	1.368277461	5	7.26344508
R	-9.233982277	2	22.4679646

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	24.06692989	6	0.00050766
2	7.977799991	3	0.04647275
3	2.862093091	2	0.23905861
4	0.000317326	1	0.98578752

Figure 2-79. Details Regarding the Selected Model (Exponential 5) for Increased Relative Liver Weight in Male Mice Exposed to 1,2-Dichloroethane Via Oral Gavage in an Acute Toxicity Study with a BMR of 1SD

Model Results

Benchmark Dose	
BMD	325.7980347
BMDL	284.922869
BMDU	377.6371666
AIC	4.990841016
Test 4 P-value	0.630790181
D.O.F.	3

Model Parameters				
# of Parameters	6			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	4.190234558	0.058404416	4.07576401	4.30470511
beta	Bounded	NA	NA	NA
beta2	Bounded	NA	NA	NA
beta3	Bounded	NA	NA	NA
rho	10.15179628	0.240897127	9.67964658	10.623946
alpha	1.523E-08	1.83E-20	1.523E-08	1.523E-08

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	5	4.190234558	4.26	4.26	0.177733	0.14	0.14	0.877722612
200	5	4.287170082	4.21	4.21	0.1996107	0.27	0.27	-0.864470458
300	5	4.517391953	4.47	4.47	0.26031146	0.2	0.2	-0.407095508
400	3	4.965718753	5.1	5.1	0.42080801	0.58	0.58	0.552703217

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-1.189417326	5	12.3788347
A2	2.79948267	8	10.4010347
A3	1.368436124	6	9.26312775
fitted	0.504579492	3	4.99084102
R	-9.233982277	2	22.4679646

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	24.06692989	6	0.00050766
2	7.977799991	3	0.04647275
3	2.862093091	2	0.23905861
4	1.727713264	3	0.63079018

Figure 2-80. Details Regarding the Selected Model (Polynomial 3-Degree) for Increased Relative Liver Weight in Male Mice Exposed to 1,2-Dichloroethane Via Oral Gavage in an Acute Toxicity Study with a BMR of 10%RD

2.1.2.1.3 Renal Effects

For acute oral exposure, EPA selected two renal endpoints for quantitative dose-response analysis with BMDS, including relative kidney weights and BUN levels following a single oral gavage exposure in male mice (Storer et al., 1984). For both data sets, only data for the control and three lowest doses (0, 200, 300, and 400 mg/kg) were modeled due to high mortality (four of five) at the two highest tested doses (500 and 600 mg/kg). EPA modeled relative kidney weight change because a statistically and biologically significant change was identified. Though not statistically significant, EPA modeled BUN in male mice from the acute oral Storer et al. (1984) study because a dose-related trend was evident in the data.

2.1.2.1.3.1 Relative Kidney Weight in Male B6C3F1 Mice – Single Oral Gavage

Relative kidney weight was significantly increased in male mice exposed to 1,2-dichloroethane following a single oral gavage exposure in an acute toxicity study by Storer et al. (1984). The dose and response data used for the modeling are presented in Table 2-63. 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 because EPA considers a 10 percent change in relative kidney weight to be biologically significant.

Table 2-63. Increased Relative Kidney Weight in Male Mice and Associated Doses Selected for Dose-Response Modeling for 1,2-Dichloroethane from an Oral Exposure Study

Dose (mg/kg)	Number of Animals	Mean (Kidney Weight/100 g Body Weight)	SD (Kidney Weight/100 g Body Weight)
0	5	1.50	0.09
200	5	1.58	0.19
300	5	1.69	0.09
400	3	1.75	0.08

The BMD modeling results for increased relative kidney weight in male mice are summarized in Table 2-64. The constant variance model provided an adequate fit to the variance data. With the constant variance model applied, all models except Exponential 5 and Hill 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 (Polynomial 2-degree) was selected.

Table 2-64. Summary of BMD Modeling Results for Increased Relative Kidney Weight in Male Mice Following a Single Oral Exposure to 1,2-Dichloroethane (Constant Variance)[a]

Model	Goodness of Fit		BMD 1SD (mg/kg)	BMDL 1SD (mg/kg)	BMD 10%RD (mg/kg)	BMDL 10%RD (mg/kg)	Basis for Model Selection
	Test 4 p-value	AIC					
Exponential 3	0.6040	−19.77	221	124	271	162	All models except Exponential 5 and Hill provided adequate fit to the means (test 4 p-value > 0.1). BMDLs for the fit models differed by < 3-fold; therefore, EPA chose the model with the lowest AIC.
Exponential 5	NA	−18.04	228	94.9	262	128	
Hill	NA	−18.04	226	89.1	260	124	
Polynomial Degree 3	0.8476	−21.71	217	117	270	153	
Polynomial Degree 2	**0.8641**	**−21.74**	**219**	**117**	**270**	**153**	
Power	0.6148	−19.78	222	118	271	154	
Linear	0.7377	−21.43	179	115	235	150	

[a] Selected model in bold.

Plots of the Polynomial 2-degree model with BMRs of one SD and 10 percent RD are shown in Figure 2-81 and Figure 2-82, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-83 (BMD and BMDL shown are for BMR of 10 percent RD; the rest is applicable to both BMRs).

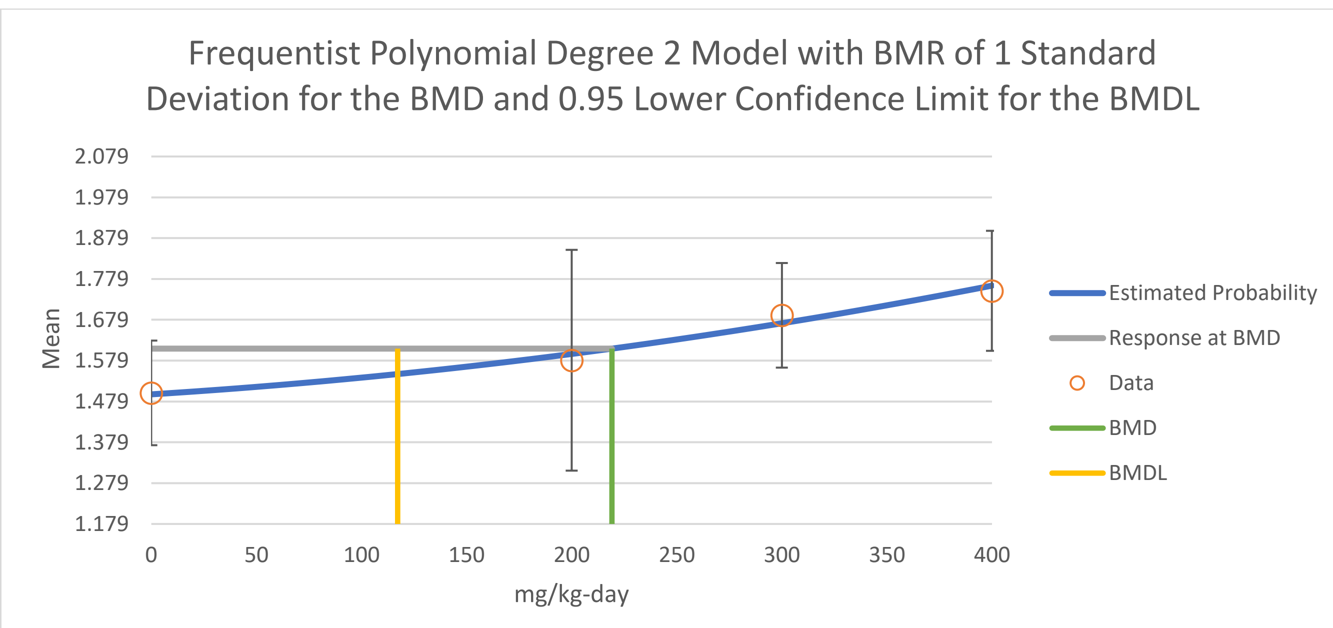

Figure 2-81. Plot of Response by Dose with Fitted Curve for the Selected Model (Polynomial 2-Degree) for Increased Relative Kidney Weight in Male Mice Exposed to 1,2-Dichloroethane Via Oral Gavage in an Acute Toxicity Study and BMR of 1SD (Constant Variance)

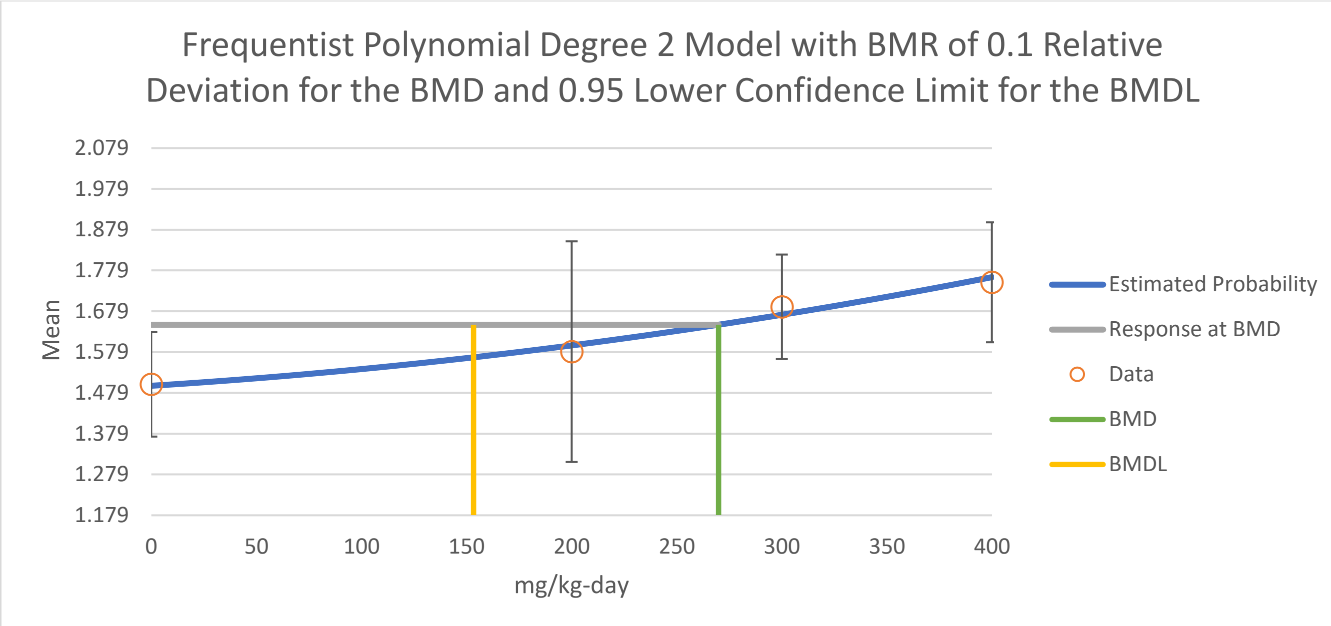

Figure 2-82. Plot of Response by Dose with Fitted Curve for the Selected Model (Polynomial 2-Degree) for Increased Relative Kidney Weight in Male Mice Exposed to 1,2-Dichloroethane Via Oral Gavage in an Acute Toxicity Study and BMR of 10%RD (Constant Variance)

Model Results

Benchmark Dose	
BMD	219.1614151
BMDL	117.214416
BMDU	380.6486941
AIC	-21.74414133
Test 4 P-value	0.8640863
D.O.F.	2

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	1.496455497	4.99E-02	1.39871499	1.594196
beta	0.000323664	5.94E-04	-0.0008398	0.00148709
beta2	Bounded	NA	NA	NA
alpha	0.012545321	5.25E-05	0.01244245	0.01264819

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	5	1.496455497	1.5	1.5	0.1120059	0.09	0.09	0.070761898
200	5	1.59539172	1.58	1.58	0.1120059	0.19	0.19	-0.307277867
300	5	1.67051238	1.69	1.69	0.1120059	0.09	0.09	0.389047757
400	3	1.762734739	1.75	1.75	0.1120059	0.08	0.08	-0.196929058

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	14.0181533	5	-18.036307
A2	16.70117875	8	-17.402358
A3	14.0181533	5	-18.036307
fitted	13.87207067	3	-21.744141
R	9.252043047	2	-14.504086

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	14.89827141	6	0.02106286
2	5.366050911	3	0.14687341
3	5.366050911	3	0.14687341
4	0.292165262	2	0.8640863

Figure 2-83. Details Regarding the Selected Model (Polynomial 2-Degree) for Increased Relative Kidney Weight in Male Mice Exposed to 1,2-Dichloroethane Via Oral Gavage in an Acute Toxicity Study

2.1.2.1.3.2 Blood Urea Nitrogen in Male B6C3F1 Mice – Single Oral Gavage

BUN levels appeared to show a dose-related increasing trend (not statistically significant) in male mice exposed to 1,2-dichloroethane following a single oral gavage exposure in an acute toxicity study by Storer et al. (1984). The doses and response data used for the modeling are presented in Table 2-65. 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.

Table 2-65. Blood Urea Nitrogen in Male Mice and Associated Doses Selected for Dose-Response Modeling for 1,2-Dichloroethane from an Oral Exposure Study

Dose (mg/kg)	Number of Animals	Mean (mg urea nitrogen/100 mL serum)	SD (mg urea nitrogen/100 mL serum)
0	5	13.4	2.3
200	5	16.6	15.1
300	5	18.5	10.3
400	3	26.2	21.8

The BMD modeling results for increased BUN levels in male mice are summarized in Table 2-66. 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 and using a BMR of one SD, only the Power model provided adequate fit to the means (test 4 p-value > 0.1) and a viable result; this model was selected for the one SD BMR. When a BMR of 10 percent RD was applied, all models, except for the Exponential 3 model, provided an adequate fit to the means (test 4 p-value > 0.1); however, the BMDL computation failed for the Hill model and BMDs and BMDLs for the Exponential 5 model were 10 times lower than the lowest non-zero dose and, therefore, not considered viable. The BMDLs for the remaining fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected for the 10 percent RD BMR (Linear).

Table 2-66. Summary of BMD Modeling Results for Increased Blood Urea Nitrogen in Male Mice Following a Single Oral Exposure to 1,2-Dichloroethane (Nonconstant Variance)[a]

Model	Goodness of Fit		BMD 1SD (mg/kg)	BMDL 1SD (mg/kg)	BMD 10%RD (mg/kg)	BMDL 10%RD (mg/kg)	Basis for Model Selection
	Test 4 p-value	AIC					
Exponential 3	0.0642	138.0	156	70.9	68.0	37.7	Using a BMR of one SD, only the Power model provided adequate fit to the means (test 4 p-value > 0.1) and a viable result; this model was selected for the one SD BMR. With a BMR of 10 percent RD, all models, except for the Exponential 3 model, provided an adequate fit to the means (test 4 p-value > 0.1); however, the Hill and Exponential 5 models were not viable. The BMDLs for the remaining viable models differed by < 3-fold; therefore, the model with the lowest AIC was selected for the 10 percent RD BMR (Linear).
Exponential 5	0.3474	134.6	35.4	0.814	19.1	0.712	
Hill	0.1560	136.5	24.7	0	12.7	0	
Polynomial Degree 3	0.1170	136.824	-	-	54.3	25.8	
Polynomial Degree 2	0.1168	136.827	-	-	53.9	25.8	
Power	**0.1072**	**136.999**	**106**	**42.8**	46.6	25.3	
Linear	**0.1171**	**136.822**	**-**	**-**	**54.9**	**25.8**	

[a] Selected model in bold.

A plot of the Power model with a BMR of one SD is shown in Figure 2-84 and a plot of the Linear model with a BMR of 10 percent RD is shown in Figure 2-85. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood for the Power model with BMR of one SD are shown in Figure 2-86 and additional modeling details for the Linear model with BMR of 10 percent RD are shown in Figure 2-87.

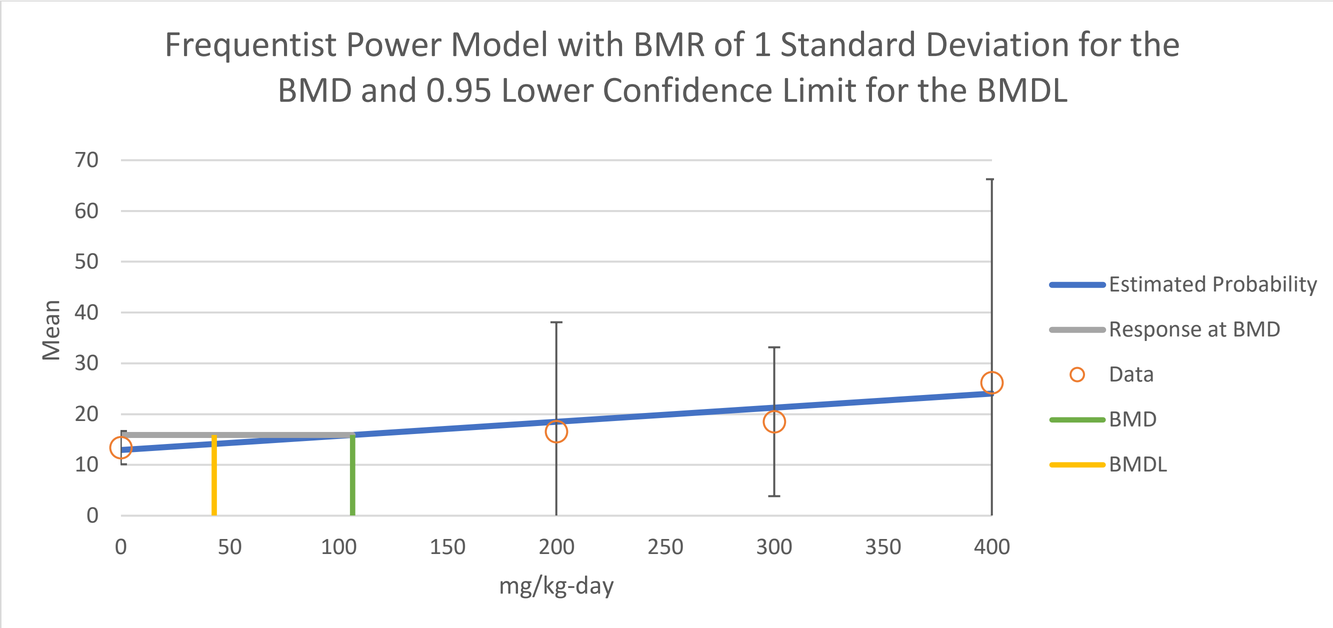

Figure 2-84. Plot of Response by Dose with Fitted Curve for the Selected Model (Power) for Increased Blood Urea Nitrogen in Male Mice Exposed to 1,2-Dichloroethane Via Oral Gavage in an Acute Toxicity Study and BMR of 1SD (Nonconstant Variance)

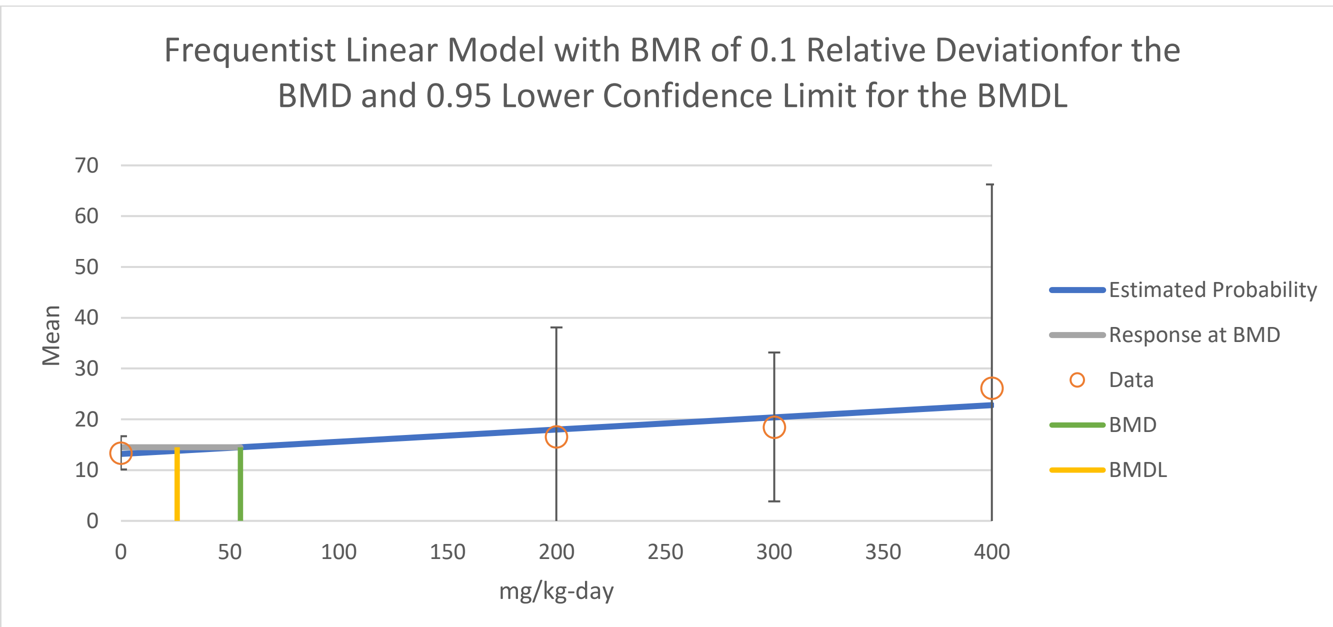

Figure 2-85. Plot of Response by Dose with Fitted Curve for the Selected Model (Linear) for Increased Blood Urea Nitrogen in Male Mice Exposed to 1,2-Dichloroethane Via Oral Gavage in an Acute Toxicity Study and BMR of 10%RD (Nonconstant Variance)

Model Results

Benchmark Dose	
BMD	106.3910977
BMDL	42.83193912
BMDU	108.5933934
AIC	136.9992953
Test 4 P-value	0.107170237
D.O.F.	2

Model Parameters				
# of Parameters	5			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	12.93552585	1.295836951	10.3957321	15.4753196
v	0.02778794	1.24E-02	0.00350199	0.05207389
n	Bounded	NA	NA	NA
rho	6.354251024	2.97E+00	0.54176928	12.1667328
alpha	7.533E-07	4.75E-12	7.5329E-07	7.5331E-07

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	5	12.93552585	13.4	13.4	2.95638946	2.3	2.3	0.351305461
200	5	18.49311389	16.6	16.6	9.2030968	15.1	15.1	-0.459968144
300	5	21.27190791	18.5	18.5	14.3579284	10.3	10.3	-0.431690029
400	3	24.05070193	26.2	26.2	21.2080278	21.8	21.8	0.175532279

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-69.2249334	5	148.449867
A2	-61.90358802	8	139.807176
A3	-62.26631094	6	136.532622
fitted	-64.49964765	4	136.999295
R	-70.38699059	2	144.773981

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	16.96680515	6	0.00940602
2	14.64269077	3	0.00214891
3	0.725445834	2	0.6957792
4	4.466673423	2	0.10717024

Figure 2-86. Details Regarding the Selected Model (Power) for Increased BUN Levels in Male Mice Exposed to 1,2-Dichloroethane Via Oral Gavage in an Acute Toxicity Study (BMR of 1SD)

Model Results

Benchmark Dose	
BMD	54.86685634
BMDL	25.80392856
BMDU	112.6650676
AIC	136.8221271
Test 4 P-value	0.117097004
D.O.F.	2

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	13.17889964	1.067007319	11.0876037	15.2701956
beta	0.024019782	8.14E-03	0.0080685	0.03997107
rho	7.756854984	3.18E-01	7.1330916	8.38061837
alpha	1.523E-08	1.81E-20	1.523E-08	1.523E-08

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	5	13.17889964	13.4	13.4	2.72094491	2.3	2.3	0.181699903
200	5	17.98285606	16.6	16.6	9.08297293	15.1	15.1	-0.340434809
300	5	20.38483427	18.5	18.5	14.7707533	10.3	10.3	-0.285335316
400	3	22.78681248	26.2	26.2	22.7523877	21.8	21.8	0.259832695

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-69.2249334	5	148.449867
A2	-61.90358802	8	139.807176
A3	-62.26631094	6	136.532622
fitted	-64.41106353	4	136.822127
R	-70.38699059	2	144.773981

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	16.96680515	6	0.00940602
2	14.64269077	3	0.00214891
3	0.725445834	2	0.6957792
4	4.289505196	2	0.117097

Figure 2-87. Details Regarding the Selected Model (Linear) for Increased BUN Levels in Male Mice Exposed to 1,2-Dichloroethane Via Oral Gavage in an Acute Toxicity Study (BMR of 10%RD)

2.1.2.2 Short-term/Intermediate

2.1.2.2.1 Mortality

NTP (1991) provided data showing increased mortality in rats following intermediate oral exposure to 1,2-dichloroethane.

2.1.2.2.1.1 Mortality in F344 Male Rats – 13-Week Gavage

There was an increased incidence of mortality in male rats exposed to 1,2-dichloroethane by gavage for 13 weeks (5 days per week) (NTP, 1991). The administered doses were duration adjusted to estimate an equivalent oral dose for animals exposed for 7 days per week. The dose and response data used for the modeling are presented in Table 2-67. Dichotomous models were used to fit dose-response data.

A BMR of 10 percent ER was chosen according to *BMD Technical Guidance* (U.S. EPA, 2012). BMRs of five and one percent ER were also selected due to severity of the endpoint.

Table 2-67. Incidence of Mortality in Male Rats and Associated Doses Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 13-Week Oral Exposure Study

Adjusted Dose (mg/kg-day)	Number of Animals	Incidence
0	10	0
21	10	0
43	10	0
86	10	0
171	10	10
343	10	10

The BMD modeling results for mortality in male rats are summarized in Table 2-68. All models provided adequate fit to the data (chi-square p-value > 0.1) except for the Multistage 1-degree/Quantal Linear model. The BMD computation failed for the Weibull model because the lower limit included zero; therefore, this model was unusable. With a BMR of 10 percent ER applied, the BMDLs for the remaining models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC (Logistic) was selected. With BMRs of five and one percent ER applied (below the observable range in the study), model uncertainty increased and the BMDLs of the fit models were not sufficiently close (differed by > 3-fold); therefore, the BMDS recommended the model with the lowest BMDL (Multistage 2-degree).

This data set is not well suited for BMD modeling; there are no data points with incidence between 0 and 100 percent, and no data to inform the shape of the curve at the region of interest, as defined by the BMR. As a result, the different models provide a broad range of BMD and BMDL estimates. For the five and one percent ER BMRs, selection of the low end of the range to represent the BMDL is not among the more realistic possibilities and involves extrapolation below the observable range in the study (1/10 = 10 percent) to generate BMD estimates well below the lowest tested dose where any mortality was observed.

Table 2-68. Summary of BMD Modeling Results for Increased Incidence of Mortality in Male Rats Following Oral Exposure to 1,2-Dichloroethane for 13 Weeks[a]

Model	Goodness of Fit (Means)		BMD 1%ER (mg/kg-day)	BMDL 1%ER (mg/kg-day)	BMD 5%ER (mg/kg-day)	BMDL 5%ER (mg/kg-day)	BMD 10%ER (mg/kg-day)	BMDL 10%ER (mg/kg-day)	Basis for Model Selection
	p-value	AIC							
Dichotomous Hill	0.9997	4.099	95	64	100	78	110	84	All models provided adequate fit to the data (chi-square p-value > 0.1) except for the Multistage 1-degree/Quantal Linear model. The BMD computation failed for the Weibull model. With a BMR of 10 percent ER applied, BMDLs for the remaining models differed by < 3-fold; therefore, EPA chose the model with the lowest AIC (Logistic). With BMRs of five and one percent ER applied, BMDLs of the fit models differed by > 3-fold; therefore, EPA chose the model with the lowest BMDL (Multistage 2-degree) for this BMR. NOTE: This data set is not well suited for BMD modeling and the results for BMR = five percent ER and one percent ER are highly unrealistic.
Gamma	0.9010	5.080	66	51	80	65	88	73	
Log-Logistic	0.9997	4.099	95	64	100	78	110	84	
Multistage 3	0.5659	8.699	29	9.0	50	34	63	50	
Multistage 2	**0.1217**	**17.01**	**14**	**6.0**	**32**	**22**	47	35	
Multistage 1	0.0028	31.61	1.7	1.2	8.7	5.9	18	12	
Weibull	0.9101	4.941	57	0	78	0	90	0	
Logistic	**1.000**	**2.098**	94	51	100	74	**110**	**83**	
Log-Probit	1.000	4.000	110	68	110	79	120	84	
Probit	0.9922	4.518	84	54	97	72	100	81	
Quantal Linear	0.0028	31.61	1.7	1.2	8.7	5.9	18	12	

[a] Selected model in bold.

A plot of the Logistic model with a BMR of 10 percent ER is shown in Figure 2-88 and plots of the Multistage (2-degree) model for BMRs of five percent ER and five percent ER are shown in Figure 2-89 and Figure 2-90, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood for the Logistic model with BMR of 10 percent ER are shown in Figure 2-91; additional modeling details for the Multistage 2-degree model are shown in Figure 2-92 (BMD and BMDL shown are for BMR of five percent ER; the rest is applicable to both BMRs).

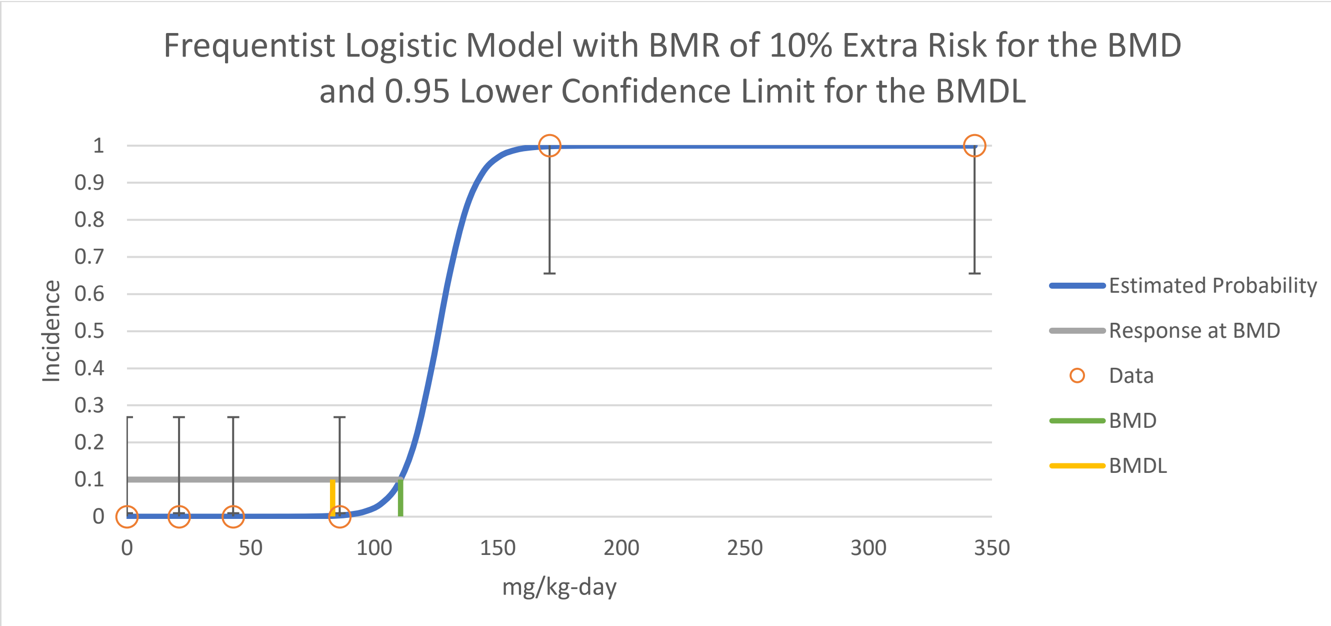

Figure 2-88. Plot of Response by Dose with Fitted Curve for the Selected Model (Logistic Model) for Mortality in Male Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks and BMR of 10%ER

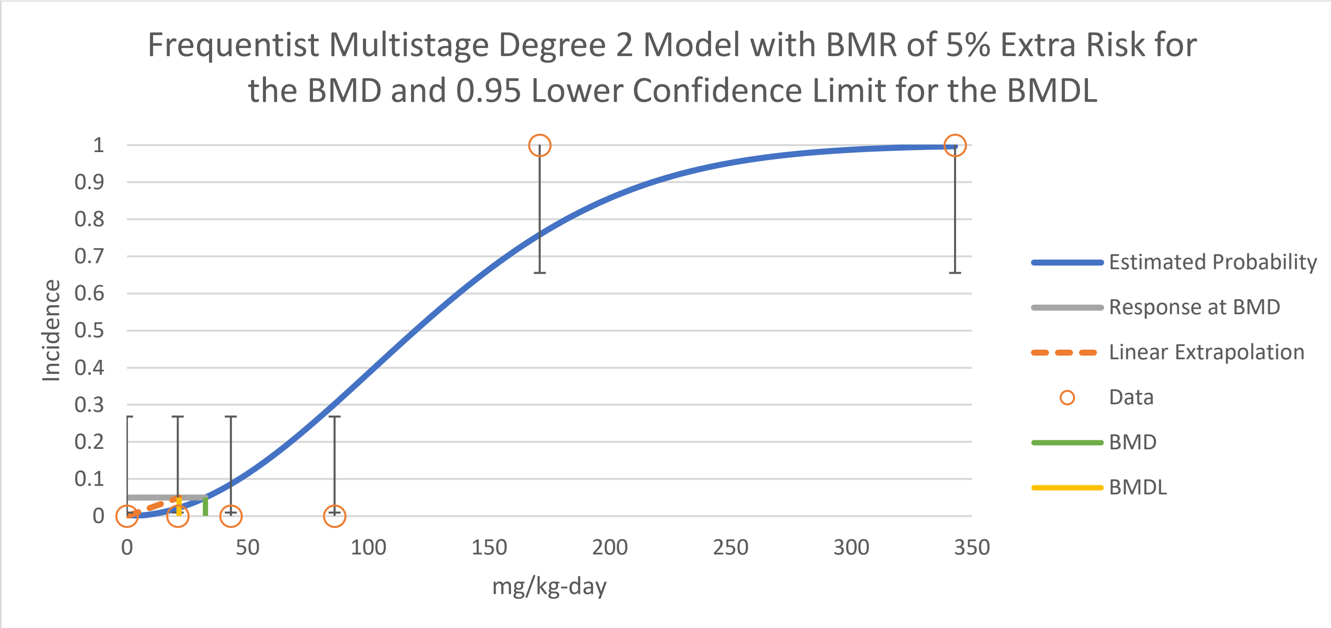

Figure 2-89. Plot of Response by Dose with Fitted Curve for the Selected Model (Multistage 2-Degree) for Mortality in Male Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks and BMR of 5%ER

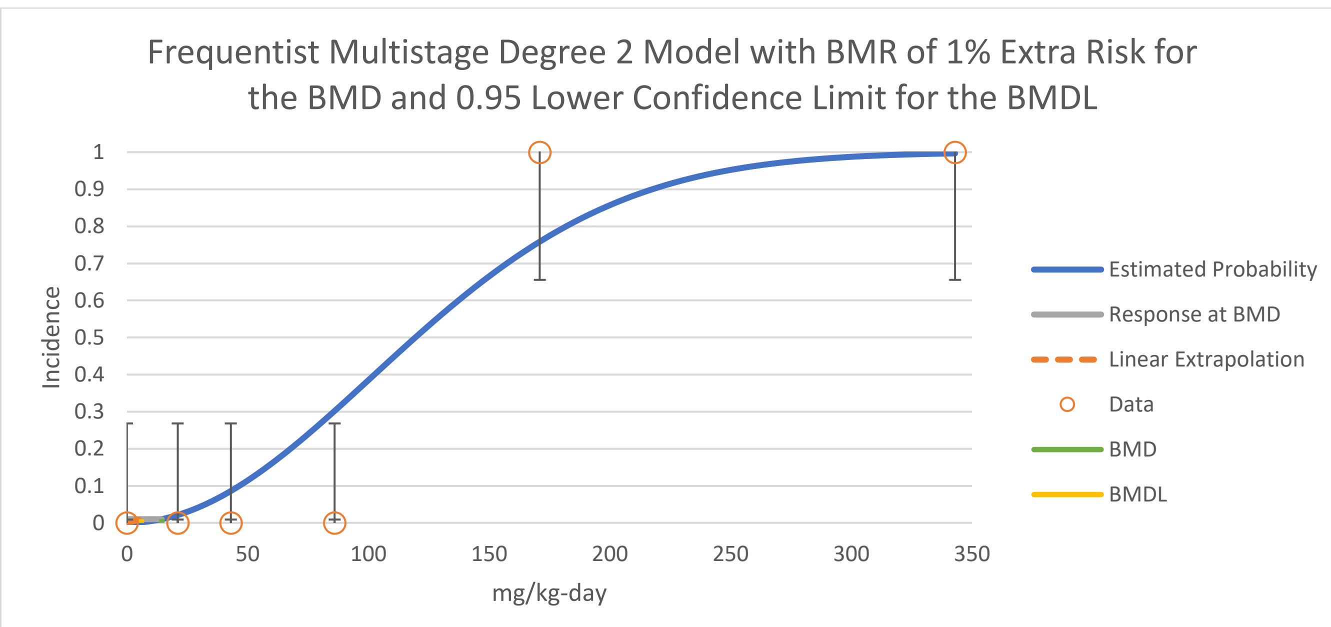

Figure 2-90. Plot of Response by Dose with Fitted Curve for the Selected Model (Multistage 2-Degree) for Mortality in Male Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks and BMR of 1%ER

Model Results

Benchmark Dose	
BMD	110.6991871
BMDL	83.20918801
BMDU	135.7943266
AIC	2.098271204
P-value	0.999971933
D.O.F.	5
Chi^2	0.049202422

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
a	Bounded	NA	NA	NA
b	0.142754215	3.73E-02	0.06967734	0.21583109

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	1.523E-07	0	10	-0.00039
21	3.05242E-07	3.05242E-06	0	10	-0.001747
43	7.0564E-06	7.0564E-05	0	10	-0.0084
86	0.003258783	0.032587826	0	10	-0.180816
171	0.998359268	9.983592681	10	10	0.1281963
343	1	10	10	10	5.972E-07

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	4.44089E-16	6	-	-	NA
Fitted Model	-0.049135602	1	0.0982712	5	0.9998445
Reduced Model	-38.1908501	1	76.283429	5	<0.0001

Figure 2-91. Details Regarding the Selected Model (Logistic) for Mortality in Male Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks

Model Results

Benchmark Dose	
BMD	32.47950141
BMDL	21.58183101
BMDU	42.58707132
AIC	17.00744744
P-value	0.121722096
D.O.F.	5
Chi^2	8.698255892
Slope Factor	0.002316764

Model Parameters				
# of Parameters	3			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	Bounded	NA	NA	NA
b2	4.8623E-05	1.850501141	-3.626867	3.62696424

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	1.523E-07	0	10	-0.00039
21	0.021214505	0.212145047	0	10	-0.465557
43	0.085981052	0.859810517	0	10	-0.969893
86	0.302055617	3.020556174	0	10	-2.080334
171	0.758717227	7.587172269	10	10	1.783295
343	0.996721763	9.967217631	10	10	0.1813565

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	4.44089E-16	6	-	-	NA
Fitted Model	-7.503723719	1	15.0074474	5	0.0103306
Reduced Model	-38.1908501	1	61.3742528	5	<0.0001

Figure 2-92. Details Regarding the Selected Model (Multistage 2-Degree) for Mortality in Male Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks

2.1.2.2.1.2 Mortality in F344 Female Rats – 13-Week Gavage

There was an increased incidence of mortality in female rats exposed to 1,2-dichloroethane by gavage for 13 weeks (5 days per week) (NTP, 1991). The administered doses were duration adjusted to estimate an equivalent oral dose for animals exposed for 7 days per week. The dose and response data used for the modeling are presented in Table 2-69. Dichotomous models were used to fit dose-response data.

A BMR of 10 percent ER was chosen according to *BMD Technical Guidance* (U.S. EPA, 2012). BMRs of five and one percent ER were also selected due to severity of the endpoint.

Table 2-69. Incidence of Mortality in Female Rats and Associated Doses Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 13-Week Oral Exposure Study

Adjusted Dose (mg/kg-day)	Number of Animals	Incidence
0	10	0
13	10	0
26	10	0
54	10	0
107	10	0
214	10	9

The BMD modeling results for increased mortality in female rats are summarized in Table 2-70. All models provided adequate fit to the data (chi-square p-value > 0.1) except for the Multistage 1-degree/Quantal Linear model. With a BMR of 10 percent ER applied, the BMDLs were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC (Weibull) was selected. With BMRs of five and one percent ER applied (below the observable range in the study), model uncertainty increased and the BMDLs of the fit models were not sufficiently close (differed by > 3-fold); therefore, the BMDS recommended the model with the lowest BMDL (Multistage 2-degree).

This data set is not well suited for BMD modeling; there are no data points with incidence between 0 and 90 percent, and there are no data to inform the shape of the curve at the region of interest, as defined by the BMR. As a result, the different models provide a broad range of BMD and BMDL estimates. For the five and one percent ER BMRs, selection of the low end of the range to represent the BMDL is not among the more realistic possibilities and involves extrapolation below the range of observation in the study (1/10 = 10 percent) to generate a BMD estimate well below the lowest tested dose where any mortality was observed.

Table 2-70. Summary of BMD Modeling Results for Increased Incidence of Mortality in Female Rats Following Oral Exposure to 1,2-Dichloroethane for 13 Weeks[a]

Model	Goodness of Fit (Means)		BMD 1%RD (mg/kg-day)	BMDL 1%RD (mg/kg-day)	BMD 5%RD (mg/kg-day)	BMDL 5%RD (mg/kg-day)	BMD 10%RD (mg/kg-day)	BMDL 10%RD (mg/kg-day)	Basis for Model Selection
	p-value	AIC							
Dichotomous Hill	1.000	8.502	150	67	160	90	168	103	All models provided adequate fit to the data (chi-square p-value > 0.1) except for the Multistage 1-degree/Quantal Linear model. With a BMR of 10 percent ER applied, BMDLs differed by < 3-fold; therefore, EPA chose the model with the lowest AIC (Weibull). With BMRs of five and one percent ER applied, BMDLs of the fit models differed by > 3-fold; therefore, the BMDS recommended the model with the lowest BMDL (Multistage 2-degree). NOTE: This data set is not well suited for BMD modeling and the results for BMR = five percent ER and one percent ER are highly unrealistic.
Gamma	0.9903	9.462	91	62	110	83	121	95.9	
Log-Logistic	1.000	8.502	150	67	160	90	168	103	
Multistage 3	0.7864	11.83	40	12	69	46	87.4	68.3	
Multistage 2	**0.2605**	**19.79**	**20**	**8.3**	**46**	**30**	65.5	48.3	
Multistage 1	0.0146	28.73	3.4	2.1	18	10	36.0	21.6	
Weibull	**1.000**	**8.502**	160	58	170	86	**180**	**102**	
Logistic	1.000	8.509	140	48	160	87	167	105	
Log-Probit	1.000	10.50	170	75	180	92	185	103	
Probit	1.000	10.50	160	56	170	87	174	103	
Quantal Linear	0.0146	28.73	3.4	2.1	18	10	36.0	21.6	

[a] Selected model in bold.

A plot of the Weibull model with a BMR of 10 percent ER is shown in Figure 2-93 and plots of the Multistage (2-degree) model with a BMR of five percent ER and one percent ER are shown in Figure 2-94 and Figure 2-95, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood for the Weibull model with BMR of 10 percent ER are shown in Figure 2-96; additional modeling details for the Multistage 2-degree model are shown in Figure 2-97 (BMD and BMDL shown are for BMR of five percent ER; the rest is applicable to both BMRs).

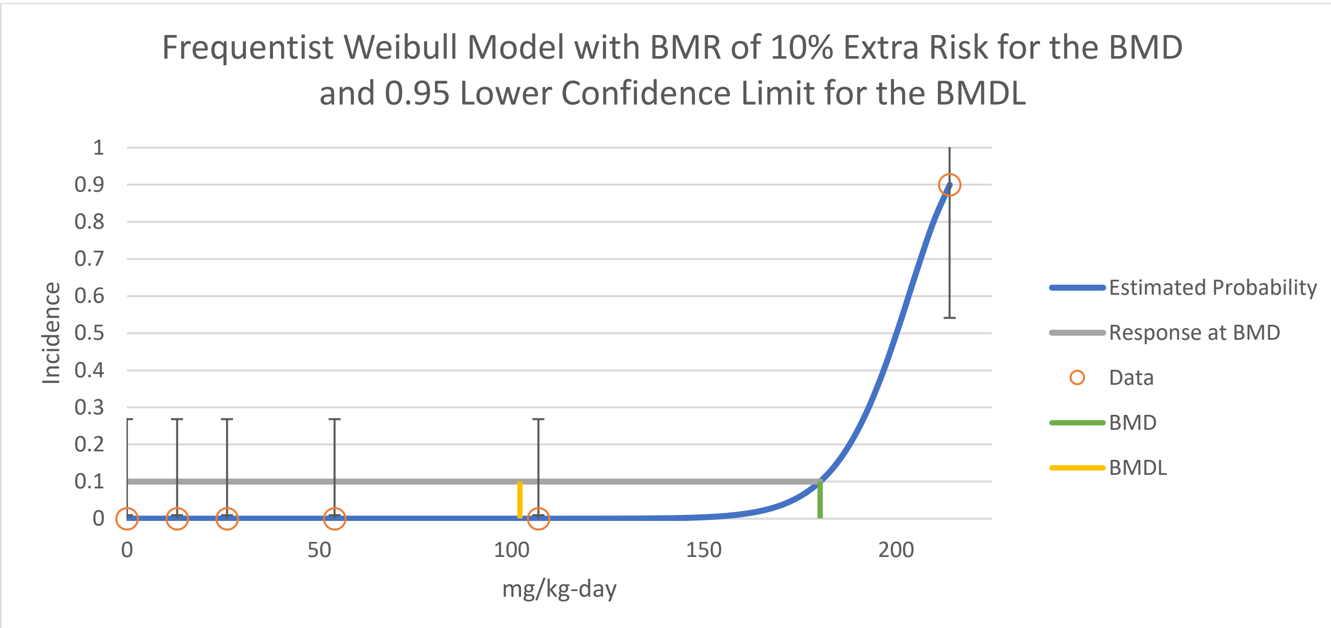

Figure 2-93. Plot of Response by Dose with Fitted Curve for the Selected Model (Weibull) for Mortality in Female Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks and BMR of 10%ER

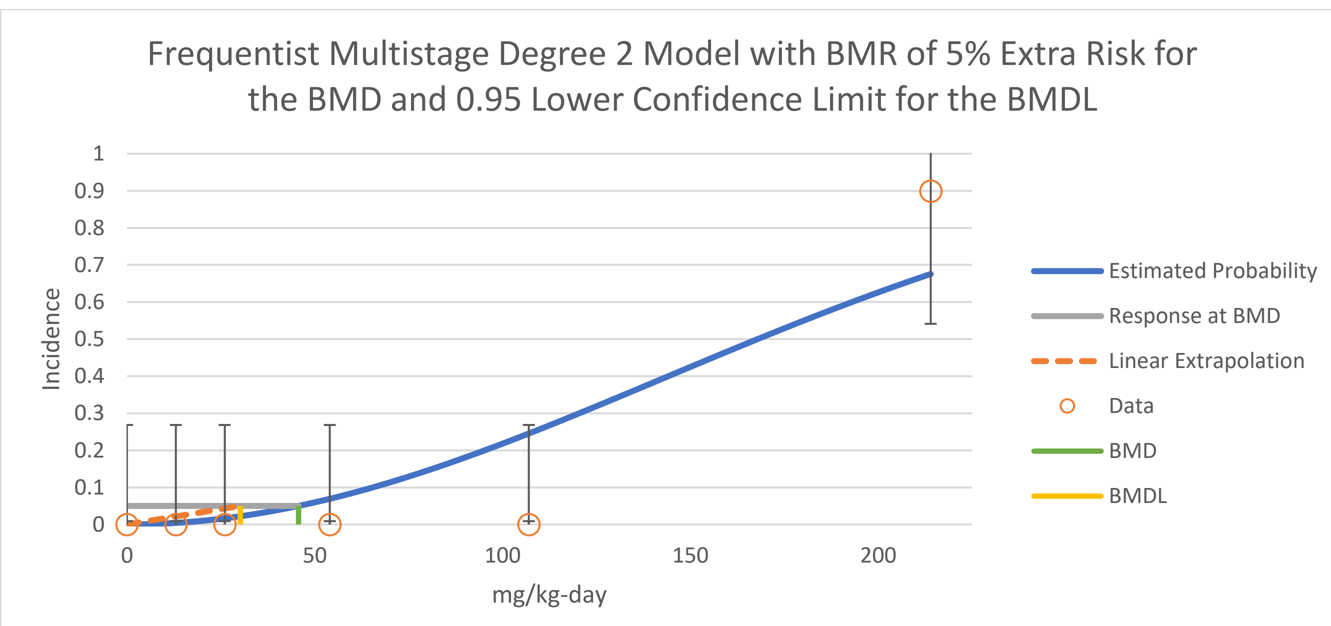

Figure 2-94. Plot of Response by Dose with Fitted Curve for the Selected Model (Multistage 2-Degree) for Mortality in Female Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks and BMR of 5%ER

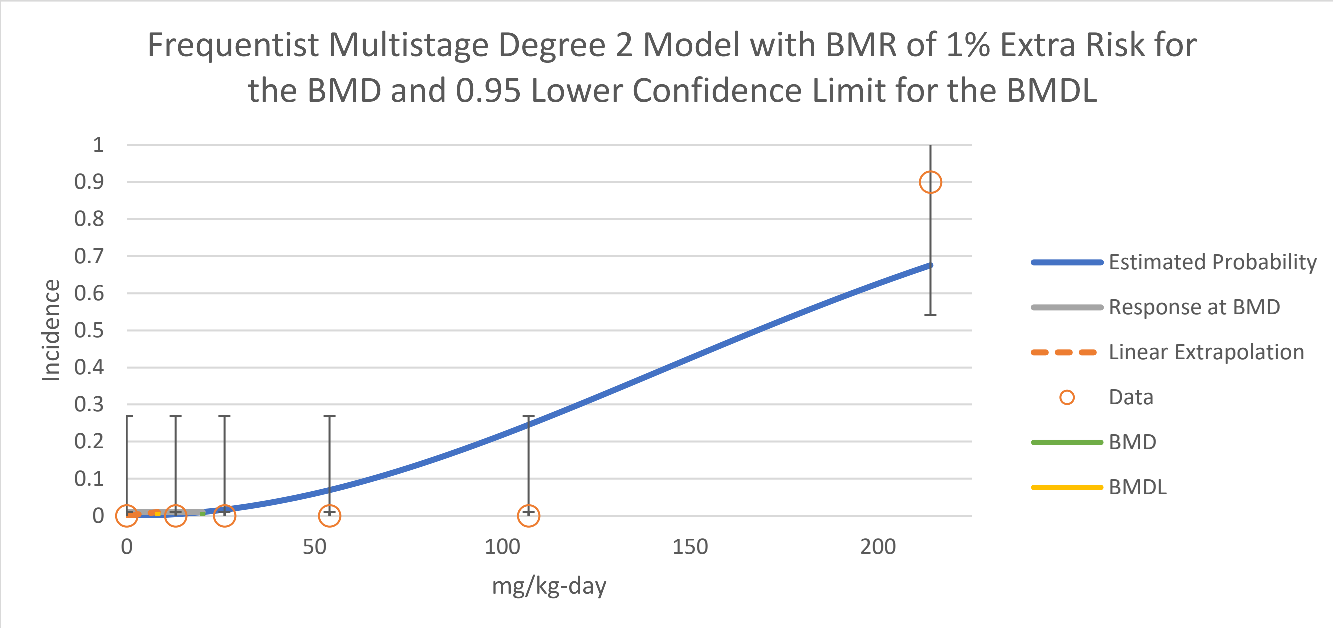

Figure 2-95. Plot of Response by Dose with Fitted Curve for the Selected Model (Multistage 2-Degree) for Mortality in Female Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks and BMR of 1%ER

Model Results

Benchmark Dose	
BMD	180.2998504
BMDL	102.2067187
BMDU	187.4610082
AIC	8.501836664
P-value	1
D.O.F.	5
Chi^2	8.8597E-05

Model Parameters				
# of Parameters	3			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
a	Bounded	NA	NA	NA
b	2.59873E-42	0.948650386	-1.8593206	1.8593206

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	1.523E-07	0	10	-0.00039
13	1.523E-08	1.523E-07	0	10	-0.00039
26	1.523E-08	1.523E-07	0	10	-0.00039
54	1.52696E-08	1.52696E-07	0	10	-0.000391
107	8.79873E-06	8.79873E-05	0	10	-0.00938
214	0.899996567	8.999965671	9	10	3.618E-05

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-3.250829734	6	-	-	NA
Fitted Model	-3.250918332	1	0.0001772	5	1
Reduced Model	-25.36254527	1	44.2232539	5	<0.0001

Figure 2-96. Details Regarding the Selected Model (Weibull) for Mortality in Female Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks

Model Results

Benchmark Dose	
BMD	45.67835414
BMDL	30.17422595
BMDU	62.50104948
AIC	18.78831282
P-value	0.260531164
D.O.F.	5
Chi^2	6.500319411
Slope Factor	0.001657043

Model Parameters				
# of Parameters	3			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	Bounded	NA	NA	NA
b2	2.45833E-05	0.395402699	-0.7749505	0.77499964

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	1.523E-07	0	10	-0.00039
13	0.00414597	0.041459704	0	10	-0.20404
26	0.016480987	0.164809869	0	10	-0.409355
54	0.069175797	0.691757972	0	10	-0.862071
107	0.245314319	2.453143191	0	10	-1.802928
214	0.675612239	6.756122394	9	10	1.5157172

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-3.250829734	6	-	-	NA
Fitted Model	-8.394156409	1	10.2866533	5	0.0675087
Reduced Model	-25.36254527	1	44.2234311	5	<0.0001

Figure 2-97. Details Regarding the Selected Model (Multistage 2-Degree) for Mortality in Female Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks

2.1.2.2.2 Body Weight Effects

One short-term/intermediate-duration inhalation study was identified for BMD modeling that showed significant changes in maternal absolute body weight gain in mice (Payan et al., 1995).

2.1.2.2.2.1 Maternal Absolute Weight Gain in Female Rats – Oral Gavage, GD 6 to 20

Absolute body weight gain was significantly increased in maternal rats exposed to 1,2-dichloroethane by gavage on GD 6 to 20 (Payan et al., 1995). Doses were reported in mmol/kg/day and converted to units of mg/kg-day. The dose and response data used for the modeling are presented in Table 2-71. Continuous models were used to fit 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.

Table 2-71. Maternal Absolute Weight Gain in Female Mice and Associated Doses Selected for Dose-Response Modeling for 1,2-Dichloroethane from an Oral Gestational Exposure Study

Dose (mg/kg-day)	Number of Animals	Mean (g)	SD (g)
0	26	43	10
119	26	39	15
158	25	33	20
198	26	30	20
238	26	22	25

The BMD modeling results for decreased maternal absolute weight gain in female rats are summarized in Table 2-72. 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 Hill model provided an adequate fit to the means (test 4 p-value > 0.1); therefore, this model was selected.

Table 2-72. Summary of BMD Modeling Results for Decreased Maternal Absolute Weight Gain in Female Rats Following Oral Exposure to 1,2-Dichloroethane on GD 6 to 20 (Nonconstant Variance)[a]

Model	Goodness of Fit		BMD 1SD (mg/kg-day)	BMDL 1SD (mg/kg-day)	BMD 10%RD (mg/kg-day)	BMDL 10%RD (mg/kg-day)	Basis for Model Selection
	test 4 p-value	AIC					
Exponential 3	0.0002	1125	224	176	118	52.7	Only the Hill model provided an adequate fit to the means (test 4 p-value > 0.1); therefore, this model was selected.
Exponential 5	< 0.0001	1127	224	176	118	52.7	
Hill	**0.3438**	**1109**	**154**	**111**	**99.1**	**41.8**	
Polynomial Degree 3	0.0005	1123	224	178	113	48.5	
Polynomial Degree 2	0.0005	1123	223	178	108	48.4	
Power	0.0002	1125	224	177	114	48.5	
Linear	0.0002	1125	221	158	54.2	42.6	

[a] Selected model in bold.

Plots of the Hill model with BMRs of one SD and 10 percent RD are shown in Figure 2-98 and Figure 2-99, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-100 (BMD and BMDL shown are for BMR of one SD; the rest is applicable to both BMRs).

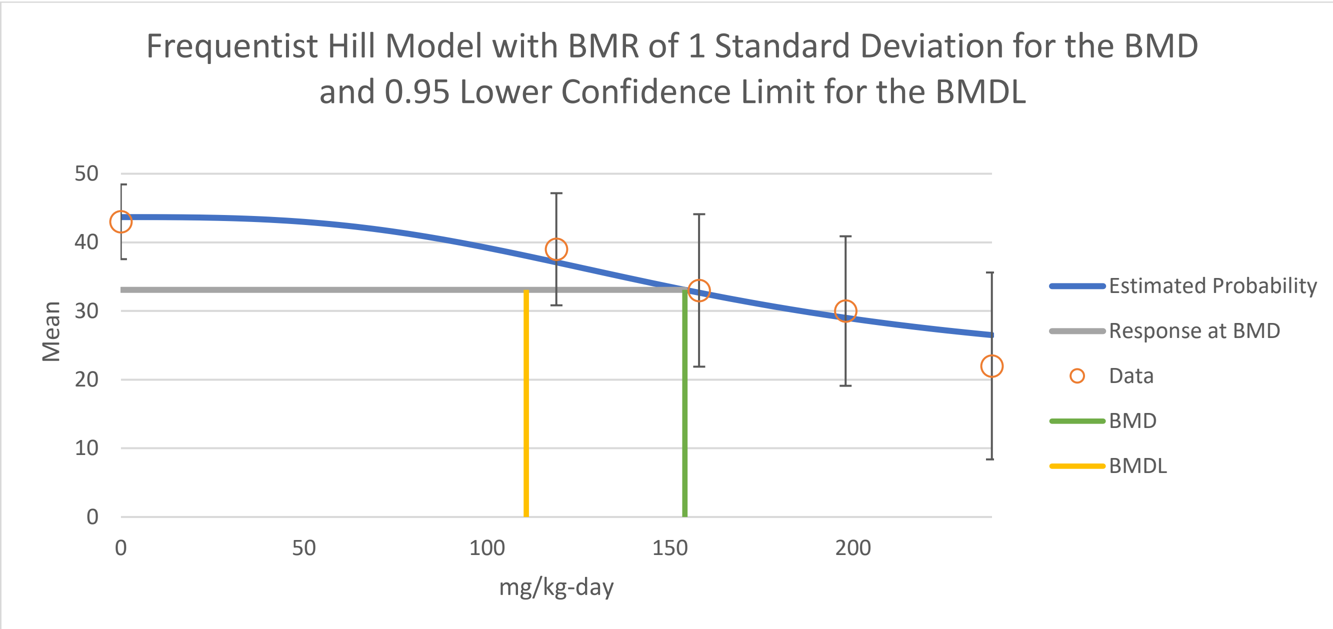

Figure 2-98. Plot of Response by Dose with Fitted Curve for the Selected Model (Hill) for Decreased Maternal Absolute Weight Gain in Female Rats Exposed to 1,2-Dichloroethane Via Oral Gavage GD 6 to 20 and BMR of 1SD (Nonconstant Variance)

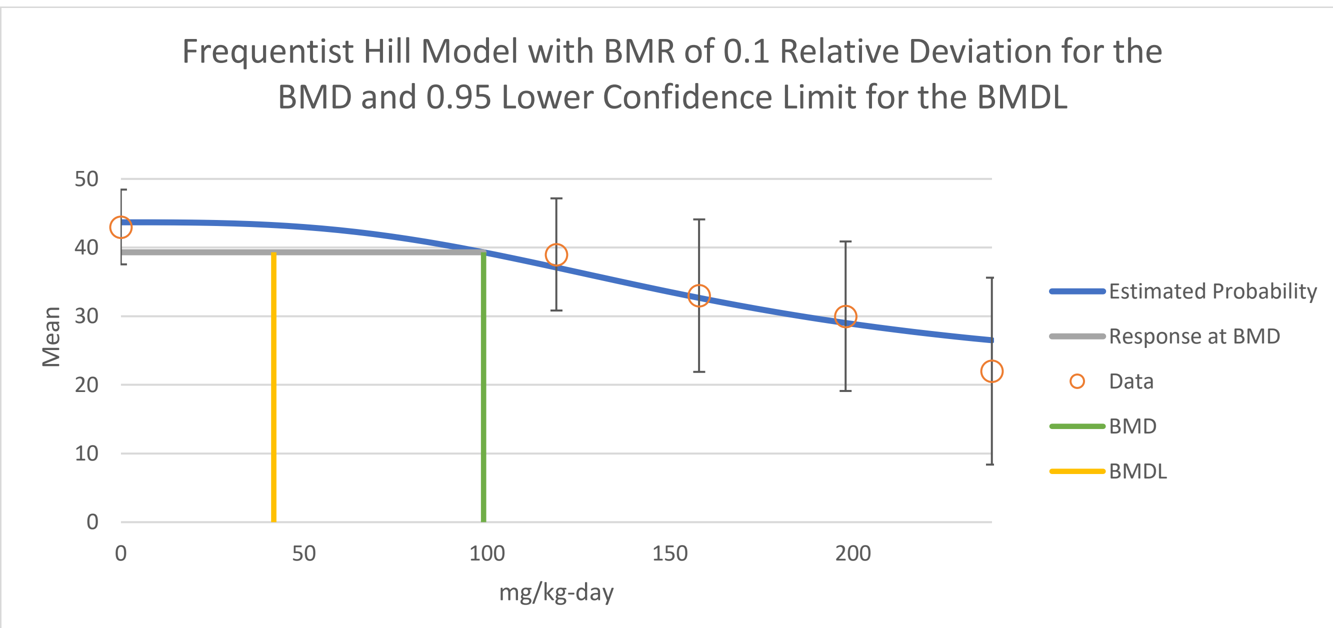

Figure 2-99. Plot of Response by Dose with Fitted Curve for the Selected Model (Hill) for Decreased Maternal Absolute Weight Gain in Female Rats Exposed to 1,2-Dichloroethane Via Oral Gavage GD 6 to 20 and BMR of 10%RD (Nonconstant Variance)

Model Results

Benchmark Dose	
BMD	154.0869579
BMDL	110.7483035
BMDU	189.773709
AIC	1109.497668
Test 4 P-value	0.343844647
D.O.F.	1

Model Parameters				
# of Parameters	6			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	43.68213907	1.959630152	39.8413345	47.5229436
v	-22.53459618	19.65018267	-61.048247	15.9790544
k	160.4215626	105.8714667	-47.082701	367.925826
n	2.957753882	3.483418283	-3.8696205	9.78512831
rho	-3.482162919	1.383320231	-6.1934208	-0.7709051
alpha	57829944.68	1.66E+16	-3.252E+16	3.2521E+16

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	26	43.68213907	43	43	10.5967743	10	10	-0.328235774
119	26	37.09148674	39	39	14.0877651	15	15	0.690779997
158	25	32.66824306	33	33	17.5735729	20	20	0.094390862
198	26	29.01694655	30	30	21.6013361	20	20	0.232050864
238	26	26.49829695	22	22	25.3010171	25	25	-0.906560548

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-558.2556686	6	1128.51134
A2	-547.2429538	10	1114.48591
A3	-548.3008121	7	1110.60162
fitted	-548.7488342	6	1109.49767
R	-567.776198	2	1139.5524

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	41.06648838	8	<0.0001
2	22.02542948	4	0.0001981
3	2.11571657	3	0.54873974
4	0.896044122	1	0.34384465

Figure 2-100. Details Regarding the Selected Model (Hill) for Decreased Maternal Absolute Weight Gain in Female Rats Exposed to 1,2-Dichloroethane Via Oral Gavage GD 6 to 20

2.1.2.2.3 Renal Effects

Data sets for changes in absolute and relative kidney weight in male and female rats orally exposed for 13 weeks were identified for BMD modeling (NTP, 1991).

Modeled results were not presented for the absolute or relative kidney weight data in female rats because neither the constant nor nonconstant variance models provided adequate fit to the variance data.

2.1.2.2.3.1 Absolute Kidney Weight in F344 Male Rats – 13-Week Gavage

Absolute kidney weight was significantly increased in male rats exposed to 1,2-dichloroethane by gavage for 13 weeks (5 days per week) (NTP, 1991). The administered doses were duration adjusted to estimate an equivalent oral dose for animals exposed for 7 days per week. The dose and response data used for the modeling are presented in Table 2-73. Continuous models were used to fit 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 because EPA considers a 10 percent change in kidney weight to be biologically significant.

Table 2-73. Absolute Kidney Weight in Male Rats and Associated Doses Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 13-Week Oral Exposure Study

Adjusted Dose (mg/kg-day)	Number of Animals	Mean (mg)	SD (mg)
0	10	1324	92
21	10	1441	82
43	10	1600	171
86	10	1653	149

The BMD modeling results for increased absolute kidney weight in male rats are summarized in Table 2-74. Both the constant and nonconstant variance models provide adequate fit to the variance data. With the constant variance model applied, none of the models provided adequate fit to the means (test 4 p-value < 0.1). With the nonconstant variance model applied, only the Exponential 5 model provided adequate fit to the means (test 4 p-value > 0.1); therefore, this model was selected.

Table 2-74. Summary of BMD Modeling Results for Increased Absolute Kidney Weight in Male Rats Following Oral Exposure to 1,2-Dichloroethane for 13 Weeks (Nonconstant Variance)[a]

Model	Goodness of Fit		BMD 1SD (mg/kg-day)	BMDL 1SD (mg/kg-day)	BMD 10%RD (mg/kg-day)	BMDL 10%RD (mg/kg-day)	Basis for Model Selection
	test 4 p-value	AIC					
Exponential 3	0.0388	507.1	27	17	35	27	Only the Exponential 5 model provided adequate fit to the means (test 4 p-
Exponential 5	**0.3660**	**503.5**	**19**	**12**	**23**	**14**	
Hill	NA	505.5	19	13	23	19	

Model	Goodness of Fit		BMD 1SD (mg/kg-day)	BMDL 1SD (mg/kg-day)	BMD 10%RD (mg/kg-day)	BMDL 10%RD (mg/kg-day)	Basis for Model Selection
	test 4 p-value	AIC					
Polynomial Degree 3	0.0268	507.9	-	-	31	0	value > 0.1); therefore, this model was selected.
Polynomial Degree 2	0.0268	507.9	-	-	31	0	
Power	0.0268	507.9	23	14	31	24	
Linear	0.0268	507.9	-	-	31	24	
[a] Selected model in bold.							

Plots of the Exponential 5 model with BMRs of one SD and 10 percent RD are shown in Figure 2-101 and Figure 2-102, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-103 (BMD and BMDL shown are for BMR of one SD; the rest is applicable to both BMRs).

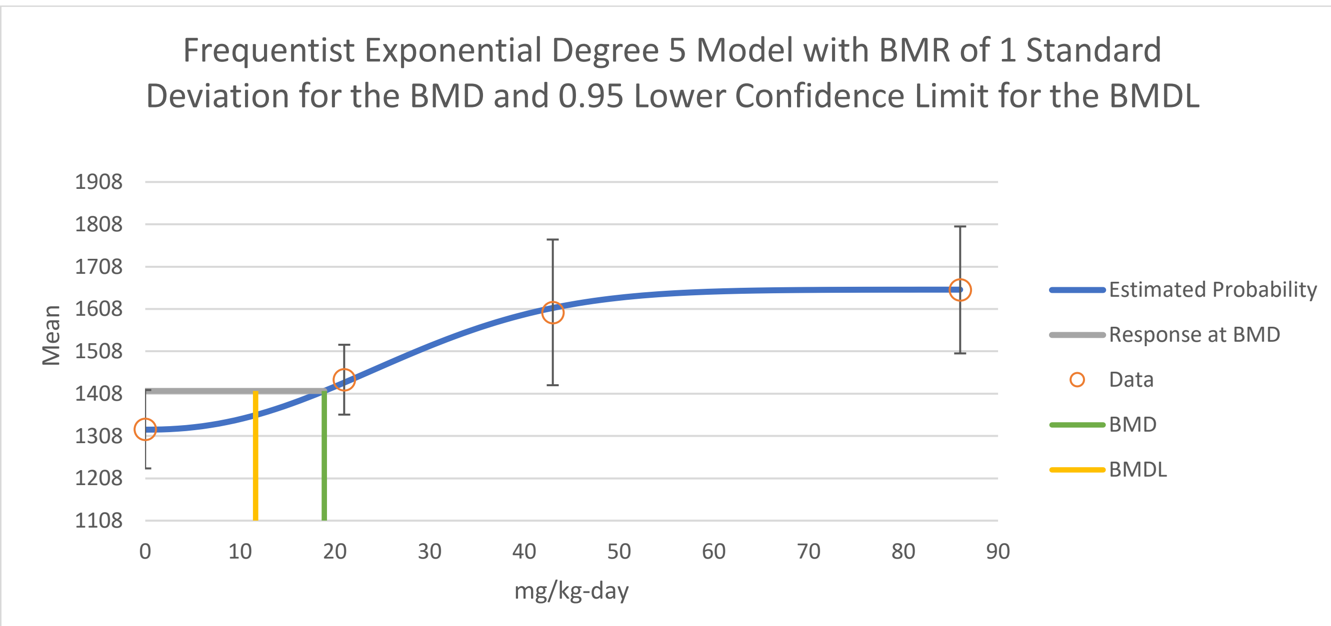

Figure 2-101. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 5) for Increased Absolute Kidney Weight in Male Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks and BMR of 1SD (Nonconstant Variance)

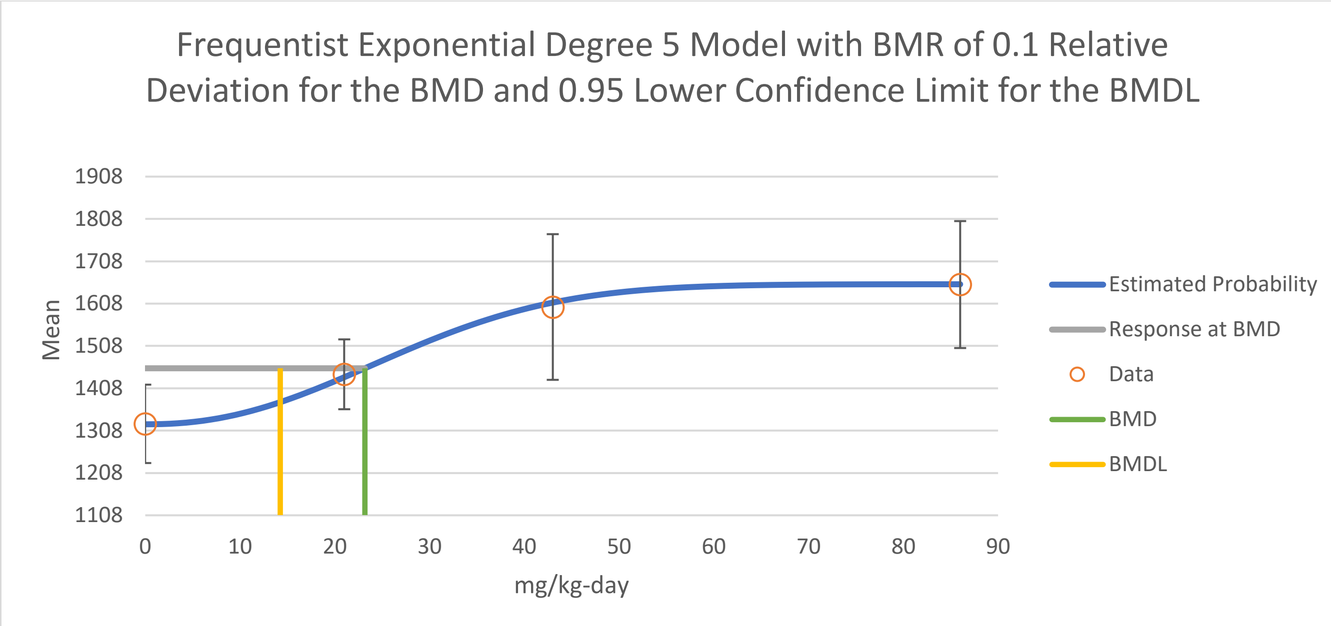

Figure 2-102. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 5) for Increased Absolute Kidney Weight in Male Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks and BMR of 10%RD (Nonconstant Variance)

Model Results

Benchmark Dose	
BMD	18.89503404
BMDL	11.64401146
BMDU	25.54732985
AIC	503.4998688
Test 4 P-value	0.366027487
D.O.F.	1

Model Parameters				
# of Parameters	6			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
a	1322.943197	28.52751242	1267.0303	1378.85609
b	0.031943071	6.44E-03	0.01931208	0.04457407
c	1.250041712	3.38E-02	1.18379403	1.31628939
d	2.234728895	9.38E-01	0.39703395	4.07242384
rho	3.760841847	3.12E-02	3.69972526	3.82195844
log-alpha	Bounded	NA	NA	NA

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	10	1322.943197	1324	1324	91.4452272	92	92	0.036545426
21	10	1434.143559	1441	1441	106.432064	82	82	0.203716537
43	10	1610.401275	1600	1600	132.353569	171	171	-0.248514042
86	10	1653.711018	1653	1653	139.126056	149	149	-0.016161145

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-249.0626479	5	508.125296
A2	-245.3915079	8	506.783016
A3	-246.3413811	6	504.682762
fitted	-246.7499344	5	503.499869
R	-264.1885774	2	532.377155

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	37.59413899	6	<0.0001
2	7.342280042	3	0.06175249
3	1.899746393	2	0.38679007
4	0.817106605	1	0.36602749

Figure 2-103. Details Regarding the Selected Model (Exponential 5) for Increased Absolute Kidney Weight in Male Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks

2.1.2.2.3.2 Relative Kidney Weight in F344 Male Rats – 13-Week Gavage

Relative kidney weight was significantly increased in male rats exposed to 1,2-dichloroethane by gavage for 13 weeks (5 days per week) (NTP, 1991). The administered doses were duration adjusted to estimate an equivalent oral dose for animals exposed for 7 days per week. The dose and response data used for the modeling are presented in Table 2-75. Continuous models were used to fit 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 because EPA considers a 10 percent change in relative kidney weight to be biologically significant.

Table 2-75. Relative Kidney Weight in Male Rats and Associated Doses Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 13-Week Oral Exposure Study

Adjusted Dose (mg/kg-day)	Number of Animals	Mean (Organ weight to body weight)	SD (Organ weight to body weight)
0	10	3.9	0.19
21	10	4.1	0.32
43	10	4.5	0.25
86	10	4.9	0.22

The BMD modeling results for increased relative kidney weight in male rats are summarized in Table 2-76. The constant variance model provided an adequate fit to the variance data. With the constant variance model applied, the goodness-of-fit p-values for the means (test 4) could not be derived for the Exponential 5 and Hill models because the models were saturated (degrees of freedom = 0). The remaining 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 (Power) was selected.

Table 2-76. Summary of BMD Modeling Results for Increased Relative Kidney Weight in Male Rats Following Oral Exposure to 1,2-Dichloroethane for 13 Weeks (Constant Variance)[a]

Model	Goodness of Fit		BMD 1SD (mg/kg-day)	BMDL 1SD (mg/kg-day)	BMD 10%RD (mg/kg-day)	BMDL 10%RD (mg/kg-day)	Basis for Model Selection
	test 4 p-value	AIC					
Exponential 3	0.2945	6.746	23	18	36	30	Goodness-of-fit p-values could not be derived for the Exponential 5 and Hill models because the models were saturated (degrees of freedom = 0). The remaining models provided adequate fit to the means (test 4 p-value > 0.1). BMDLs for the fit models differed by < 3-fold; therefore, EPA chose the model with the lowest AIC.
Exponential 5	NA	8.301	23	13	32	21	
Hill	NA	8.301	23	13	31	21	
Polynomial Degree 3	0.3915	6.1763	20	16	33	27	
Polynomial Degree 2	0.3908	6.180	20	16	33	27	
Power	**0.3916**	**6.1758**	**20**	**16**	**33**	**27**	
Linear	0.3916	6.1758	20	16	33	27	

[a] Selected model in bold.

Plots of the Power model with BMRs of one SD and 10 percent RD are shown in Figure 2-104 and Figure 2-105, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-106 (BMD and BMDL shown are for BMR of one SD; the rest is applicable to both BMRs).

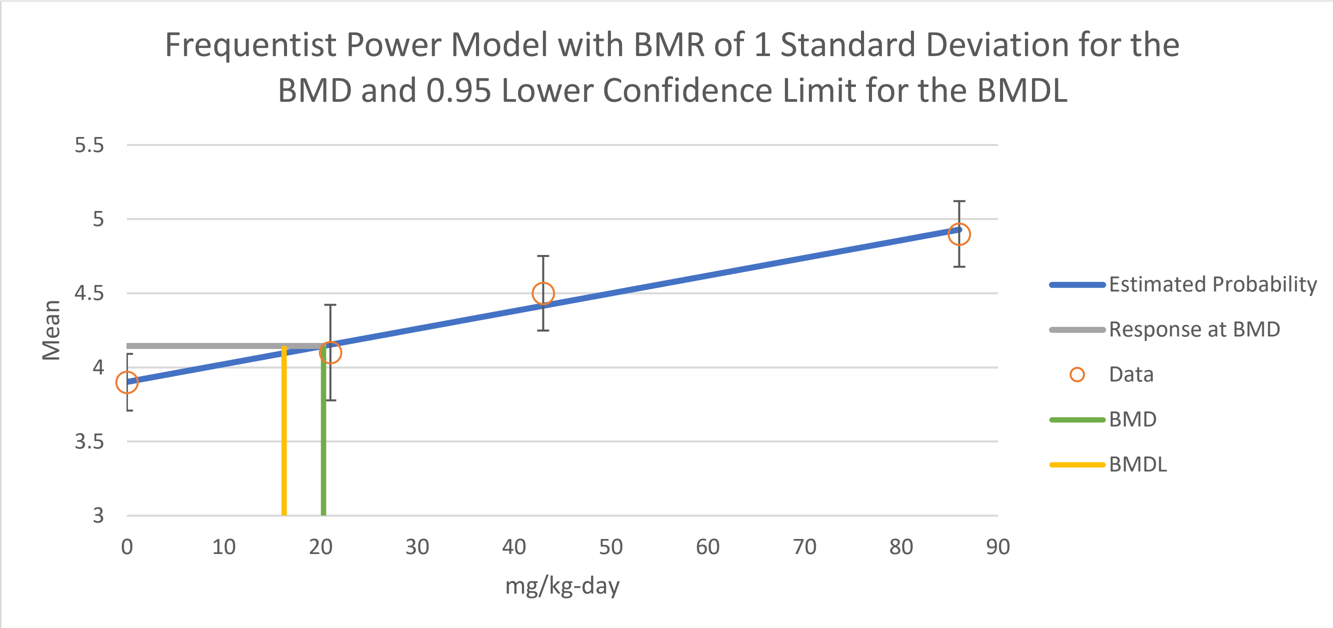

Figure 2-104. Plot of Response by Dose with Fitted Curve for the Selected Model (Power) for Increased Absolute Kidney Weight in Male Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks and BMR of 1SD (Constant Variance)

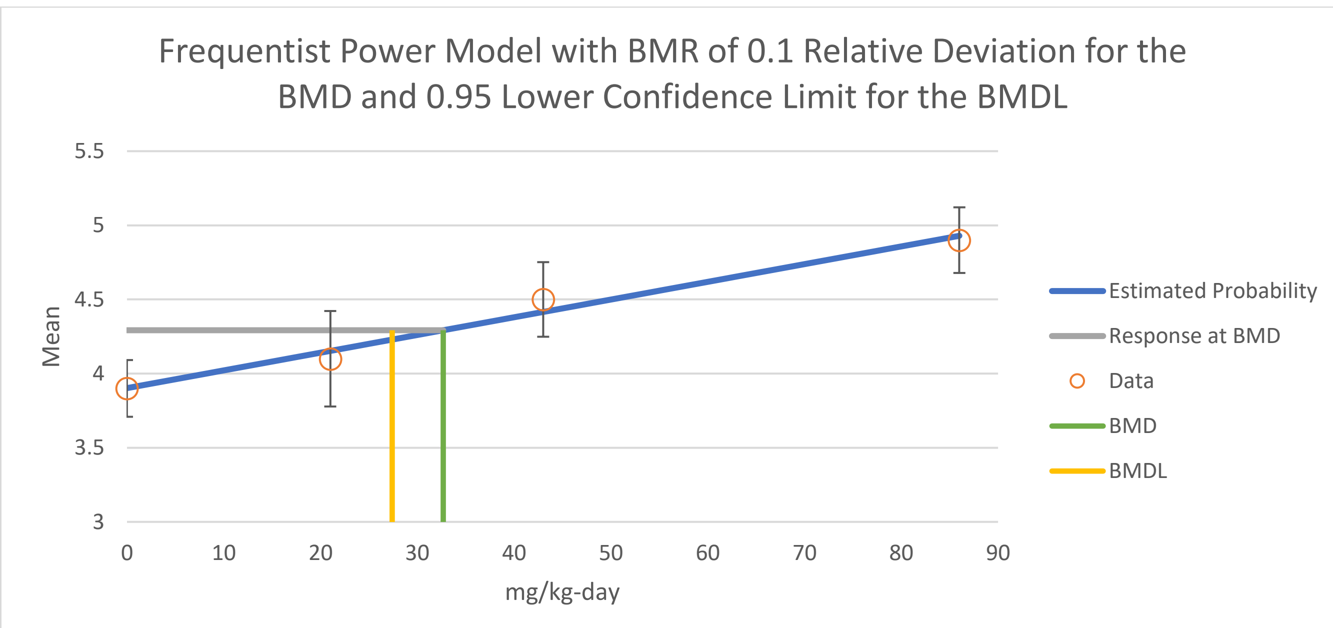

Figure 2-105. Plot of Response by Dose with Fitted Curve for the Selected Model (Power) for Increased Absolute Kidney Weight in Male Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks and BMR of 10%RD (Constant Variance)

Model Results	

Benchmark Dose	
BMD	20.30524804
BMDL	16.22947938
BMDU	31.96250624
AIC	6.175774284
Test 4 P-value	0.391649386
D.O.F.	2

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	3.902142333	0.059216216	3.78608068	4.01820398
v	0.011942871	1.20E-03	0.00958432	0.01430142
n	Bounded	NA	NA	NA
alpha	0.058807687	7.73E-04	0.05729203	0.06032334

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	10	3.902142333	3.9	3.9	0.24250296	0.19	0.19	-0.027936363
21	10	4.152942628	4.1	4.1	0.24250296	0.32	0.32	-0.690380391
43	10	4.415685794	4.5	4.5	0.24250296	0.25	0.25	1.099470812
86	10	4.929229256	4.9	4.9	0.24250296	0.22	0.22	-0.381154207

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	0.849501122	5	8.30099776
A2	2.355544823	8	11.2889104
A3	0.849501122	5	8.30099776
fitted	-0.087887142	3	6.17577428
R	-24.92705487	2	53.8541097

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	54.56519938	6	<0.0001
2	3.012087401	3	0.38976529
3	3.012087401	3	0.38976529
4	1.874776528	2	0.39164939

Figure 2-106. Details Regarding the Selected Model (Power) for Increased Relative Kidney Weight in Male Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks

2.1.2.2.4 Immune Effects

Data sets identified for BMD modeling for immune effects in a 14-day gavage study (Munson et al., 1982) include changes in leukocyte count, antibody-forming cells/spleen, and antibody-forming cells/10^6 cells in male mice. Data sets for the incidence of thymus necrosis in male and female rats in a 13-week gavage study (NTP, 1991) were also identified for BMD modeling.

Modeled results were not presented for the antibody-forming cells/spleen or antibody-forming cells/10^6 cells in male mice data sets (Munson et al., 1982) because none of the models provided adequate fits to the means (test 4 p-value < 0.1) either assuming constant or nonconstant variance.

2.1.2.2.4.1 Leukocyte Count in CD-1 Male Mice – 14-day Gavage Study

Leukocyte counts were significantly decreased in male mice exposed to 1,2-dichloroethane by gavage daily for 14 days (Munson et al., 1982). The dose and response data used for the modeling are presented in Table 2-77. Continuous models were used to fit 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 because EPA considers a 10 percent change in leukocyte counts to be biologically relevant.

Table 2-77. Leukocytes in Male Mice and Associated Doses Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 14-Day Oral Exposure Study

Dose (mg/kg-day)	Number of Animals	Mean	SD
0	12	8.24	3.26
4.89	10	7.60	1.64
48.9	10	5.76	1.55

The BMD modeling results for decreased leukocyte count in male mice are summarized in Table 2-78. 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, all models except 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 (Exponential 3) was selected.

Table 2-78. Summary of BMD Modeling Results for Decreased Leukocytes in Male Mice Following Oral Exposure to 1,2-Dichloroethane for 14 Days (Nonconstant Variance)[a]

Model	Goodness of Fit		BMD 1SD (mg/kg-day)	BMDL 1SD (mg/kg-day)	BMD 10%RD (mg/kg-day)	BMDL 10%RD (mg/kg-day)	Basis for Model Selection
	test 4 p-value	AIC					
Exponential 3	**0.1556**	**146.8**	**56.1**	**30.9**	**15.2**	**9.75**	All models except the Exponential 5 and Hill models provided adequate fit to the means (test 4 p-value < 0.1). BMDLs for the fit models differed by < 3-fold; therefore, EPA chose the model with the lowest AIC.
Exponential 5	NA	148.8	-	-	3.69	0.980	
Hill	NA	148.8	-	-	3.14	0.480	
Polynomial Degree 2	0.1435	147.0	55.4	34.0	17.2	12.0	
Power	0.1435	147.0	55.8	34.0	17.3	12.0	

Model	Goodness of Fit		BMD 1SD (mg/kg-day)	BMDL 1SD (mg/kg-day)	BMD 10%RD (mg/kg-day)	BMDL 10%RD (mg/kg-day)	Basis for Model Selection
	test 4 p-value	AIC					
Linear	0.1435	147.0	55.4	34.0	17.2	12.0	
[a] Selected model in bold.							

Plots of the Exponential 3 model with BMRs of one SD and 10 percent RD are shown in Figure 2-107 and Figure 2-108, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-109 (BMD and BMDL shown are for BMR of one SD; the rest is applicable to both BMRs).

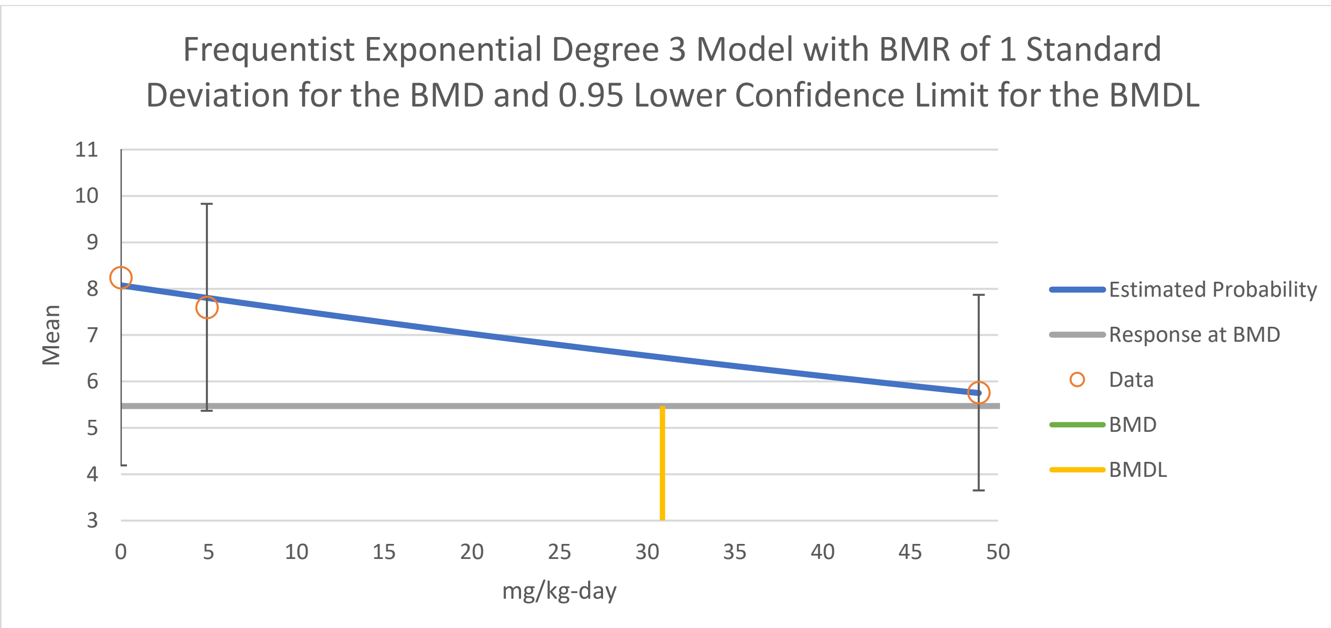

Figure 2-107. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 3) for Decreased Leukocytes in Male Mice Exposed to 1,2-Dichloroethane Via Oral Gavage for 14 Days and BMR of 1SD (Nonconstant Variance)

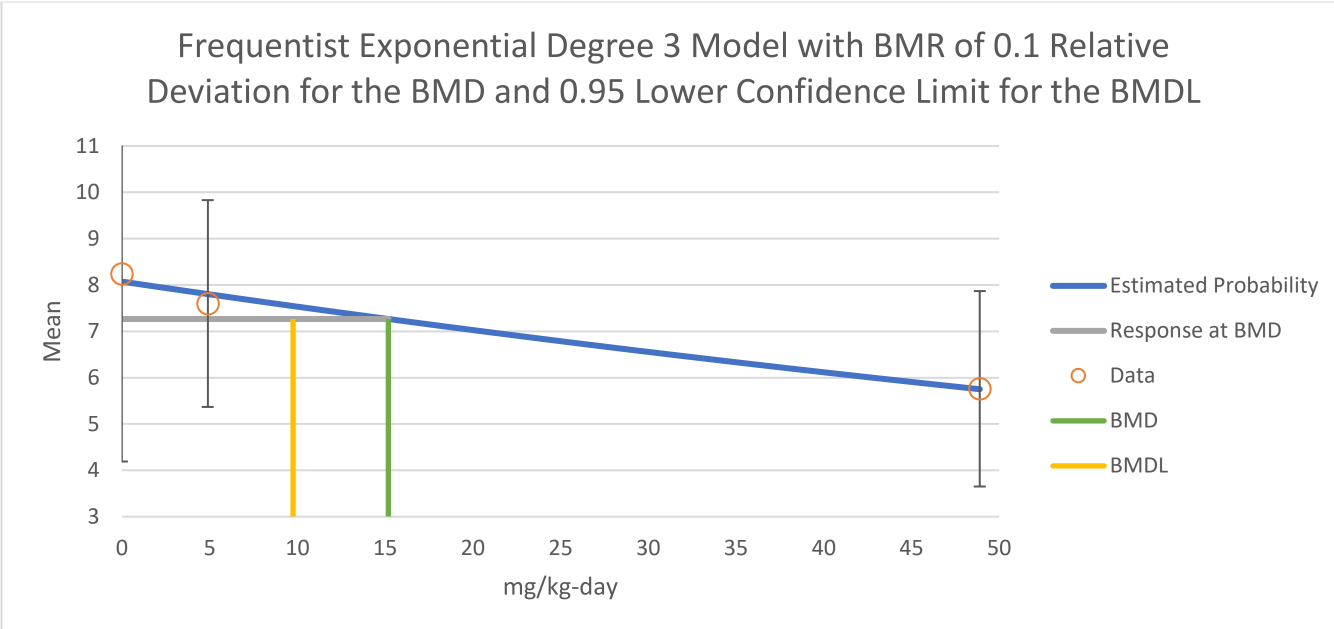

Figure 2-108. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 3) for Decreased Leukocytes in Male Mice Exposed to 1,2-Dichloroethane Via Oral Gavage for 14 Days and BMR of 10%RD (Nonconstant Variance)

Model Results

Benchmark Dose	
BMD	56.08674721
BMDL	30.86793476
BMDU	149.2332182
AIC	146.8344073
Test 4 P-value	0.155640847
D.O.F.	1

Model Parameters				
# of Parameters	5			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
a	8.073279139	0.575470972	6.94537675	9.20118153
b	0.006937773	2.22E-03	0.00257845	0.0112971
d	Bounded	NA	NA	NA
rho	3.534193135	1.97E+00	-0.3223061	7.39069233
log-alpha	-5.468519023	3.87E+00	-13.048931	2.11189326

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	12	8.073279139	8.24	8.24	2.60238213	3.26	3.26	0.221926671
4.89	10	7.803981293	7.6	7.6	2.45095372	1.64	1.64	-0.263181422
48.9	10	5.750590964	5.76	5.76	1.42893177	1.55	1.55	0.020822538

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-71.42798259	4	150.855965
A2	-67.34059772	6	146.681195
A3	-68.40916542	5	146.818331
fitted	-69.41720367	4	146.834407
R	-74.55945884	2	153.118918

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	14.43772225	4	0.00602144
2	8.174769753	2	0.01678307
3	2.137135415	1	0.14377013
4	2.016076497	1	0.15564085

Figure 2-109. Details Regarding the Selected Model (Exponential 3) for Decreased Leukocytes in Male Mice Exposed to 1,2-Dichloroethane Via Oral Gavage for 14 Days

2.1.2.2.4.2 Thymus Necrosis in F344 Male Rats – One Time per Day, 5 days per Week

There was an increased incidence of thymus necrosis in male rats exposed to 1,2-dichloroethane by gavage for 13 weeks (5 days per week) (NTP, 1991). The administered doses were duration adjusted to estimate an equivalent oral dose for animals exposed for 7 days per week. The dose and response data used for the modeling are presented in Table 2-79. Dichotomous models were used to fit dose-response data.

A BMR of 10 percent ER was chosen according to *BMD Technical Guidance* (U.S. EPA, 2012).

Table 2-79. Incidence of Thymus Necrosis in Male Rats and Associated Doses Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 13-Week Oral Exposure Study

Adjusted Dose (mg/kg-day)	Number of Animals	Incidence
0	10	0
86	10	0
171	10	4
343	10	10

The BMD modeling results for increased incidence of thymus necrosis in male rats are summarized in Table 2-80. All models provided adequate fit to the data (chi-square p-value > 0.1) except for the Multistage 1-degree/Quantal Linear model. The BMD computation failed for the Weibull model because the lower limit included zero; therefore, this model was unusable. BMDLs for the remaining models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Multistage 3-degree).

Table 2-80. Summary of BMD Modeling Results for Increased Incidence of Thymus Necrosis in Male Rats Following Oral Exposure to 1,2-Dichloroethane for 13 Weeks[a]

Model	Goodness of Fit		BMD 10%ER (mg/kg-day)	BMDL 10%ER (mg/kg-day)	Basis for Model Selection
	p-value	AIC			
Dichotomous Hill	1.000	15.46	160	100	All models provided adequate fit to the data (chi-square p-value > 0.1) except for the Multistage 1-degree/Quantal Linear model. The BMD computation failed for the Weibull model and was unusable. BMDLs differed by < 3-fold; therefore, EPA chose the model with the lowest AIC (Multistage Degree 3).
Gamma	0.9979	15.54	130	92	
Log-Logistic	1.000	15.46	160	100	
Multistage 3	**0.9335**	**15.09**	**100**	**59**	
Multistage 2	0.4338	20.47	71	44	
Multistage 1	0.0490	28.56	27	17	
Weibull	0.9988	15.52	140	0	
Logistic	1.000	15.46	150	93	
Log-Probit	1.000	17.46	160	97	
Probit	1.000	17.46	150	87	
Quantal Linear	0.0490	28.56	27	17	

[a] Selected model in bold.

A plot of the Multistage 3-degree model with a BMR of 10 percent ER is shown in Figure 2-110. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-111.

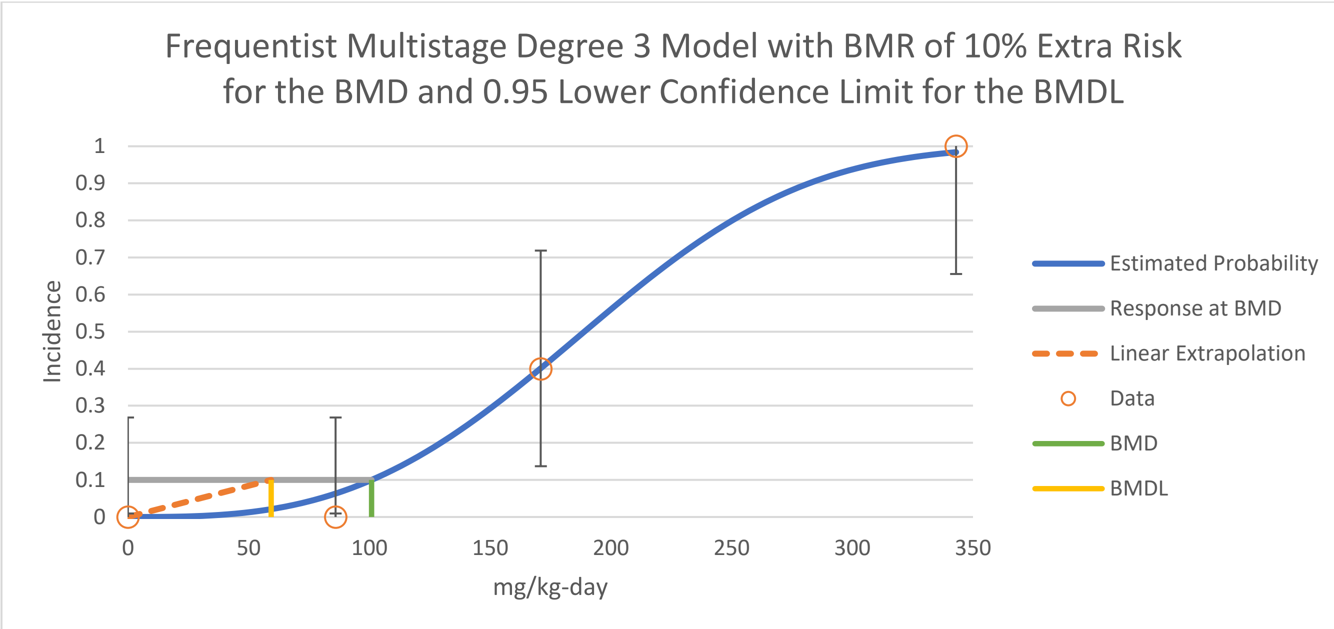

Figure 2-110. Plot of Response by Dose with Fitted Curve for the Selected Model (Multistage 3-Degree) for Increased Incidence of Thymus Necrosis in Male Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks and BMR of 10%ER

Model Results	

Benchmark Dose	
BMD	100.8873865
BMDL	59.30171288
BMDU	124.622876
AIC	15.08642199
P-value	0.933531247
D.O.F.	4
Chi^2	0.836191799
Slope Factor	0.001686292

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	Bounded	NA	NA	NA
b2	Bounded	NA	NA	NA
b3	Bounded	NA	NA	NA

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	1.523E-07	0	10	-0.00039
86	0.063178343	0.631783434	0	10	-0.821213
171	0.401330243	4.013302431	4	10	-0.008582
343	0.984084626	9.840846256	10	10	0.4021538

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-6.73011667	4	-	-	NA
Fitted Model	-7.543210994	0	1.62618865	4	0.8040777
Reduced Model	-25.89786556	1	38.3354978	3	<0.0001

Figure 2-111. Details Regarding the Selected Model (Multistage 3-Degree) for Increased Incidence of Thymus Necrosis in Male Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks

2.1.2.2.4.3 Thymus Necrosis in F344 Female Rats – 13-Week Gavage

There was an increased incidence of thymus necrosis in female rats exposed to 1,2-dichloroethane by gavage for 13 weeks (5 days per week) (NTP, 1991). The administered doses were duration adjusted to estimate an equivalent oral dose for animals exposed for 7 days per week. The dose and response data used for the modeling are presented in Table 2-81. Dichotomous models were used to fit the dose-response data.

A BMR of 10 percent ER was chosen according to *BMD Technical Guidance* (U.S. EPA, 2012).

Table 2-81. Increased Incidence of Thymus Necrosis in Female Rats and Associated Doses Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 13-Week Oral Exposure Study

Adjusted Dose (mg/kg-day)	Number of Animals	Incidence
0	10	0
107	10	0
214	10	5

The BMD modeling results for increased incidence of thymus necrosis in female rats are summarized in Table 2-82. All models provided adequate fit to the data (chi-square p-value > 0.1). BMDLs were not sufficiently close (differed by > 3-fold); therefore, the model with the lowest BMDL was selected (Multistage 1-degree).

This data set is not well suited for BMD modeling; there is a single non-zero data point and no data to inform the shape of the curve at the region of interest, as defined by the BMR. As a result, the different models provide a broad range of BMD and BMDL estimates. Selection of the low end of the range to represent the BMDL is not among the more realistic possibilities and in this case involves extrapolation below the range of observation to generate a BMD estimate well below the lowest tested dose.

Table 2-82. Summary of BMD Modeling Results for Increased Incidence of Thymus Necrosis in Female Rats Following Oral Exposure to 1,2-Dichloroethane for 13 Weeks[a]

Model	Goodness of Fit		BMD 10%ER (mg/kg-day)	BMDL 10%ER (mg/kg-day)	Basis for Model Selection
	p-value	AIC			
Dichotomous Hill	1.000	15.86	189	97.1	All models provided adequate fit to the data (chi-square p-value > 0.1). BMDLs differed by > 3-fold; therefore, EPA chose the model with the lowest BMDL. NOTE: This data set is not well suited for BMD modeling and the results should be interpreted with caution.
Gamma	0.9780	15.95	156	95.7	
Log-Logistic	1.000	15.86	189	97.1	
Multistage 2	0.4109	18.83	97.2	41.9	
Multistage 1	**0.1740**	**21.10**	**55.6**	**28.7**	
Weibull	1.000	15.86	193	96.1	
Logistic	0.9994	15.87	188	107	
Log-Probit	0.9996	17.86	199	98.2	
Probit	1.000	17.86	193	102	
Quantal Linear	0.1740	21.10	55.6	28.7	

[a] Selected model in bold.

A plot of the Multistage 1-degree model with a BMR of 10 percent ER is shown in Figure 2-112. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-113.

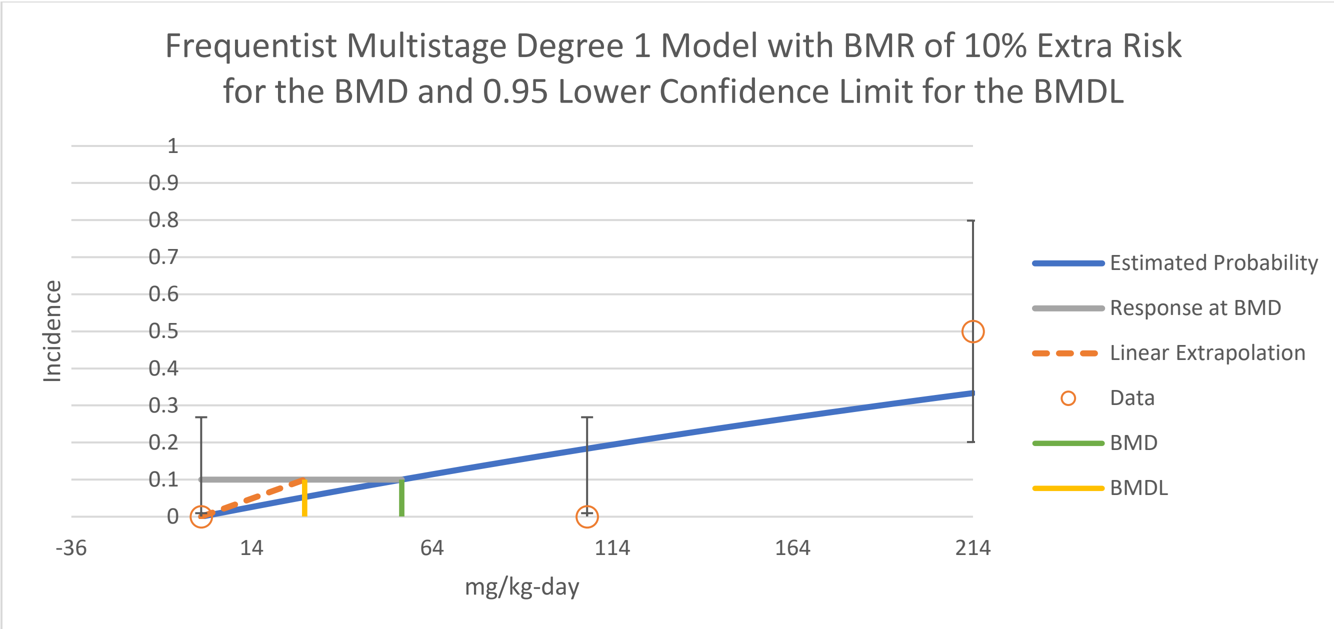

Figure 2-112. Plot of Response by Dose with Fitted Curve for the Selected Model (Quantal Linear) for Increased Incidence of Thymus Necrosis in Female Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks and BMR of 10%ER

Model Results

Benchmark Dose	
BMD	55.60812223
BMDL	28.68887964
BMDU	129.2673929
AIC	21.09542551
P-value	0.173995734
D.O.F.	2
Chi^2	3.49744899
Slope Factor	0.003485671

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	0.001894697	0.182567022	-0.3559301	0.35971949

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	1.523E-07	0	10	-0.00039
107	0.183503423	1.835034229	0	10	-1.499149
214	0.333333329	3.333333294	5	10	1.118034

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-6.931471806	3	-	-	NA
Fitted Model	-9.547712753	1	5.23248189	2	0.073077
Reduced Model	-13.51683627	1	13.1707289	2	0.0013804

Figure 2-113. Details Regarding the Selected Model (Quantal Linear) for Increased Incidence of Thymus Necrosis in Female Rats Exposed to 1,2-Dichloroethane Via Oral Gavage for 13 Weeks

2.2 Cancer Endpoints – 1,2-Dichloroethane

EPA used the oral cancer slope factors from 1,2-dichloroethane, based on hepatocellular carcinomas in male mice (NTP (1978) as cited in the IRIS 1987 assessment on 1,2-dichloroethane), for read across to 1,1-dichloroethane, and no additional modeling was performed for the oral route. The inhalation unit risk for 1,1-dichloroethane was based on read-cross from an inhalation study for 1,2-dichloroethane by Nagano et al. (2006). EPA conducted BMD modeling on these data as described below.

The BMD modeling of cancer incidence data was conducted with the EPA's BMD software (BMDS, version 3.3). Modeled concentrations were in units of ppm. For these data, the Multistage model was fit to the incidence data using a BMR of 10 percent ER. The Multistage cancer model was run for all polynomial degrees up to n–1 (where n is the number of dose groups including control). Adequacy of model fit was judged based on the chi-square 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 BMDL from the model with the lowest AIC was selected if the BMDLs were sufficiently close (< 3-fold); if the BMDLs were not sufficiently close (> 3-fold), model-dependence is indicated, and the model with the lowest reliable BMDL was selected.

Where applicable, the MS Combo model was used to evaluate the combined cancer risk of tumors observed in multiple tissues in a test group, assuming that the tumors in the different tissues occurred independently. MS Combo was run using the incidence data for the individual tumors and the polydegrees identified in the model runs for the individual tumors.

2.2.1 Rat Data

2.2.1.1 Tumor Incidence in Male Rats

2.2.1.1.1 Subcutaneous Fibromas in Male Rats

Male rats exhibited a significantly increased trend for the incidence of subcutaneous fibromas in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). For BMD modeling, the exposure concentrations were first duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week rather than 6 hours per day, 5 days per week. Then, the Multistage cancer models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentration and response data used for the modeling are presented in Table 2-83.

Table 2-83. Increased Incidence of Subcutaneous Fibromas in Male Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 2-Year Chronic Bioassay

Adjusted Concentration (ppm)	Number of Animals	Incidence
0	50	6
2	50	9
7	50	12
29	50	15

The BMD modeling results for subcutaneous fibromas in male rats are summarized in Table 2-84. All Multistage models provided an adequate fit (chi-square p-value > 0.1) to the data. The Multistage 2- and 3-degree models converged on the 1-degree model; therefore, the 1-degree Multistage model was selected as the more parsimonious choice. A plot of the Multistage 1 model with a BMR of 10 percent ER is shown in Figure 2-114. Additional modeling details, including model parameters, goodness of fit at each concentration, and log likelihood are shown in Figure 2-115.

Table 2-84. Summary of BMD Modeling Results for Increased Incidence of Subcutaneous Fibromas in Male Rats Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay[a]

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 3	0.6229	205.2	14	7.3	0.014	

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 2	0.6229	205.2	14	7.3	0.014	All the Multistage models provided adequate fit (chi-square p-value > 0.1). The 2- and 3-degree models converged on the 1-degree model; therefore, EPA chose the 1-degree Multistage model.
Multistage 1	**0.6229**	**205.2**	**14**	**7.3**	**0.014**	
[a] Selected model in bold.						

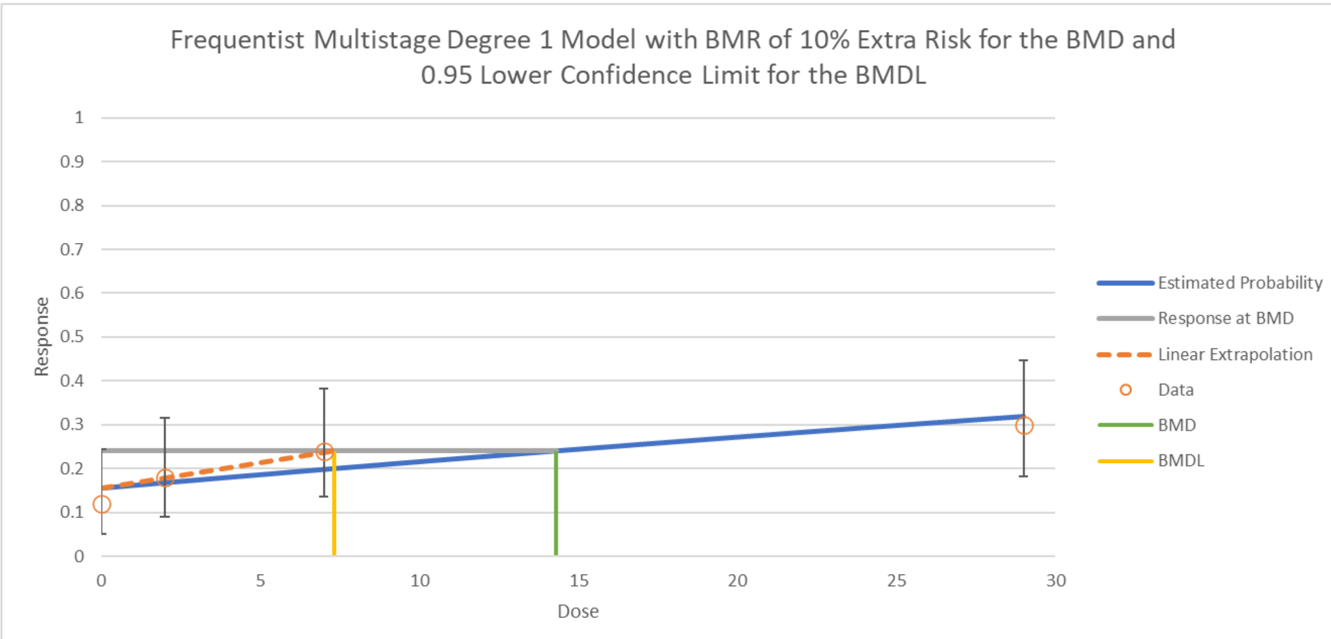

Figure 2-114. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 1-Degree) for the Increased Incidence of Subcutaneous Fibromas in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

Benchmark Dose	
BMD	14.31033134
BMDL	7.324332663
BMDU	Infinity
AIC	205.197232
P-value	0.622942744
D.O.F.	2
Chi^2	0.946601335
Slope Factor	0.013653121

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.155527448	1.70E-02	0.122295876	0.188759019
b1	0.007362549	0.108083178	-0.204476589	0.219201687

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.155527448	7.776372388	6	50	-0.637008884
2	0.167871284	8.393564185	9	50	0.209320438
7	0.19794724	9.89736201	12	50	0.668351272
29	0.317884967	15.89424837	15	50	-0.224304589

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-100.0131354	4	-	-	NA
Fitted Model	-100.598616	2	1.170961199	2	0.556838181
Reduced Model	-102.7913341	1	4.385436226	3	0.222739593

Figure 2-115. Details Regarding the Selected Model (Multistage 1-Degree) for the Increased Incidence of Subcutaneous Fibromas in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.1.1.2 Mammary Gland Fibroadenomas in Male Rats

Male rats exhibited significantly increased incidences of mammary gland fibroadenomas in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). For BMD modeling, the exposure concentrations were first duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week rather than 6 hours per day, 5 days per week. Then, the Multistage cancer models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentration and response data used for the modeling are presented in Table 2-85.

Table 2-85. Increased Incidence of Mammary Gland Fibroadenomas in Male Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 2-Year Chronic Bioassay

Adjusted Concentration (ppm)	Number of Animals	Incidence
0	50	0
2	50	0
7	50	1
29	50	5

The BMD modeling results for mammary gland fibroadenomas in male rats are summarized in Table 2-86. All Multistage models provided an adequate fit (chi-square p-value > 0.1) to the data. The Multistage 3-degree model converged on the 2-degree model. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Multistage 1-degree). A plot of the Multistage 1-degree model with a BMR of 10 percent ER is shown in Figure 2-116. Additional modeling details, including model parameters, goodness of fit at each concentration, and log likelihood are shown in Figure 2-117.

Table 2-86. Summary of BMD Modeling Results for Increased Incidence of Mammary Gland Fibroadenomas in Male Rats Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay[a]

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 3	0.8739	46.8	29	18	0.0056	All the Multistage models provided adequate fit (chi-square p-value > 0.1). The 3-degree model converged on the 2-degree model. The BMDLs were sufficiently close (differed by < 3-fold); therefore, EPA chose the 1-degree Multistage model, which had the lowest AIC.
Multistage 2	0.8739	46.8	29	18	0.0056	
Multistage 1	**0.9425**	**45.0**	**32**	**17**	**0.0057**	

[a] Selected model in bold.

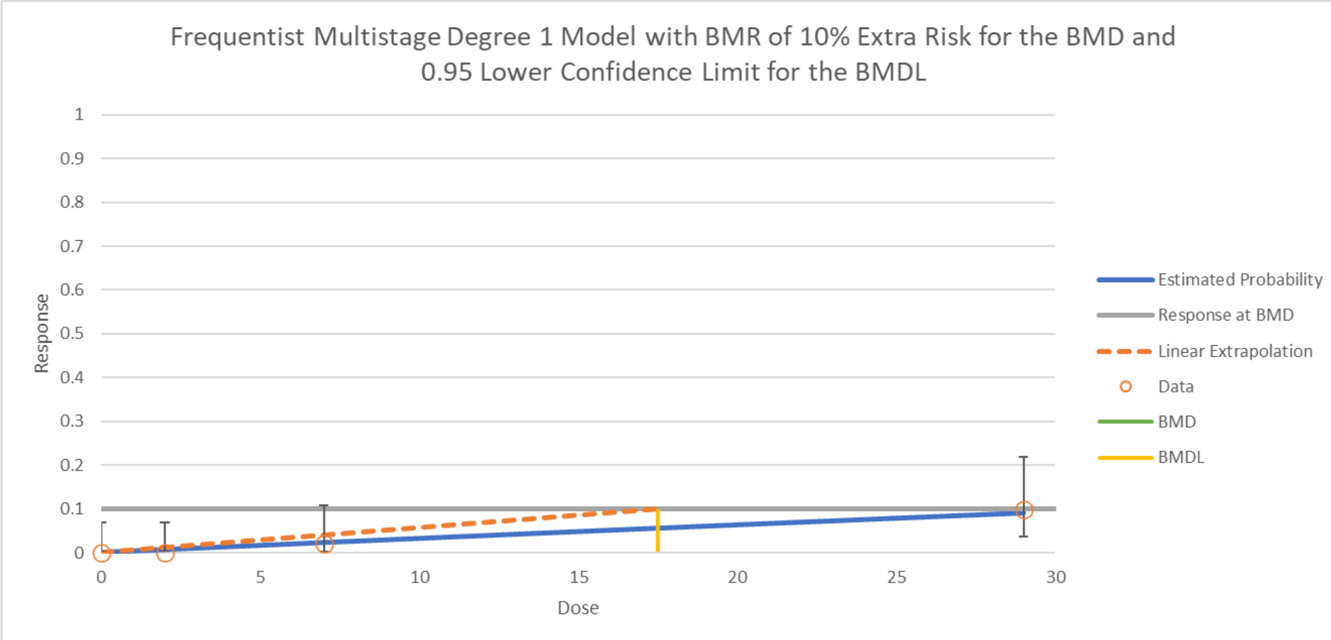

Figure 2-116. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 1-Degree) for the Increased Incidence of Mammary Gland Fibroadenomas in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

Benchmark Dose	
BMD	32.00911617
BMDL	17.49222195
BMDU	68.22514663
AIC	45.03571882
P-value	0.942486739
D.O.F.	3
Chi^2	0.389090832
Slope Factor	0.005716827

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	0.003291578	3.90E-02	-0.073102918	0.079686075

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	7.61499E-07	0	50	-0.001
2	0.00656155	0.328077513	0	50	-0.573
7	0.022777645	1.138882259	1	50	-0.130
29	0.091041451	4.55207255	5	50	0.210

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-21.15610433	4	-	-	NA
Fitted Model	-21.51785941	1	0.723510151	3	0.867660684
Reduced Model	-26.94843364	1	10.86114845	3	0.012500888

Figure 2-117. Details Regarding the Selected Model (Multistage 1-Degree) for the Increased Incidence of Mammary Gland Fibroadenomas in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.1.1.3 Mammary Gland Adenomas and Fibroadenomas (Combined) in Male Rats

Male rats exhibited significantly increased incidences of mammary gland adenomas and fibroadenomas (combined) in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). For BMD modeling, the exposure concentrations were first duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week rather than 6 hours per day, 5 days per week. Then, the Multistage cancer models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentration and response data used for the modeling are presented in Table 2-87.

Table 2-87. Increased Incidence of Mammary Gland Adenomas and Fibroadenomas (Combined) in Male Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 2-Year Chronic Bioassay

Adjusted Concentration (ppm)	Number of Animals	Incidence
0	50	1
2	50	2
7	50	1
29	50	7

The BMD modeling results for mammary gland adenomas and fibroadenomas (combined) in male rats are summarized in Table 2-88. All Multistage models provided an adequate fit (chi-square p-value > 0.1) to the data. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Multistage 3-degree). A plot of the Multistage 3-degree model with a BMR of 10 percent ER is shown in Figure 2-118. Additional modeling details, including model parameters, goodness of fit at each concentration, and log likelihood are shown in Figure 2-119.

Table 2-88. Summary of BMD Modeling Results for Increased Incidence of Mammary Gland Adenomas and Fibroadenomas (Combined) in Male Rats Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay[a]

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 3	**0.7617**	**81.43**	**27**	**15**	**0.0065**	All the Multistage models provided adequate fit (chi-square p-value > 0.1). The BMDLs were sufficiently close (differed by < 3-fold); therefore, EPA chose the 3-degree Multistage model, which had the lowest AIC.
Multistage 2	0.7116	81.58	27	15	0.0066	
Multistage 1	0.5722	82.24	27	14	0.0072	

[a] Selected model in bold.

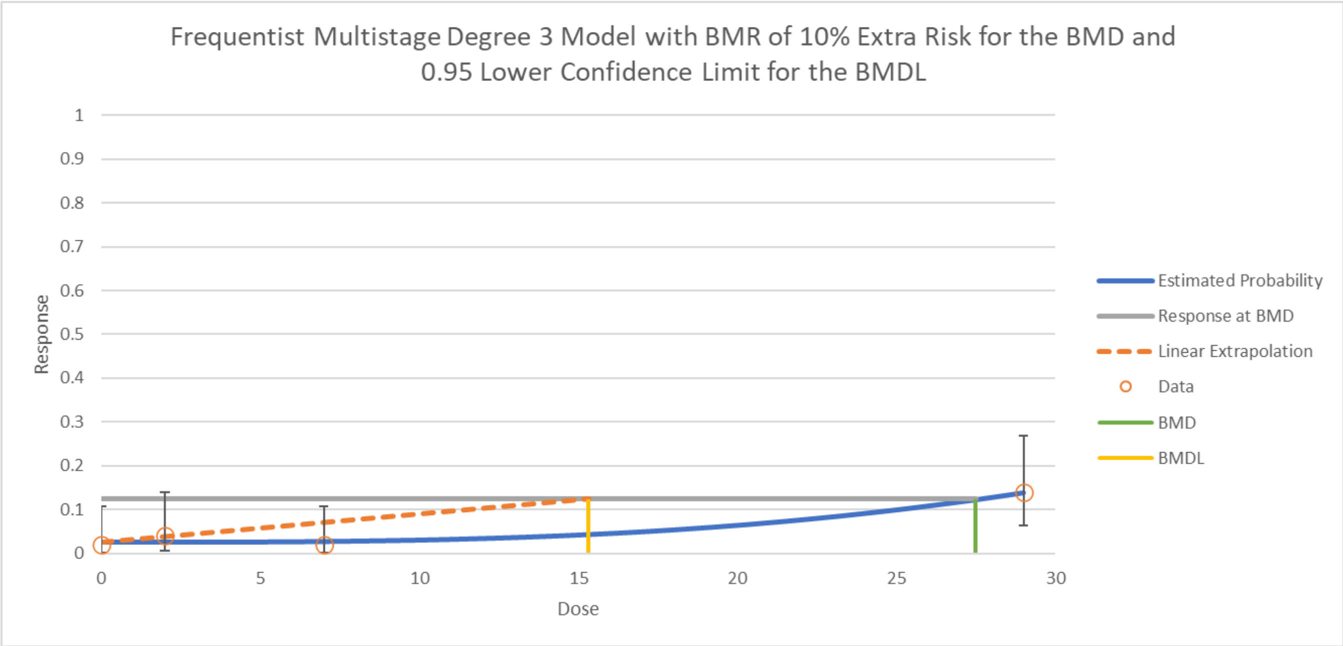

Figure 2-118. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 3-Degree) for the Increased Incidence of Mammary Gland Adenomas and Fibroadenomas (Combined) in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

Benchmark Dose	
BMD	27.49900097
BMDL	15.31882395
BMDU	61.22780582
AIC	81.42793799
P-value	0.761735667
D.O.F.	2
Chi^2	0.544311354
Slope Factor	0.006527916

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.026277252	3.23E-02	-0.036979536	0.089534039
b1	Bounded	NA	NA	NA
b2	Bounded	NA	NA	NA
b3	5.06672E-06	5.86E-02	-0.114805797	0.11481593

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.026277252	1.313862577	1	50	-0.273819621
2	0.026316719	1.31583597	2	50	0.596429835
7	0.027968001	1.398400056	1	50	-0.336902066
29	0.13946499	6.973249521	7	50	0.010130105

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-38.44929297	4	-	-	NA
Fitted Model	-38.71396899	2	0.529352051	2	0.767454546
Reduced Model	-42.59643946	1	7.764940939	3	0.051127864

Figure 2-119. Details Regarding the Selected Model (Multistage 3-Degree) for the Increased Incidence of Mammary Gland Adenomas and Fibroadenomas (Combined) in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.1.1.4 Peritoneal Mesothelioma in Male Rats

Male rats exhibited a significantly increased trend for incidence of peritoneal mesothelioma in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). For BMD modeling, the exposure concentrations were first duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week rather than 6 hours per day, 5 days per week. Then, the Multistage cancer models were fit to the dose-response data.

A BMR of 10 percent ER 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 2-89.

Table 2-89. Increased Incidence of Peritoneal Mesothelioma in Male Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 2-Year Chronic Bioassay

Adjusted Concentration (ppm)	Number of Animals	Incidence
0	50	1
2	50	1
7	50	1
29	50	5

The BMD modeling results for peritoneal mesothelioma in male rats are summarized in Table 2-90. All Multistage models provided an adequate fit (chi-square p-value > 0.1) to the data. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Multistage 3-degree). A plot of the Multistage 3-degree model with a BMR of 10 percent ER is shown in Figure 2-120. Additional modeling details, including model parameters, goodness of fit at each concentration, and log likelihood are shown in Figure 2-121.

Table 2-90. Summary of BMD Modeling Results for Increased Incidence of Peritoneal Mesothelioma in Male Rats Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay[a]

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 3	**0.9989**	**65.92**	**31**	**19**	**0.0052**	All the Multistage models provided adequate fit (chi-square p-value > 0.1). The BMDLs were sufficiently close (differed by < 3-fold); therefore, EPA chose the 3-degree Multistage model, which had the lowest AIC.
Multistage 2	0.9830	65.96	32	19	0.0052	
Multistage 1	0.8132	66.39	38	18	0.0055	

[a] Selected model in bold.

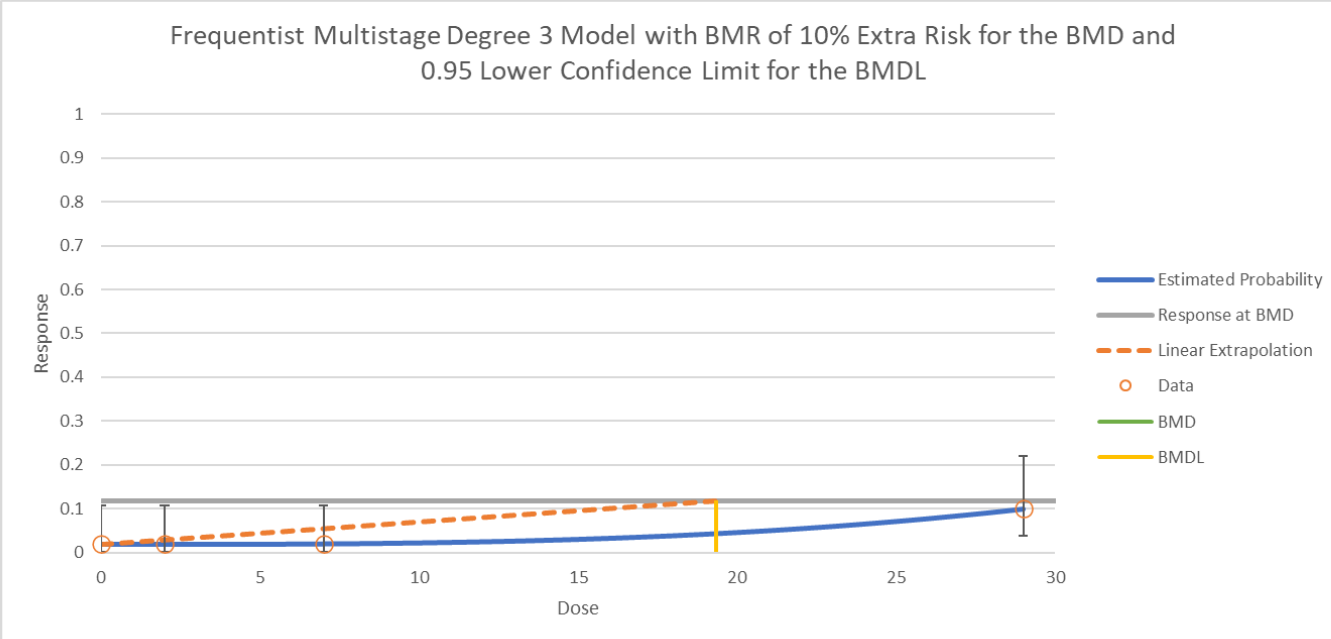

Figure 2-120. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 3-Degree) for the Increased Incidence of Peritoneal Mesothelioma in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

Benchmark Dose	
BMD	31.09224433
BMDL	19.32721096
BMDU	Infinity
AIC	65.92230974
P-value	0.998892256
D.O.F.	2
Chi^2	0.002216716
Slope Factor	0.005174052

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.019616475	3.73E-02	-0.053527977	0.092760928
b1	Bounded	NA	NA	NA
b2	Bounded	NA	NA	NA
b3	3.50527E-06	4.87E-02	-0.095482039	0.095489049

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.019616475	0.980823761	1	50	0.01936279
2	0.019643967	0.982198346	1	50	0.017962251
7	0.02079449	1.039724502	1	50	-0.038958239
29	0.099946886	4.997344318	5	50	0.001187972

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-30.96001566	4	-	-	NA
Fitted Model	-30.96115487	2	0.002278419	2	0.998861439
Reduced Model	-33.58882955	1	5.255349352	3	0.154026085

Figure 2-121. Details Regarding the Selected Model (Multistage 3-Degree) for the Increased Incidence of Peritoneal Mesothelioma in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.1.1.5 Combined Mammary Gland, Subcutaneous, and Peritoneal Tumors in Male Rats

Male rats exhibited significantly increased incidences of subcutaneous fibromas, mammary gland adenomas and fibroadenomas, and peritoneal mesothelioma in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). The MS Combo model was applied to the incidence data for the individual tumors and polydegrees identified for the individual tumor models, shown above (Sections 2.2.1.1.1 through 2.2.1.1.4), using a BMR of 10 percent ER.

The BMD Multistage Cancer/Multi-tumor modeling results for combined subcutaneous fibromas, mammary gland adenomas and fibroadenomas, and peritoneal mesothelioma in male rats are summarized in Table 2-91. A plot of the dose-response curves for the incidence of individual tumor types with a BMR of 10 percent ER is shown in Figure 2-122. Additional modeling details, including the cancer slope factor and log likelihood are shown in Figure 2-123.

Table 2-91. Summary of BMD Multi-Tumor (MS Combo) Modeling Results for Increased Incidence of Subcutaneous Fibromas, Mammary Gland Adenomas and Fibroadenomas, and Peritoneal Mesothelioma (Combined) in Male Rats Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay

Model	BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)
Multi-tumor (MS Combo)	**12**	**5.3**	**0.019**
Subcutaneous fibroma Multistage 1	14	7.3	0.014
Mammary gland adenoma and fibroadenoma Multistage 3	27	15	0.0065
Peritoneal mesothelioma Multistage 3	31	19	0.0052

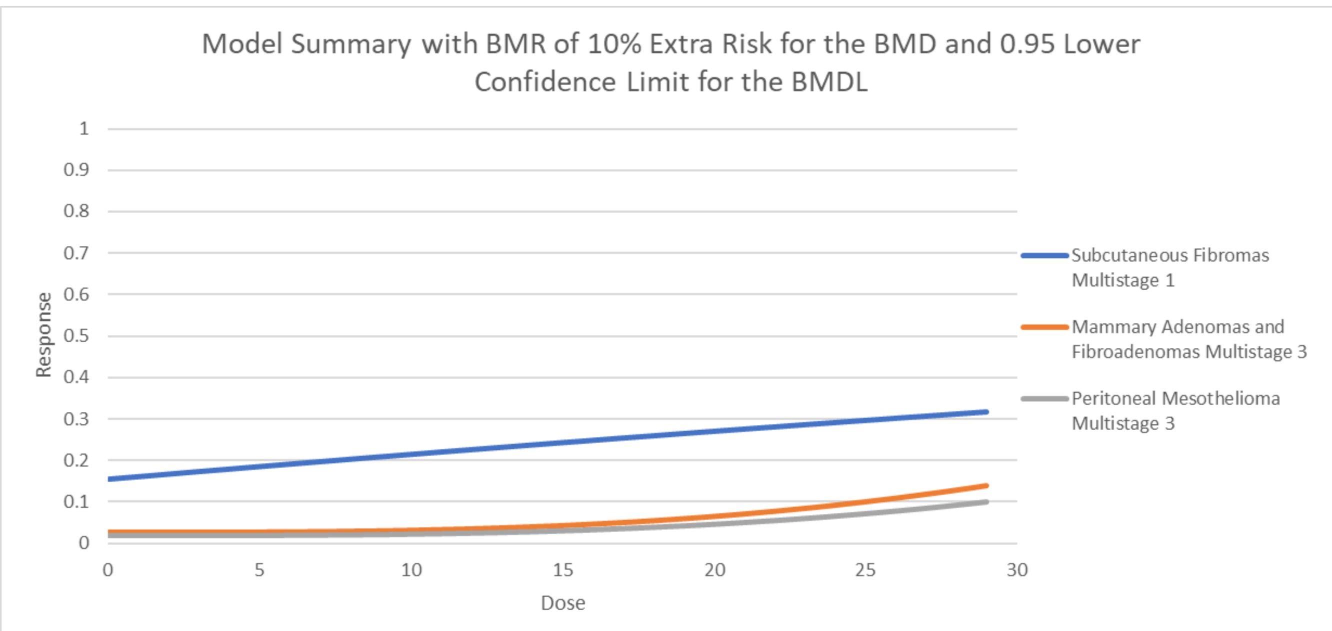

Figure 2-122. Plot of Response by Concentration with Fitted Curve for Selected Models used for the Multi-Tumor (MS Combo) Model for Increased Incidence of Subcutaneous Fibromas, Mammary Gland Adenomas and Fibroadenomas, and Peritoneal Mesothelioma (Combined) in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

User Input	
Info	
Model	frequentist Multi-tumor v1.0
Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	

Model Results	
Benchmark Dose	
BMD	12.19749412
BMDL	5.303369371
BMDU	21.35824384
Slope Factor	0.018855937
Combined Log-Likelihood	-170.2737399
Combined Log-Likelihood Constant	151.8443229

Figure 2-123. Details Regarding the Multi-Tumor (MS Combo) Model for the Increased Incidence of Subcutaneous Fibromas, Mammary Gland Adenomas and Fibroadenomas, and Peritoneal Mesothelioma (Combined) in Male Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.1.2 Tumor Incidence in Female Rats

2.2.1.2.1 Subcutaneous Fibromas in Female Rats

Female rats exhibited significantly increased incidences of subcutaneous fibromas in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). For BMD modeling, the exposure concentrations were first duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week rather than 6 hours per day, 5 days per week. Then, the Multistage cancer models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentration and response data used for the modeling are presented in Table 2-92.

Table 2-92. Increased Incidence of Subcutaneous Fibromas in Female Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 2-Year Chronic Bioassay

Adjusted Concentration (ppm)	Number of Animals	Incidence
0	50	0
2	50	0
7	50	1
29	50	5

The BMD modeling results for subcutaneous fibromas in female rats are summarized in Table 2-93. All Multistage models provided an adequate fit (chi-square p-value > 0.1) to the data. The Multistage 3-degree model converged on the 2-degree model. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Multistage 1-degree). A plot of the Multistage 1-degree model with a BMR of 10 percent ER is shown in Figure 2-124. Additional modeling details, including model parameters, goodness of fit at each concentration, and log likelihood are shown in Figure 2-125.

Table 2-93. Summary of BMD Modeling Results for Increased Incidence of Subcutaneous Fibromas in Female Rats Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay[a]

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 3	0.8739	46.75	29	18	0.0056	All the Multistage models provided adequate fit (chi-square p-value > 0.1). The 3-degree model converged on the 2-degree model. The BMDLs were sufficiently close (differed by < 3-fold); therefore, EPA chose the 1-degree Multistage model, which had the lowest AIC.
Multistage 2	0.8739	46.75	29	18	0.0056	
Multistage 1	**0.9425**	**45.04**	**32**	**17**	**0.0057**	

[a] Selected model in bold.

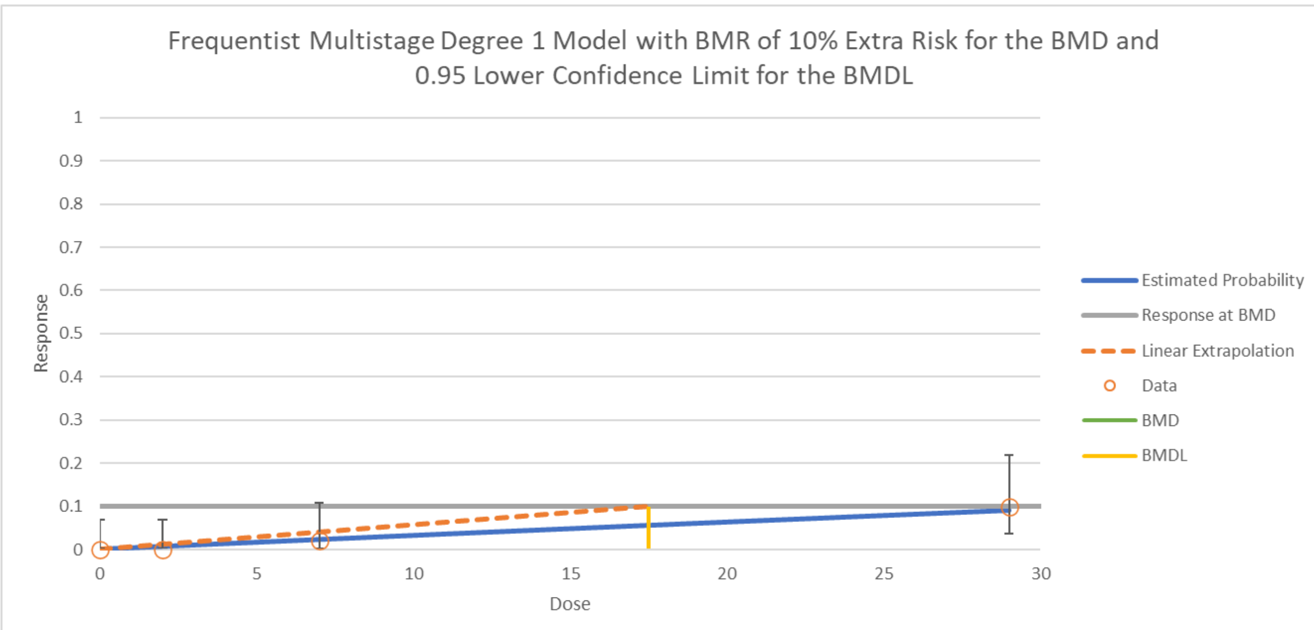

Figure 2-124. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 1-Degree) for the Increased Incidence of Subcutaneous Fibromas in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

Benchmark Dose	
BMD	32.00911617
BMDL	17.49222195
BMDU	68.22514663
AIC	45.03571882
P-value	0.942486739
D.O.F.	3
Chi^2	0.389090832
Slope Factor	0.005716827

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	0.003291578	3.90E-02	-0.073102918	0.079686075

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	7.61499E-07	0	50	-0.000872639
2	0.00656155	0.328077513	0	50	-0.572780511
7	0.022777645	1.138882259	1	50	-0.130138968
29	0.091041451	4.55207255	5	50	0.209943818

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-21.15610433	4	-	-	NA
Fitted Model	-21.51785941	1	0.723510151	3	0.867660684
Reduced Model	-26.94843364	1	10.86114845	3	0.012500888

Figure 2-125. Details Regarding the Selected Model (Multistage 1-Degree) for the Increased Incidence of Subcutaneous Fibromas in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.1.2.2 Mammary Gland Adenomas in Female Rats

Female rats exhibited significantly increased incidences of mammary gland adenomas in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). For BMD modeling, the exposure concentrations were first duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week rather than 6 hours per day, 5 days per week. Then, the Multistage cancer models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentration and response data used for the modeling are presented in Table 2-94.

Table 2-94. Increased Incidence of Mammary Gland Adenomas in Female Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 2-Year Chronic Bioassay

Adjusted Concentration (ppm)	Number of Animals	Incidence
0	50	3
2	50	5
7	50	5
29	50	11

The BMD modeling results for mammary gland adenomas in female rats are summarized in Table 2-95. All Multistage models provided an adequate fit (chi-square p-value > 0.1) to the data. The Multistage 3-degree model converged on the 1-degree model. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected. The 1-degree Multistage model was selected as the more parsimonious choice. A plot of the Multistage 1-degree model with a BMR of 10 percent ER is shown in Figure 2-126. Additional modeling details, including model parameters, goodness of fit at each concentration, and log likelihood are shown in Figure 2-127.

Table 2-95. Summary of BMD Modeling Results for Increased Incidence of Mammary Gland Adenomas in Female Rats Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay[a]

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 3	0.8523	144.7	18	9.4	0.011	All the Multistage models provided adequate fit (chi-square p-value > 0.1). The 3-degree model converged on the 1-degree model. The BMDLs were sufficiently close (differed by < 3-fold); therefore, EPA chose the 1-degree Multistage model, which had the lowest AIC and was the more parsimonious choice.
Multistage 2	0.5709	146.7	18	9.4	0.011	
Multistage 1	**0.8516**	**144.7**	**18**	**9.4**	**0.011**	

[a] Selected model in bold.

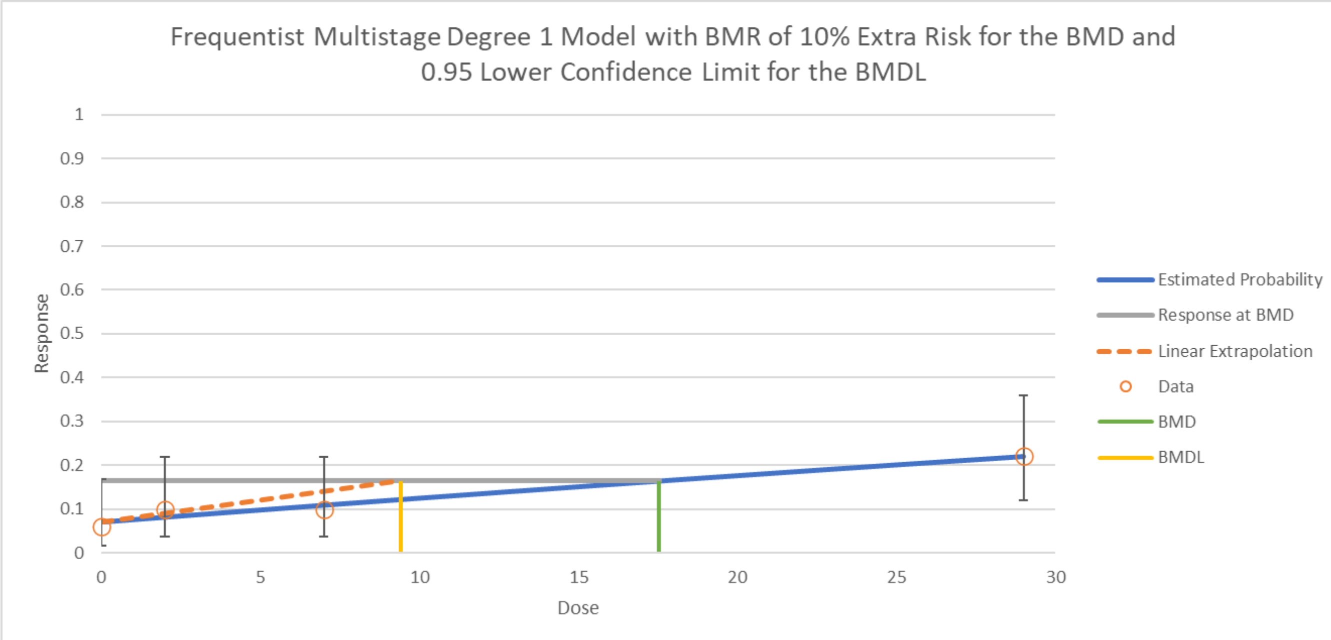

Figure 2-126. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 1-Degree) for the Increased Incidence of Mammary Gland Adenomas in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

Benchmark Dose	
BMD	17.53354728
BMDL	9.407667481
BMDU	58.29776202
AIC	144.7453231
P-value	0.851617435
D.O.F.	2
Chi^2	0.321235746
Slope Factor	0.010629627

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.070489692	2.44E-02	0.022654769	0.118324615
b1	0.006009082	7.59E-02	-0.142761504	0.154779667

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.070489692	3.524484591	3	50	-0.279373318
2	0.081593839	4.079691958	5	50	0.455637574
7	0.108777313	5.438865655	5	50	-0.188181718
29	0.219141052	10.95705262	11	50	0.012974475

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-70.20207154	4	-	-	NA
Fitted Model	-70.37266157	2	0.341180063	2	0.843167175
Reduced Model	-73.38499825	1	6.024673375	3	0.110415963

Figure 2-127. Details Regarding the Selected Model (Multistage 1-Degree) for the Increased Incidence of Mammary Gland Adenomas in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.1.2.3 Mammary Gland Fibroadenomas in Female Rats

Female rats exhibited significantly increased incidences of mammary gland fibroadenomas in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). For BMD modeling, the exposure concentrations were first duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week rather than 6 hours per day, 5 days per week. Then, the Multistage cancer models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentration and response data used for the modeling are presented in Table 2-96.

Table 2-96. Increased Incidence of Mammary Gland Fibroadenomas in Female Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 2-Year Chronic Bioassay

Adjusted Concentration (ppm)	Number of Animals	Incidence
0	50	4
2	50	1
7	50	6
29	50	13

The BMD modeling results for mammary gland fibroadenomas in female rats are summarized in Table 2-97. All Multistage models provided an adequate fit (chi-square p-value > 0.1) to the data. The Multistage 3-degree model converged on the 2-degree model. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Multistage 1-degree). A plot of the Multistage 1-degree model with a BMR of 10 percent ER is shown in Figure 2-128. Additional modeling details, including model parameters, goodness of fit at each concentration, and log likelihood are shown in Figure 2-129.

Table 2-97. Summary of BMD Modeling Results for Increased Incidence of Mammary Gland Fibroadenomas in Female Rats Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay[a]

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 3	0.1157	140.8	15	7.8	0.013	All the Multistage models provided adequate fit (chi-square p-value > 0.1). The 3-degree model converged on the 2-degree model. The BMDLs were sufficiently close (differed by < 3-fold); therefore, EPA chose the 1-degree Multistage model, which had the lowest AIC.
Multistage 2	0.1157	140.8	15	7.8	0.013	
Multistage 1	**0.2797**	**138.9**	**13**	**7.7**	**0.013**	

[a] Selected model in bold.

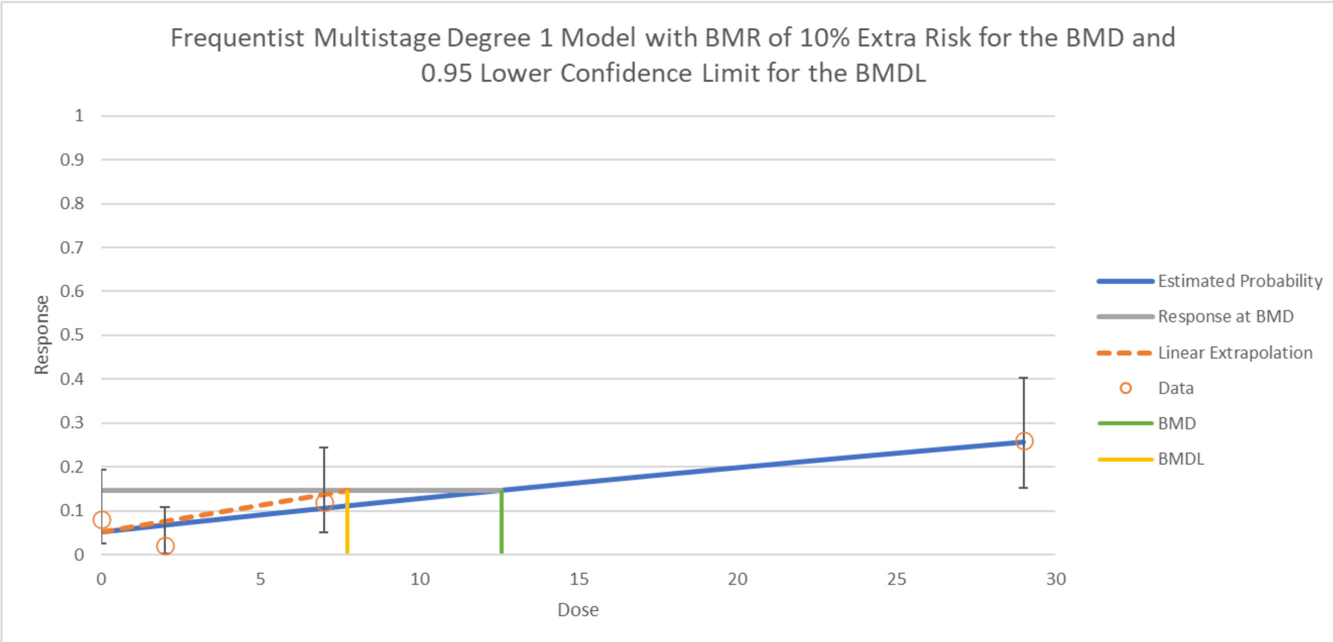

Figure 2-128. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 1-Degree) for the Increased Incidence of Mammary Gland Fibroadenomas in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

Benchmark Dose	
BMD	12.58447242
BMDL	7.741278443
BMDU	26.11089254
AIC	138.9247592
P-value	0.279716095
D.O.F.	2
Chi^2	2.547960275
Slope Factor	0.012917763

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.051585929	2.83E-02	-0.003958966	0.107130823
b1	0.008372264	7.82E-02	-0.144863436	0.161607964

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.051585929	2.579296433	4	50	0.884612032
2	0.067334456	3.3667228	1	50	-1.289863384
7	0.105571164	5.278558204	6	50	0.314010118
29	0.256033853	12.80169265	13	50	0.055424925

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-65.83951967	4	-	-	NA
Fitted Model	-67.46237958	2	3.245719818	2	0.197333535
Reduced Model	-73.38499825	1	11.84523735	3	0.007932559

Figure 2-129. Details Regarding the Selected Model (Multistage 1-Degree) for the Increased Incidence of Mammary Gland Fibroadenomas in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.1.2.4 Mammary Gland Adenomas and Fibroadenomas (Combined) in Female Rats

Female rats exhibited significantly increased incidences of mammary gland adenomas and fibroadenomas (combined) in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). For BMD modeling, the exposure concentrations were first duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week rather than 6 hours per day, 5 days per week. Then, the Multistage cancer models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentration and response data used for the modeling are presented in Table 2-98.

Table 2-98. Increased Incidence of Mammary Gland Adenomas and Fibroadenomas (Combined) in Female Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 2-Year Chronic Bioassay

Adjusted Concentration (ppm)	Number of Animals	Incidence
0	50	7
2	50	6
7	50	11
29	50	22

The BMD modeling results for mammary gland adenomas and fibroadenomas (combined) in female rats are summarized in Table 2-99. All Multistage models provided an adequate fit (chi-square p-value > 0.1) to the data. The Multistage 3-degree model converged on the 2-degree model. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Multistage 1-degree). A plot of the Multistage 1-degree model with a BMR of 10 percent ER is shown in Figure 2-130. Additional modeling details, including model parameters, goodness of fit at each concentration, and log likelihood are shown in Figure 2-131.

Table 2-99. Summary of BMD Modeling Results for Increased Incidence of Mammary Gland Adenomas and Fibroadenomas (Combined) in Female Rats Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay[a]

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 3	0.5222	205.0	7.5	4.5	0.022	All the Multistage models provided adequate fit (chi-square p-value > 0.1). The 3-degree model converged on the 2-degree model. The BMDLs were sufficiently close (differed by < 3-fold); therefore, EPA chose the 1-degree Multistage model, which had the lowest AIC.
Multistage 2	0.5222	205.0	7.5	4.5	0.022	
Multistage 1	**0.8084**	**203.0**	**7.5**	**4.5**	**0.022**	

[a] Selected model in bold.

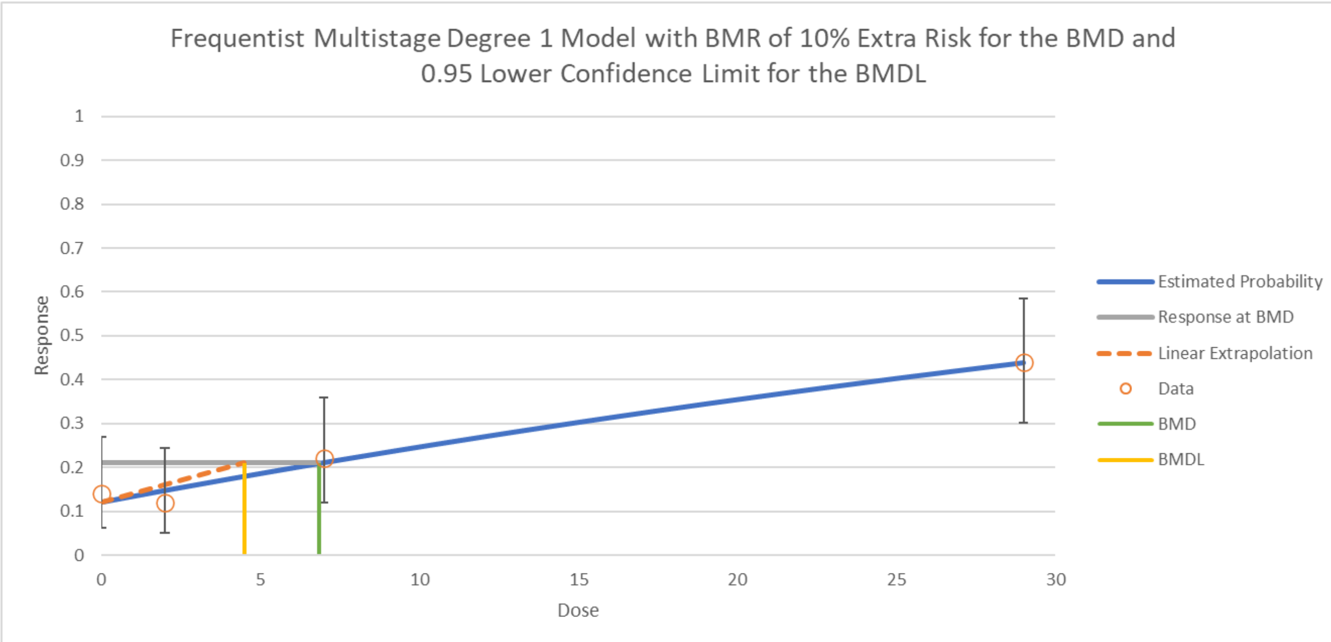

Figure 2-130. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 1-Degree) for the Increased Incidence of Mammary Gland Adenomas and Fibroadenomas (Combined) in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

Benchmark Dose	
BMD	6.836211264
BMDL	4.501066127
BMDU	12.30383058
AIC	202.9818151
P-value	0.808367209
D.O.F.	2
Chi^2	0.425477713
Slope Factor	0.022216959

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.121858132	1.93E-02	0.083957729	0.159758535
b1	0.015412121	0.125543163	-0.230647959	0.261472202

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.121858132	6.092906583	7	50	0.367485117
2	0.148513267	7.425663362	6	50	-0.523177864
7	0.211664854	10.5832427	11	50	0.12810729
29	0.438362491	21.91812455	22	50	0.017488478

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-99.2363119	4	-	-	NA
Fitted Model	-99.49090755	2	0.509191289	2	0.775229903
Reduced Model	-107.8552683	1	16.72872151	3	0.000803582

Figure 2-131. Details Regarding the Selected Model (Multistage 1-Degree) for the Increased Incidence of Mammary Gland Adenomas and Fibroadenomas (Combined) in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.1.2.5 Mammary Gland Adenocarcinomas in Female Rats

Female rats exhibited a significantly increased trend for the incidence of mammary gland adenocarcinomas in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). For BMD modeling, the exposure concentrations were first duration adjusted to estimate an equivalent inhalation dose for animals exposed for 24 hours per day, 7 days per week rather than 6 hours per day, 5 days per week. Then, the Multistage cancer models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentration and response data used for the modeling are presented in Table 2-100.

Table 2-100. Increased Incidence of Mammary Gland Adenocarcinomas in Female Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 2-Year Chronic Bioassay

Adjusted Concentration (ppm)	Number of Animals	Incidence
0	50	1
2	50	2
7	50	0
29	50	5

The BMD modeling results for mammary gland adenocarcinomas in female rats are summarized in Table 2-101. All Multistage models provided an adequate fit (chi-square p-value > 0.1) to the data. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Multistage 3-degree). A plot of the Multistage 3-degree model with a BMR of 10 percent ER is shown in Figure 2-132. Additional modeling details, including model parameters, goodness of fit at each concentration, and log likelihood are shown in Figure 2-133.

Table 2-101. Summary of BMD Modeling Results for Increased Incidence of Mammary Gland Adenocarcinomas in Female Rats Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay[a]

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 3	**0.3593**	**66.04**	**31**	**23**	**0.0043**	All the Multistage models provided adequate fit (chi-square p-value > 0.1). The BMDLs were sufficiently close (differed by < 3-fold); therefore, EPA chose the 3-degree Multistage model, which had the lowest AIC.
Multistage 2	0.3371	66.36	33	22	0.0045	
Multistage 1	0.2854	67.32	44	20	0.0050	

[a] Selected model in bold.

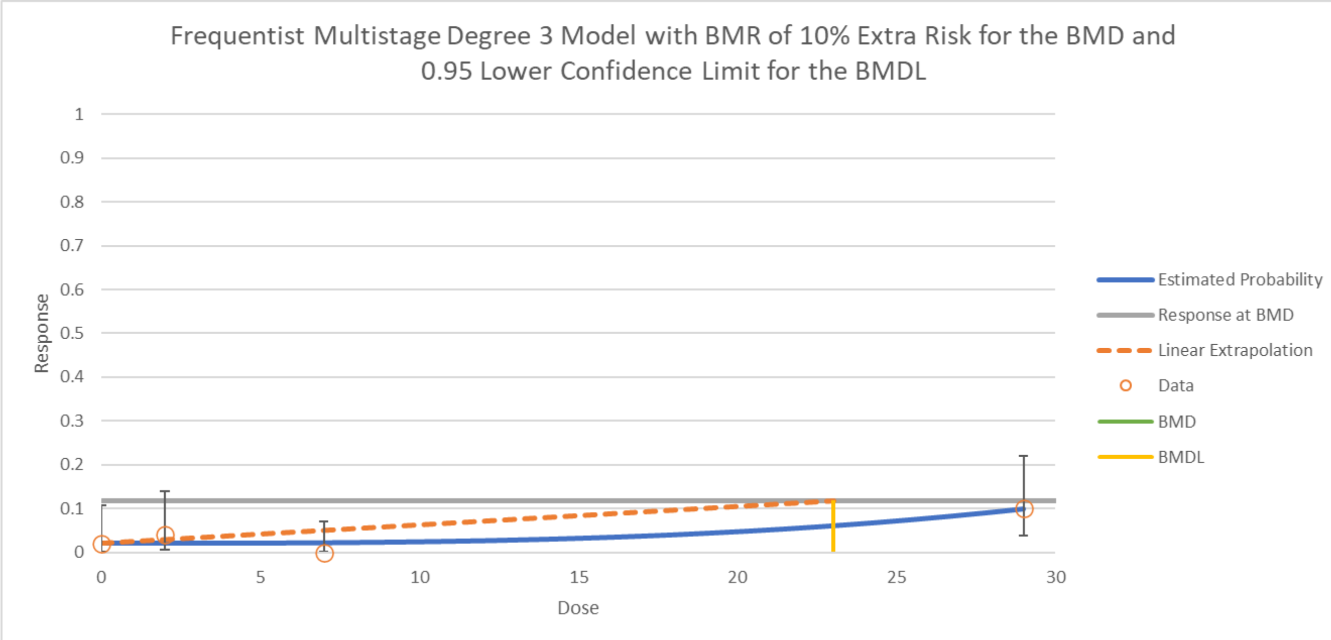

Figure 2-132. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 3-Degree) for the Increased Incidence of Mammary Gland Adenocarcinomas in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

Benchmark Dose	
BMD	31.32763273
BMDL	23.02143452
BMDU	Infinity
AIC	66.03592535
P-value	0.35930595
D.O.F.	2
Chi^2	2.04716205
Slope Factor	0.004343778

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.020074114	3.65E-02	-0.051434256	0.091582483
b1	Bounded	NA	NA	NA
b2	Bounded	NA	NA	NA
b3	3.42685E-06	4.79E-02	-0.093905886	0.09391274

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.020074114	1.003705676	1	50	-0.003698829
2	0.020100978	1.005048882	2	50	0.992448894
7	0.021225251	1.061262562	0	50	-1.030175986
29	0.098644728	4.932236411	5	50	0.030512266

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-29.55331172	4	-	-	NA
Fitted Model	-31.01796267	2	2.929301905	2	0.231158663
Reduced Model	-33.58882955	1	5.141733748	3	0.161708073

Figure 2-133. Details Regarding the Selected Model (Multistage 3-Degree) for the Increased Incidence of Mammary Gland Adenocarcinomas in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.1.2.6 Mammary Gland Adenomas, Fibroadenomas, and Adenocarcinomas (Combined) in Female Rats

Female rats exhibited significantly increased incidences of mammary gland adenomas, fibroadenomas, and adenocarcinomas (combined) in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). For BMD modeling, the exposure concentrations were first duration adjusted to estimate an equivalent inhalation dose for animals exposed for 24 hours per day, 7 days per week rather than 6 hours per day, 5 days per week. Then, the Multistage cancer models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentration and response data used for the modeling are presented in Table 2-102.

Table 2-102. Increased Incidence of Mammary Gland Adenomas, Fibroadenomas, and Adenocarcinomas (Combined) in Female Rats and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 2-Year Chronic Bioassay

Adjusted Concentration (ppm)	Number of Animals	Incidence
0	50	8
2	50	8
7	50	11
29	50	25

The BMD modeling results for mammary gland adenomas, fibroadenomas, and adenocarcinomas (combined) in female rats are summarized in Table 2-103. All Multistage models provided an adequate fit (chi-square p-value > 0.1) to the data. The Multistage 3-degree model converged on the 2-degree model. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Multistage 1-degree). A plot of the Multistage 1-degree model with a BMR of 10 percent ER is shown in Figure 2-134. Additional modeling details, including model parameters, goodness of fit at each concentration, and log likelihood are shown in Figure 2-135.

Table 2-103. Summary of BMD Modeling Results for Increased Incidence of Mammary Gland Adenomas, Fibroadenomas, and Adenocarcinomas (Combined) in Female Rats Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay[a]

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 3	0.8383	216.0	9.2	4.1	0.025	All the Multistage models provided adequate fit (chi-square p-value > 0.1). The 3-degree model converged on the 2-degree model. The BMDLs were sufficiently close (differed by < 3-fold); therefore, EPA chose the 1-degree Multistage model, which had the lowest AIC.
Multistage 2	0.8383	216.0	9.2	4.1	0.025	
Multistage 1	**0.8714**	**214.3**	**5.9**	**4.0**	**0.025**	

[a] Selected model in bold.

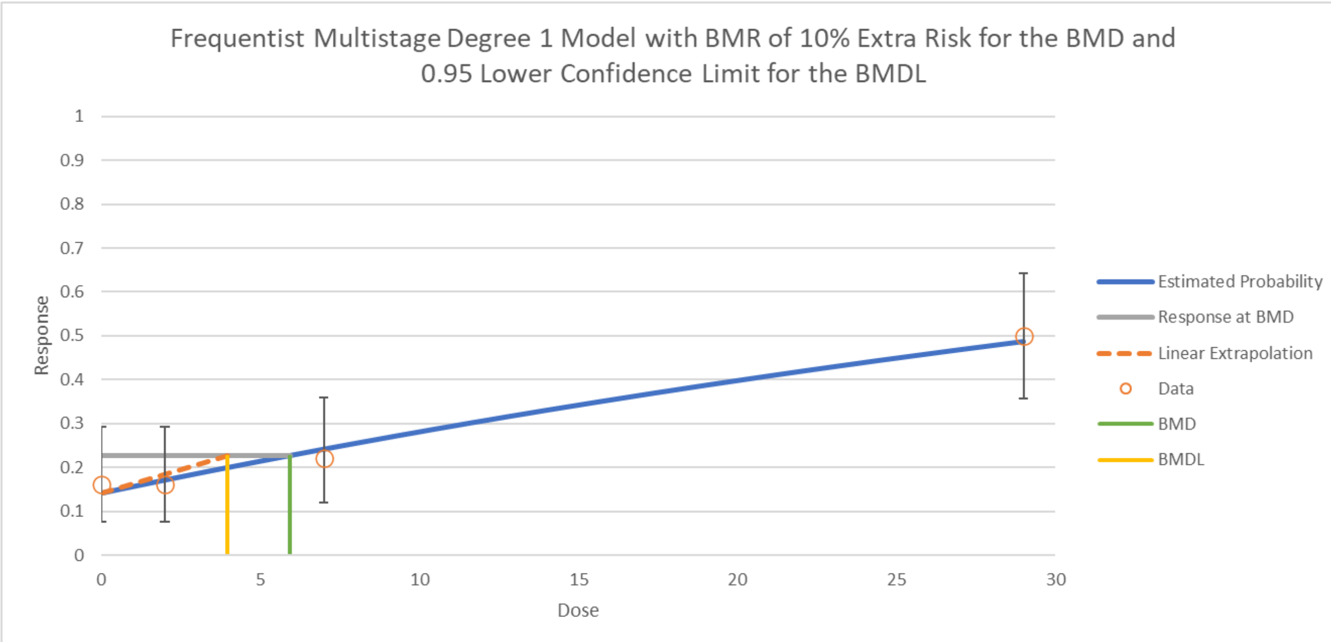

Figure 2-134. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 1-Degree) for the Increased Incidence of Mammary Gland Adenomas, Fibroadenomas, and Adenocarcinomas (Combined) in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

Benchmark Dose	
BMD	5.931093454
BMDL	3.976641889
BMDU	10.25361658
AIC	214.2892161
P-value	0.871412464
D.O.F.	2
Chi^2	0.275279724
Slope Factor	0.025146846

Model Parameters				
# of Parameters	2			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.141490568	1.79E-02	0.106338916	0.176642219
b1	0.017764096	0.1380138	-0.252737984	0.288266175

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.141490568	7.074528384	8	50	0.34794801
2	0.171456388	8.572819379	8	50	-0.195639194
7	0.241874456	12.09372282	11	50	-0.314504792
29	0.487121544	24.35607719	25	50	0.130475851

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-104.969745	4	-	-	NA
Fitted Model	-105.1446081	2	0.349726056	2	0.839572011
Reduced Model	-114.6113834	1	18.93355072	3	0.000282186

Figure 2-135. Details Regarding the Selected Model (Multistage 1-Degree) for the Increased Incidence of Mammary Gland Adenomas, Fibroadenomas, and Adenocarcinomas (Combined) in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.1.2.7 Combined Mammary Gland and Subcutaneous Tumors in Female Rats

Female rats exhibited significantly increased incidences of subcutaneous fibromas and mammary gland adenomas, fibroadenomas, and adenocarcinomas in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). The MS Combo model was applied to the incidence data for the individual tumors and polydegrees identified for the individual tumor models, shown above (Sections 2.2.1.2.1 through 2.2.1.2.6), using a BMR of 10 percent ER.

The BMD Multistage Cancer/Multi-tumor modeling results for combined subcutaneous fibromas and mammary gland adenomas, fibroadenomas, and adenocarcinomas in female rats are summarized in

Table 2-104. A plot of the dose-response curves for the incidence of individual tumor types with a BMR of 10 percent ER is shown in Figure 2-136. Additional modeling details, including the cancer slope factor and log likelihood are shown in Figure 2-137.

Table 2-104. Summary of BMD Multi-Tumor (MS Combo) Modeling Results for Increased Incidence of Subcutaneous Fibromas and Mammary Gland Adenomas, Fibroadenomas, and Adenocarcinomas (Combined) in Female Rats Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay

Model	BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)
Multi-tumor (MS Combo)	**5.0**	**3.5**	**0.029**
Subcutaneous fibroma Multistage 1	32	17	0.0057
Mammary gland adenoma, fibroadenoma, and adenocarcinoma Multistage 1	5.9	4.0	0.025

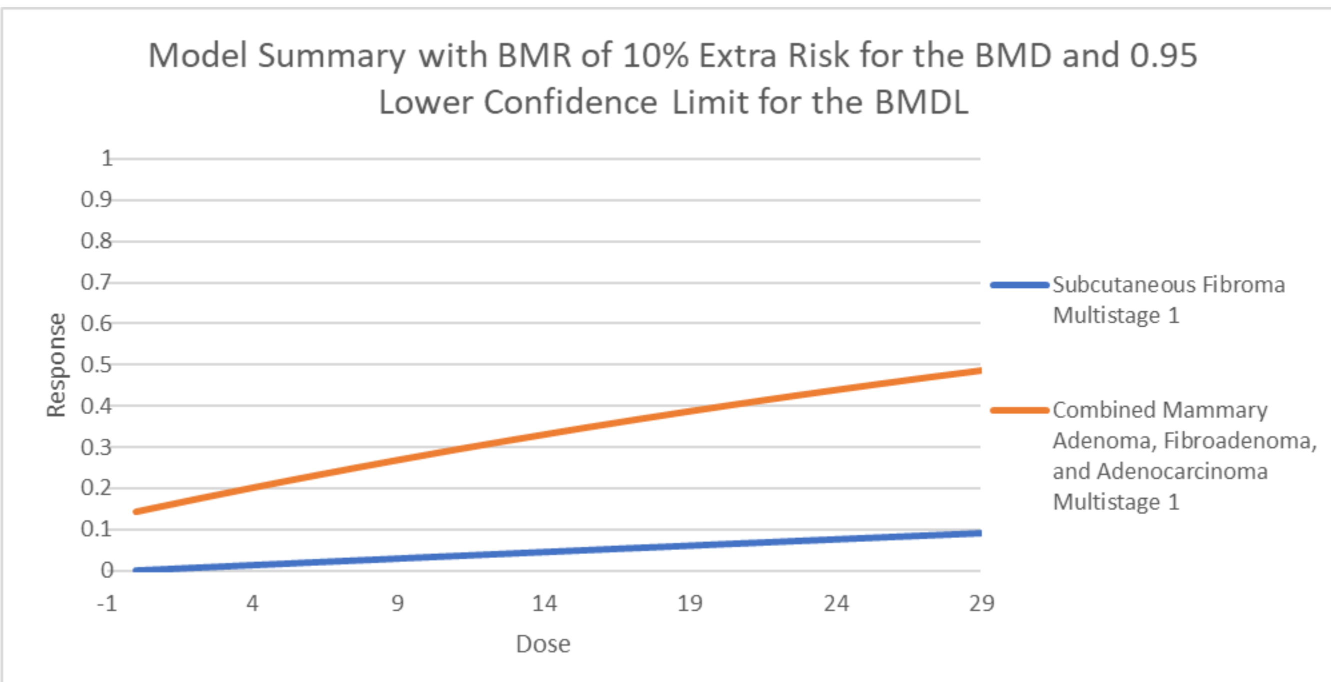

Figure 2-136. Plot of Response by Concentration with Fitted Curve for Selected Models Used for the Multi-Tumor (MS Combo) Model for Increased Incidence of Subcutaneous Fibromas and Mammary Gland Adenomas, Fibroadenomas, and Adenocarcinomas (Combined) in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

User Input	
Info	
Model	frequentist Multi-tumor v1.0
Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	

Model Results	
Benchmark Dose	
BMD	5.003900592
BMDL	3.50357935
BMDU	7.943159365
Slope Factor	0.028542239
Combined Log-Likelihood	-126.6624659
Combined Log-Likelihood Constant	115.4951852

Figure 2-137. Details Regarding the Multi-Tumor (MS Combo) Model for the Increased Incidence of Subcutaneous Fibromas and Mammary Gland Adenomas, Fibroadenomas, and Adenocarcinomas (Combined) in Female Rats Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.2 Mouse Data

2.2.2.1 Bronchiolo-Alveolar Adenomas in Female Mice

Female mice exhibited a significantly increased trend for the incidence of bronchiolo-alveolar adenomas in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). For BMD modeling, the exposure concentrations were first duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week rather than 6 hours per day, 5 days per week. Then, the Multistage cancer models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentration and response data used for the modeling are presented in Table 2-105.

Table 2-105. Increased Incidence of Bronchiolo-Alveolar Adenomas in Female Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 2-Year Chronic Bioassay

Adjusted Concentration (ppm)	Number of Animals	Incidence
0	49	4
2	50	1
5	50	3
16	50	8

The BMD modeling results for bronchiolo-alveolar adenomas in female mice are summarized in Table 2-106. All Multistage models provided an adequate fit (chi-square p-value > 0.1) to the data. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Multistage 3-degree). A plot of the Multistage 3-degree model with a BMR of 10 percent ER is shown in Figure 2-138. Additional modeling details, including model parameters, goodness of fit at each concentration, and log likelihood are shown in Figure 2-139.

Table 2-106. Summary of BMD Modeling Results for Increased Incidence of Bronchiolo-Alveolar Adenomas in Female Mice Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay[a]

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 3	**0.4013**	**110.3**	**15**	**9.4**	**0.011**	All the Multistage models provided adequate fit (chi-square p-value > 0.1). The BMDLs were sufficiently close (differed by < 3-fold); therefore, EPA chose the 3-degree Multistage model, which had the lowest AIC.
Multistage 2	0.3754	110.4	15	9.3	0.011	
Multistage 1	0.2359	111.5	17	8.1	0.012	

[a] Selected model in bold.

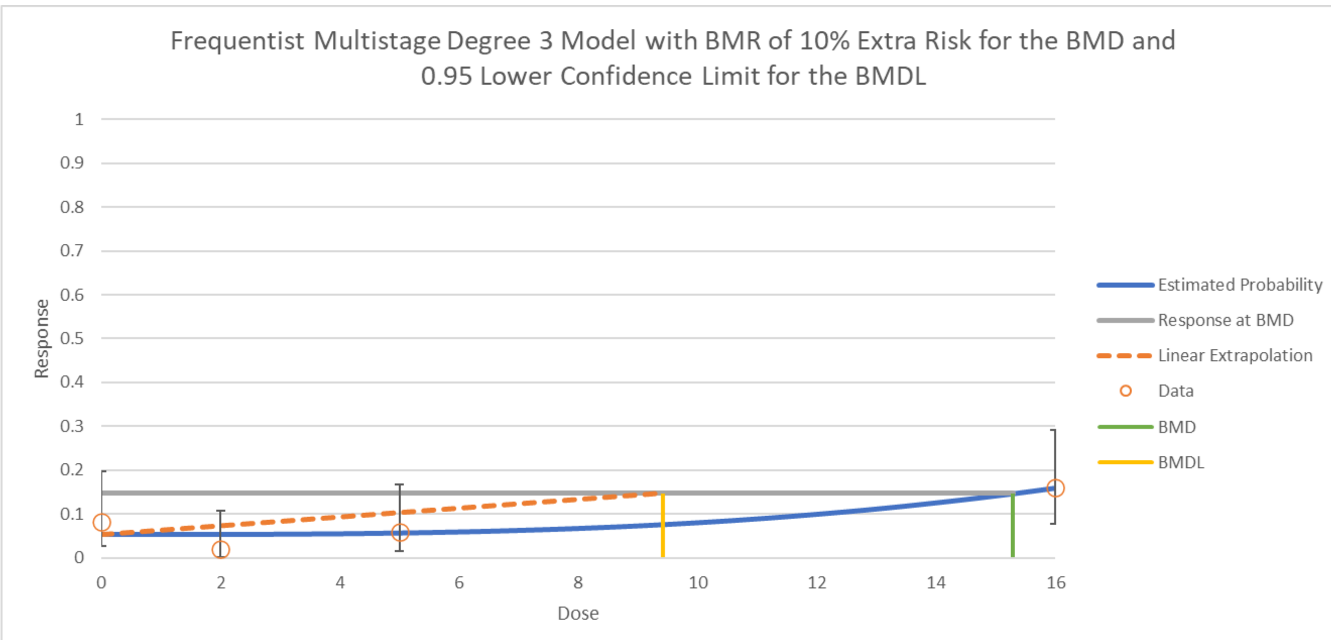

Figure 2-138. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 3-Degree) for the Increased Incidence of Bronchiolo-Alveolar Adenomas in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

Benchmark Dose	
BMD	15.28951263
BMDL	9.41161009
BMDU	Infinity
AIC	110.3012141
P-value	0.401340961
D.O.F.	2
Chi^2	1.825887871
Slope Factor	0.010625175

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.052388509	2.35E-02	0.0063456	0.098431418
b1	Bounded	NA	NA	NA
b2	Bounded	NA	NA	NA
b3	2.94779E-05	6.54E-02	-0.128136264	0.12819522

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.052388509	2.567036922	4	49	0.894373541
2	0.052611951	2.630597564	1	50	-1.005355325
5	0.055873787	2.793689339	3	50	0.123433378
16	0.160167058	8.00835292	8	50	-0.002951663

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-52.08803088	4	-	-	NA
Fitted Model	-53.15060707	2	2.125152373	2	0.345564424
Reduced Model	-55.67027459	1	5.039335051	3	0.168939394

Figure 2-139. Details Regarding the Selected Model (Multistage 3-Degree) for the Increased Incidence of Bronchiolo-Alveolar Adenomas in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.2.2 Bronchiolo-Alveolar Carcinomas in Female Mice

Female mice exhibited a significantly increased trend for the incidence of bronchiolo-alveolar carcinomas in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). For BMD modeling, the exposure concentrations were first duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week rather than 6 hours per day, 5 days per week. Then, the Multistage cancer models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentration and response data used for the modeling are presented in Table 2-107.

Table 2-107. Increased Incidence of Bronchiolo-Alveolar Carcinomas in Female Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 2-year Chronic Bioassay

Adjusted Concentration (ppm)	Number of Animals	Incidence
0	49	1
2	50	0
5	50	1
16	50	3

The BMD modeling results for bronchiolo-alveolar carcinomas in female mice are summarized in Table 2-108. All Multistage models provided an adequate fit (chi-square p-value > 0.1) to the data. The Multistage 3-degree model converged on the 2-degree model. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected. The 2-degree Multistage model was selected as the more parsimonious choice. A plot of the Multistage 2-degree model with a BMR of 10 percent ER is shown in Figure 2-140. Additional modeling details, including model parameters, goodness of fit at each concentration, and log likelihood are shown in Figure 2-141.

Table 2-108. Summary of BMD Modeling Results for Increased Incidence of Bronchiolo-Alveolar Carcinomas in Female Mice Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay[a]

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 3	0.6059	47.82	23	14	0.0069	All the Multistage models provided adequate fit (chi-square p-value > 0.1). The Multistage 3-degree model converged on the 2-degree model. The BMDLs were sufficiently close (differed by < 3-fold); therefore, EPA chose the 2-degree Multistage model, which had the lowest AIC and was the more parsimonious choice.
Multistage 2	**0.6059**	**47.82**	**23**	**14**	**0.0070**	
Multistage 1	0.5056	48.31	40	16	0.0062	

[a] Selected model in bold.

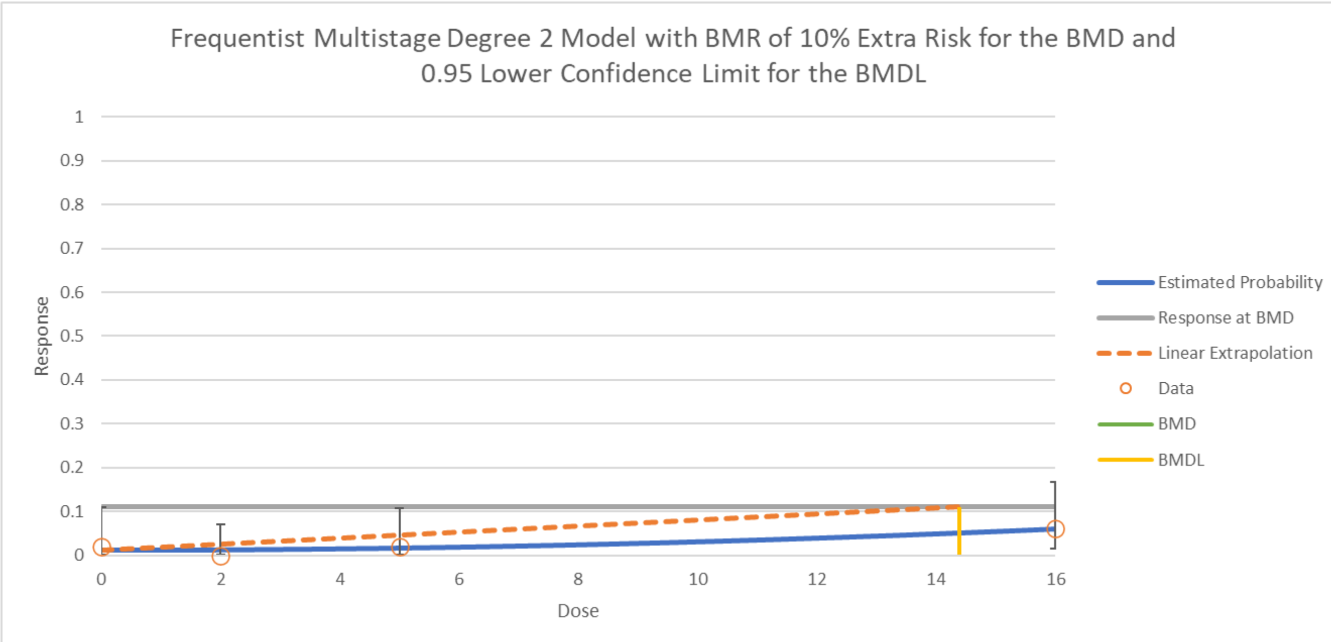

Figure 2-140. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 2-Degree) for the Increased Incidence of Bronchiolo-Alveolar Carcinomas in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

Benchmark Dose	
BMD	23.02764702
BMDL	14.38723029
BMDU	Infinity
AIC	47.81567877
P-value	0.605883382
D.O.F.	2
Chi^2	1.002135499
Slope Factor	0.006950608

Model Parameters				
# of Parameters	3			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.0113772	0.053529952	-0.093539578	0.116293979
b1	Bounded	NA	NA	NA
b2	0.000198691	3.67E-02	-0.071651227	0.072048609

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.0113772	0.557482822	1	49	0.592671971
2	0.012162611	0.608130555	0	50	-0.77982726
5	0.016275792	0.813789577	1	50	0.206418171
16	0.060405966	3.020298307	3	50	-0.011679786

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-21.13187787	4	-	-	NA
Fitted Model	-21.90783939	2	1.551923026	2	0.460261021
Reduced Model	-23.3559877	1	2.896296628	3	0.407892098

Figure 2-141. Details Regarding the Selected Model (Multistage 2-Degree) for the Increased Incidence of Bronchiolo-Alveolar Carcinomas in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.2.3 Bronchiolo-Alveolar Adenomas and Carcinomas (Combined) in Female Mice

Female mice exhibited a significantly increased trend for the incidence of bronchiolo-alveolar adenomas and carcinomas (combined) in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). For BMD modeling, the exposure concentrations were first duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week rather than 6 hours per day, 5 days per week. Then, the Multistage cancer models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentration and response data used for the modeling are presented in Table 2-109.

Table 2-109. Increased Incidence of Bronchiolo-Alveolar Adenomas and Carcinomas (Combined) in Female Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 2-Year Chronic Bioassay

Adjusted Concentration (ppm)	Number of Animals	Incidence
0	49	5
2	50	1
5	50	4
16	50	11

The BMD modeling results for bronchiolo-alveolar adenomas and carcinomas (combined) in female mice are summarized in Table 2-110. All Multistage models provided an adequate fit (chi-square p-value > 0.1) to the data. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Multistage 2-degree). A plot of the Multistage 2-degree model with a BMR of 10 percent ER is shown in Figure 2-142. Additional modeling details, including model parameters, goodness of fit at each concentration, and log likelihood are shown in Figure 2-143.

Table 2-110. Summary of BMD Modeling Results for Increased Incidence of Bronchiolo-Alveolar Adenomas and Carcinomas (Combined) in Female Mice Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay[a]

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 3	0.1016	132.0	13	7.6	0.013	All the Multistage models provided adequate fit (chi-square p-value > 0.1). The BMDLs were sufficiently close (differed by < 3-fold); therefore, EPA chose the 2-degree Multistage model, which had the lowest AIC.
Multistage 2	**0.2413**	**130.0**	**12**	**7.5**	**0.013**	
Multistage 1	0.1217	131.7	11	6.1	0.016	

[a] Selected model in bold.

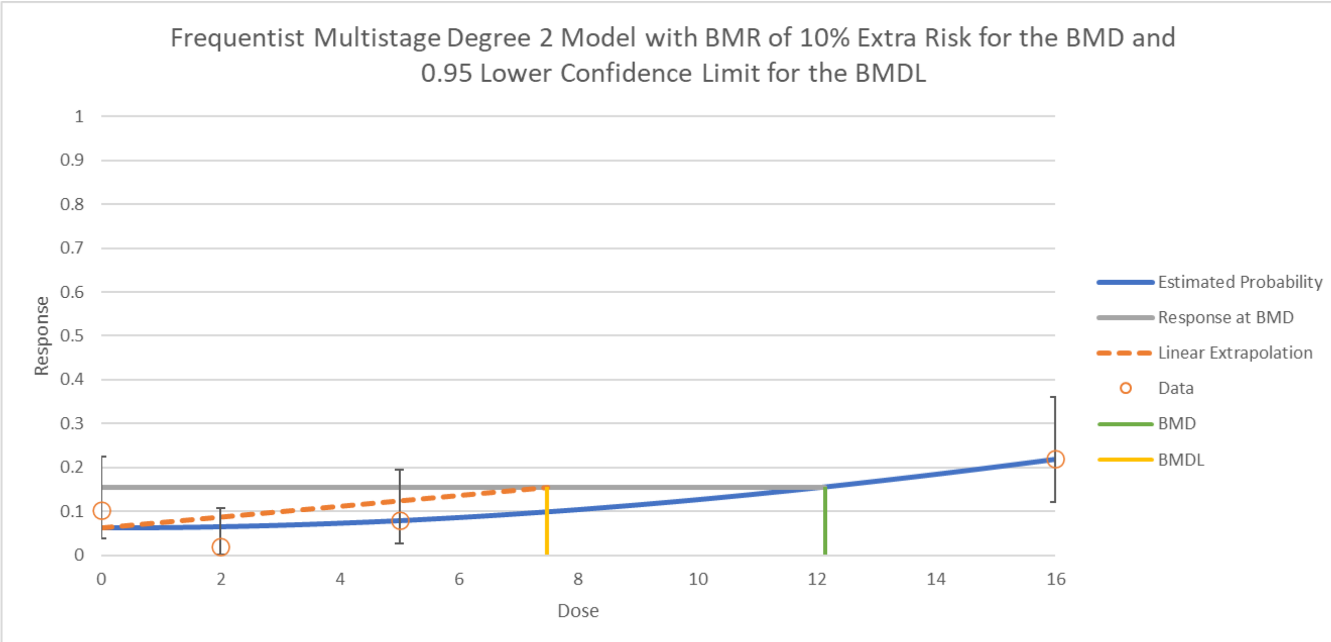

Figure 2-142. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 2-Degree) for the Increased Incidence of Bronchiolo-Alveolar Adenomas and Carcinomas (Combined) in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

Benchmark Dose	
BMD	12.14137745
BMDL	7.47918985
BMDU	19.79664615
AIC	130.0361342
P-value	0.241329764
D.O.F.	2
Chi^2	2.843181935
Slope Factor	0.013370432

Model Parameters				
# of Parameters	3			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.061269856	2.31E-02	0.016075343	0.10646437
b1	Bounded	NA	NA	NA
b2	0.00071473	7.85E-02	-0.153059287	0.154488747

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.061269856	3.002222954	5	49	1.15299002
2	0.063949778	3.197488882	1	50	-1.228915905
5	0.077894352	3.894717584	4	50	0.053347965
16	0.218232649	10.91163246	11	50	0.026751484

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-61.33348348	4	-	-	NA
Fitted Model	-63.01806711	2	3.369167271	2	0.185521661
Reduced Model	-67.07521698	1	8.114299727	3	0.043707604

Figure 2-143. Details Regarding the Selected Model (Multistage 2-Degree) for the Increased Incidence of Bronchiolo-Alveolar Adenomas and Carcinomas (Combined) in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.2.4 Endometrial Stromal Polyps in Female Mice

Female mice exhibited a significantly increased trend for the incidence of endometrial stromal polyps in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). For BMD modeling, the exposure concentrations were first duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week rather than 6 hours per day, 5 days per week. Then, the Multistage cancer models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentration and response data used for the modeling are presented in Table 2-111.

Table 2-111. Increased Incidence of Endometrial Stromal Polyps in Female Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 2-Year Chronic Bioassay

Adjusted Concentration (ppm)	Number of Animals	Incidence
0	49	2
2	50	0
5	50	1
16	50	6

The BMD modeling results for endometrial stromal polyps in female mice are summarized in Table 2-112. All Multistage models provided an adequate fit (chi-square p-value > 0.1) to the data. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Multistage 3-degree). A plot of the Multistage 3-degree model with a BMR of 10 percent ER is shown in Figure 2-144. Additional modeling details, including model parameters, goodness of fit at each concentration, and log likelihood are shown in Figure 2-145.

Table 2-112. Summary of BMD Modeling Results for Increased Incidence of Endometrial Stromal Polyps in Female Mice Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay[a]

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 3	**0.3370**	**70.10**	**16**	**12**	**0.0086**	All the Multistage models provided adequate fit (chi-square p-value > 0.1). The BMDLs were sufficiently close (differed by < 3-fold); therefore, EPA chose the 3-degree Multistage model, which had the lowest AIC.
Multistage 2	0.2839	70.39	16	11	0.0087	
Multistage 1	0.1521	72.23	21	11	0.0094	

[a] Selected model in bold.

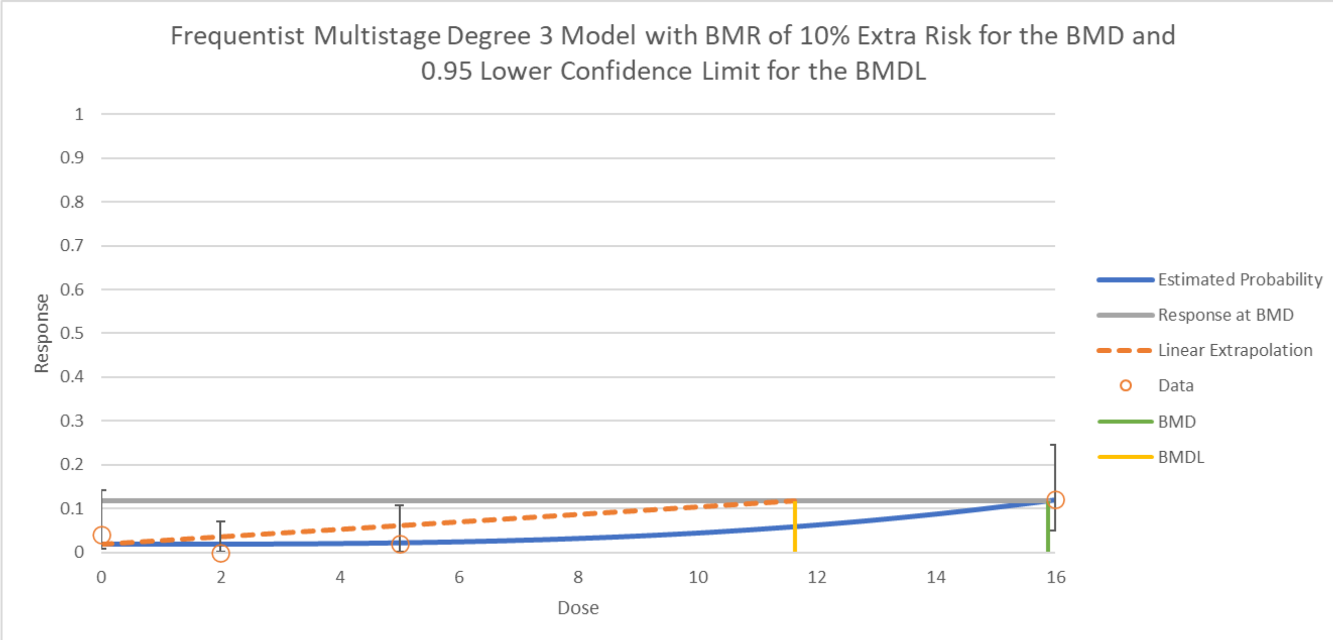

Figure 2-144. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 3-Degree) for the Increased Incidence of Endometrial Stromal Polyps in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

Benchmark Dose	
BMD	15.88183212
BMDL	11.62829155
BMDU	33.54474972
AIC	70.10389143
P-value	0.336969894
D.O.F.	2
Chi^2	2.175523375
Slope Factor	0.008599716

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.019204564	3.85E-02	-0.056279724	0.094688853
b1	Bounded	NA	NA	NA
b2	Bounded	NA	NA	NA
b3	2.63012E-05	5.35E-02	-0.10487753	0.104930133

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.019204564	0.941023655	2	49	1.091656458
2	0.019410912	0.970545585	0	50	-0.98516272
5	0.022423786	1.121189281	1	50	-0.114452357
16	0.119373076	5.968653792	6	50	0.012830596

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-31.60416819	4	-	-	NA
Fitted Model	-33.05194571	2	2.895555043	2	0.235092195
Reduced Model	-36.65806521	1	7.212238997	3	0.065432012

Figure 2-145. Details Regarding the Selected Model (Multistage 3-Degree) for the Increased Incidence of Endometrial Stromal Polyps in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.2.5 Mammary Gland Adenocarcinomas in Female Mice

Female mice exhibited a significantly increased trend for the incidence of mammary gland adenocarcinomas in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). For BMD modeling, the exposure concentrations were first duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week rather than 6 hours per day, 5 days per week. Then, the Multistage cancer models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentration and response data used for the modeling are presented in Table 2-113.

Table 2-113. Increased Incidence of Mammary Gland Adenocarcinomas in Female Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 2-Year Chronic Bioassay

Adjusted Concentration (ppm)	Number of Animals	Incidence
0	49	1
2	50	2
5	50	1
16	50	6

The BMD modeling results for mammary gland adenocarcinomas in female mice are summarized in Table 2-114. All Multistage models provided an adequate fit (chi-square p-value > 0.1) to the data. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Multistage 3-degree). A plot of the Multistage 3-degree model with a BMR of 10 percent ER is shown in Figure 2-146. Additional modeling details, including model parameters, goodness of fit at each concentration, and log likelihood are shown in Figure 2-147.

Table 2-114. Summary of BMD Modeling Results for Increased Incidence of Mammary Gland Adenocarcinomas in Female Mice Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay[a]

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 3	**0.7560**	**77.60**	**16**	**9.9**	**0.010**	All the Multistage models provided adequate fit (chi-square p-value > 0.1). The BMDLs were sufficiently close (differed by < 3-fold); therefore, EPA chose the 3-degree Multistage model, which had the lowest AIC.
Multistage 2	0.7044	77.77	17	9.7	0.010	
Multistage 1	0.5949	78.34	18	9.1	0.011	

[a] Selected model in bold.

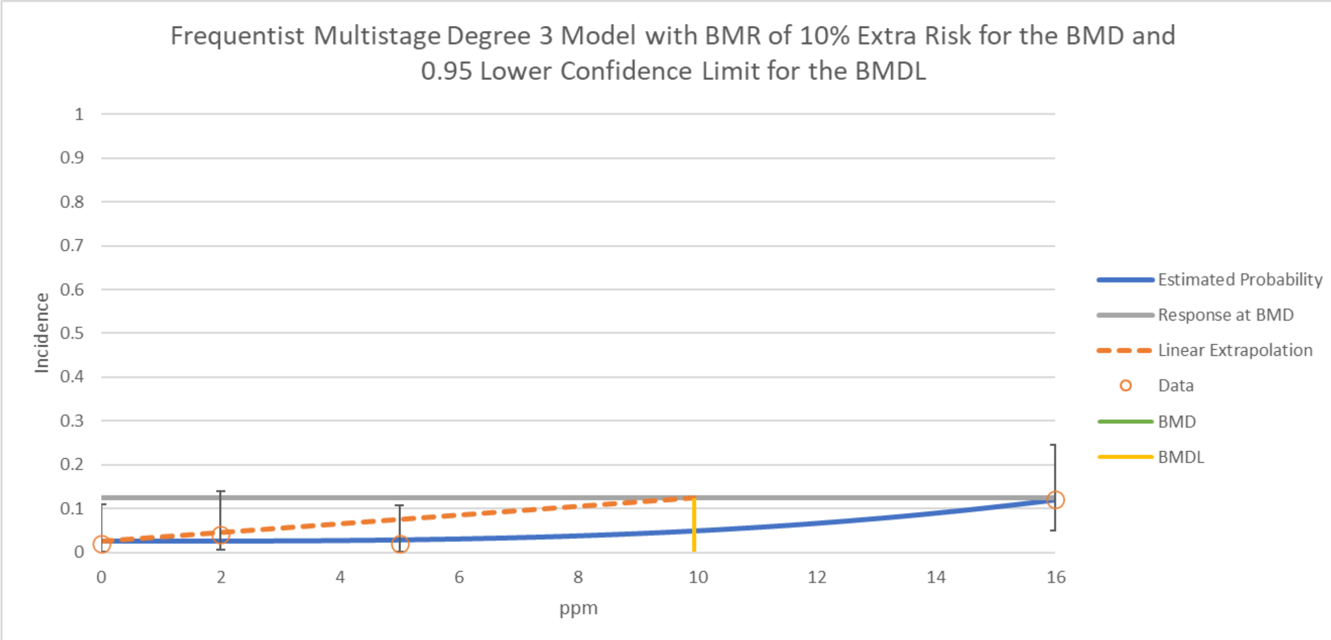

Figure 2-146. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 3-Degree) for the Increased Incidence of Mammary Gland Adenocarcinomas in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

Benchmark Dose	
BMD	16.27040863
BMDL	9.941820292
BMDU	Infinity
AIC	77.60267152
P-value	0.755966155
D.O.F.	2
Chi^2	0.559517345
Slope Factor	0.01005852

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.026137909	3.28E-02	-0.038234568	0.090510386
b1	Bounded	NA	NA	NA
b2	Bounded	NA	NA	NA
b3	2.44615E-05	5.38E-02	-0.105461386	0.105510309

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.026137909	1.280757549	1	49	-0.248083557
2	0.026328467	1.316423363	2	50	0.595784802
5	0.029111123	1.455556151	1	50	-0.377596042
16	0.118984218	5.949210887	6	50	0.020822887

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-36.5269587	4	-	-	NA
Fitted Model	-36.80133576	2	0.548754125	2	0.760045437
Reduced Model	-39.65162334	1	5.700575167	3	0.127122222

Figure 2-147. Details Regarding the Selected Model (Multistage 3-Degree) for the Increased Incidence of Mammary Gland Adenocarcinomas in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.2.6 Hepatocellular Adenomas in Female Mice

Female mice exhibited a significantly increased trend for the incidence of hepatocellular adenomas in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). For BMD modeling, the exposure concentrations were first duration adjusted to estimate an equivalent inhalation dose for animals exposed for 24 hours per day, 7 days per week rather than 6 hours per day, 5 days per week. Then, the Multistage cancer models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentration and response data used for the modeling are presented in Table 2-115.

Table 2-115. Increased Incidence of Hepatocellular Adenomas in Female Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 2-Year Chronic Bioassay

Adjusted Concentration (ppm)	Number of Animals	Incidence
0	49	1
2	50	1
5	50	1
16	50	6

The BMD modeling results for hepatocellular adenomas in female mice are summarized in Table 2-116. All Multistage models provided an adequate fit (chi-square p-value > 0.1) to the data. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Multistage 3-degree). A plot of the Multistage 3-degree model with a BMR of 10 percent ER is shown in Figure 2-148. Additional modeling details, including model parameters, goodness of fit at each concentration, and log likelihood are shown in Figure 2-149.

Table 2-116. Summary of BMD Modeling Results for Increased Incidence of Hepatocellular Adenomas in Female Mice Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay[a]

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 3	**0.9911**	**70.08**	**16**	**11**	**0.0093**	All the Multistage models provided adequate fit (chi-square p-value > 0.1). The BMDLs were sufficiently close (differed by < 3-fold); therefore, EPA chose the 3-degree Multistage model, which had the lowest AIC.
Multistage 2	0.9337	70.21	16	11	0.0095	
Multistage 1	0.6159	71.18	18	9.5	0.011	

[a] Selected model in bold.

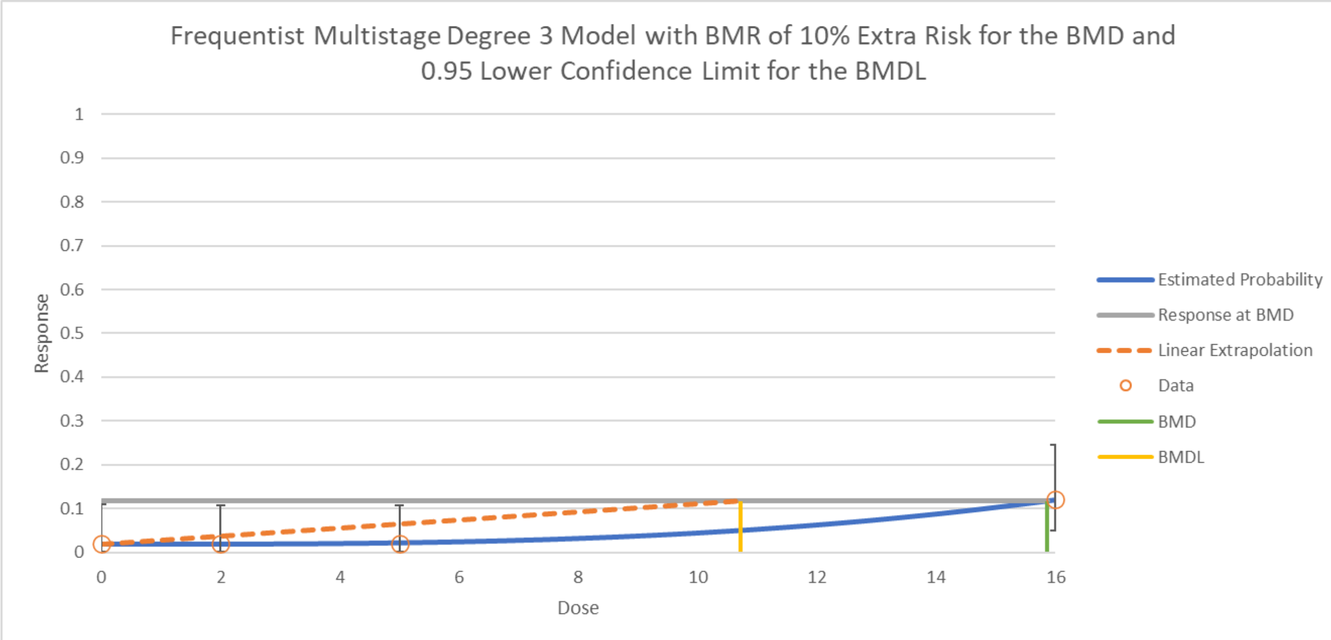

Figure 2-148. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 3-Degree) for the Increased Incidence of Hepatocellular Adenomas in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

Benchmark Dose	
BMD	15.86314678
BMDL	10.72443119
BMDU	Infinity
AIC	70.08200509
P-value	0.991114758
D.O.F.	2
Chi^2	0.017849902
Slope Factor	0.009324504

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.019111852	3.87E-02	-0.056762546	0.09498625
b1	Bounded	NA	NA	NA
b2	Bounded	NA	NA	NA
b3	2.63943E-05	0.053688515	-0.105201162	0.105253951

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.019111852	0.936480755	1	49	0.065638085
2	0.019318949	0.96594745	1	50	0.034647579
5	0.022342749	1.117137467	1	50	-0.11082622
16	0.119625443	5.981272148	6	50	0.007657574

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-33.03170698	4	-	-	NA
Fitted Model	-33.04100255	2	0.018591143	2	0.990747499
Reduced Model	-36.65806521	1	7.234125334	3	0.064798208

Figure 2-149. Details Regarding the Selected Model (Multistage 3-Degree) for the Increased Incidence of Hepatocellular Adenomas in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.2.7 Hepatocellular Adenomas and Carcinomas (Combined) in Female Mice

Female mice exhibited a significantly increased trend for the incidence of hepatocellular adenomas and carcinomas (combined) in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). For BMD modeling, the exposure concentrations were first duration adjusted to estimate an equivalent inhalation concentration for animals exposed for 24 hours per day, 7 days per week rather than 6 hours per day, 5 days per week. Then, the Multistage cancer models were fit to the dose-response data.

A BMR of 10 percent ER was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The concentration and response data used for the modeling are presented in Table 2-117.

Table 2-117. Increased Incidence of Hepatocellular Adenomas and Carcinomas (Combined) in Female Mice and Associated Concentrations Selected for Dose-Response Modeling for 1,2-Dichloroethane from a 2-Year Chronic Bioassay

Adjusted Concentration (ppm)	Number of Animals	Incidence
0	49	2
2	50	1
5	50	2
16	50	6

The BMD modeling results for hepatocellular adenomas and carcinomas (combined) in female mice are summarized in Table 2-118. All Multistage models provided an adequate fit (chi-square p-value > 0.1) to the data. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Multistage 2-degree). A plot of the Multistage 2-degree model with a BMR of 10 percent ER is shown in Figure 2-150. Additional modeling details, including model parameters, goodness of fit at each concentration, and log likelihood are shown in Figure 2-151.

Table 2-118. Summary of BMD Modeling Results for Increased Incidence of Hepatocellular Adenomas and Carcinomas (Combined) in Female Mice Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay[a]

Model	Goodness of Fit		BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)	Basis for Model Selection
	p-value	AIC				
Multistage 3	0.5369	86.42	17	10	0.0097	All the Multistage models provided adequate fit (chi-square p-value > 0.1). The BMDLs were sufficiently close (differed by < 3-fold); therefore, EPA chose the 2-degree Multistage model, which had the lowest AIC.
Multistage 2	**0.8193**	**84.43**	**17**	**10**	**0.0097**	
Multistage 1	0.6051	85.07	20	9.5	0.011	

[a] Selected model in bold.

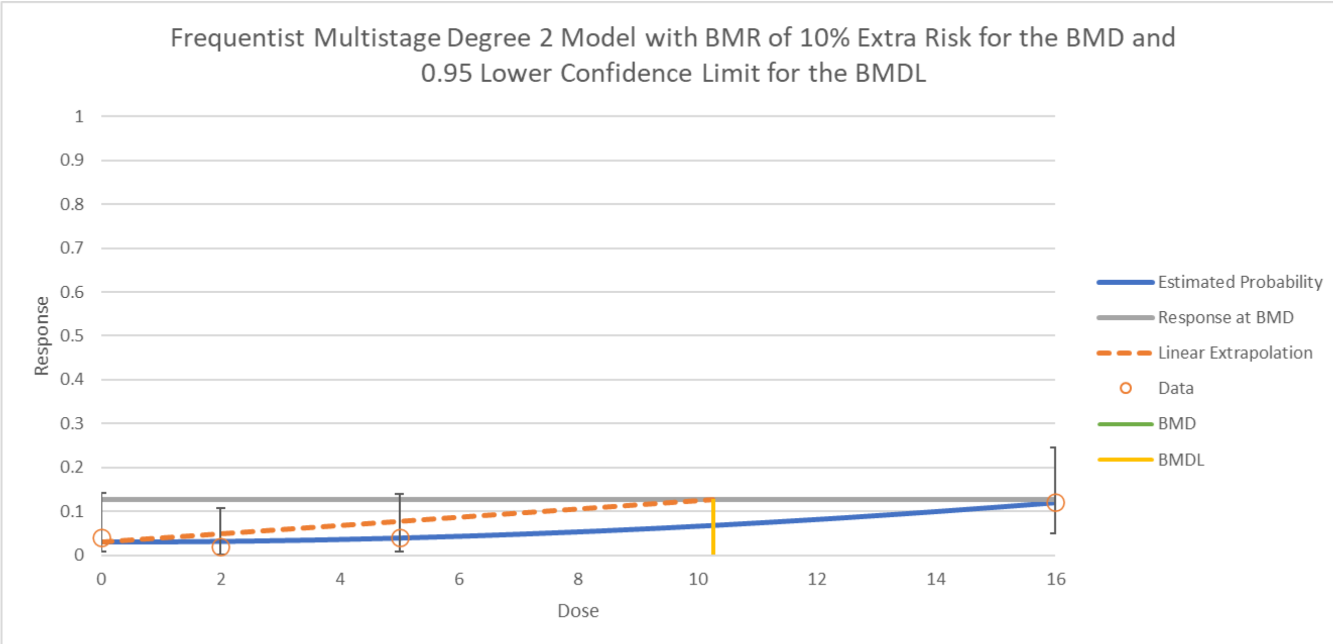

Figure 2-150. Plot of Response by Concentration with Fitted Curve for the Selected Model (Multistage 2-Degree) for the Increased Incidence of Hepatocellular Adenomas and Carcinomas (Combined) in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

Benchmark Dose	
BMD	16.704916
BMDL	10.26208393
BMDU	Infinity
AIC	84.42822854
P-value	0.81925885
D.O.F.	2
Chi^2	0.398710378
Slope Factor	0.009744609

Model Parameters				
# of Parameters	3			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.030173657	3.26E-02	-0.03365823	0.094005545
b1	Bounded	NA	NA	NA
b2	0.000377563	5.45E-02	-0.106466417	0.107221543

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.030173657	1.478509213	2	49	0.428878843
2	0.031637234	1.581861679	1	50	-0.462631823
5	0.039284849	1.964242466	2	50	0.025513498
16	0.119525528	5.976276377	6	50	0.009704333

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-40.00137558	4	-	-	NA
Fitted Model	-40.21411427	2	0.42547738	2	0.808367344
Reduced Model	-42.53972311	1	4.651217674	3	0.199192151

Figure 2-151. Details Regarding the Selected Model (Multistage 2-Degree) for the Increased Incidence of Hepatocellular Adenomas and Carcinomas (Combined) in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.2.8 Combined Lung, Uterine, Mammary Gland, and Liver Tumors in Female Mice

Female mice exhibited significantly increased incidences of bronchiolo-alveolar adenomas and carcinomas, uterine endometrial stromal polyps, mammary gland adenocarcinomas, and hepatocellular adenomas and carcinomas in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). The MS Combo model was applied to the incidence data for the individual tumors and polydegrees identified for the individual tumor models, shown above (Sections 2.2.2.1 through 2.2.2.7), using a BMR of 10 percent ER.

The BMD Multistage Cancer/Multi-tumor modeling results for combined bronchiolo-alveolar adenomas and carcinomas, uterine endometrial stromal polyps, mammary gland adenocarcinomas, and hepatocellular adenomas and carcinomas in female mice are summarized in Table 2-119. A plot of the dose-response curves for the incidence of individual tumor types with a BMR of 10 percent ER is shown in Figure 2-152. Additional modeling details, including the cancer slope factor and log likelihood are shown in Figure 2-153.

Table 2-119. Summary of BMD Multi-Tumor (MS Combo) Modeling Results for Increased Incidence of Bronchiolo-alveolar Adenomas and Carcinomas, Uterine Endometrial Stromal Polyps, Mammary Gland Adenocarcinomas, and Hepatocellular Adenomas and Carcinomas (Combined) in Female Mice Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay

Model	BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)
Multi-tumor (MS Combo)	**8.3**	**4.6**	**0.022**
Bronchiolo-alveolar carcinomas and adenomas in the lungs Multistage 2	12	7.5	0.013
Endometrial stromal polyp in the uterus Multistage 3	16	12	0.0086
Adenocarcinoma in the mammary gland Multistage 3	16	9.9	0.010
Hepatocellular adenomas and carcinomas in the liver Multistage 2	17	10	0.0097

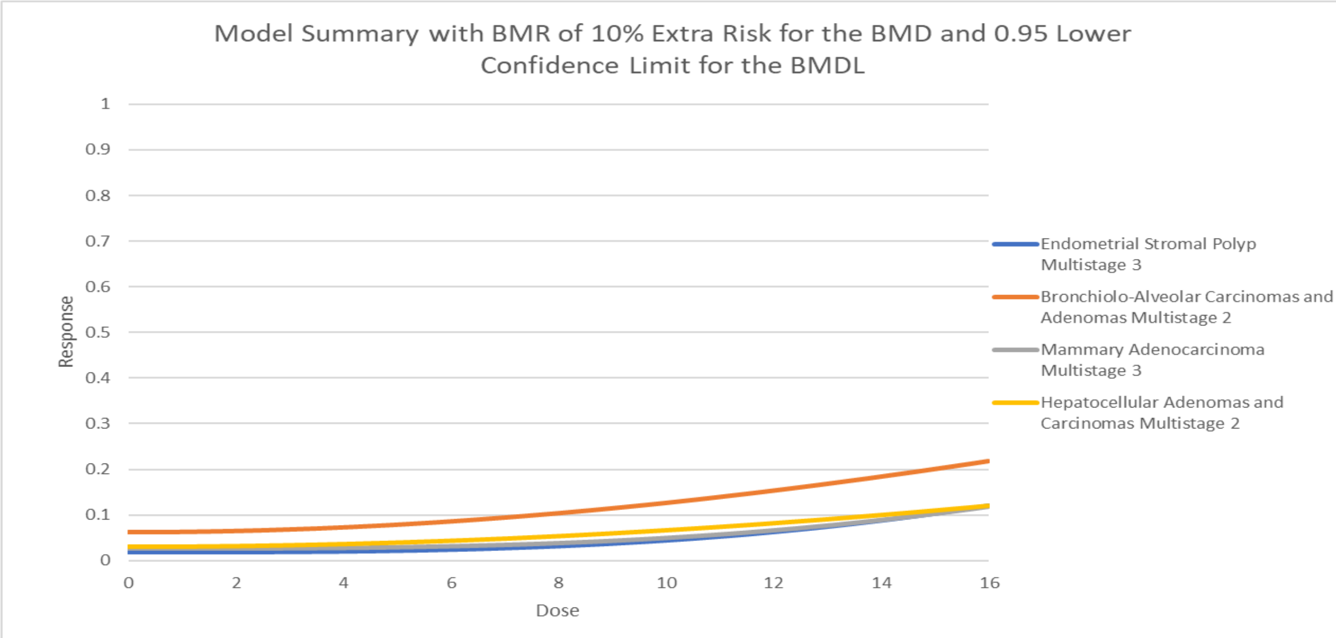

Figure 2-152. Plot of Response by Concentration with Fitted Curve for Selected Models used for the Multi-Tumor (MS Combo) Model for Increased Incidence of Bronchiolo-alveolar Adenomas and Carcinomas, Uterine Endometrial Stromal Polyps, Mammary Gland Adenocarcinomas, and Hepatocellular Adenomas and Carcinomas (Combined) in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

User Input

Info	
Model	frequentist Multi-tumor v1.0

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

Model Results

Benchmark Dose	
BMD	8.337858446
BMDL	4.613136813
BMDU	10.36198116
Slope Factor	0.021677224
Combined Log-Likelihood	-173.0854629
Combined Log-Likelihood Constant	148.7966046

Figure 2-153. Details Regarding the Multi-Tumor (MS Combo) Model for the Increased Incidence of Bronchiolo-alveolar Adenomas and Carcinomas, Uterine Endometrial Stromal Polyps, Mammary Gland Adenocarcinomas, and Hepatocellular Adenomas and Carcinomas (Combined) in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

2.2.2.9 Combined Lung, Mammary Gland, and Liver Tumors in Female Mice (Alternate Analysis of Combined Tumors with Uterine Polyps Excluded)

This section presents an alternate analysis of combined tumors in female mice that excludes uterine polyps because these lesions are considered preneoplastic by some researchers. Female mice exhibited significantly increased incidences of bronchiolo-alveolar adenomas and carcinomas, mammary gland adenocarcinomas, and hepatocellular adenomas and carcinomas in a 2-year inhalation toxicity study of 1,2-dichloroethane (Nagano et al., 2006). The MS Combo model was applied to the incidence data for the individual tumors and polydegrees identified for the individual tumor models, shown above (Sections 2.2.2.1 through 2.2.2.7), using a BMR of 10 percent ER.

The BMD Multistage Cancer/Multi-tumor modeling results for combined bronchiolo-alveolar adenomas and carcinomas, mammary gland adenocarcinomas, and hepatocellular adenomas and carcinomas in female mice are summarized in Table 2-120. A plot of the dose-response curves for the incidence of individual tumor types with a BMR of 10 percent ER is shown in Figure 2-154. Additional modeling details, including the cancer slope factor and log likelihood are shown in Figure 2-155.

Table 2-120. Summary of BMD Multi-Tumor (MS Combo) Modeling Results for Increased Incidence of Bronchiolo-alveolar Adenomas and Carcinomas, Mammary Gland Adenocarcinomas, and Hepatocellular Adenomas and Carcinomas (Combined) in Female Mice Following Inhalation Exposure to 1,2-Dichloroethane in a 2-Year Chronic Bioassay

Model	BMD 10%ER (ppm)	BMDL 10%ER (ppm)	Slope Factor (per ppm)
Multi-tumor (MS Combo)	**9.0**	**4.8**	**0.021**
Bronchiolo-alveolar carcinomas and adenomas in the lungs Multistage 2	12	7.5	0.013
Adenocarcinoma in the mammary gland Multistage 3	16	9.9	0.010
Hepatocellular adenomas and carcinomas in the liver Multistage 2	17	10	0.0097

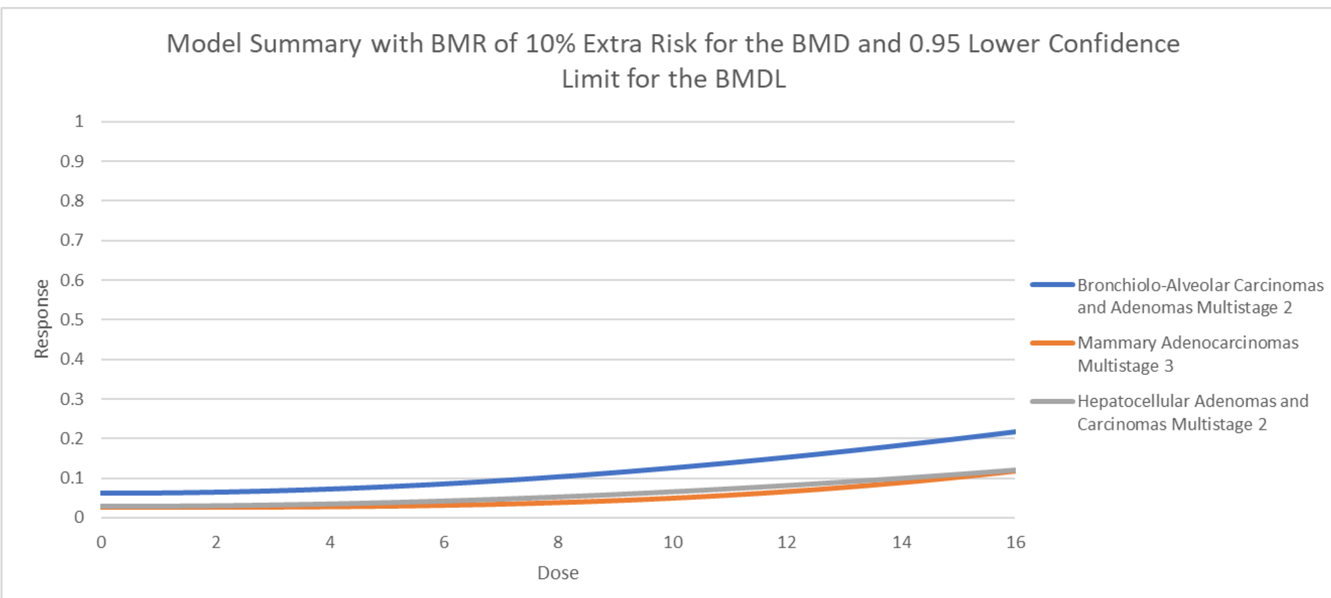

Figure 2-154. Plot of Response by Concentration with Fitted Curve for Selected Models Used for the Multi-Tumor (MS Combo) Model for Increased Incidence of Bronchiolo-alveolar Adenomas and Carcinomas, Mammary Gland Adenocarcinomas, and Hepatocellular Adenomas and Carcinomas (Combined) in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

User Input

Info	
Model	frequentist Multi-tumor v1.0

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

Model Results

Benchmark Dose	
BMD	8.96289734
BMDL	4.755620898
BMDU	11.70062473
Slope Factor	0.021027748
Combined Log-Likelihood	-140.0335171
Combined Log-Likelihood Constant	121.2334629

Figure 2-155. Details Regarding the Multi-Tumor (MS Combo) Model for the Increased Incidence of Bronchiolo-alveolar Adenomas and Carcinomas, Mammary Gland Adenocarcinomas, and Hepatocellular Adenomas and Carcinomas (Combined) in Female Mice Exposed to 1,2-Dichloroethane Via Inhalation (2-Year Study)

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