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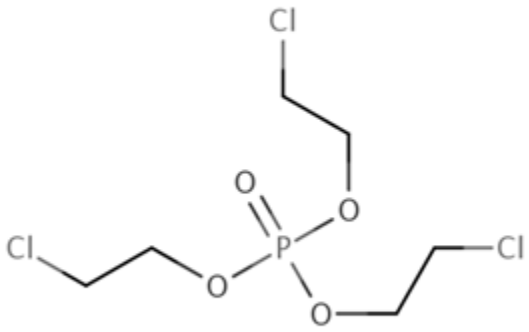
Environmental Protection Agency

December 2023
Office of Chemical Safety and
Pollution Prevention

Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP)

Supplemental File:

Benchmark Dose Modeling Results for TCEP CASRN: 115-96-8



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1 BENCHMARK DOSE MODELING RESULTS

EPA performed benchmark dose (BMD) modeling using EPA's BMD modeling software (BMDS Version 3.2.0.1) for the health domains that were identified during hazard identification and that received a judgment of likely ("evidence indicates that TCEP exposure likely causes [health effect]") and suggests ("evidence suggests but is not sufficient to conclude that TCEP exposure causes [health effect]") during evidence integration. EPA considered that TCEP is likely to cause the following health endpoints for which BMD modeling is presented: reproductive/developmental, neurological/behavioral, and cancer (kidney tumors). EPA considered that TCEP exposure results in a suggests conclusion for: hepatic and renal effects and mortality. 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 karyomegaly) and continuous models to fit continuous data (*e.g.,* kidney weights), as recommended by EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The BMD/BMDLs are provided based on a daily exposure (*i.e.,* seven 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 datasets could be fit using models after dropping doses (either 1, 2 or 3 of the highest doses), EPA considered only modeling results from full datasets 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 datasets. Several additional endpoints evaluated in various TCEP toxicity studies were not considered for BMD modeling because the changes were observed only at the highest dose. Studies were also not considered for BMD modeling if the lowest-observed-adverse-effect-levels (LOAELs) were more than 10-times greater than the most sensitive LOAEL for the health domain. If BMD modeling was not possible or when data did not fit the available models, EPA used no-observed-adverse-effect-levels (NOAELs) and LOAELs during point of departure (POD) selection for the risk evaluation.

EPA relied on the BMD guidance and other information to choose benchmark responses (BMRs) appropriate for each endpoint. Although the *BMD Technical Guidance* doesn't recommend default BMRs, it describes how various BMD modeling results compare with NOAEL values, and the guidance recommends 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 TCEP 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 extra risk (ER) 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]

Of the modeled BMDLs, critical endpoints and their PODs used as the basis of risk estimates are decreased numbers of seminiferous tubules (Section 1.1.1), changes in path length in the Morris water maze (Section 1.3.1) and increased incidence of renal tubule adenomas and carcinomas (Section 1.5.1).

1.1 Reproductive Effects

EPA modeled endpoints when one or more doses showed pairwise differences from controls and/or when a dose-response trend was evident in the data. EPA modeled litter data separately by sex as well as combined (males and females) as well as effects on male reproductive organs.

EPA did not present the BMD modeling results for several endpoints from NTP (1991a) that resulted in inadequate model fits. These endpoints included several for the F0 animals: cumulative days to litter (litter numbers 2 and 3); mean litters per pair; and live F1 pups per litter (both sexes and females). Also, although F1 fertility was modeled due to a statistically significant dose-response trend, the results are not presented because the BMD/BMDL ratio was greater than three and the BMDL was more than three times lower than the lowest dose tested. Testicular testosterone levels from Chen et al. (2015) were modeled but didn't fit any of the constant or nonconstant variance models.

EPA also identified an anomaly in the data presented Table 4-4 within NTP (1991a) that affects the measures of sex of F2 pups born alive and live male F2 pups per litter (difference in proportion of males at 350 mg/kg-day). Therefore, although EPA modeled both effects (with an adequate model fit for live male F2 pups per litter), EPA is not presenting the results base on the identified error.

1.1.1 Decreased Numbers of Seminiferous Tubules (Mice)

Chen et al. (2015) found decreases in numbers of seminiferous tubules in adolescent ICR mice after 35 days of exposure. Continuous models were used to fit data, and BMDLs based on BMRs of one SD and five percent RD from the best fit model are both presented. Based on the severity of the endpoint (considering EPA's *BMD Technical Guidance* (U.S. EPA, 2012)), EPA is using the BMDL based on a lower BMR (EPA used five percent RD) for this endpoint in the risk calculation. The doses and response data used for the modeling are presented in Table 1-1. There is uncertainty in using the BMDL based on a BMR of 5 percent because this BMR is lower than the responses observed in the study (decreases of 22.2 and 40.7 percent at 100 and 300 mg/kg-day, respectively).

Table 1-1. Decreased Numbers of Seminiferous Tubules in Mice and Associated Doses Selected for Dose-Response Modeling for TCEP

Dose (mg/kg-day)	Number of Mice	Mean	SD
0	7	24.3	5.29
100	7	18.9	3.17
300	7	14.4	2.65

[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 1-2 summarizes the BMD modeling results for decreased numbers of seminiferous tubules from Chen et al. (2015). The constant variance model provided adequate fit to the variance data and with this model applied, all models except the Exponential 4 and 5 models, provided adequate fit to the means (p-value > 0.1). BMDLs for the fit models were sufficiently close (< 3-fold difference). Therefore, EPA selected the model with the lowest Akaike information criterion (AIC). The software selected the Exponential 3 model, but EPA chose the Exponential 2 as the more parsimonious choice because Exponential 3 defaulted to the Exponential 2 model by bounding variable d at a value of one.

Table 1-2. Summary of BMD Modeling Results for Decreased Numbers of Seminiferous Tubules in Mice Following Oral Exposure to TCEP in a 35-Day Study (Constant Variance)[ab]

Model	Goodness of Fit		BMD 1SD (mg/kg-day)	BMDL 1SD (mg/kg-day)	BMD 5%RD (mg/kg-day)	BMDL 5%RD (mg/kg-day)	Basis for Model Selection
	P-value	AIC					
Exponential 2	**0.343**	**120**	**94.0**	**61.2**	**28.8**	**20.8**	For the constant variance model, all models except the Exponential 4 and 5 models, provided adequate fit to the means (p-value > 0.1). BMDLs were < 3-fold difference. EPA selected the Exponential 2, the model with the lowest AIC (along with Exponential 3). Exponential 2 is the more parsimonious.
Exponential 3	0.343	120	94.0	61.2	28.8	20.9	
Exponential 4	NA	121	59.3	26.2	17.8	7.70	
Exponential 5	< 0.0001	123	59.2	26.2	17.8	7.70	
Polynomial 2	0.223	121	118	82.7	37.1	29.0	
Power	0.223	121	118	82.7	37.1	29.0	
Linear	0.223	121	118	82.7	37.1	29.0	

[a] Three significant figures
[b] Selected model in bold; scaled residuals for selected model for doses 0, 100, and 300 mg/kg-day were 0.397, 0.711, and 0.338 respectively.

Plots of the Exponential 2 model with BMRs of one SD and five percent RD are shown in Figure 1-1 and Figure 1-2, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown below in Figure 1-3.

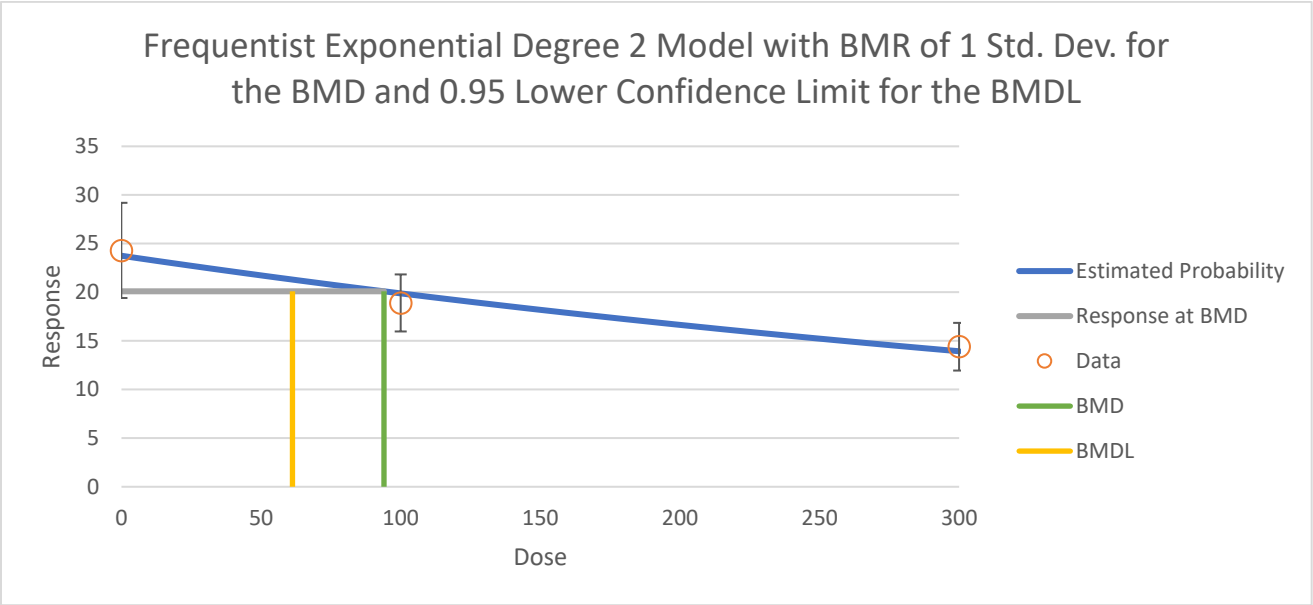

Figure 1-1. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 2) for Decreased Numbers of Seminiferous Tubules in Mice Exposed to TCEP Via Oral Gavage in a 35-Day Study and BMR of 1SD (Constant Variance)

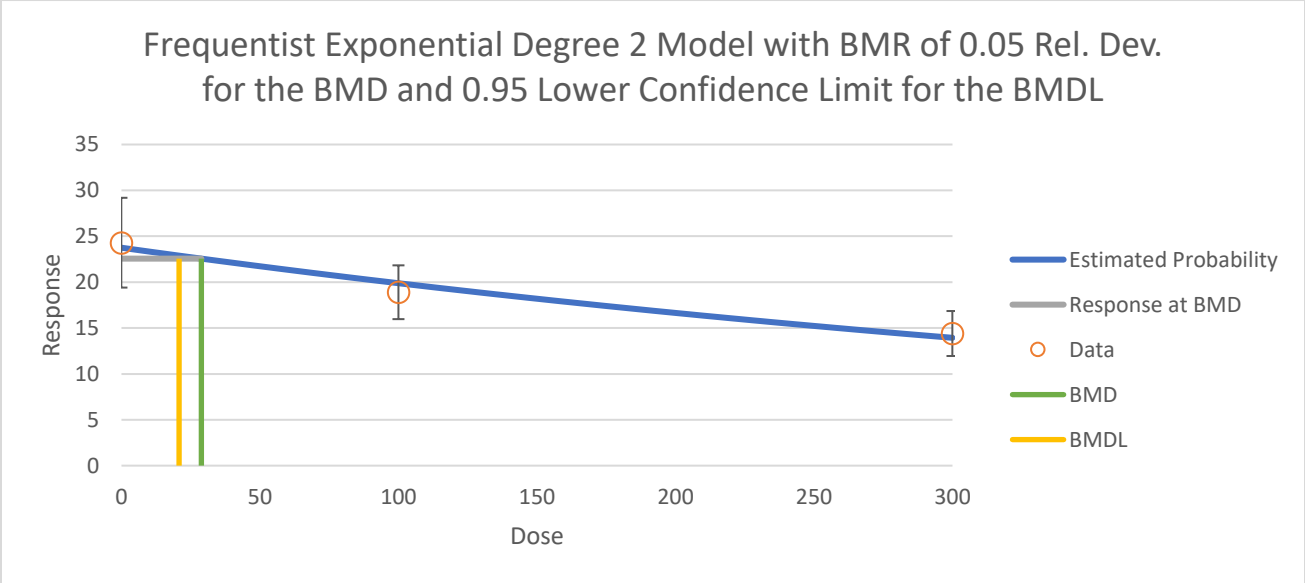

Figure 1-2. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 2) for Decreased Numbers of Seminiferous Tubules in Mice Exposed to TCEP Via Oral Gavage in a 35-Day Study and BMR of 5 Percent Relative Deviation (Constant Variance)

Model Results

Benchmark Dose	
BMD	94.01164055
BMDL	61.23672499
BMDU	177.5203492
AIC	120.0453798
Test 4 P-value	0.373439526
D.O.F.	1

Model Parameters	
# of Parameters	3
Variable	Estimate
a	23.75164316
b	0.001778069

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	7	23.75164316	24.3	24.3	3.65621204	5.29	5.29	0.396808451
100	7	19.88259622	18.9	18.9	3.65621204	3.17	3.17	–0.711037874
300	7	13.93259326	14.4	14.4	3.65621204	2.65	2.65	0.33823038

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	–56.62659619	4	121.253192
A2	–54.73789338	6	121.475787
A3	–56.62659619	4	121.253192
fitted	–57.02268989	3	120.04538
R	–65.24552159	2	134.491043

Tests of Interest

Test	–2*Log(Likelihood Ratio)	Test d.f.	P-value
1	21.01525643	4	0.00031447
2	3.777405633	2	0.1512679
3	3.777405633	2	0.1512679
4	0.792187387	1	0.37343953

Figure 1-3. Details Regarding the Selected Model (Exponential 2) for Decreased Numbers of Seminiferous Tubules in Mice in a 35-Day Study

1.1.2 Decreases in Testes Weights (Mice)

Chen et al. (2015) identified decreased testes weights in adolescent ICR mice after 35 days exposure to TCEP. Continuous models were used to fit dose-response data. BMDLs based on BMRs of one SD and

five percent RD from the best fit model are both presented. Based on EPA's *BMD Technical Guidance* (U.S. EPA, 2012), EPA is using the BMDL based on a BMR of one SD for this endpoint when comparing with other points of departure. The doses and response data used for modeling this endpoint are presented in Table 1-3.

Table 1-3. Decreased Testes Weights in Mice and Associated Doses Selected for Dose-Response Modeling for TCEP

Dose (mg/kg-day)	Number of Fertile Pairs	Mean	SD
0	7	0.32	0.053
100	7	0.28	0.04
300	7	0.27	0.019

Table 1-4 summarizes the BMD modeling results for decreased testes weights from Chen et al. (2015). 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 4 and 5 models provided adequate fit to the means. The BMDLs for the fit models were sufficiently close (< 3-fold difference). therefore, EPA chose the Exponential 3 model, the one with the lowest AIC was selected.

Table 1-4. Summary of BMD Modeling Results for Decreased Testes Weights in Mice Following Oral Exposure to TCEP in a 35-Day Study (Constant Variance)[ab]

Model	Goodness of Fit		BMD 1SD (mg/kg-day)	BMDL 1SD (mg/kg-day)	BMD 5%RD (mg/kg-day)	BMDL 5%RD (mg/kg-day)	Basis for Model Selection
	P-value	AIC					
Exponential 2	0.659	–75.9	459	214	123	69.7	The nonconstant variance model fit, and all models, except the Exponential 4 and 5, provided adequate fit to the means. The BMDLs for the fit models were < 3-fold different; EPA chose the model with the lowest AIC, the Exponential 3.
Exponential 3	**0.660**	**–75.9**	**467**	**214**	**125**	**69.7**	
Exponential 4	NA	–73.9	469	34.8	125	0	
Exponential 5	65535	–72.0	–9999	0	81.4	0	
Polynomial 2	0.630	–75.8	460	224	131	77.0	
Power	0.630	–75.8	460	224	131	77.0	
Linear	0.630	–75.8	460	225	131	77.0	

[a] Three significant figures
[b] Selected model in bold; scaled residuals for selected model for doses 0, 100, and 300 mg/kg-day were 0.778, 0.859, and 0.155 respectively

Plots of the Exponential 3 model with BMRs of one SD and five percent RD are shown in Figure 1-4 and Figure 1-5, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown below in Figure 1-6.

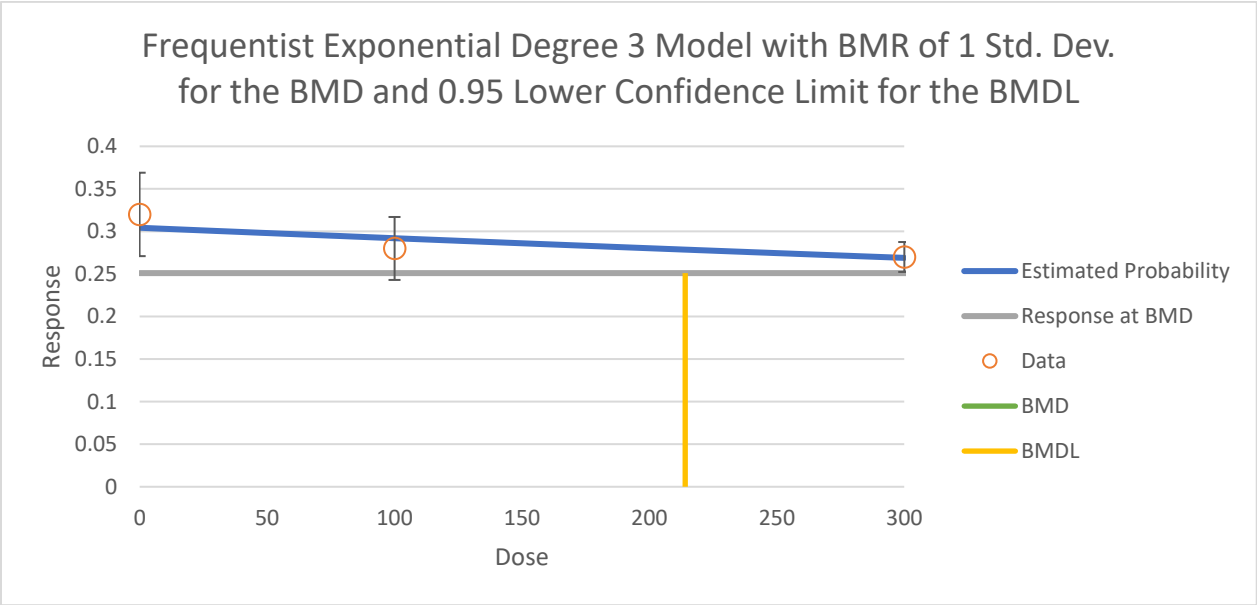

Figure 1-4. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 3) for Decreased Testes Weights in Mice Exposed to TCEP Via Oral Gavage in a 35-Day Study and BMR of 1SD (Nonconstant Variance)

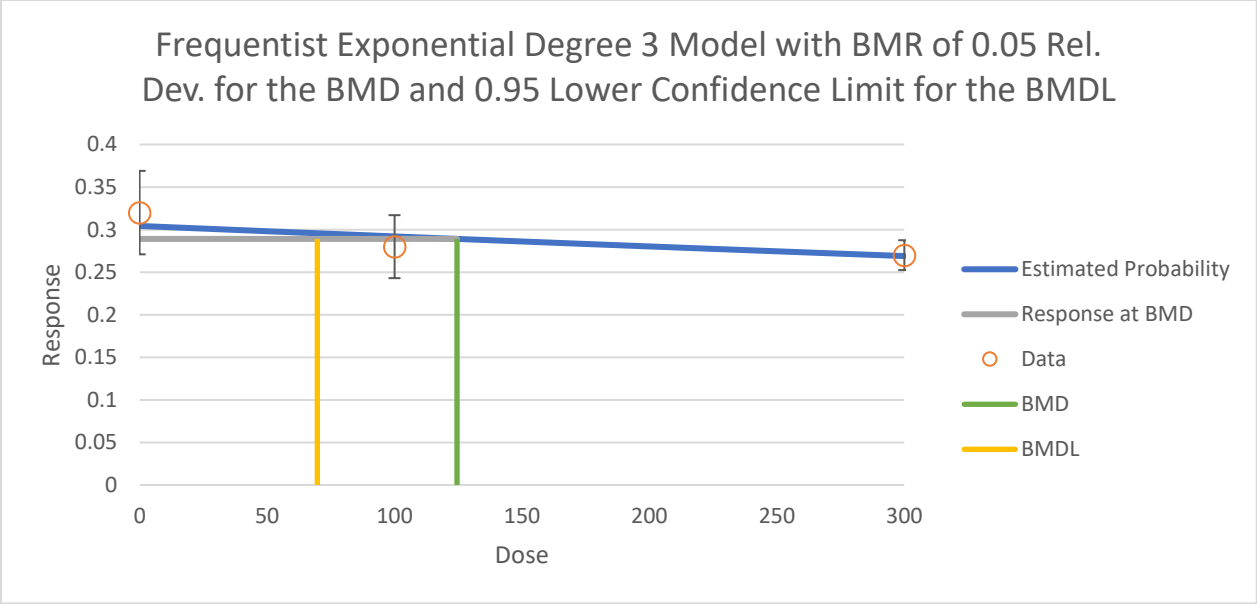

Figure 1-5. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 3) for Decreased Testes Weights in Mice Exposed to TCEP Via Oral Gavage in a 35-Day Study and BMR of 5 Percent Relative Deviation (Nonconstant Variance)

Model Results

Benchmark Dose	
BMD	467.3440933
BMDL	214.0626432
BMDU	792.6585915
AIC	–75.85266567
Test 4 P-value	0.660168789
D.O.F.	1

Model Parameters	
# of Parameters	5
Variable	Estimate
a	0.304323078
b	0.000411915
d	Bounded
rho	17.60378098

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	7	0.304323078	0.32	0.32	0.05329016	0.053	0.053	0.778328256
100	7	0.292042232	0.28	0.28	0.03708412	0.04	0.04	–0.859148124
300	7	0.268947308	0.27	0.27	0.01795849	0.019	0.019	0.155088856

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	39.4830962	4	–70.966192
A2	42.65846137	6	–73.316923
A3	42.02299215	5	–74.045984
fitted	41.92633284	4	–75.852666
R	36.39113618	2	–68.782272

Tests of Interest

Test	–2*Log(Likelihood Ratio)	Test d.f.	P-value
1	12.53465039	4	0.01378827
2	6.350730343	2	0.04177884
3	1.270938445	1	0.2595907
4	0.193318625	1	0.66016879

Figure 1-6. Details Regarding the Selected Model (Exponential 3) for Decreased Testes Weights in Mice in a 35-Day Study

1.1.3 Live Male F1 Pups per Litter (Mice)

NTP (1991a) identified decreases in the number of live male F1 mouse pups per litter. BMDLs based on BMRs of one SD and five percent RD from the best fit model are both presented. Based on the severity of the endpoint that was observed in offspring and considering EPA's *BMD Technical Guidance* (U.S. EPA, 2012), EPA is using the BMDL based on a BMR of five percent RD for this endpoint when comparing with other points of departure. Continuous models were used to fit dose-response data. The doses and response data used for the modeling are presented in Table 1-5.

Table 1-5. F1 Live Male F1 Pups per Litter in Mice and Associated Doses Selected for Dose-Response Modeling for TCEP

Dose (mg/kg-day)	Number of Fertile Pairs	Mean	SD
0	37	6.4	1.82
175	18	6.1	1.27
350	18	5.1	1.7
700	18	3.9	1.27

Table 1-6 summarizes the BMD modeling results for live male F1 mice per litter from NTP (1991a). 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. The BMDLs for the fit models were sufficiently close (differed by < 3-fold). The 2-degree and 3-degree Polynomial models converged on the same model and had the lowest AIC. EPA chose the 2-degree Polynomial model because it had the lowest AIC and was the more parsimonious choice.

Table 1-6. Summary of BMD Modeling Results for Live Male F1 Pups per Litter in Mice Following Oral Exposure to TCEP in a Continuous Breeding Study (Constant Variance)[ab]

Model	Goodness of Fit		BMD 1SD (mg/kg-day)	BMDL 1SD (mg/kg-day)	BMD 5%RD (mg/kg-day)	BMDL 5%RD (mg/kg-day)	Basis for Model Selection
	P-value	AIC					
Exponential 2	0.583	347	402	286	74.3	56.1	With constant variance option, all models (except Exponential 5 and Hill) provided adequate fit to the means and had BMDLs that were sufficiently close (< 3-fold difference). The 2-degree and 3-degree Polynomial models converged and had the lowest AIC. EPA chose the 2-degree Polynomial model as most parsimonious.
Exponential 3	0.529	348	447	298	125	58.3	
Exponential 4	0.583	347	402	286	74.3	56.1	
Exponential 5	NA	350	393	281	180	59.5	
Hill	NA	350	398	275	180	50.6	
Polynomial 3	0.747	346	455	330	103	71.5	
Polynomial 2	**0.747**	**346**	**455**	**330**	**103**	**71.5**	
Power	0.475	348	457	331	115	71.7	
Linear	0.717	347	431	329	88.7	71.3	

[a] Three significant figures
[b] Selected model in bold; scaled residuals for selected model for doses 0, 175, 350, and 700 mg/kg-day were 0.155, 0.594, 0.446, and 0.0743, respectively.

Plots of the Polynomial 2 model with BMRs of one SD and five percent RD are shown in Figure 1-7 and Figure 1-8, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown below in Figure 1-9.

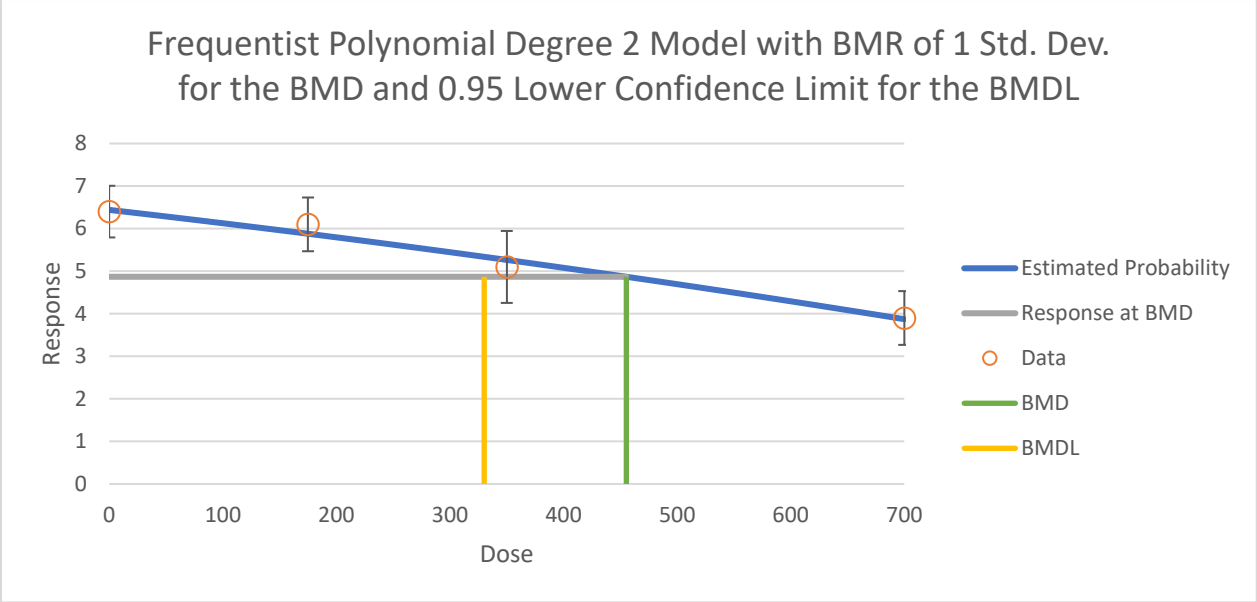

Figure 1-7. Plot of Response by Dose with Fitted Curve for the Selected Model (Polynomial 2) for Live Male F1 Pups per Litter in Mice Exposed to TCEP Via Oral Gavage in a Continuous Breeding Study and BMR of 1SD (Constant Variance)

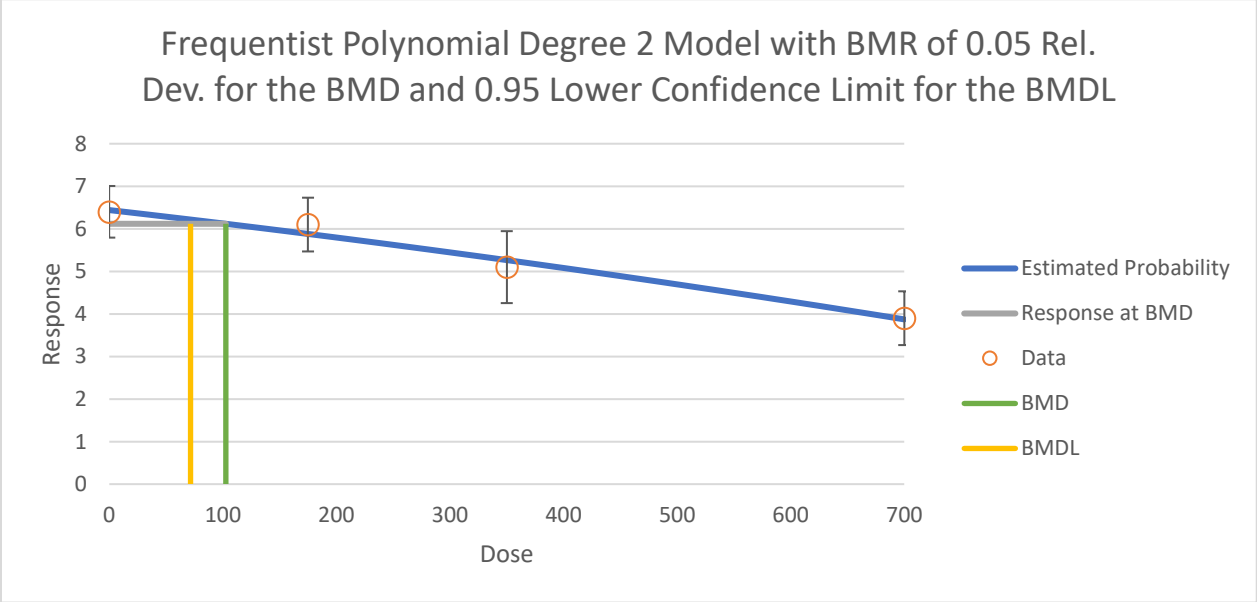

Figure 1-8. Plot of Response by Dose with Fitted Curve for the Selected Model (Polynomial 2) for Live Male F1 Pups per Litter in Mice Exposed to TCEP Via Oral Gavage in a Continuous Breeding Study and BMR of 5 Percent Relative Deviation (Constant Variance)

Model Results

Benchmark Dose	
BMD	455.3158283
BMDL	330.1312755
BMDU	636.807465
AIC	346.4826916
Test 4 P-value	0.746854679
D.O.F.	2

Model Parameters	
# of Parameters	4
Variable	Estimate
g	6.440162141
beta1	–0.003046379
beta2	Bounded

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	37	6.440162141	6.4	6.4	1.57120085	1.82	1.82	–0.155484111
175	18	5.879844619	6.1	6.1	1.57120085	1.27	1.27	0.59447535
350	18	5.265124542	5.1	5.1	1.57120085	1.7	1.7	–0.445878131
700	18	3.872476719	3.9	3.9	1.57120085	1.27	1.27	0.074319837

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	–169.9494612	5	349.898922
A2	–167.3861158	8	350.772232
A3	–169.9494612	5	349.898922
fitted	–170.2413458	3	346.482692
R	–184.5846567	2	373.169313

Tests of Interest

Test	–2*Log(Likelihood Ratio)	Test d.f.	P-value
1	34.39708179	6	< 0.0001
2	5.126690709	3	0.16275184
3	5.126690709	3	0.16275184
4	0.583769305	2	0.74685468

Figure 1-9. Details Regarding the Selected Model (Polynomial 2) for Live Male F1 Pups per Litter in a Continuous Breeding Study

1.1.4 Live F2 Pups per Litter (Mice)

NTP (1991a) identified decreased mean numbers of F2 mice pups per litter in the F2 generation. Continuous models were used to fit dose-response data. BMDLs based on BMRs of one SD and five percent RD from the best fit model are both presented. Based on the severity of this effect in offspring and considering EPA's *BMD Technical Guidance* (U.S. EPA, 2012), EPA is using the BMDL based on a BMR of five percent RD for this endpoint when comparing with other points of departure. The doses and response data used for the modeling are presented in Table 1-7.

Table 1-7. Live F2 Pups per Litter in Mice and Associated Doses Selected for Dose-Response Modeling for TCEP

Dose (mg/kg-day)	Number of Fertile Pairs	Mean	SD
0	17	11.4	2.06
175	18	11	2.12
350	14	7.6	4.12

Table 1-8 summarizes the BMD modeling results for live pups per litter from NTP (1991a). The constant variance model did not provide adequate fit to the variance data but the nonconstant variance model did provide an adequate fit. Applying the nonconstant variance model, only the 2-degree Polynomial provided adequate fit to the means (test 4 p-value > 0.1); therefore, this model was selected.

Table 1-8. Summary of BMD Modeling Results for Live F2 Pups per Litter in Mice Following Oral Exposure to TCEP in a Continuous Breeding Study (Nonconstant Variance)[ab]

Model	Goodness of Fit		BMD 1SD (mg/kg-day)	BMDL 1SD (mg/kg-day)	BMD 5%RD (mg/kg-day)	BMDL 5%RD (mg/kg-day)	Basis for Model Selection
	P-value	AIC					
Exponential 2	0.0157	241	230	133	67.3	40.9	Of the non-constant variance models (the only ones that adequately fit the variance data), the 2-degree Polynomial provided adequate fit to the means (test 4 p-value > 0.1) and EPA selected this model.
Exponential 3	NA	237	284	203	198	102	
Exponential 4	0.0157	241	230	133	67.4	40.9	
Exponential 5	NA	237	284	203	198	102	
Hill	< 0.0001	239	223	180	185	155	
Polynomial 2	**0.335**	**236**	**252**	**192**	**139**	**76.5**	
Power	NA	238	343	199	326	301	
Linear	0.0232	240	223	140	69.3	45.7	

[a] Three significant figures
[b] Selected model in bold; scaled residuals for selected model for doses 0, 175, and 350 mg/kg-day were 0.418, 0.624, and 0.293, respectively.

Plots of the Polynomial 2 model with BMRs of one SD and five percent RD are shown in Figure 1-10 and Figure 1-11, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown below in Figure 1-12.

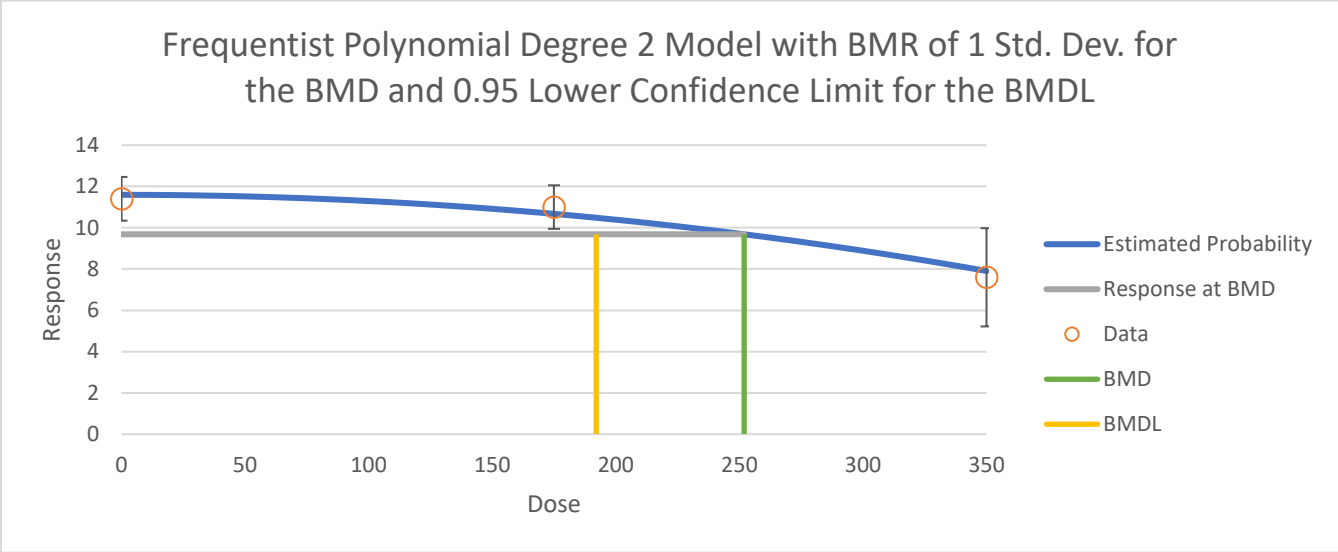

Figure 1-10. Plot of Response by Dose with Fitted Curve for the Selected Model (Polynomial 2) for Live F2 Pups per Litter in Mice Exposed to TCEP Via Oral Gavage in a Continuous Breeding Study and BMR of 1SD (Nonconstant Variance)

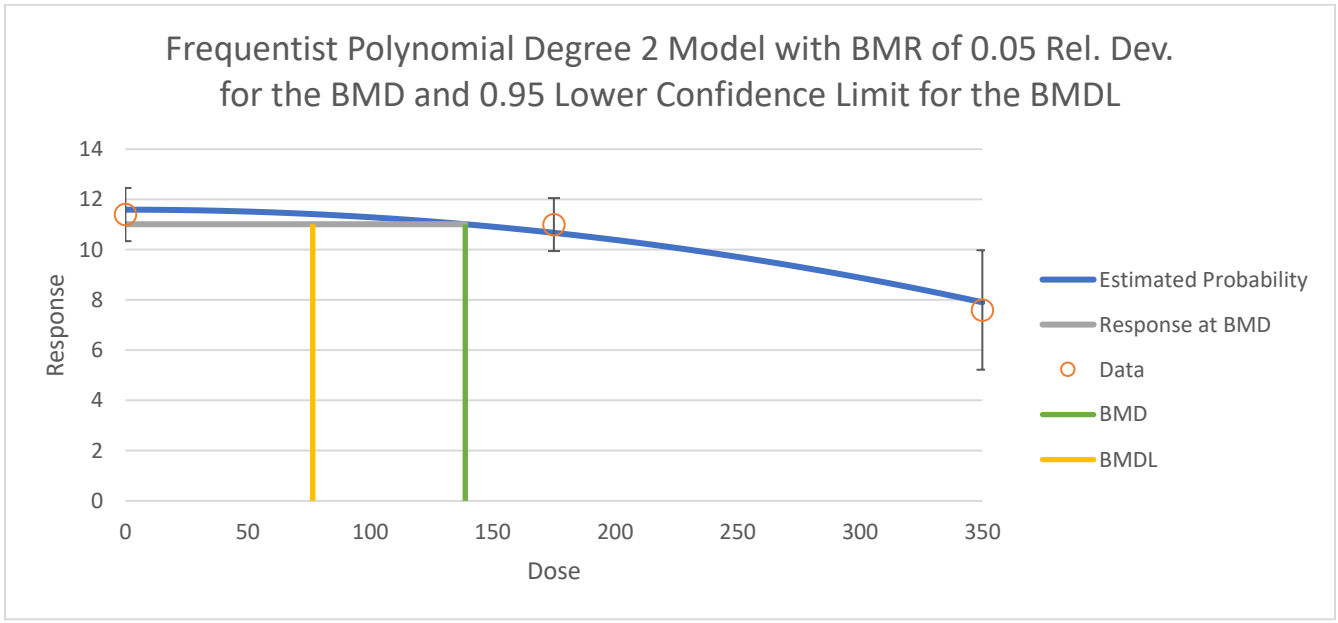

Figure 1-11. Plot of Response by Dose with Fitted Curve for the Selected Model (Polynomial 2) for Live F2 Pups per Litter in Mice Exposed to TCEP Via Oral Gavage in a Continuous Breeding Study and BMR of 5 Percent Relative Deviation (Nonconstant Variance)

Model Results

Benchmark Dose (1 SD)	
BMD	251.9403458
BMDL	192.0823998
BMDU	367.1866626
AIC	236.1697373
Test 4 P-value	0.334975944
D.O.F.	1

Model Parameters	
# of Parameters	5
Variable	Estimate
g	11.5935616
beta1	Bounded
beta2	–3.01002E-05
rho	–3.746949647

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	17	11.5935616	11.4	11.4	1.91057668	2.06	2.06	–0.417714158
175	18	10.67174339	11	11	2.23138704	2.12	2.12	0.624129657
350	14	7.906288771	7.6	7.6	3.91398177	4.12	4.12	–0.292803521

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	–118.7238354	4	245.447671
A2	–113.6129329	6	239.225866
A3	–113.6200861	5	237.240172
fitted	–114.0848686	4	236.169737
R	–126.2176267	2	256.435253

Tests of Interest

Test	–2*Log(Likelihood Ratio)	Test d.f.	P-value
1	25.20938769	4	< 0.0001
2	10.2218049	2	0.00603064
3	0.014306312	1	0.90479289
4	0.929565159	1	0.33497594

Figure 1-12. Details Regarding the Selected Model (Polynomial 2) for Live F2 Pups per Litter in Mice in a Continuous Breeding Study

1.1.5 F0 Fertility in Mice

NTP (1991a) identified increases in the number of non-fertile pairs per number of cohabiting mice for litter five from the F0 generation. Dichotomous models were fit to the incidence data. EPA chose a BMR of five percent ER according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012) to compare with other points of departure. The doses and response data used for the modeling are presented in Table 1-9.

Table 1-9. F0 Non-fertility in Mice and Associated Doses Selected for Dose-Response Modeling for TCEP

Dose (mg/kg-day)	Number of Animals Cohabiting	Incidence of Nonfertility
0	38	3
175	19	2
350	18	5
700	18	18

Table 1-10 summarizes the BMD modeling results for F0 nonfertile mice from NTP (1991a). The Dichotomous Hill, Gamma, Log-logistic, 3-degree Multistage, Weibull, and Log-probit 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, EPA chose the model with the lowest AIC.

Table 1-10. Summary of BMD Modeling Results for F0 Nonfertile Mice Following Oral Exposure to TCEP in a Continuous Breeding Study[ab]

Model	Goodness of Fit		BMD (mg/kg/day)	BMDL (mg/kg/day)	Basis for Model Selection
	P-value	AIC			
Dichotomous Hill	0.947	59.2	320	225	The Dichotomous Hill, Gamma, Log-logistic, 3-degree Multistage, Weibull, and Log-probit models provided adequate fits to the data (chi-square p-value > 0.1). The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, EPA selected the model with the lowest AIC.
Gamma	0.863	59.5	275	200	
Log-Logistic	**0.947**	**59.2**	**320**	**225**	
Multistage 3	0.456	61.3	175	82.4	
Multistage 2	0.0697	66.5	108	65.9	
Multistage 1	0.000911	78.7	29.6	20.7	
Weibull	0.773	61.1	271	161	
Logistic	0.0878	64.8	108	72.9	
Log-Probit	0.741	61.2	329	229	
Probit	0.0609	65.6	90.6	62.5	

[a] Three significant figures
[b] Selected model in bold; scaled residuals for selected model for doses 0, 175, 350, and 700 mg/kg-day were −0.191, 0.270, −1.7E−04, and 1.54E−02, respectively.

Figure 1-13 shows the log-logistic model, the chosen model for F0 fertility with a BMR of five percent RD. shows additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood.

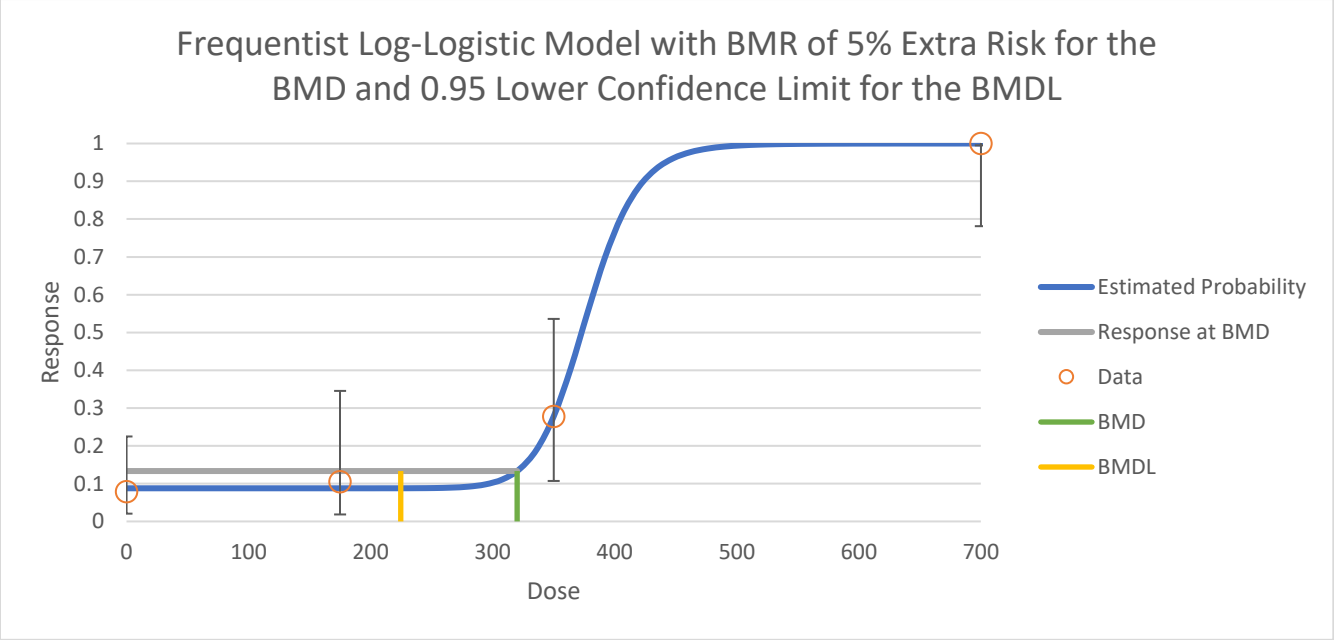

Figure 1-13. Plot of Response by Dose with Fitted Curve for the Selected Model (Log-Logistic) for F0 Nonfertile Mice Exposed to TCEP Via Oral Gavage in a Continuous Breeding Study and BMR of 5 Percent Extra Risk

Model Results

Benchmark Dose	
BMD	320.0613905
BMDL	224.693377
BMDU	362.8647716
AIC	59.15490795
P-value	0.946557537
D.O.F.	2
Chi^2	0.109847042

Model Parameters	
# of Parameters	3
Variable	Estimate
G	0.08771758
A	–106.7776698
B	Bounded

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.08771758	3.333268046	3	38	–0.191115
175	0.087718496	1.666651425	2	19	0.2703409
350	0.277795687	5.000322359	5	18	–0.00017
700	0.999986778	17.999762	18	18	0.0154275

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P-Value
Full Model	–27.52383488	4	-	-	NA
Fitted Model	–27.57745398	2	0.1072382	2	0.9477931
Reduced Model	–56.89485404	1	58.7420383	3	< 0.0001

Figure 1-14. Details Regarding the Selected Model (Log-Logistic) for F0 Nonfertile Mice in a Continuous Breeding Study

1.2 Liver Effects

EPA modeled liver effects when a pairwise change from controls and/or dose-response trend was evident in the data (*e.g.*, a statistically significant change was identified).

When modeling liver weight changes, the best measures are changes relative to body weight (to account for any changes that are primarily related to body weight changes). However, EPA modeled both relative and absolute liver weight changes in male rats at 66 weeks in the 2-year cancer bioassay and in female rats and mice from 16-week studies (NTP, 1991b) because body weights didn't change or because the percent change in relative liver weight was 30 percent greater than changes in body weight in female rats at 350 mg/kg-day after 16 weeks.

All modeled results from the NTP studies are presented except the relative liver weight changes in male rats at 66 weeks because neither the constant nor the nonconstant variance models provided adequate fit to the variance data. The female rat data could not be modeled without dropping doses and therefore, EPA is not presenting these data. EPA also modeled decreased absolute liver weight in male ICR mice in a 35-day study (Chen et al., 2015) as a comparison with liver weight changes from other studies, but these results are not shown because none of the models provided adequate fits to the data either assuming constant or non-constant variance.

1.2.1 Eosinophilic Foci in Male Mice

Male mice exhibited an increase in eosinophilic liver foci after two years of exposure to TCEP (NTP, 1991b). As inputs to BMD modeling and for consistency across endpoints, administered doses were first duration adjusted to estimate an equivalent oral dose for animals exposed for seven days per week rather than five days per week. Then, dichotomous models were used to fit dose-response data.

EPA presents the BMDL based on a BMR of 10 percent ER from the best fit model and based on the severity of the endpoint and considering EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The doses and response data used for the modeling are presented in Table 1-11.

Table 1-11. Male Mouse Eosinophilic Foci in Livers and Associated Doses Selected for Dose-Response Modeling for TCEP in the Two-Year Bioassay

Dose (mg/kg-day)	Number of Animals	Incidence
0	50	0
125	50	3
250	50	8

Table 1-12 summarizes the BMD modeling results for eosinophilic foci in male mice. The Log-logistic, Multistage 2- and 1-degree, Logistic, and Probit models all provided adequate fits to the data (chi-square p-value > 0.1). BMDLs among the fit models were sufficiently close (< 3-fold difference). Therefore, EPA chose the model with the lowest AIC – the Multistage 1-degree model.

Table 1-12. BMD Modeling Results for Eosinophilic Liver Foci in Male Mice in the Two-Year Bioassay[ab]

Model	Goodness of Fit (Means)		BMD 10%ER (mg/kg-day)	BMDL 10%ER (mg/kg-day)	Basis for Model Selection
	P-value	AIC			
Dichotomous Hill	NA	72.7	169	0	Of the models with adequate fits (Log-logistic, Multistage 2- and 1-degree, Logistic, and Probit models), EPA chose the model with the lowest AIC.
Gamma	NA	72.7	178	108	
Log-Logistic	0.999	70.7	178	104	
Multistage 2	0.999	70.7	180	108	
Multistage 1	**0.878**	**68.9**	**168**	**106**	
Weibull	NA	72.7	178	108	
Logistic	0.339	72.0	208	172	
Log-Probit	NA	76.9	244	0	
Probit	0.398	71.7	202	163	

[a] Three significant figures
[b] Selected model in bold; scaled residuals for selected model for doses 0, 125, and 250 mg/kg-day were –8.73E–04, –0.413, and 0.298 respectively.

Plots of the Multistage 2-degree model with BMR 10 percent ER is shown in Figure 1-15. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 1-16.

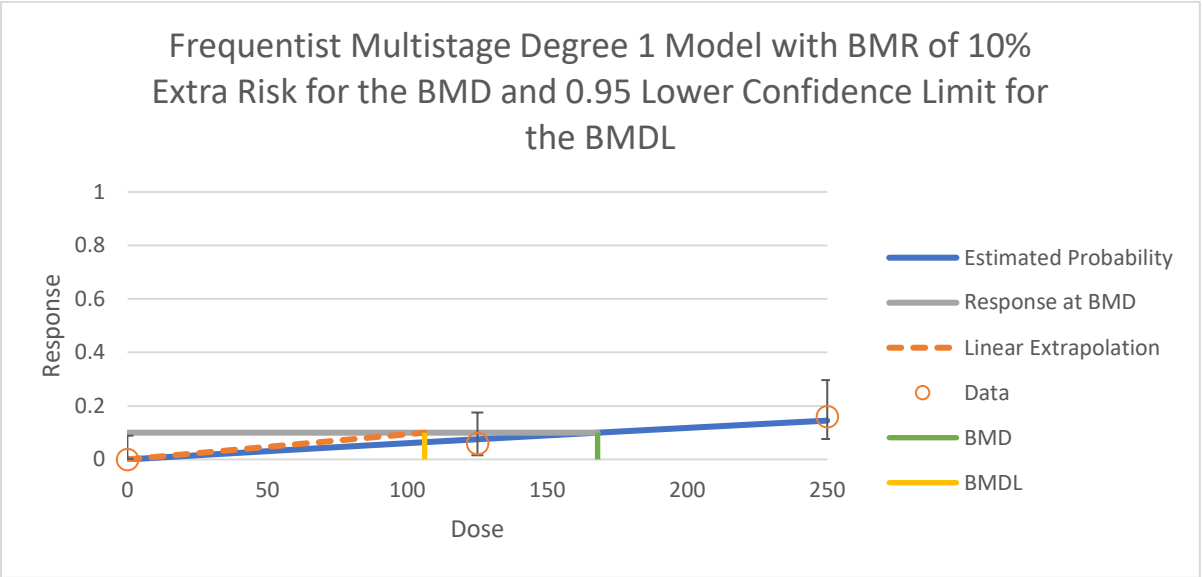

Figure 1-15. Plot of Response by Dose with Fitted Curve for the Selected Model (Multistage 1-Degree) for Eosinophilic Foci in Livers of Male Mice Exposed to TCEP Via Oral Gavage (Two-Year Bioassay) and BMR of 10 Percent

Model Results

Benchmark Dose	
BMD	167.9439247
BMDL	106.14906
BMDU	289.6913765
AIC	68.93261182
P-value	0.878392643
D.O.F.	2
Chi^2	0.259323168
Slope Factor	0.000942071

Model Parameters	
# of Parameters	2
Variable	Estimate
g	Bounded
b1	0.000627355

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E–08	7.61499E–07	0	50	–0.000873
125	0.075423454	3.771172705	3	50	–0.412992
250	0.145158198	7.257909888	8	50	0.2979257

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P-Value
Full Model	–33.3318701	3	-	-	NA
Fitted Model	–33.46630591	1	0.26887163	2	0.874209
Reduced Model	–39.32656941	1	11.9893986	2	0.0024919

Figure 1-16. Details Regarding the Selected Model (Multistage 1-Degree) for Eosinophilic Foci in Livers of Male Mice in the Two-Year Bioassay

1.2.2 Absolute Liver Weight in Male Rats

Absolute liver weights increased in male rats exposed to TCEP at 66 weeks (NTP, 1991b). As inputs to BMD modeling and for consistency across endpoints, administered doses were first duration adjusted to estimate an equivalent oral dose for animals exposed for seven days per week rather than five days per week. Then, continuous models were used to fit dose-response data.

BMRs of one SD and ten percent RD were chosen according to EPA's *BMD Technical Guidance* (**U.S. EPA, 2012**). EPA considers the BMR of ten percent RD to be adverse and used the BMDL associated with this BMR for consideration within the risk evaluation and when comparing with other PODs. The doses and response data used for the modeling are presented in Table 1-13.

Table 1-13. Male Rat Absolute Liver Weights and Associated Doses Selected for Dose-Response Modeling for TCEP at 66 Weeks

Dose (mg/kg-day)	Number of Animals	Mean	SD
0	9	14.9	2.52
31	10	16.2	1.04
63	10	17.9	1.11

Table 1-14 summarizes the BMD modeling results for increased absolute liver weight in male rats at 66 weeks in the NTP 2-year chronic bioassay. Although the constant variance model did not provide adequate fit to the variance data, the nonconstant variance model provided an adequate fit. With the nonconstant variance model applied, the Exponential 2, Exponential 3, 2-degree Polynomial, Power and Linear models provided adequate fit to the means (test 4 p-value > 0.1). The BMDLs for the fit models with adequate fit were sufficiently close (< 3-fold difference). The Power and 2-degree Polynomial models converged on the Linear model; these had the lowest AICs, and the Linear model was selected as the most parsimonious choice.

Table 1-14. Summary of BMD Modeling Results for Increased Absolute Liver Weights in Male Rats Following Oral Exposure to TCEP at 66 Weeks (Nonconstant Variance)[ab]

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
	P-value	AIC					
Exponential 2	0.587	109	45.0	30.3	32.2	23.0	Among the non-constant variance models with adequate fit (test 4 p-value > 0.1), the Linear model is recommended because it is the most parsimonious of the three converged models with the lowest AICs.
Exponential 3	0.591	109	44.3	30.3	31.9	23.0	
Exponential 4	NA	111	39.1	19.5	24.9	9.83	
Exponential 5	NA	111	39.0	19.5	24.8	9.83	
Hill	65535	113	31.9	18.8	30.3	28.2	
Polynomial 2	0.694	109	42.7	28.3	29.8	20.4	
Power	0.694	109	42.7	28.3	29.8	20.4	
Linear	**0.694**	**109**	**42.7**	**28.3**	**29.8**	**20.4**	

[a] Three significant figures
[b] Selected model in bold; scaled residuals for selected model for doses 0, 31, and 63 mg/kg-day were 0.200, 0.216, and 0.0636, respectively.

Plots of the Linear model with BMRs of one SD and ten percent RD are shown in Figure 1-17 and Figure 1-18, respectively. Additional modeling details, including model parameters, goodness of fit at each dose and log likelihood are shown in Figure 1-19.

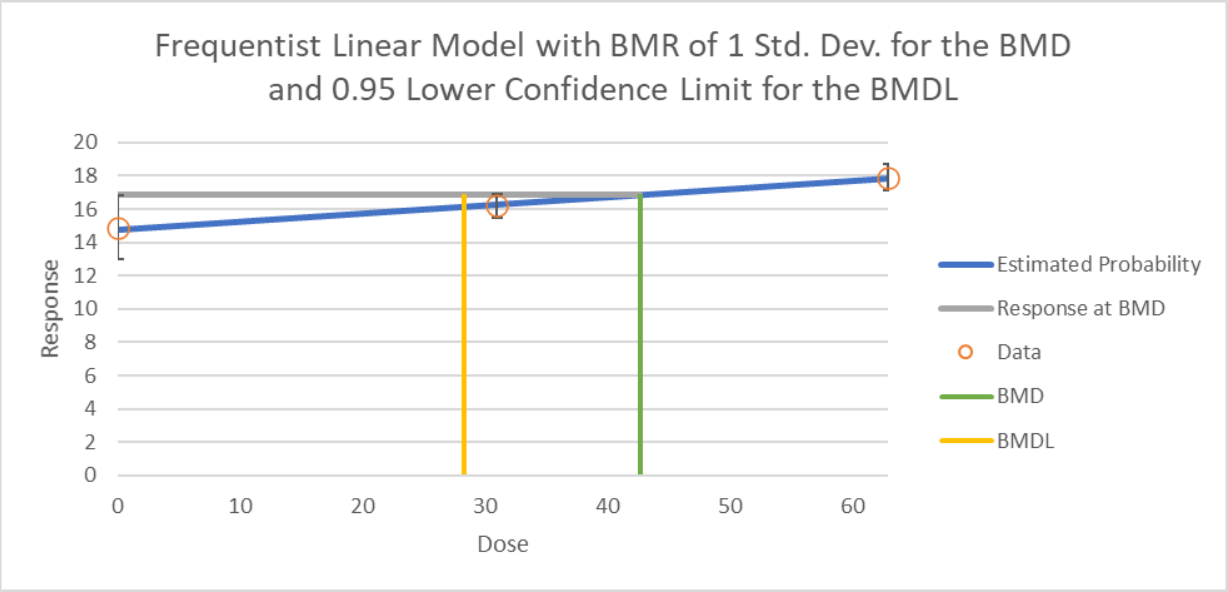

Figure 1-17. Plot of Response by Dose with Fitted Curve for the Selected Model (Linear) for Absolute Liver Weight Increases in Male Rats Exposed to TCEP Via Oral Gavage (at 66 Weeks) and BMR of 1SD (Nonconstant Variance)

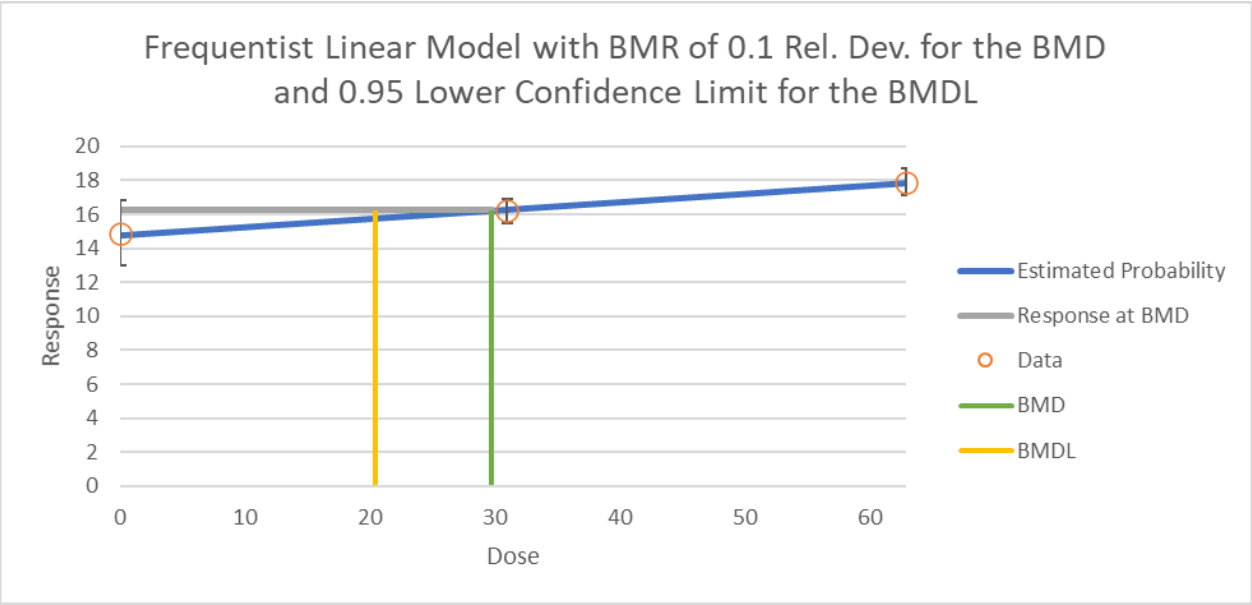

Figure 1-18. Plot of Response by Dose with Fitted Curve for the Selected Model (Linear) for Absolute Liver Weight Increases in Male Rats Exposed to TCEP Via Oral Gavage (at 66 Weeks) and BMR of 10 Percent (Nonconstant Variance)

Model Results

Benchmark Dose	
BMD	42.69774628
BMDL	28.32874416
BMDU	76.64400531
AIC	109.1787602
Test 4 P-value	0.694137339
D.O.F.	1

Model Parameters	
# of Parameters	4
Variable	Estimate
g	14.75901536
beta1	0.049556637
rho	–8.45314728

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	9	14.75901536	14.9	14.9	2.11595582	2.52	2.52	0.199887879
31	10	16.29527111	16.2	16.2	1.39234274	1.04	1.04	–0.216378973
63	10	17.88108349	17.9	17.9	0.94032713	1.11	1.11	0.063615366

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	–54.25967213	4	116.519344
A2	–49.31972604	6	110.639452
A3	–50.51205867	5	111.024117
fitted	–50.58938012	4	109.17876
R	–61.09564682	2	126.191294

Tests of Interest			
Test	–2*Log(Likelihood Ratio)	Test d.f.	P-value
1	23.55184155	4	< 0.0001
2	9.87989217	2	0.00715498
3	2.384665249	1	0.12253114
4	0.154642905	1	0.69413734

Figure 1-19. Details Regarding the Selected Model (Linear) for Absolute Liver Weight Increases in Male Rats at 66 Weeks

1.2.3 Absolute Liver Weight in Female Mice

Absolute liver weights increased in female mice exposed to TCEP for 16 weeks (NTP, 1991b). For BMD modeling, the administered doses were first duration adjusted to estimate an equivalent oral dose for animals exposed for seven days per week rather than five days per week. Then, continuous models were used to fit dose-response data.

BMRs of one SD and ten percent RD were chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). EPA considers the BMR of ten percent RD to be adverse and used the BMDL associated with this BMR for consideration within the risk evaluation and when comparing with other PODs. The doses and response data used for the modeling are presented in Table 1-15.

Table 1-15. Female Mouse Absolute Liver Weights and Associated Doses Selected for Dose-Response Modeling for TCEP From a 16-Week Study

Dose (mg/kg-day)	Number of Animals	Mean	SD
0	10	1.07	0.09
31	10	1.11	0.13
63	10	1.16	0.09
125	9	1.22	0.12
250	9	1.29	0.12
500	10	1.21	0.06

Table 1-16 summarizes the BMD modeling results for increased absolute liver weight in female mice in the 16-week study. The constant variance model provided adequate fit to the variance data. With the constant variance model applied, the Exponential 4 and 5 models and the Hill model provided adequate fit to the means. The BMDLs for these models were sufficiently close (< 3-fold difference). Therefore, EPA selected the Exponential 4 model because it has the lowest AIC.

Table 1-16. Summary of BMD Modeling Results for Increased Absolute Liver Weights in Female Mice Following Oral Exposure to TCEP in a 16-Week Study (Constant Variance)[abc]

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
	P-value	AIC					
Exponential 2	0.00233	−81.9	447	294	446	291	The Exponential 4 and 5 models and the Hill model provided adequate fit to the means (test 4 p-values > 0.1). The BMDLs for the fit models were sufficiently close (< 3-fold difference). Therefore, EPA chose the Exponential 4 model, which has the lowest AIC.
Exponential 3	0.00233	−81.9	447	294	447	292	
Exponential 4	**0.268**	**−92.5**	**57.8**	**27.7**	**61.5**	**28.0**	
Exponential 5	0.211	−91.4	71.2	31.2	75.7	32.3	
Hill	0.174	−91.0	68.9	31.3	73.0	36.3	
Polynomial 5	0.00269	−82.2	428	275	428	273	
Polynomial 4	0.00269	−82.2	428	275	428	273	
Polynomial 3	0.00269	−82.2	428	275	428	273	
Polynomial 2	0.00269	−82.2	428	275	428	273	
Power	0.00269	−82.2	428	276	428	273	
Linear	0.00269	−82.2	428	275	428	273	

[a] Three significant figures
[b] Based on test 2 p-values > 0.05 for all models, EPA determined that the constant variance model assumption may be suitable for dose-response modeling.
[c] Selected model in bold; scaled residuals for selected model for doses 0, 31, 63, 125, 250, and 500 mg/kg-day were 0.311, 0.442, 0.236, 0.201, 1.43, and 1.18, respectively.

Plots of the Exponential 4 model with BMRs of one SD and 10 percent RD are shown in Figure 1-20 and Figure 1-21, respectively. Additional modeling details, including model parameters, goodness of fit at each dose and log likelihood are shown in Figure 1-22.

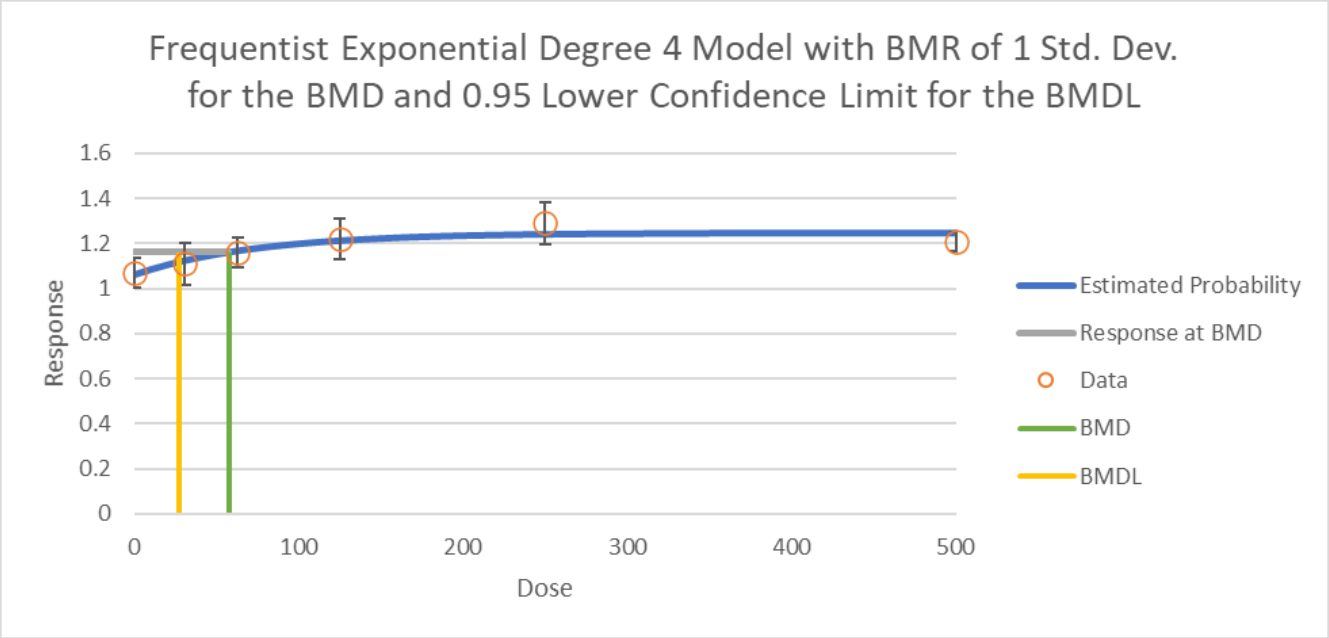

Figure 1-20. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 4) for Absolute Liver Weight Increases in Female Mice Exposed to TCEP Via Oral Gavage (16-Week Study) and BMR of 1SD (Constant Variance)

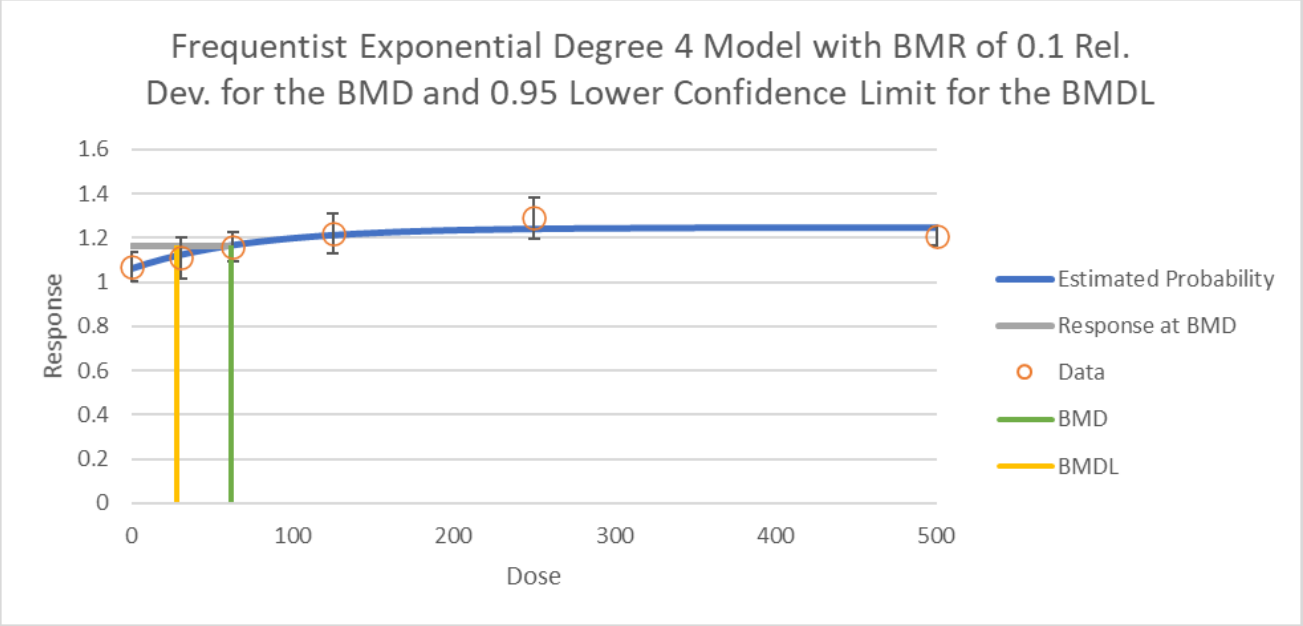

Figure 1-21. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 4) for Absolute Liver Weight Increases in Female Mice Exposed to TCEP Via Oral Gavage (16-Week Study) and BMR of 10 Percent Rel Dev (Constant Variance)

Model Results

Benchmark Dose	
BMD	57.75678158
BMDL	27.71499956
BMDU	163.5531039
AIC	–92.52408587
Test 4 P-value	0.267822421
D.O.F.	3

Model Parameters	
# of Parameters	4
Variable	Estimate
a	1.059984909
b	0.013471904
c	1.177474954

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	10	1.059984909	1.07	1.07	0.10172056	0.09	0.09	0.311348069
31	10	1.124208116	1.11	1.11	0.10172056	0.13	0.13	–0.441700389
63	10	1.167597871	1.16	1.16	0.10172056	0.09	0.09	–0.236201795
125	9	1.21318441	1.22	1.22	0.10172056	0.12	0.12	0.201009221
250	9	1.24162317	1.29	1.29	0.10172056	0.12	0.12	1.426756755
500	10	1.2478823	1.21	1.21	0.10172056	0.06	0.06	–1.17768084

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	52.23292131	7	–90.465843
A2	55.72879398	12	–87.457588
A3	52.23292131	7	–90.465843
fitted	50.26204294	4	–92.524086
R	39.66391724	2	–75.327834

Tests of Interest

Test	–2*Log(Likelihood Ratio)	Test d.f.	P-value
1	32.12975349	10	0.00038098
2	6.991745356	5	0.22125494
3	6.991745356	5	0.22125494
4	3.941756742	3	0.26782242

Figure 1-22. Details Regarding the Selected Model (Exponential 4) for Absolute Liver Weight Increases for Female Mice Exposed in a 16-Week Study

1.2.4 Relative Liver Weight in Female Mice

Relative liver weights increased in female mice exposed to TCEP for 16 weeks (NTP, 1991b). For BMD modeling, the administered doses were first duration adjusted to estimate an equivalent oral dose for animals exposed for seven days per week rather than five days per week. Then, continuous models were used to fit dose-response data.

BMRs of one SD and 10 percent RD were chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). EPA considers the BMR of ten percent RD to be adverse and used the BMDL associated with this BMR for consideration within the risk evaluation and when comparing with other PODs. The doses and response data used for the modeling are presented in Table 1-17.

Table 1-17. Female Mouse Relative Liver Weights and Associated Doses Selected for Dose-Response Modeling for TCEP From a 16-Week Study

Dose (mg/kg-day)	Number of Animals	Mean	SD
0	10	41.5	3.64
31	10	41.7	5
63	10	42.8	4.02
125	9	45.9	3.69
250	9	48.6	4.05
500	10	47.4	3.29

Table 1-18 summarizes the BMD modeling results for increased relative liver weight in female mice in the 16-week study. The Exponential 4 and 5 models and the Hill model provided adequate fit to the means (test 4 p values > 0.1) using the constant variance model. The BMDLs for these models differed by less than 3-fold, and therefore, EPA chose the Exponential 5 model because it has the lowest AIC.

Table 1-18. Summary of BMD Modeling Results for Increased Relative Liver Weights in Female Mice Following Oral Exposure to TCEP in a 16-Week Study (Constant Variance)[abc]

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
	P-value	AIC					
Exponential 2	0.0349	335	334	240	344	247	The Exponential 4 and 5 models and the Hill model 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,
Exponential 3	0.0349	335	334	240	344	247	
Exponential 4	0.409	330	89.7	44.4	96.7	46.2	
Exponential 5	**0.783**	**329**	**112**	**61.0**	**119**	**64.4**	
Hill	0.706	329	109	61.3	116	69.2	
Polynomial 5	0.0419	335	317	223	327	229	
Polynomial 4	0.0419	335	317	223	327	229	
Polynomial 3	0.0419	335	317	223	327	229	

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
	P-value	AIC					
Polynomial Degree 2	0.0419	335	317	223	327	229	EPA chose the Exponential 5 model, which had the lowest AIC.
Power	0.0419	335	317	223	327	229	
Linear	0.0419	335	317	223	327	229	

[a] Three significant figures
[b] Based on test 2 p-values > 0.05 for all models, EPA determined that the constant variance model assumption may be suitable for dose-response modeling.
[c] Selected model in bold; scaled residuals for selected model for doses 0, 31, 63, 125, 250, and 500 mg/kg-day were 0.00298, 0.0292, 0.0424, 0.0332, 0.512, and 0.470, respectively.

Plots of the Exponential 5 model with BMRs of one SD and ten percent RD are shown in Figure 1-23 and Figure 1-24, respectively. Additional modeling details, including model parameters, goodness of fit at each dose and log likelihood are shown in Figure 1-25.

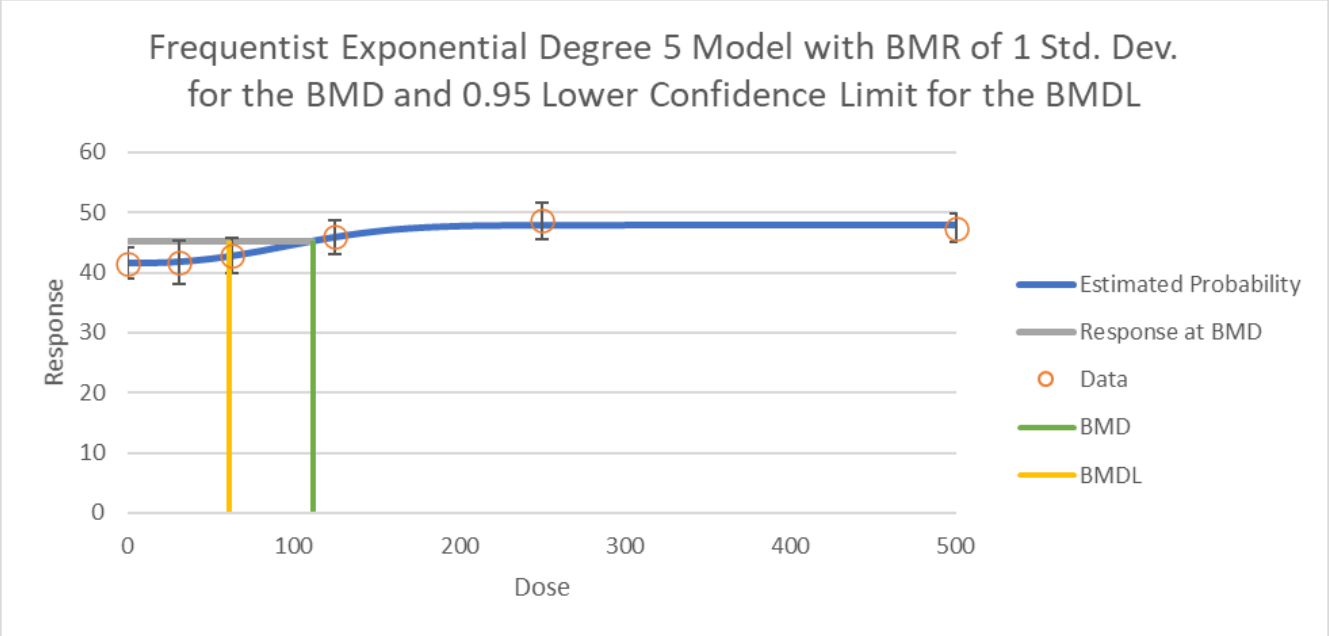

Figure 1-23. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 5) for Relative Liver Weight Increases in Female Mice Exposed to TCEP Via Oral Gavage (16-Week Study) and BMR of 1SD (Constant Variance)

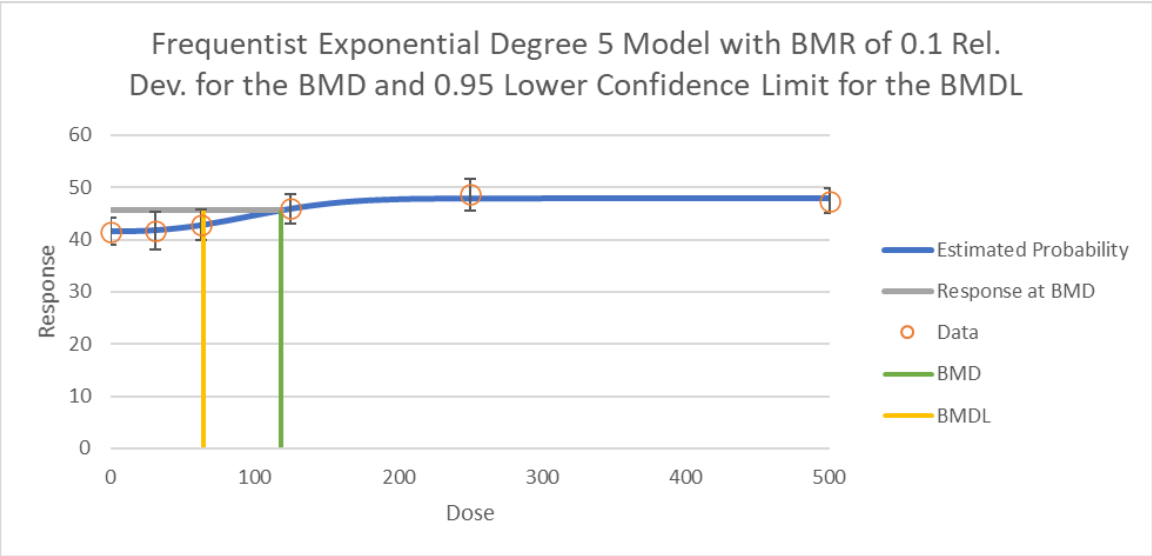

Figure 1-24. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 5) for Relative Liver Weight Increases in Female Mice Exposed to TCEP Via Oral Gavage (16-Week Study) and BMR of 10 Percent Rel. Dev. (Constant Variance)

Model Results

Benchmark Dose	
BMD	111.7706299
BMDL	60.96094969
BMDU	189.8088568
AIC	329.2304296
Test 4 P-value	0.783232337
D.O.F.	2

Model Parameters	
# of Parameters	5
Variable	Estimate
a	41.49642547
b	0.008505426
c	1.155854346
d	2.461378592

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	10	41.49642547	41.5	41.5	3.79258592	3.64	3.64	0.00298046
31	10	41.7349856	41.7	41.7	3.79258592	5	5	–0.029171173
63	10	42.74919598	42.8	42.8	3.79258592	4.02	4.02	0.04236065
125	9	45.94195855	45.9	45.9	3.79258592	3.69	3.69	–0.033189926
250	9	47.95311831	48.6	48.6	3.79258592	4.05	4.05	0.511694425
500	10	47.96382372	47.4	47.4	3.79258592	3.29	3.29	–0.470119116

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	–159.3708889	7	332.741778
A2	–158.306178	12	340.612356
A3	–159.370889	7	332.741778
fitted	–159.6152148	5	239.23043
R	–171.9698877	2	347.939775

Tests of Interest			
Test	–2*Log(Likelihood Ratio)	Test d.f.	P-value
1	27.32741956	10	0.00231098
2	2.129421912	5	0.83096277
3	2.129421912	5	0.83096277
4	0.488651801	2	0.78323234

Figure 1-25. Details Regarding the Selected Model (Exponential 5) for Relative Liver Weight Increases for Female Mice Exposed in a 16-Week Study

1.3 Neurological and Behavioral Effects

1.3.1 Path Length in the Morris Water Maze Test in Female Rats

Path length in the Morris water maze test decreased in female rats exposed to TCEP for 60 days (Yang et al., 2018). First, the administered doses were duration adjusted to estimate an equivalent oral dose for animals exposed for seven rather than five days per week. Then, dichotomous models were used to fit dose response data.

A BMR of 1 SD, 10, 20, and 30 percent relative deviations were modeled according to EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012). EPA chose the BMR of 20 percent RD as the most appropriate measure of relevant biological change (U.S. EPA, 2022) when comparing with other PODs. The doses and response data used for the modeling are presented in Table 1-19.

Table 1-19. Path Length Decreased in the Morris Water Maze Test Selected for Dose-Response Modeling for TCEP from a 60-Day Study

Dose (mg/kg/day)	Number of Animals	Mean	SD
0	10	685	144.90
50	10	602	106.12
100	10	470	114.28
250	10	317	110.20

The BMD modeling results for path length in the Morris water maze test are summarized below in Table 1-20. 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. The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected. The Exponential 2 and 3 models converged on the same model and had the lowest AIC; the Exponential 2 model is the more parsimonious choice.

Table 1-20. Summary of the BMD Modeling Results for Path Length in the Morris Water Maze Test in Female Rats in the 60-Day Study

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)	BMD 20%RD (mg/kg-day)	BMDL 20%RD (mg/kg-day)	BMD 30%RD (mg/kg-day)	BMDL 30%RD (mg/kg-day)	Basis for Model Selection
	Test 4 P-value	AIC									
Exponential 2	**0.636723**	**499**	**57**	**41**	**33**	**26**	**69**	**55**	**111**	**87**	
Exponential 3	0.636723	499	57	41	33	26	69	55	111	87	
Exponential 4	0.394512	501	50	29	29	18	62	40	102	68	
Exponential 5	NA	502	61	32	44	19	70	42	96	71	
Hill	NA	502	61	31	45	18	69	41	96	70	
Polynomial Degree 3	0.298849	501	80	62	46	39	91	77	137	116	
Polynomial Degree 2	0.298849	501	80	62	46	39	91	77	137	116	
Power	0.298849	501	80	62	46	39	91	77	137	116	
Linear	0.298849	501	80	62	46	39	91	77	137	116	

The Exponential 2 Exponential 3 converged on the same model and had the lowest AIC; the Exponential 2 model is the parsimonious choice.

Plots of the Exponential 2 model with BMRs of one SD, or 10, 20, or 30 percent RD are shown in Figure 1-26, Figure 1-27, Figure 1-28 and Figure 1-29, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown below in Figure 1-30.

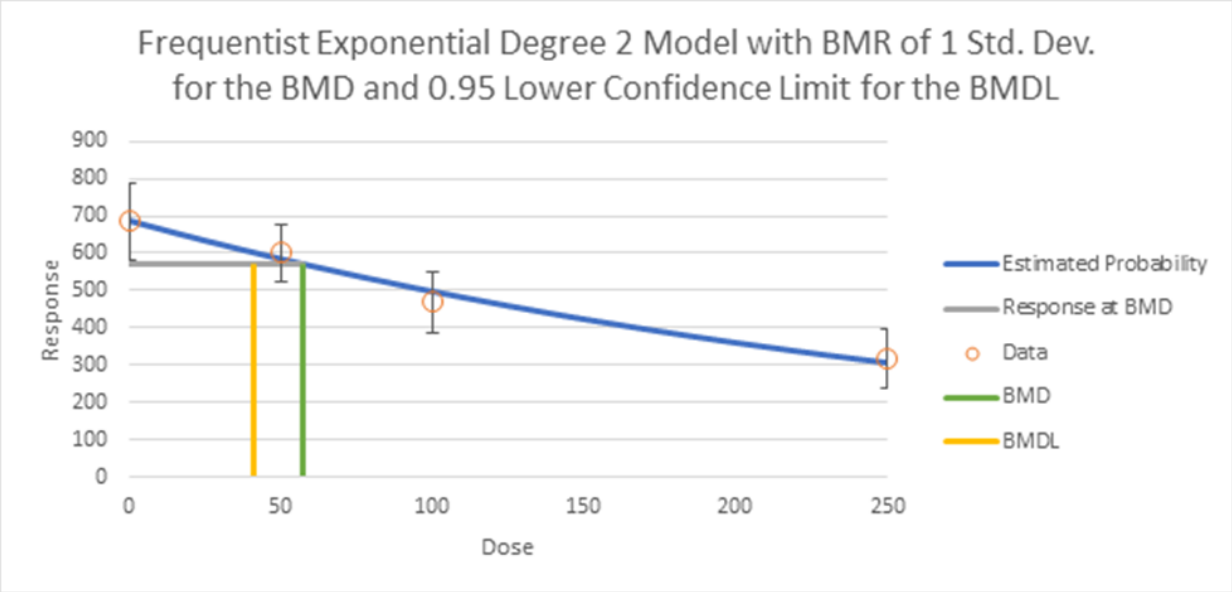

Figure 1-26. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 2) for Path Length in the Morris Water Maze Test in Female Rats Exposed to TCEP Via Oral Gavage (60-Day Study) and BMR of 1SD (Constant Variance Assumed)

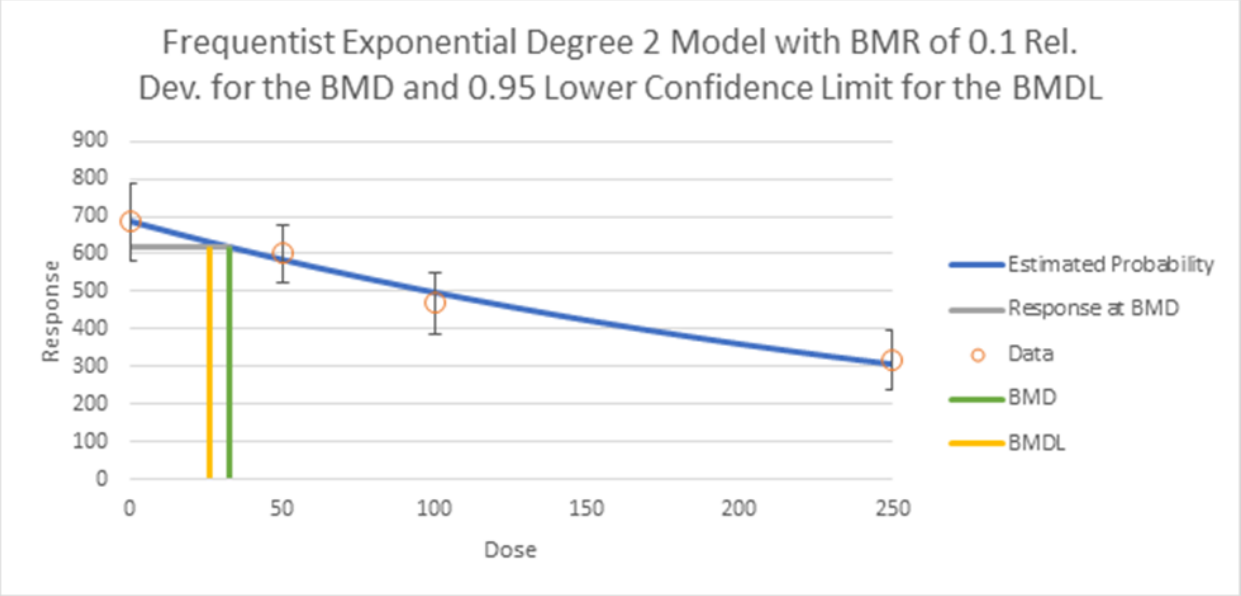

Figure 1-27. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 2) for Path Length in the Morris Water Maze Test in Female Rats Exposed to TCEP Via Oral Gavage (Sixty Days Study) and BMR of 10 percent Relative Deviation (Constant Variance Assumed)

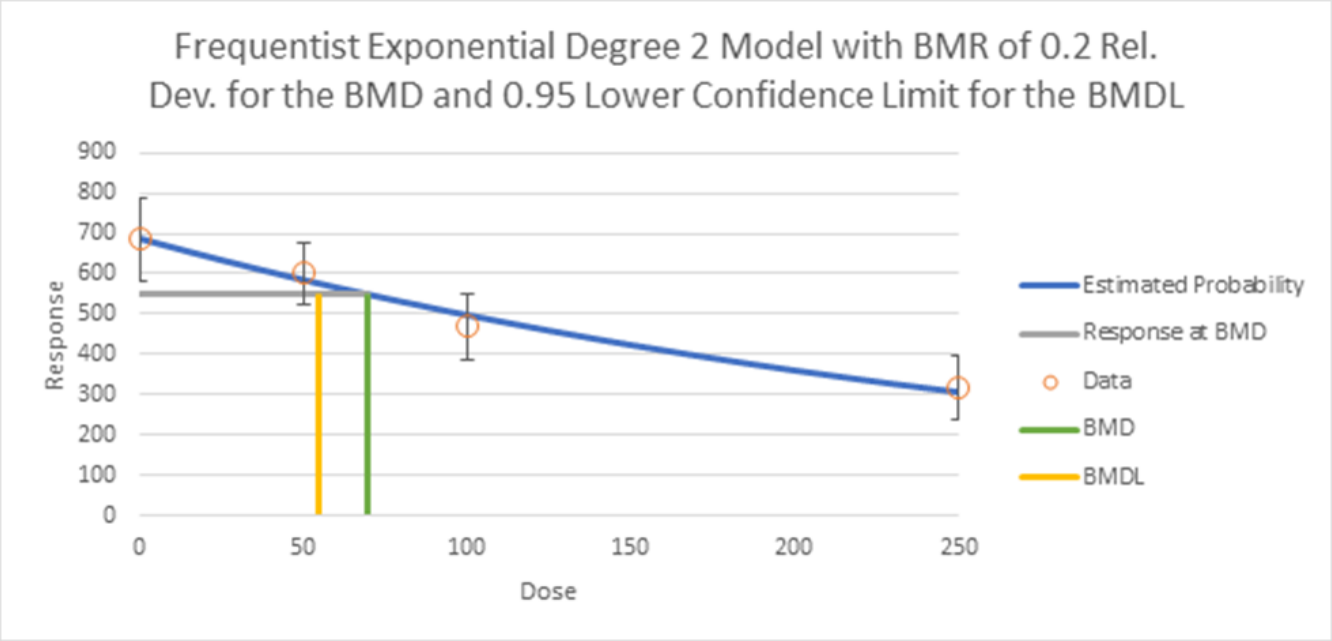

Figure 1-28. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 2) for Path Length in the Morris Water Maze Test in Female Rats Exposed to TCEP Via Oral Gavage (60-Day Study) and BMR of 20 Percent Relative Deviation (Constant Variance Assumed)

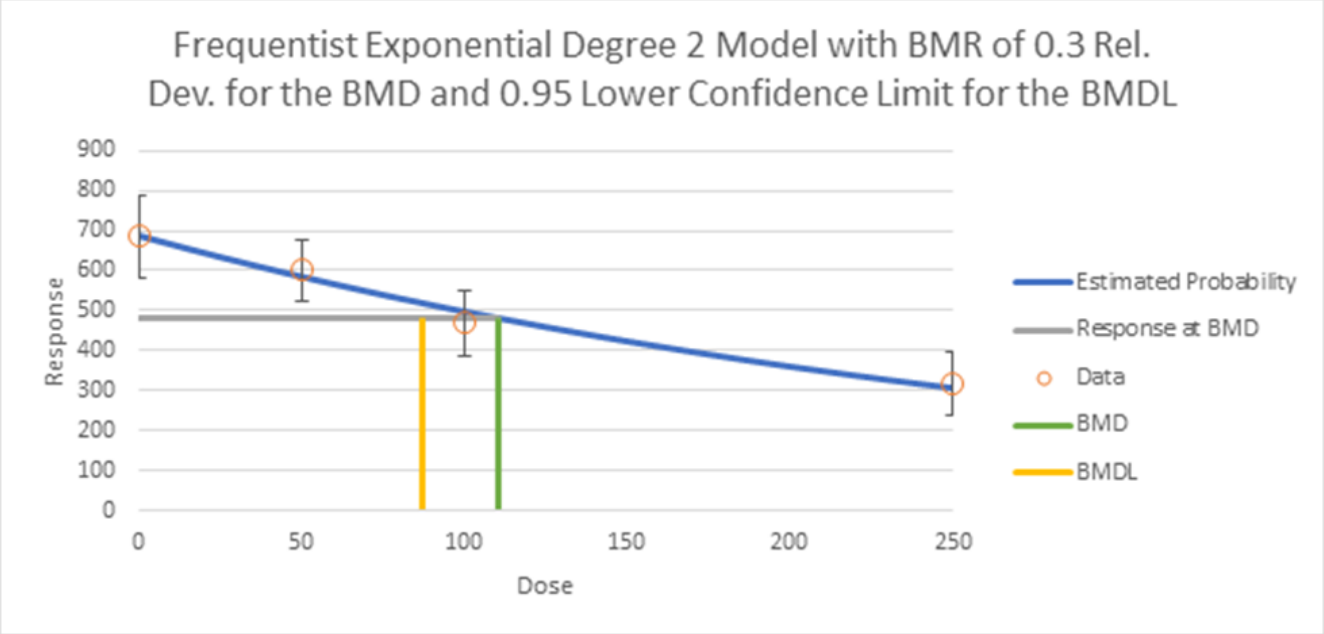

Figure 1-29. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 2) for Path Length in the Morris Water Maze Test in Female Rats Exposed to TCEP Via Oral Gavage (60-Day Study) and BMR of 30 Percent Relative Deviation (Constant Variance Assumed)

Model Results

Benchmark Dose	
BMD	56.99372292
BMDL	40.99542231
BMDU	87.274695
AIC	499.106493
Test 4 P-value	0.636722823
D.O.F.	2

Model Parameters	
# of Parameters	3
Variable	Estimate
a	685.5495504
b	0.003221614

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	10	685.5495504	684.94	684.94	144.994889	144.9	144.9	–0.016762203
50	10	583.5558003	601.76	601.76	144.994889	106.12	106.12	0.500602545
100	10	496.7363363	469.62	469.62	144.994889	114.28	114.28	–0.745679962
250	10	306.3772749	317.03	317.03	144.994889	110.2	110.2	0.292942362

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	–246.1018257	5	502.203651
A2	–245.4659596	8	506.931919
A3	–246.1018257	5	502.203651
fitted	–246.5532465	3	499.106493
R	–264.4339647	2	532.867929

Tests of Interest

Test	–2*Log(Likelihood Ratio)	Test d.f.	P-value
1	37.93601035	6	< 0.0001
2	1.271732238	3	0.73585623
3	1.271732238	3	0.73585623
4	0.902841695	2	0.63672282

Figure 1-30. Details Regarding the Selected Model (Exponential 2) for Path Length in the Morris Water Maze Test in Female Rats Following Oral Exposure to TCEP in a 60-Day Toxicity Study

1.3.2 Necrosis of the Neurons of the Hippocampus in Female Rats

Increased necrosis of the neurons of hippocampus was observed in female rats exposed to TCEP for 16 weeks (NTP, 1991b; Matthews et al., 1990). First, the administered doses were duration adjusted to estimate an equivalent oral dose for animals exposed for seven rather than five days per week. Then, dichotomous models were used to fit dose-response data.

EPA presents BMDLs based on BMRs of 5 and 10 percent ER from the best fit model. Based on the severity of the endpoint and considering EPA's *BMD Technical Guidance* (U.S. EPA, 2012), EPA is using the BMDL based on a BMR of 5 percent ER for this endpoint in the risk calculation. The doses and response data used for the modeling are presented in Table 1-21.

Table 1-21. Necrosis of the Neurons of the Hippocampus Selected for Dose-Response Modeling for TCEP from a 16-Week Study

Dose (mg/kg/day)	Number of Animals	Incidence
0	10	0
16	10	0
31	10	0
63	10	0
125	10	8
250	10	10

The BMD modeling results for the necrosis of neurons in the hippocampus are summarized in Table 1-22. All models, except for the 1-degree multistage model, provided an adequate fit (chi-square p-value > 0.1) to the data. Using a BMR of 10 percent extra risk, the BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC (Probit) was selected. Using a BMR of 5 percent extra risk, however, BMDLs for the fit models differed by > 3-fold and the BMDS software recommended selection of the 2-degree multistage model because it estimated the lowest BMDL. Although the 2-degree multistage model provided overall adequate fit to the data, in the context of this dataset, the high residuals at the key datapoints (−1.7 and 1.1) indicate a relatively poor fit in the key part of the dose-response curve. For this reason, the 2-degree multistage was dropped from consideration. The BMDLs of the remaining models are sufficiently close (differed by < 3-fold), and the model with the lowest AIC (Probit) was selected.

Table 1-22. BMD Modeling Results for Necrosis of the Neurons of the Hippocampus in Female Rats in the 16-Week Study

Model	Goodness of Fit (Means)		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	1.00	14.01	98	52	102	61	The Probit model is selected because
Gamma	0.99	14.52	69	49	76	57	
Log-Logistic	1.00	14.01	98	52	102	61	

Model	Goodness of Fit (Means)		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					
Multistage 5	0.99	13.04	64	38	74	55	of the lowest AIC.
Multistage 4	0.95	14.05	55	34	66	50	
Multistage 3	0.80	16.02	44	27	56	42	
Multistage 2	0.41	20.35	28	18	40	30	
Multistage 1	0.01	35.31	8	5	16	11	
Weibull	0.99	14.52	72	70	81	79	
Logistic	1.00	12.01	97	51	102	63	
Log-Probit	1.00	14.01	104	53	107	60	
Probit	**1.00**	**12.01**	**90**	**50**	**96**	**61**	

Plots of the Probit model with BMRs of 10 or 5 percent ER are shown in Figure 1-31 and Figure 1-32, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown below in Figure 1-33.

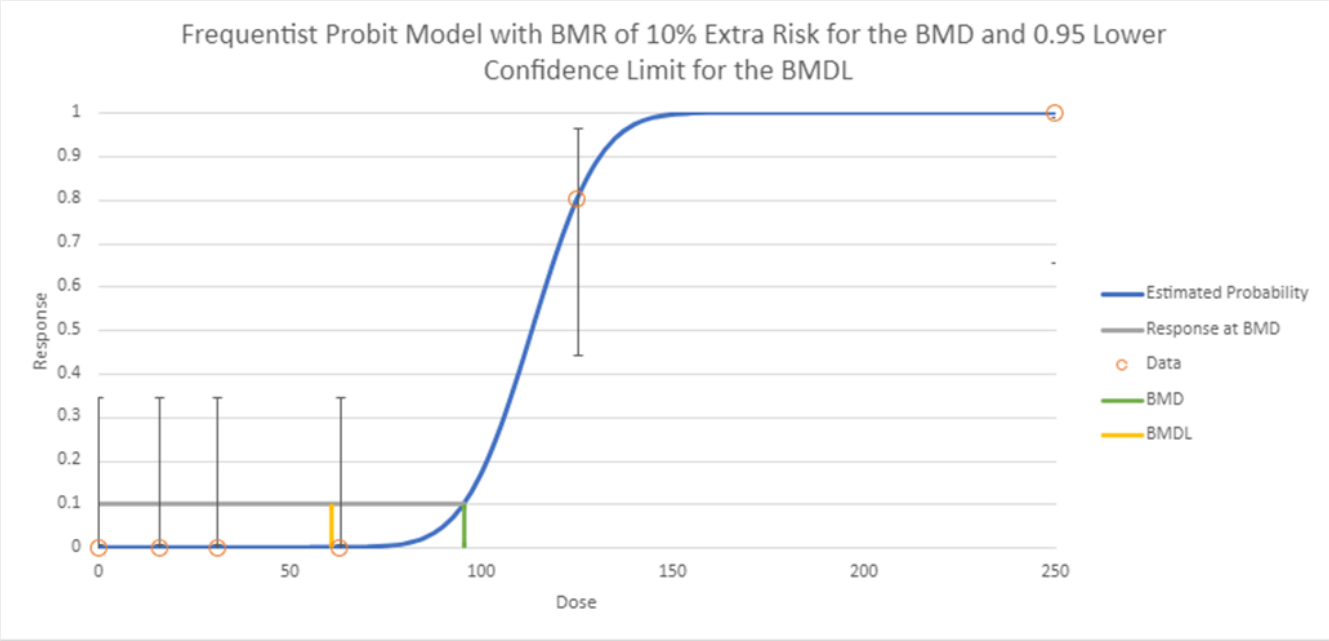

Figure 1-31. Plot of Response by Dose with Fitted Curve for the Selected Model (Probit) for Necrosis of the Neurons in the Hippocampus in Female Rats Exposed to TCEP Via Oral Gavage (16-Week Study) and BMR of 10 Percent Extra Risk

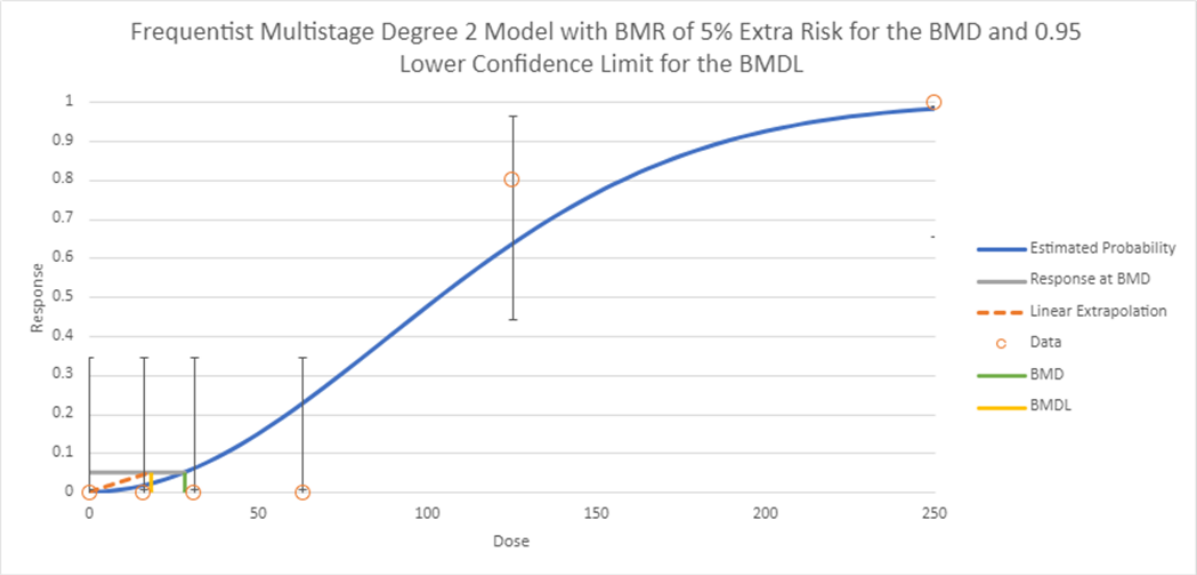

Figure 1-32. Plot of Response by Dose with Fitted Curve for the Selected Model (Multistage 2) for Necrosis of the Neurons in the Hippocampus in Female Rats Exposed to TCEP Via Oral Gavage (16-Week Study) and BMR of 5 Percent Extra Risk

Model Results

Benchmark Dose	
BMD	95.52742296
BMDL	60.85124313
BMDU	105.2988529
AIC	12.01096127
P–value	0.999999996
D.O.F.	5
Chi^2	0.001459742

Model Parameters	
# of Parameters	2
Variable	Estimate
a	–8.159526019
b	Bounded

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.68171E–16	1.68171E–15	0	10	–4.1E–08
16	1.21284E–12	1.21284E–11	0	10	–3.48E–06
31	1.53766E–09	1.53766E–08	0	10	–0.000124
63	0.000145307	0.00145307	0	10	–0.038122
125	0.799678658	7.996786579	8	10	0.0025389
250	1	10	10	10	0

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P-value
Full Model	–5.004024235	6	-	-	NA
Fitted Model	–5.005480635	1	0.0029128	5	1
Reduced Model	–36.65185812	1	63.2956678	5	< 0.0001

Figure 1-33. Details Regarding the Selected Model (Probit) for Necrosis of the Neurons in the Hippocampus in Female Rats Following Oral Exposure to TCEP in a 16-Week Chronic Toxicity Study

1.3.3 Serum Cholinesterase Activity in Female Rats

Serum cholinesterase activity was decreased in female rats that were exposed to TCEP for 16 weeks (NTP, 1991b). First, the administered doses were duration adjusted to estimate an equivalent oral dose for animals exposed for seven rather than five days per week. Then, continuous models were used to fit dose-response data.

EPA modeled serum cholinesterase activity for BMRs of 1 SD and 10 percent RD according to EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012). The doses and response data used for the modeling are presented in Table 1-23.

Table 1-23. Decrease of Serum Cholinesterase Activity Selected for Dose-Response Modeling for TCEP from a 16-Week Study

Dose (mg/kg/day)	Number of Animals	Mean	SD
0	10	2064	354.18
16	8	1946	353.55
31	10	1808	332.04
63	10	1873	332.04
125	8	1550	294.16
250	5	1226	62.61

The BMD modeling results for serum cholinesterase activity are summarized in Table 1-24. The constant variance model did not provide adequate fit to the variance data, but the nonconstant variance model did fit. With the nonconstant variance model applied, all the 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.

Table 1-24. Summary of BMD Modeling Results for Decreased of Serum Cholinesterase Activity in Female Rats Following Oral Exposure to TCEP in a 16-Week Study

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 2	0.634687	730	110.5	77.5	52.3	43.9	The Linear model is recommended because it is the only model that 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.
Exponential 3	0.712137	730	147.3	84.7	87.0	45.9	
Exponential 4	0.634686	730	110.5	77.5	52.3	43.9	
Exponential 5	0.503801	732	148.2	84.7	87.6	46.3	
Hill	0.515392	732	147.4	83.0	82.8	41.1	
Polynomial Degree 5	0.538459	732	154.1	98.5	84.2	58.1	
Polynomial Degree 4	0.744042	730	153.7	98.5	84.4	57.3	
Polynomial Degree 3	0.744042	730	153.7	98.5	84.4	57.3	
Polynomial Degree 2	0.744042	730	153.7	98.5	84.4	57.3	
Power	0.726725	730	150.0	98.0	84.7	57.2	
Linear	**0.803824**	**729**	**129.6**	**96.3**	**64.3**	**56.8**	

[a] Three significant figures
[b] Selected model in bold; scaled residuals for selected model for doses 0, 16, 31, 63, 125, and 250 mg/kg-day were 0.555, 0.0167, –0.8154, 0.857, –0.7530, and 0.1978, respectively.

Plots of the linear model with BMRs of one SD and 10 percent RD are shown in Figure 1-34 and Figure 1-35, respectively. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown below in Figure 1-36.

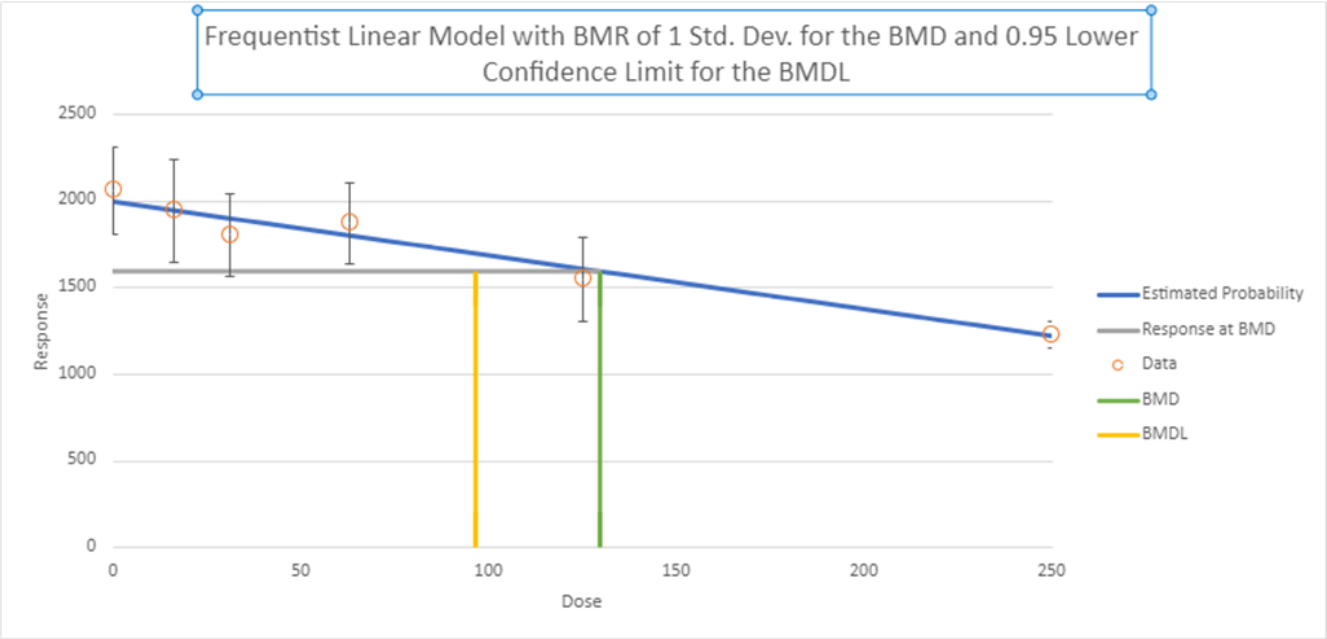

Figure 1-34. Plot of Response by Dose with Fitted Curve for the Selected Model (Linear) for Serum Cholinesterase Activity Decreases in Female Rats Exposed to TCEP Via Oral Gavage (16-Week Study) and BMR of 1SD (Nonconstant Variance Assumed)

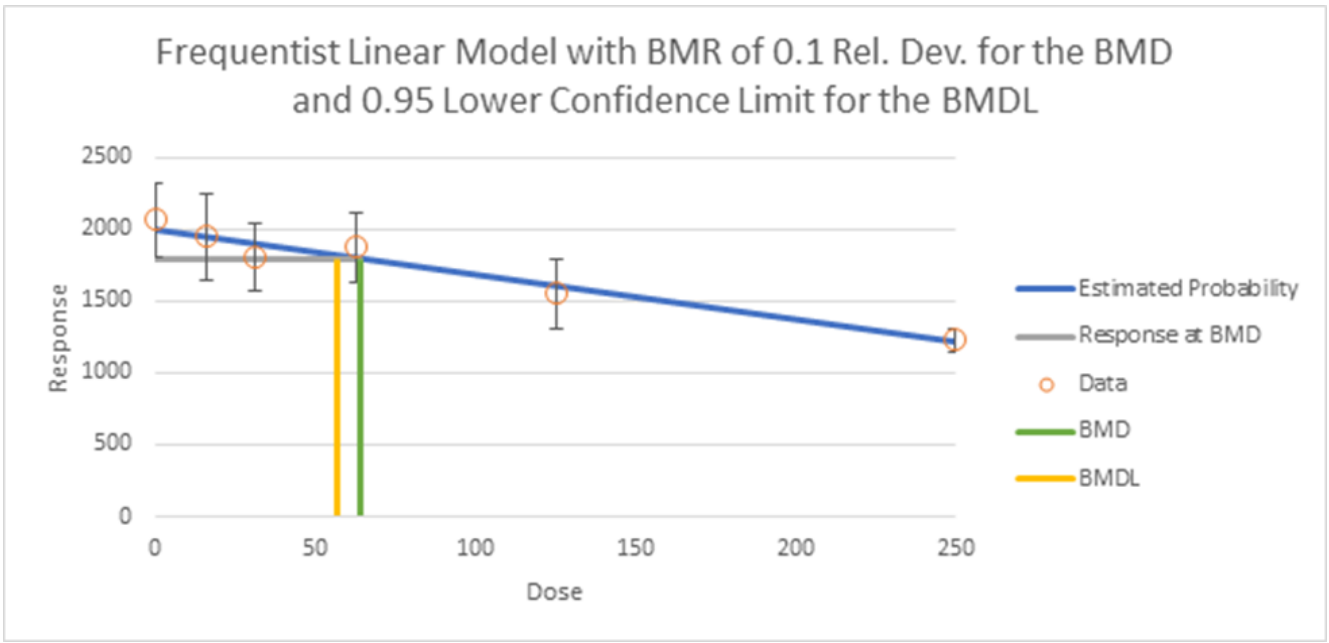

Figure 1-35. Plot of Response by Dose with Fitted Curve for the Selected Model (Linear) for Serum cholinesterase activity decreases in Female Rats Exposed to TCEP Via Oral Gavage (16-Week Study) and BMR of 10 Percent Relative Deviation (Nonconstant Variance Assumed)

Model Results

Benchmark Dose	
BMD	129.5518875
BMDL	96.29342612
BMDU	178.1793969
AIC	728.5938025
P-value	0.803823971
D.O.F.	4

Model Parameters	
# of Parameters	4
Variable	Estimate
g	1993.420713
beta1	–3.101835334
rho	6.036517732

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	10	1993.420713	2064	2064	401.848517	354.18	354.18	0.555411536
16	8	1943.791348	1946	1946	372.404125	353.55	353.55	0.016774819
31	10	1897.263818	1808	1808	346.143837	332.04	332.04	–0.815490402
63	10	1798.005087	1873	1873	294.320203	332.04	332.04	0.805771181
125	8	1605.691296	1550	1550	209.187846	294.16	294.16	–0.753001553
250	5	1217.96188	1226	1226	90.836375	62.61	62.61	0.197869889

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	–363.3689517	7	740.737903
A2	–357.064324	12	738.128648
A3	–359.4831033	8	734.966207
fitted	–360.2969012	4	728.593802
R	–376.3760886	2	756.752177

Tests of Interest

Test	–2*Log(Likelihood Ratio)	Test d.f.	P-value
1	38.62352921	10	< 0.0001
2	12.60925548	5	0.027329
3	4.837558645	4	0.3043747
4	1.62759584	4	0.80382397

Figure 1-36. Details Regarding the Selected Model (Linear) for Serum Cholinesterase Activity Decreases in Female Rats Following Oral Exposure to TCEP in a 16-Week Chronic Toxicity Study

1.4 Kidney Effects

EPA selected multiple kidney endpoints for quantitative dose-response analysis with BMDS, including histopathological lesions and kidney weights. EPA modeled kidney weight changes when a pairwise change from controls and/or dose-response trend was evident in the data (*e.g.*, a statistically significant change was identified). The best measures are kidney weight changes relative to body weight (to account for any changes that are primarily related to body weight changes). EPA presents the female rat relative kidney weight data from the 16-week NTP (1991b) study after dropping the highest dose from the models and considers this to be appropriate due to the decreased survival at the highest dose (5 of 10 animals died). However, EPA could not model the female rat absolute kidney without dropping the *two* highest doses and therefore, EPA is not presenting these data. In the 16-week study (NTP, 1991b), male kidney weights were increased only at the highest doses and therefore, EPA did not conduct BMD modeling for these changes.

1.4.1 Renal Tubule Hyperplasia in Male Rats

There was an increased incidence of renal tubule hyperplasia in male rats exposed to TCEP for two years in a chronic toxicity study by NTP (1991b). First, the administered doses were duration adjusted to estimate an oral dose for animals exposed for seven days per week rather than five days per week. Then, 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). The doses and response data used for the modeling are presented in Table 1-25.

Table 1-25. Incidence of Renal Tubule Hyperplasia Selected for Dose-Response Modeling for TCEP

Dose (mg/kg/day)	Number of Animals	Incidence
0	50	0
31	50	2
63	50	24

The BMD modeling results for renal tubule hyperplasia are summarized in Table 1-26. The best fitting model was the Gamma based on the AIC (lower values indicate a better fit), chi-square goodness of fit p-value (higher value indicates a better fit) and visual inspection. A plot of the model is shown in Figure 1-37. The model version number, model form, benchmark dose calculation, parameter estimates, and estimated values are shown below in Figure 1-38.

Table 1-26. Summary of BMD Modeling Results for Renal Tubule Hyperplasia in Male Rats Following Oral Exposure to TCEP in a 2-Year Chronic Study[a]

Model	Goodness of fit		BMD (mg/kg/day)	BMDL (mg/kg/day)	Basis for Model Selection
	P-value	AIC			
Dichotomous Hill	NA	92.0	38.6	30.9	The Gamma, Logistic, and Probit models provided adequate fit to the data (chi-square p-value > 0.1). The
Gamma	**0.999**	**90.0**	**38.3**	**30.7**	
Log-Logistic	NA	92.0	38.8	30.7	

Model	Goodness of fit		BMD (mg/kg/day)	BMDL (mg/kg/day)	Basis for Model Selection
	P-value	AIC			
Multistage 2	0.0452	95.0	28.0	22.4	BMDLs were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected.
Multistage 1	0.000826	104	15.6	11.5	
Weibull	NA	92.0	39.5	30.7	
Logistic	0.749	90.2	41.9	34.2	
Log-Probit	NA	94.8	53.7	27.0	
Probit	0.896	90.1	40.0	32.4	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 31, 63 were −8.73E−04, 1.40E−05, 4.49E–05, respectively.

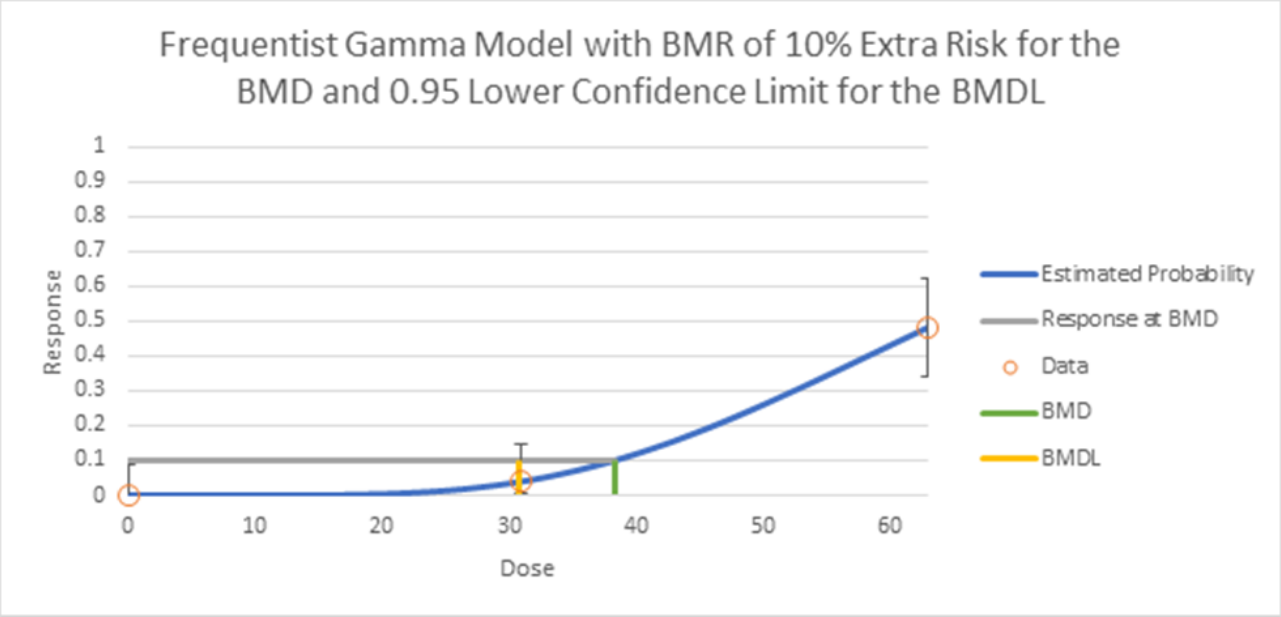

Figure 1-37. Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Gamma) for Renal Tubule Hyperplasia in Male Rats Exposed to TCEP Via Oral Gavage in mg/kg/day; BMR 10 Percent Extra Risk

Model Results

Benchmark Dose	
BMD	38.3027844
BMDL	30.70367203
BMDU	44.21349368
AIC	90.02911301
P-value	0.999302723
D.O.F.	1
Chi^2	7.63714E–07

Model Parameters	
# of Parameters	3
Variable	Estimate
g	Bounded
a	7.529213517
b	0.112149316

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E–08	7.61499E–07	0	50	–0.000873
31	0.039999613	1.999980646	2	50	1.397E–05
63	0.479996825	23.99984124	24	50	4.494E–05

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P-value
Full Model	–43.01455574	3	-	-	NA
Fitted Model	–43.0145565	2	1.5252E–06	1	0.9990146
Reduced Model	–69.16986999	1	52.3106285	2	< 0.0001

Figure 1-38. Details Regarding the Selected Model (Gamma) for Renal Tubule Hyperplasia in Male Rats Following Oral Exposure to TCEP in a 2-Year Chronic Toxicity Study

1.4.2 Renal Tubule Hyperplasia in Female Rats

There was an increased incidence of renal tubule hyperplasia in female rats exposed to TCEP for two years in a chronic toxicity study by NTP (1991b). First, the administered doses were duration adjusted to estimate an equivalent oral dose for animals exposed for seven days per week rather than five days per week. Then, dichotomous models were used to fit dose-response data.

A BMR of 10 percent extra risk was chosen according to *BMD Technical Guidance* (U.S. EPA, 2012). The doses and response data used for the modeling are presented in Table 1-27.

Table 1-27. Incidence of Renal Tubule Hyperplasia Selected for Dose-Response Modeling for TCEP

Dose (mg/kg/day)	Number of Animals	Incidence
0	50	0
31	50	3
63	50	16

The BMD modeling results for renal tubule hyperplasia are summarized in Table 1-28. The best fitting model was the Multistage Degree 2 based on the AIC (lower values indicate a better fit), chi-square goodness of fit p-value (a higher value indicates a better fit) and visual inspection. A plot of the model is shown in Figure 1-39. The model version number, model form, benchmark dose calculation, parameter estimates, and estimated values are shown below in Figure 1-40.

Table 1-28. Summary of BMD Modeling Results for Renal Tubule Hyperplasia in Female Rats Following Oral Exposure to TCEP in a 2-Year Chronic Study[a]

Model	Goodness of Fit		BMD	BMDL	Basis for Model Selection
	P-value	AIC			
Dichotomous Hill	NA	91.4	37.1	25.5	The Log-logistic, Multistage 1- and 2-degree, Logistic, and Probit models provided adequate fit to the data (chi-square p-value > 0.1). The BMDLs were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected.
Gamma	NA	91.4	37.6	25.3	
Log-Logistic	0.999	89.4	37.7	25.5	
Multistage 2	**0.804**	**87.9**	**34.2**	**23.2**	
Multistage 1	0.170	91.4	22.9	16.0	
Weibull	NA	91.4	38.1	25.2	
Logistic	0.509	90.1	42.9	35.3	
Log-Probit	NA	95.6	56.9	12.5	
Probit	0.642	89.7	40.8	33.2	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 31, 63 were −8.73E−04, –0.584, and 0.308, respectively.

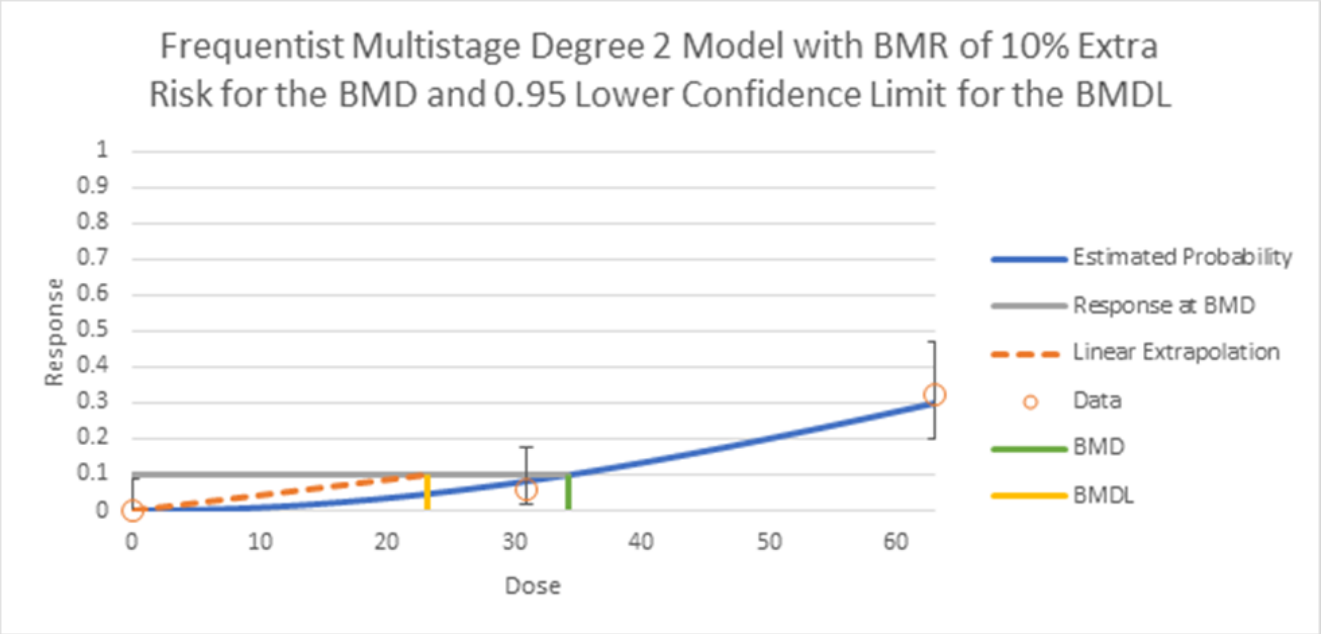

Figure 1-39. Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Multistage Degree 2) for Renal Tubule Hyperplasia in Female Rats Exposed to TCEP Via Oral Gavage in mg/kg/day; BMR 10 Percent Extra Risk

Model Results

Benchmark Dose	
BMD	34.23865288
BMDL	23.23697912
BMDU	41.90302307
AIC	87.85147946
P-value	0.80421339
D.O.F.	2
Chi^2	0.435781269
Slope Factor	0.004303485

Model Parameters	
# of Parameters	3
Variable	Estimate
g	Bounded
b1	Bounded
b2	8.98762E–05

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E–08	7.61499E–07	0	50	–0.000873
31	0.082746138	4.13730689	3	50	–0.583813
63	0.300030485	15.00152425	16	50	0.3081274

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P-value
Full Model	–42.691849	3	-	-	NA
Fitted Model	–42.92573973	1	0.46778145	2	0.7914483
Reduced Model	–57.00010417	1	28.6165103	2	< 0.0001

Figure 1-40. Details Regarding the Selected Model (Gamma) for Renal Tubule Hyperplasia in Female Rats Following Oral Exposure to TCEP in a 2-Year Chronic Toxicity Study

1.4.3 Renal Tubule Karyomegaly in Male Mice

There was an increased incidence of renal tubule karyomegaly (nuclear enlargement) in male mice exposed to TCEP for two years in a chronic toxicity study by NTP (1991b). First, the administered doses were duration adjusted to estimate an equivalent oral dose for animals exposed for seven days per week rather than five days per week. Then, dichotomous models were used to fit dose-response data.

A BMR of ten percent ER was chosen according to *BMD Technical Guidance* (U.S. EPA, 2012). The doses and response data used for the modeling are presented in Table 1-29.

Table 1-29. Incidence of Renal Tubule Karyomegaly Selected for Dose-Response Modeling for TCEP

Dose (mg/kg-day)	Number of Animals	Incidence
0	50	2
125	50	16
250	50	39

The BMD modeling results for renal tubule karyomegaly (nuclear enlargement) are summarized in Table 1-30. The best fitting model was the Probit based on the AIC (lower values indicate a better fit), chi-square goodness of fit p-value (higher value indicates a better fit) and visual inspection. A plot of the Probit model is shown in Figure 1-41. The model version number, model form, benchmark dose calculation, parameter estimates, and estimated values are shown below in Figure 1-42.

Table 1-30. Summary of BMD Modeling Results for Renal Tubule Karyomegaly (Nuclear Enlargement) in Male Mice Following Oral Exposure to TCEP in a 2-Year Chronic Toxicity Study[a]

Model	Goodness of Fit		BMD (mg/kg-day)	BMDL (mg/kg-day)	Basis for Model Selection
	P-value	AIC			
Dichotomous Hill	65535	140	81.6	50.8	The Multistage 2-degree, Logistic, and Probit models provided adequate fit to the data (chi-square p-value > 0.1). The BMDLs were sufficiently close (differed by
Gamma	NA	138	77.9	42.3	
Log-Logistic	NA	138	81.1	50.8	
Multistage 2	0.846	136	67.5	32.0	

Model	Goodness of Fit		BMD (mg/kg-day)	BMDL (mg/kg-day)	Basis for Model Selection
	P-value	AIC			
Multistage 1	0.0194	142	23.7	18.7	< 3-fold); therefore, the model with the lowest AIC was selected.
Weibull	NA	138	71.0	38.6	
Logistic	0.686	136	69.4	54.5	
Log-Probit	NA	153	224	0	
Probit	**0.935**	**136**	**63.9**	**50.5**	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 125, 250, were –0.0493, 0.0573, and –0.0307, respectively.

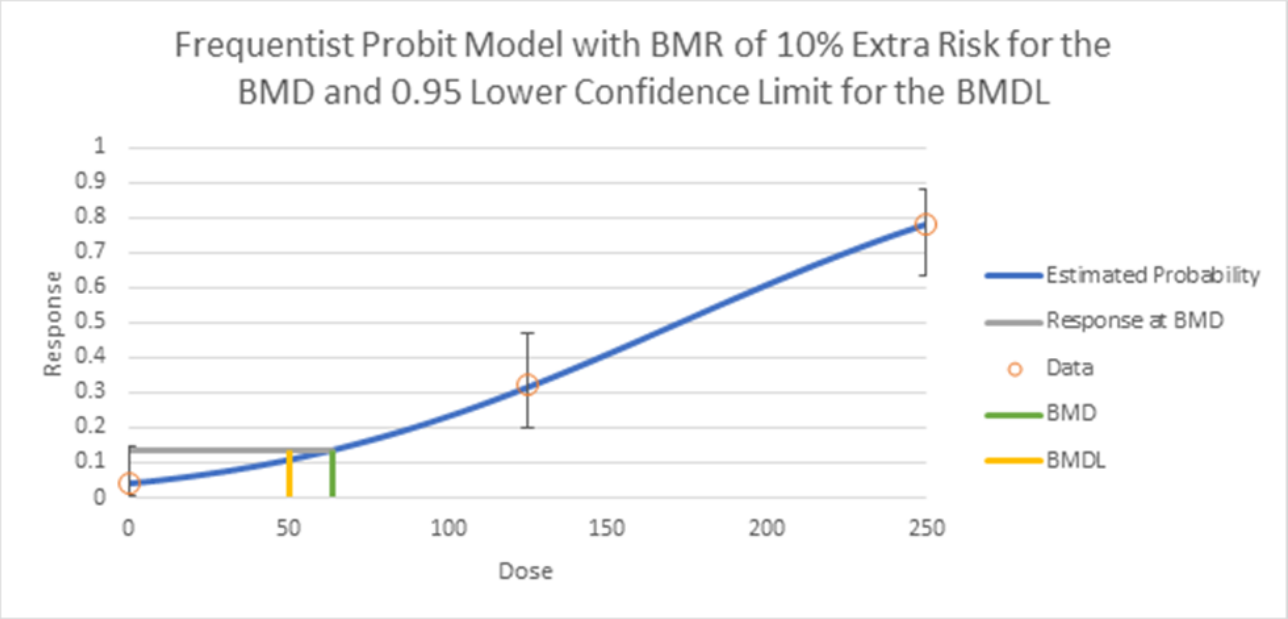

Figure 1-41. Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Probit) for Renal Tubule Karyomegaly (Nuclear Enlargement) in Male Mice Exposed to TCEP Via Oral Gavage in mg/kg/day; BMR 10 Percent Extra Risk

Model Results

Benchmark Dose	
BMD	63.86977148
BMDL	50.49773419
BMDU	80.89809675
AIC	136.1788322
P-value	0.934968193
D.O.F.	1
Chi^2	0.006657864

Model Parameters	
# of Parameters	2
Variable	Estimate
a	–1.734794541
b	0.010052255

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.041388602	2.069430088	2	50	–0.049295
125	0.31623162	15.81158102	16	50	0.0573037
250	0.781794818	39.0897409	39	50	–0.030727

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P-value
Full Model	–66.08607834	3	-	-	NA
Fitted Model	–66.08941609	2	0.0066755	1	0.9348823
Reduced Model	–99.60961898	1	67.0470813	2	< 0.0001

Figure 1-42. Details Regarding the Selected Model (Probit) for Renal Tubule Karyomegaly (Nuclear Enlargement) in Male Mice Following Oral Exposure to TCEP in a 2-Year Chronic Toxicity Study

1.4.4 Renal Tubule Karyomegaly in Female Mice

There was an increased incidence of renal tubule karyomegaly (nuclear enlargement) in female mice exposed to TCEP for 2-years in a chronic toxicity study by NTP (1991b). First, the administered doses were duration adjusted to estimate an equivalent oral dose for animals exposed for seven days per week rather than five days per week. Then, 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). The doses and response data used for the modeling are presented in Table 1-31.

Table 1-31. Incidence of Renal Tubule Karyomegaly Selected for Dose-Response Modeling for TCEP

Dose (mg/kg/day)	Number of Animals	Incidence
0	50	0
125	49	5
250	50	44

The BMD modeling results for renal tubule karyomegaly (nuclear enlargement) are summarized in Table 1-32. The best fitting model was the Gamma based on the AIC (lower values indicate a better fit), chi-square goodness of fit p-value (higher value indicates a better fit) and visual inspection. A plot of the

Gamma model is shown in Figure 1-43. The model version number, model form, benchmark dose calculation, parameter estimates, and estimated values are shown below in Figure 1-44.

Table 1-32. Summary of BMD Modeling Results for Renal Tubule Karyomegaly (nuclear enlargement) in Female Mice Following Oral Exposure to TCEP in a 2-Year Chronic Toxicity Study[a]

Model	Goodness of Fit		BMD (mg/kg/day)	BMDL (mg/kg/day)	Basis for Model Selection
	P-value	AIC[c]			
Dichotomous Hill	NA	75.0	125	108	The Gamma, Logistic, and Probit models provided adequate fit to the data (chi-square p-value > 0.1). The BMDLs were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected.
Gamma	**0.999**	**73.0**	**125**	**107**	
Log-Logistic	NA	75.0	125	108	
Multistage 2	0.00143	86.7	68.1	57.1	
Multistage 1	< 0.0001	110	25.5	20.1	
Weibull	NA	75.0	124	102	
Logistic	0.767	73.2	126	103	
Log-Probit	NA	75.0	125	109	
Probit	0.943	73.0	125	102	

[a] Three significant figures
[b] Selected model in bold; scaled residuals for selected model for doses 0, 125, and 250, were −8.73E–04, 5.93E–07, and 4.52E–07, respectively.
[c] Gamma has the lowest AIC when considering 5 significant figures (72.988) vs. the Probit model that had an AIC of 72.998.

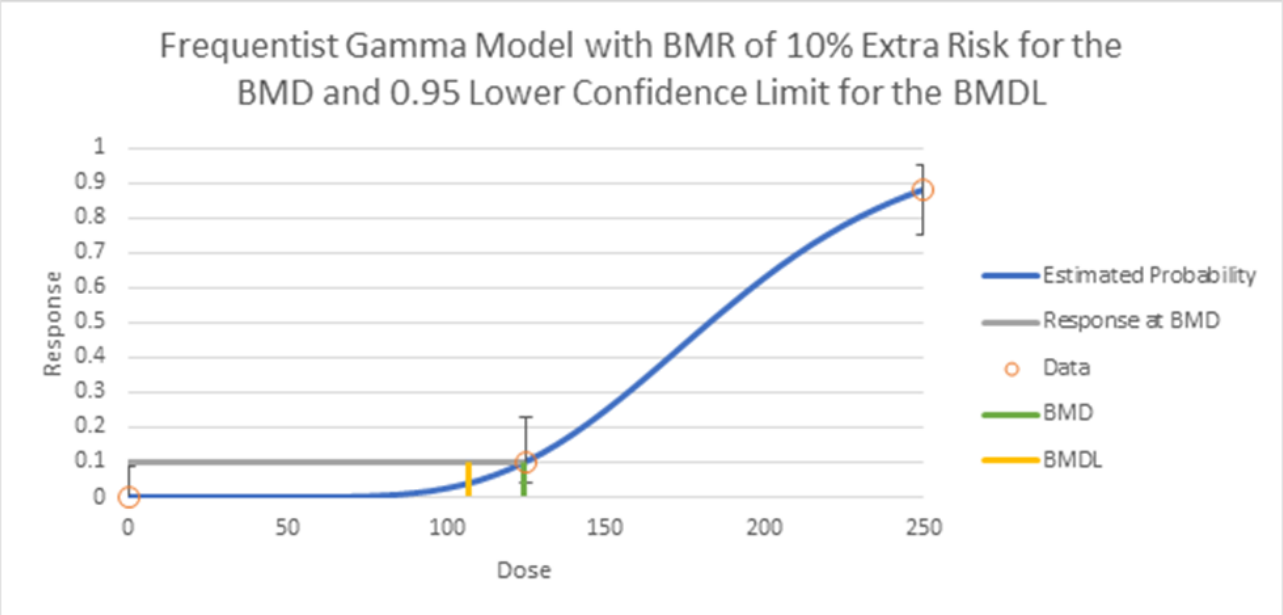

Figure 1-43. Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Gamma) for Renal Tubule Karyomegaly (Nuclear Enlargement) in Female Mice Exposed to TCEP Via Oral Gavage in mg/kg/day; BMR 10 Percent Extra Risk

Model Results

Benchmark Dose	
BMD	124.5420284
BMDL	107.145575
BMDU	139.3151775
AIC	72.98782296
P-value	0.999303735
D.O.F.	1
Chi^2	7.615E–07

Model Parameters	
# of Parameters	3
Variable	Estimate
g	Bounded
a	12.91059878
b	0.068833285

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E–08	7.61499E–07	0	50	–0.00873
125	0.102040791	4.999998743	5	49	5.932E–07
250	0.879999979	43.99999896	44	50	4.524E–07

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P-value
Full Model	–34.49391072	3	-	-	NA
Fitted Model	–34.49391148	2	1.523E–06	1	0.9990153
Reduced Model	–94.37178638	1	119.755751	2	< 0.0001

Figure 1-44. Details Regarding the Selected Model (Gamma) for Renal Tubule Karyomegaly (Nuclear Enlargement) in Female Mice Following Oral Exposure to TCEP in a 2-Year Chronic Toxicity Study

1.4.5 Relative Kidney Weight in Female Rats

Relative kidney weights increased in female mice exposed to TCEP for 16 weeks (NTP, 1991b). For BMD modeling, the administered doses were first duration adjusted to estimate an equivalent oral dose for animals exposed for seven days per week rather than five days per week. Then, continuous models were used to fit dose-response data.

A BMR of one SD were chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012). EPA did not identify a specific magnitude of change in relative kidney weight (*e.g.,* 10 percent) that would be

considered biologically significant. The doses and response data used for the modeling are presented in Table 1-33.

Table 1-33. Female Rat Relative Kidney Weights and Associated Doses Selected for Dose-Response Modeling for TCEP From a 16-Week Study[a]

Dose (mg/kg-day)	Number of Animals	Mean	SD
0	10	3.69	0.13
16	8	3.83	0.17
31	10	4.03	0.13
63	10	4.1	0.22
125	8	4.18	0.17

[a] The following data for the top dose of 250 mg/kg-day was not used: 5 animals, mean and SD of 4.51 and 0.13.

Table 1-34 summarizes the BMD modeling results for increased relative kidney weight in female rats in the 16-week study. For the full dataset (using all dose groups), none of the available models provided adequate fit to the means (test 4 p-value < 0.1). Survival was decreased at the highest dose and EPA considered that the models could be run using the control and four lower doses. Although data are not available on the cause of all the deaths, two females died after receiving double doses for three days and several of the overdosed animals; the cause of deaths of three other female rats was not stated. Without the highest dose, the constant variance model provided adequate fit to the variance data (test 2 p-values > 0.05) and with the model applied, the Exponential 4 and 5 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, EPA selected the model with the lowest AIC (Exponential 4).

Table 1-34. Summary of BMD Modeling Results for Increased Relative Kidney Weights in Female Rats Following Oral Exposure to TCEP in a 16-Week Study (Highest Dose Group Dropped; Constant Variance Assumed)[ab]

Model	Goodness of Fit (Means)		BMD 1SD (mg/kg-day)	BMDL 1SD (mg/kg-day)	Basis for Model Selection
	Test 4 P-value	AIC			
Exponential 2	0.00430	−20.2	51.9	39.5	The Exponential 4 model is recommended because it provided adequate fit to the means (test 4 p-value > 0.1) and resulted in the lowest AIC.
Exponential 3	0.00430	−20.2	51.9	39.5	
Exponential 4	**0.496**	**−30.0**	**12.5**	**7.41**	
Exponential 5	0.297	−28.3	16.9	7.64	
Hill	0.448	−28.8	16.5	7.02	
Polynomial Degree 4	0.00569	−20.8	49.0	36.9	
Polynomial Degree 3	0.00569	−20.8	49.0	36.9	
Polynomial Degree 2	0.00569	−20.8	49.0	36.9	

Model	Goodness of Fit (Means)		BMD 1SD (mg/kg-day)	BMDL 1SD (mg/kg-day)	Basis for Model Selection
	Test 4 P-value	AIC			
Power	0.00569	−20.8	49.0	36.9	
Linear	0.00569	−20.8	49.0	36.8	

[a] Three significant figures
[b] Selected model in bold; scaled residuals for selected model for doses 0, 13, 31, 63, and 125 mg/kg-day were 0.176, –0.808, 0.790, –0.271, and 0.0317, respectively.

A plot of the Exponential 4 model with a BMR of 1 SD is shown in Figure 1-45. Additional modeling details, including model parameters, goodness of fit at each dose and log likelihood are shown in Figure 1-46.

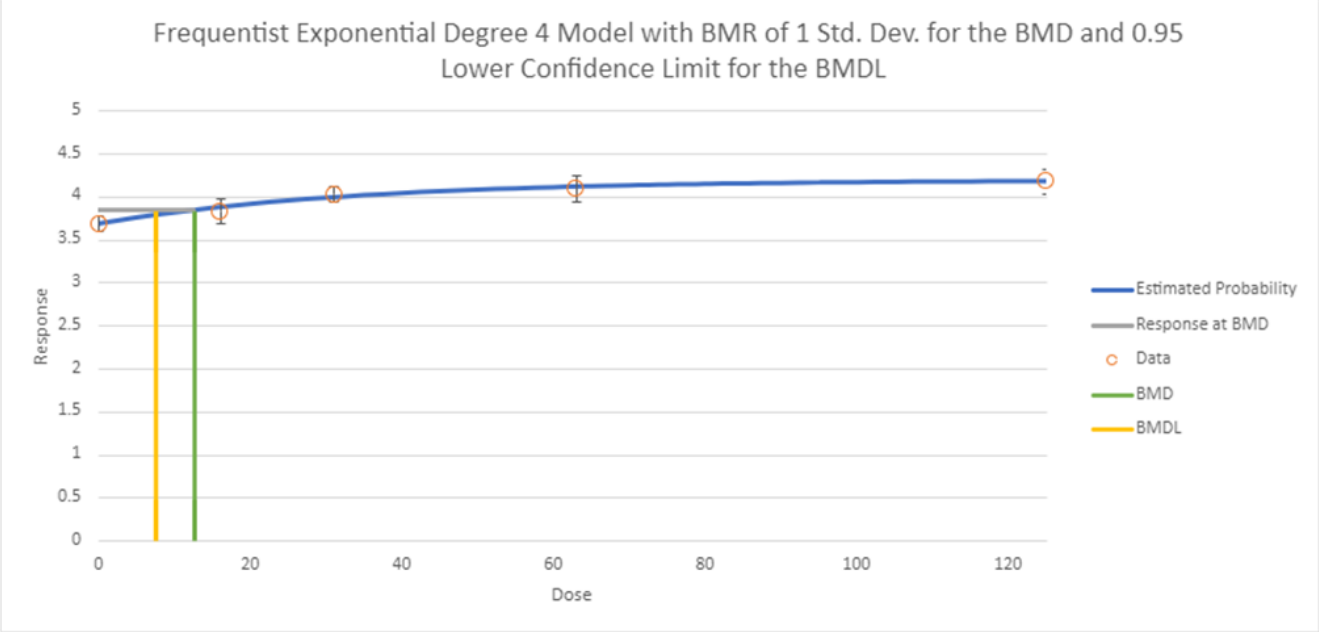

Figure 1-45. Plot of Response by Dose with Fitted Curve for the Selected Model (Exponential 4) for Relative Kidney Weight Increases in Female Rats Exposed to TCEP Via Oral Gavage (16-Week Study) and BMR of 1SD (Constant Variance Assumed)

Model Results

Benchmark Dose	
BMD	12.54183054
BMDL	7.407226907
BMDU	23.99667514
AIC	–29.96772649
Test 4 P-value	0.495858212
D.O.F.	2

Model Parameters	
# of Parameters	4
Variable	Estimate
a	3.68108785
b	0.030132406
c	1.13824347

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	10	3.68108785	3.69	3.69	0.16015224	0.13	0.13	0.175974389
16	8	3.87575017	3.83	3.83	0.16015224	0.17	0.17	–0.807987573
31	10	3.99001365	4.03	4.03	0.16015224	0.13	0.13	0.78954838
63	10	4.113734445	4.1	4.1	0.16015224	0.22	0.22	–0.271192763
125	8	4.178202794	4.18	4.18	0.16015224	0.17	0.17	0.031740207

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	19.6853285	6	–27.370657
A2	21.67448971	10	–23.348979
A3	19.6853285	6	–27.370657
fitted	18.98386324	4	–29.967726
R	0.455422464	2	3.08915507

Tests of Interest

Test	–2*Log(Likelihood Ratio)	Test d.f.	P-value
1	42.4381345	8	< 0.0001
2	3.978322428	4	0.40894754
3	3.978322428	4	0.40894754
4	1.402930511	2	0.49585821

Figure 1-46. Details Regarding the Selected Model (Exponential 4) for Relative Kidney Weight Increases in Female Rats Following Oral Exposure to TCEP in a 16-Week Toxicity Study

1.5 Cancer

EPA modeled endpoints for kidney tumors, the only tumors that had robust evidence if one or more doses resulting in pairwise differences from controls and/or if a dose-response trend was evident in the two-year cancer bioassay (NTP, 1991b). Evidence for tumors at other target organs was slight. The BMD/BMDLs chosen for tumor incidence were based on animals still alive at the time the first incidence of cancer was observed. Also, preference was given to presenting BMD models that included both adenomas and carcinomas because benign tumors (adenomas) are expected to lead to malignant tumors (carcinomas).[2]

EPA did not present BMD modeling after combining tumors from multiple target organs, because the combinations would include tumors for which evidence was slight.

1.5.1 Renal Tubule Adenomas and Carcinomas (Combined) in Male Rats

Male rats exhibited increased incidences of renal tubule carcinomas and adenomas in the two-year NTP bioassay (NTP, 1991b). For BMD modeling, the administered doses were first duration adjusted to estimate an equivalent oral dose for animals exposed for seven rather than five days per week. Then, two multistage models were used to fit dose-response data.

EPA chose a BMR of 10 percent ER to model the tumor data according to EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012). The doses and response data used for the modeling using both kidney adenomas and carcinomas are presented in Table 1-35. The numbers of animals were adjusted for mortality. Specifically, the modeling included only the animals still alive when the first tumor was observed (day 575).

Table 1-35. Male Rat Renal Tubule Adenomas or Carcinomas (Combined) and Associated Doses Selected for Dose-Response Modeling for TCEP from a 2-Year Chronic Bioassay

Dose (mg/kg-day)	Number of Animals	Incidence[a]
0	40	2
31	44	5
63	44	25

[a] Increased incidence of carcinoma was identified - 1 control and 1 high-dose rat.

Table 1-36 summarizes the BMD modeling results for combined renal tubule adenomas and carcinomas in male rats. EPA selected the 2-degree multistage model because it was the only model that provided an adequate fit (chi-square p-value > 0.1) to the data.

[2] As a comparison, EPA also conducted BMD modeling of tumor incidence from an 18-month dietary study using ddY mice (Takada et al., 1989) (not shown). Tumors included: Renal cell adenomas and carcinomas in males; hepatocellular adenomas and carcinomas in males; leukemia in females; and forestomach papillomas and squamous cell carcinomas in females. Takada et al. (1989) is in a foreign language and was not critical to using quantitatively in the risk evaluation; furthermore, EPA did not evaluate it for data quality. One or more of the multistage models fit each of these tumor type/sex combinations but ddY mice were less sensitive than the species used by NTP (1991b) based on the resulting cancer slope factors (CSFs).

Table 1-36. Summary of BMD Modeling Results for the Combined Incidence of Renal Tubule Adenomas and Carcinomas in Male Rats Following Oral Exposure to TCEP in a 2-Year Chronic Bioassay[ab]

Model	Goodness of Fit		BMD 10%ER (mg/kg-day)	BMDL 10% ER (mg/kg-day)	CSF (per mg/kg-day)	Basis for Model Selection
	P-value	AIC				
Multistage 2	**0.144**	**114**	**24.6**	**17.2**	**0.0058**	EPA chose the 2-degree Multistage model because it was the only model that provided an adequate fit (chi-square p-value > 0.1) to the data
Multistage 1	0.00439	120	12.1	8.83	ND[c]	

[a] Three significant figures
[b] Selected model in bold; scaled residuals for selected model for doses 0, 31, and 63 mg/kg-day were 0.408, −0.124, and 0.652, respectively.
[c] ND = not determined

EPA also modeled adenomas alone and identified a CSF of 6.0E–03 per mg/kg-day but considered the slope factor based on both adenomas and carcinomas to be the most appropriate for the risk evaluation. A plot of the multistage 2 model with a BMR of 10 percent ER is shown in Figure 1-47. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 1-48.

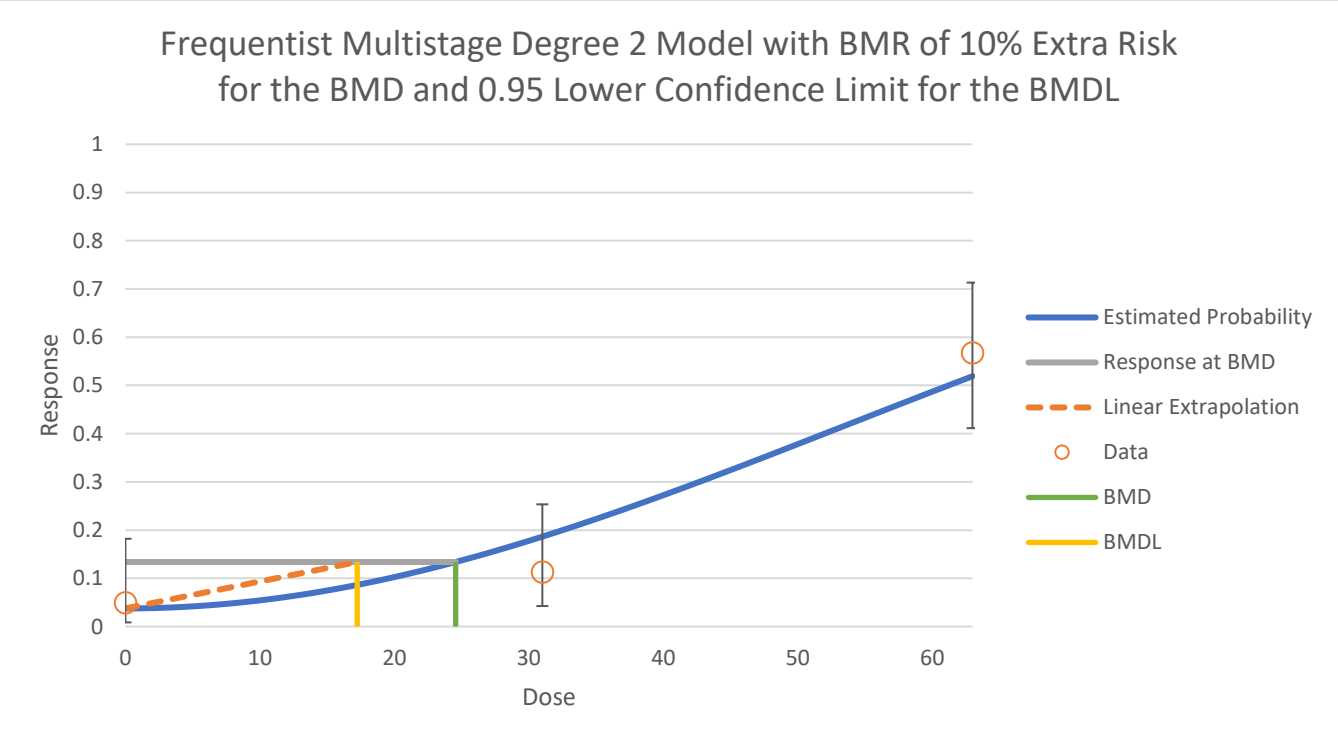

Figure 1-47. Plot of Response by Dose with Fitted Curve for the Selected Model (Multistage 2) for the Combined Incidence of Renal Tubule Adenomas and Carcinomas in Male Rats

Model Results

Benchmark Dose	
BMD	24.55384094
BMDL	17.23177476
BMDU	29.64335493
AIC	113.527872
P-value	0.144414026
D.O.F.	1
Chi^2	2.130283692
Slope Factor	0.005803233

Model Parameters	
# of Parameters	3
Variable	Estimate
g	0.037717037
b1	Bounded
b2	0.000174759

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.037717037	1.508681474	2	40	0.4077678
31	0.186484185	8.205304142	5	44	–1.24062
63	0.519084789	22.83973072	25	44	0.6518207

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P-value
Full Model	–53.60696754	3	-	-	NA
Fitted Model	–54.76393601	2	2.31393695	1	0.1282189
Reduced Model	–71.97889851	1	36.7438619	2	< 0.0001

Figure 1-48. Details Regarding the Selected Model (Multistage 2) for the Combined Incidence of Renal Tubule Adenomas and Carcinomas in Male Rats

1.5.2 Renal Tubule Adenomas in Female Rats

Female rats exhibited increased incidences of renal tubule adenomas in the two-year NTP bioassay (NTP, 1991b). For BMD modeling, the administered doses were first duration adjusted to estimate an equivalent oral dose for animals exposed for seven rather than five days per week. Then, two multistage models were used to fit dose-response data.

EPA chose a BMR of 10 percent ER to model the tumor data according to EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012). The doses and response data used for the modeling are presented in Table 1-37. The numbers of animals were adjusted for mortality. Specifically, the modeling included only the animals still alive when the first tumor was observed (day 729).

Table 1-37. Female Rat Renal Tubule Adenomas and Associated Doses Selected for Dose-Response Modeling for TCEP from 2-Year Chronic Bioassay

Dose (mg/kg-day)	Number of Animals	Incidence[a]
0	32	0
31	33	2
63	17	5

[a] Female rats had no renal tubule carcinomas

Table 1-38 summarizes the BMD modeling results for renal tubule adenomas in female rats. Both multistage models provided an adequate fit to the data (chi-square p-value > 0.1), and the BMDLs for the models were sufficiently close (< 3-fold difference). Therefore, EPA selected the Multistage 2 model, which had the lowest AIC.

Table 1-38. Summary of BMD Modeling Results for the Incidence of Renal Tubule Adenomas in Female Rats Following Oral Exposure to TCEP in a 2-Year Chronic Bioassay[ab]

Model	Goodness of Fit		BMD 10% ER (mg/kg-day)	BMDL 10% ER (mg/kg-day)	CSF (per mg/kg-day)	Basis for Model Selection
	P-value	AIC				
Multistage 2	**0.938**	**37.8**	**36.3**	**19.3**	0.0052	Both models provided an adequate fit (chi-square p-value > 0.1), and the BMDLs were sufficiently close (< 3-fold difference). Thus, EPA chose the Multistage 2 model, which had the lowest AIC.
Multistage 1	0.213	41.3	28.6	16.2	ND[c]	

[a] Three significant figures
[b] Selected model in bold; scaled residuals for selected model for doses 0, 31, and 63 mg/kg-day were −0.000698, −0.290, and 0.211, respectively.
[c] ND = not determined

A plot of the Multistage 2 model with a BMR of 10 percent ER is shown in Figure 1-49. Additional modeling details, including model parameters, goodness of fit at each dose and log likelihood are shown in Figure 1-50.

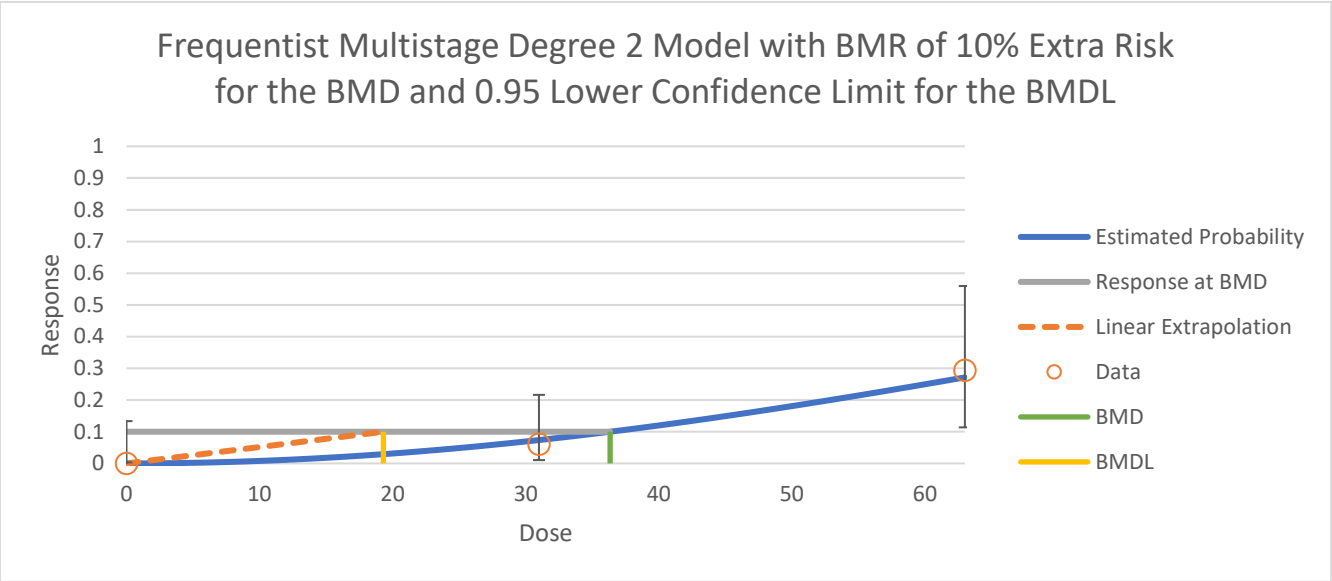

Figure 1-49. Plot of Response by Dose with Fitted Curve for the Selected Model (Multistage 2) for the Incidence of Renal Tubule Adenomas in Female Rats

Model Results

Benchmark Dose	
BMD	36.34603715
BMDL	19.30952154
BMDU	51.52675798
AIC	37.81956123
P-value	0.937802873
D.O.F.	2
Chi^2	0.128431017
Slope Factor	0.005178792

Model Parameters	
# of Parameters	3
Variable	Estimate
g	Bounded
b1	Bounded
b2	7.97561E–05

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E–08	4.87359E–07	0	32	–0.000698
31	0.073781956	2.434804551	2	33	–0.289538
63	0.27134279	4.612827437	5	17	0.2111832

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P-value
Full Model	–17.84340932	3	-	-	NA
Fitted Model	–17.90978062	1	0.1327426	2	0.9357833
Reduced Model	–23.91799872	1	12.1491788	2	0.0023006

Figure 1-50. Details Regarding the Selected Model (Multistage 2) for the Incidence of Renal Tubule Adenomas in Female Rats

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