United States
Environmental Protection Agency

June 2026
Office of Chemical Safety and
Pollution Prevention

Draft Benchmark Dose Modeling Results for *trans*-1,2-Dichloroethylene

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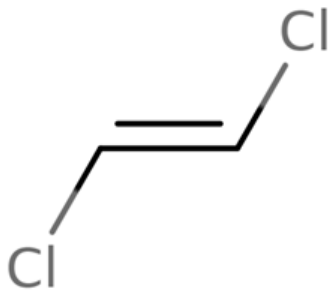

June 2026

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1 BENCHMARK DOSE MODELING RESULTS FOR *trans*-1,2-DICHLOROETHYLENE

EPA performed BMD modeling using EPA's BMD modeling software (BMDS Online Version 25.1 for continuous and dichotomous non-cancer data) for the health domains that were identified during hazard identification and that received a judgment of "likely" ("evidence indicates that *trans*-1,2-dichloroethylene exposure likely causes [health effect]") or "suggestive" ("evidence suggests but is not sufficient to conclude that *trans*-1,2-dichloroethylene exposure causes [health effect]") during evidence integration, ocular and immune effects. EPA conducted BMD modeling in a manner consistent with EPA's *Benchmark Dose (BMD) Technical Guidance* (U.S. EPA, 2012).

EPA used dichotomous models to fit quantal data (*e.g.*, incidences of tumors) and continuous models to fit continuous data (*e.g.*, body and organ weights), as recommended by EPA's *BMD Technical Guidance* (U.S. EPA, 2012). The BMDs/BMDLs are provided based on a daily exposure (*i.e.,* 7 days per week) for easier comparison across all hazard endpoints and thus, doses were adjusted as needed before BMD modeling. EPA modeled endpoints that had statistically significant pairwise comparisons between individual doses and controls or significant dose-response trends. EPA also considered potential biologically significant changes from controls where possible and/or changes that appeared to exhibit a dose-response relationship upon visual inspection. Multiple health endpoints may have been modeled from each study, depending on the relevance of the data to adverse health outcomes and to identify sensitive health endpoints for each domain.

Although some of the data sets could be fit using models after dropping doses (either one, two, or three of the highest doses), EPA considered only modeling results from full data sets for use in quantifying risk. This document does not present results of modeling exercises in which none of the models in the BMD suite provided an adequate fit to the full data sets. Endpoints were also not considered for BMD modeling if changes were observed only at the highest dose. Studies with LOAELs more than 10 times greater than the most sensitive LOAEL for the health domain were also not considered for BMD modeling. For non-cancer endpoints, if BMD modeling was not possible or when data did not fit the available models, EPA used NOAELs and LOAELs during POD selection for the risk evaluation.

EPA relied on the BMD guidance and other information to choose BMRs appropriate for each endpoint. Although the *BMD Technical Guidance* doesn't recommend default BMRs, it describes how various BMD modeling results compare with NOAEL values, and the guidance does recommend calculating10% ER for quantal data and one SD for continuous data to compare modeling results across endpoints. EPA also modeled percent RD for certain continuous endpoints. EPA's choice of BMRs for the *trans*-1,2-dichloroethylene health endpoints is described in more detail in the following sections that present BMD modeling results for each health domain.

When modeling dose-response relationships, the data can be modeled as either ER or additional risk. EPA modeled the data as ER. EPA's *BMD Technical Guidance* defines ER as "a measure of the proportional increase in risk of an adverse effect adjusted for the background incidence of the same effect." Mathematically, ER is equal to $[P(d) - P(0)]/[1 - P(0)]$. P(d) is the probability of the effect at dose d, and P(0) is the probability of risk with no exposure to a hazard (U.S. EPA, 2012).

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

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

2 INDIVIDUAL STUDY RESULTS

2.1 Hurtt et al. (1993)

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Analysis URL: View
BMDS Online Version: 25.1 (pybmds 25.1; bmdscore 25.1)

Hurtt et al. (1993) provided data showing increased incidence of lacrimation and periocular (brown) staining in female rats following acute inhalation exposure to *trans*-1,2-dichloroethylene.

2.1.1 Lacrimation in Female Crl:CD (SD) BR Rats

Increased incidence of lacrimation was observed in female rats exposed to *trans*-1,2-dichloroethylene via inhalation on gestational days (GDs) 7-16 (6 hours/day). The measured exposure concentrations (reported in units of ppm) were converted to units of mg/m^3 but duration was not adjusted from 6 hours/day to a continuous duration based on the assumption that effects are concentration-dependent, not duration-dependent. The concentration and response data used for the modeling are presented in Table 2-1. Dichotomous models were fit to the incidence data. EPA chose a BMR of 10% ER according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012) to compare with other PODs.

Table 2-1. Lacrimation Incidences in Female Crl:CD (SD) BR Rats (Hurtt et al., 1993)

Concentration (mg/m^3)	Number of Animals	Incidence of Lacrimation
0	24	0
7,930	24	13
23,800	24	22
47,580	24	24

The BMD modeling results for increased incidence of lacrimation is summarized in Table 2-2 and a summary plot of model fits is presented in Figure 2-1. For the lacrimation effects, there are limited data to inform the shape of the curve in the region of interest (10% ER) due to the concentration spacing of the study design, resulting in some uncertainty in the BMD/BMDL values. The Log Probit, Dichotomous Hill, and Log Logistic models provided adequate fit to the data (chi-square p-value > 0.1) and were considered viable. The BMDLs of the viable models were sufficiently close (differed by <3-fold); therefore, the model with the lowest AIC (Log Probit) was selected.

The Gamma, Multistage 1-, 2-, and 3-degree, Weibull, Quantal linear, Logistic, and Probit models were questionable as the BMDL were more than 3-fold below the lowest dose tested.

Table 2-2. Summary of BMD Modeling Results for Lacrimation in Female Rats Exposed to *trans*-1,2-Dichloroethylene via Inhalation for Six Hours (Hurtt et al., 1993)

Model	BMDL	BMD	BMDU	*P*-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD	Recommendation and Notes
Restricted Models								
Hill	1016.39	2934.402	4724.107	0.778	51.668	-6.05E–4	-6.05E–4	**Viable** lowest dose/BMDL ratio > 3.0
Gamma	752.463	1473.323	3734.227	0.933	51.104	-6.05E–4	-6.05E–4	**Questionable** lowest dose/BMDL ratio > 3.0 lowest dose/BMDL ratio > 10.0 lowest dose/BMD ratio > 3.0
LogLogistic	1016.39	2934.402	4724.106	0.778	51.668	-6.05E–4	-6.05E–4	**Viable** lowest dose/BMDL ratio > 3.0
Multistage 1	746.338	1006.405	1361.84	0.975	49.252	-6.05E–4	-6.05E–4	**Questionable** lowest dose/BMDL ratio > 3.0 lowest dose/BMDL ratio > 10.0 lowest dose/BMD ratio > 3.0
Multistage 2	756.509	1172.688	2630.167	0.993	49.01	-6.05E–4	-6.05E–4	**Questionable** lowest dose/BMDL ratio > 3.0 lowest dose/BMDL ratio > 10.0 lowest dose/BMD ratio > 3.0
Multistage 3	759.75	1115.846	2596.93	0.998	48.936	-6.05E–4	-6.05E–4	**Questionable** lowest dose/BMDL ratio > 3.0 lowest dose/BMDL ratio > 10.0

Model	BMDL	BMD	BMDU	*P*-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD	Recommendation and Notes
								lowest dose/BMD ratio > 3.0
Weibull	753.631	1365.554	3159.395	0.938	51.077	-6.05E–4	-6.05E–4	**Questionable** lowest dose/BMDL ratio > 3.0 lowest dose/BMDL ratio > 10.0 lowest dose/BMD ratio > 3.0
Unrestricted Models								
Logistic	2336.027	3327.37	4721.413	0.047	58.785	-1.584	-1.584	**Questionable** lowest dose/BMDL ratio > 3.0 Goodness of fit p-value < 0.1
LogProbit[ab]	913.896	2768.901	4611.214	0.851	51.379	-6.05E–4	-6.05E–4	**Recommended - Lowest AIC** lowest dose/BMDL ratio > 3.0 BMD/BMDL ratio > 3.0
Probit	2410.85	3328.427	4674.016	0.045	58.932	-1.548	-1.548	**Questionable** lowest dose/BMDL ratio > 3.0 Goodness of fit p-value < 0.1
Quantal Linear	746.337	1006.405	1361.828	0.975	49.252	-6.08E–4	-6.08E–4	**Questionable** lowest dose/BMDL ratio > 3.0 lowest dose/BMDL ratio > 10.0 lowest dose/BMD ratio > 3.0

[a] BMDS recommended best fitting model

[b] The BMDLs of the viable models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected.

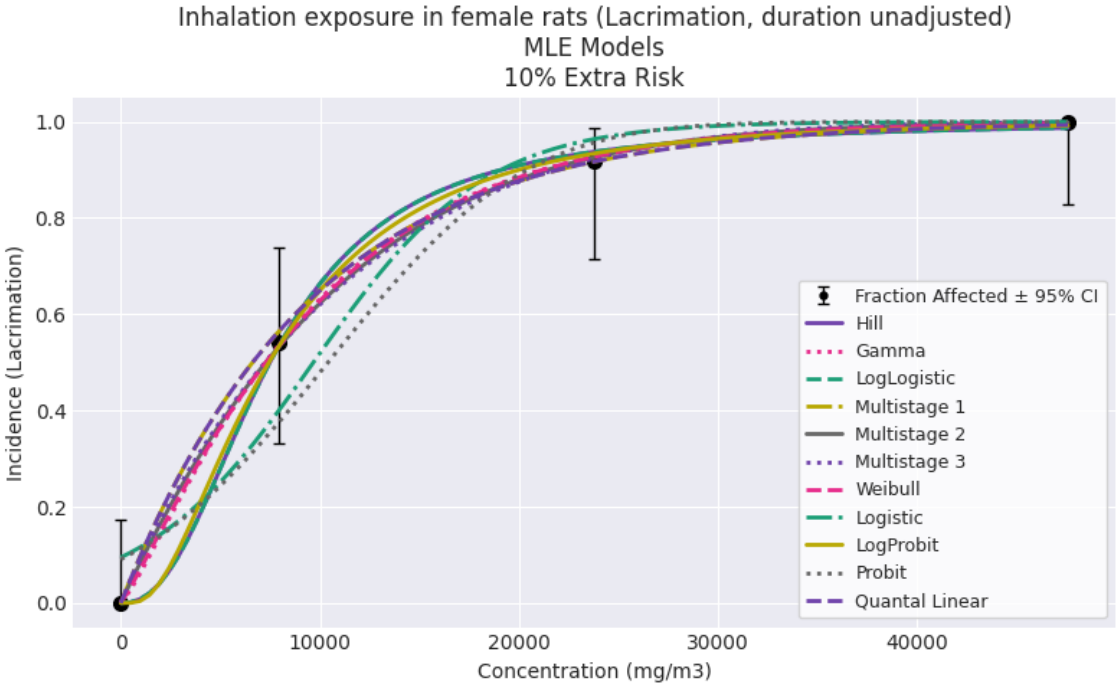

Figure 2-1. Summary Plot of Response by Concentration with Fitted Curves for Model Outputs for Lacrimation in Female Rats Exposed to *trans*-1,2-Dichloroethylene Via Inhalation for Six Hours and BMR of 10%ER (Hurtt et al., 1993)

A plot of selected Log Probit model with a BMR of 10% ER is shown in Figure 2-2. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-3.

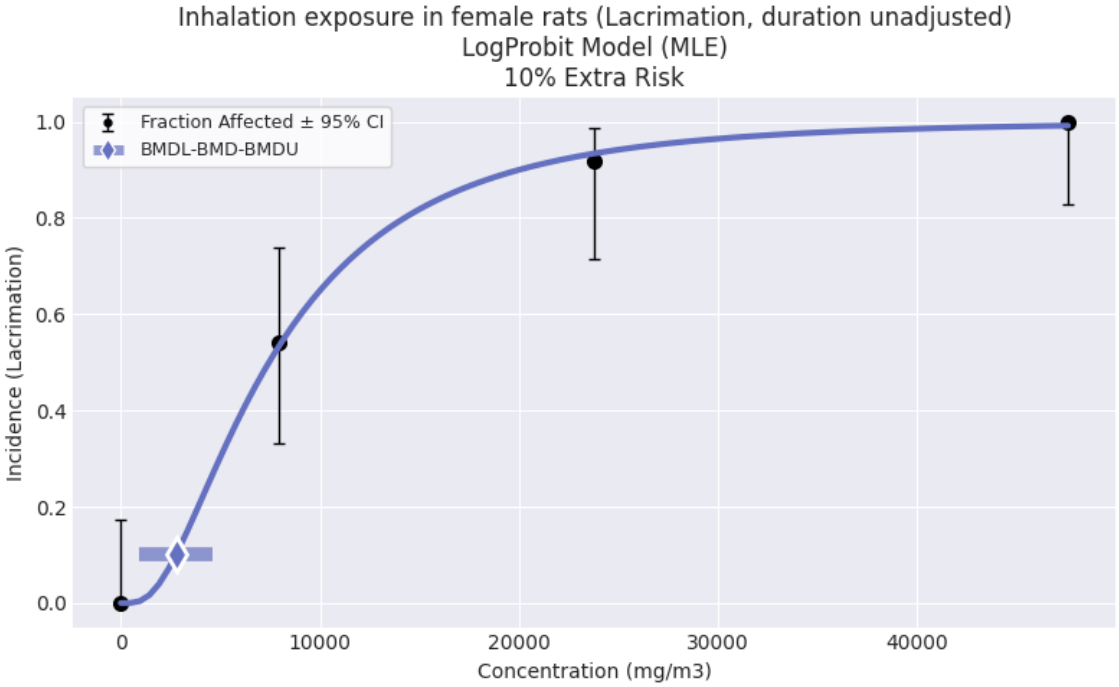

Figure 2-2. Plot of Response by Concentration with Fitted Curve for the Selected Model (Log Probit) for Lacrimation in Female Rats Exposed to *trans*-1,2-Dichloroethylene Via Inhalation for Six Hours and BMR of 10%ER (Hurtt et al., 1993)

Model Results

Benchmark Dose	
BMD	2768.9
BMDL	913.896
BMDU	4611.21
AIC	51.3795
Log-Likelihood	-23.6897
P-value	0.851362
Overall d.f.	2
Chi^2	0.321837

Model Parameters			
# of Parameters	3		
Variable	Estimate	On Bound	Std Error
g	1.523E–08	yes	Not Reported
a	-11.5568	no	3.28648
b	1.29636	no	0.349132

Goodness of Fit					
Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	24	0	3.6552E–07	1.523E–08	-0.000604582
7930	24	13	12.7889	0.532869	0.086385
23800	24	22	22.419	0.934124	-0.344759
47580	24	24	23.8061	0.991919	0.442171

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P-Value
Full model	-23.4362	4	–	–	–
Fitted model	-23.6897	2	0.507139	2	0.776026
Reduced Model	-63.9988	1	81.1252	3	0

Figure 2-3. Details Regarding the Selected Model (Log Probit) for Lacrimation in Female Rats Exposed to *trans*-1,2-Dichloroethylene Via Inhalation for Six Hours (Hurtt et al., 1993)

2.1.2 Periocular (Brown) Staining in Female Crl:CD (SD) BR Rats

Increased incidence of periocular (brown) staining was observed in female rats exposed to *trans*-1,2-dichloroethylene via inhalation on gestational days (GDs) 7-16 (6 hours/day). The measured exposure concentrations (reported in units of ppm) were converted to units of mg/m^3 but duration was not adjusted from 6 hours/day to a continuous duration based on the assumption that effects are concentration-dependent, not duration-dependent. The concentration and response data used for the modeling are presented in Table 2-3. Dichotomous models were fit to the incidence data. EPA chose a BMR of 10% ER according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012) to compare with other PODs.

Table 2-3. Periocular (Brown) Staining Incidences in Female Crl:CD (SD) BR Rats (Hurtt et al., 1993)

Concentration (mg/m^3)	Number of Animals	Incidence of Periocular (Brown) Staining
0	24	1
7,930	24	3
23,800	24	18
47,580	24	22

The BMD modeling results for incidence of periocular (brown) staining are summarized in Table 2-4 and a summary plot of model fits is presented in Figure 2-4. The Log Logistic, Gamma, Multistage 2- and 3-degree, Weibull, and Log Probit models provided adequate fit to the data (chi-square p-value > 0.1); therefore, the model with the lowest AIC (Log Logistic) was selected. The Multistage 1-degree, Quantal Linear model, Logistic, Probit, and Dichotomous Hill was considered questionable because the BMD and BMDL were 10 times lower than the lowest non-zero concentration.

Table 2-4. Summary of BMD Modeling Results for Periocular (Brown) Staining in Female Rats Exposed to *trans*-1,2-Dichloroethylene via Inhalation for Six Hours and BMR of 10%ER (Hurtt et al., 1993)

Model	BMDL	BMD	BMDU	*P*-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD	Recommendation and Notes
Restricted Models								
Hill	4706.628	8315.713	20,438.032	–	75.159	2.28E–8	1.35E–7	**Questionable** Zero degrees of freedom; saturated model
Gamma	3151.728	6740.865	11039.484	0.184	74.89	0.146	-0.55	**Viable**
LogLogistic[ab]	4443.638	7614.762	12197.511	0.493	73.614	0.099	-0.263	**Recommended - Lowest AIC**
Multistage 1	1781.101	2359.1	3194.302	0.07	77.268	0.374	0.374	**Questionable** lowest dose/BMDL ratio > 3.0 lowest dose/BMD ratio > 3.0 Goodness of fit p-value < 0.1
Multistage 2	2245.718	5210.542	9559.898	0.197	74.432	0.187	-0.877	**Viable** lowest dose/BMDL ratio > 3.0

Model	BMDL	BMD	BMDU	*P*-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD	Recommendation and Notes
Multistage 3	2238.271	5210.542	9702.612	0.197	74.432	0.187	-0.877	**Viable** lowest dose/BMDL ratio > 3.0
Weibull	2641.968	5629.165	9470.039	0.294	73.672	0.205	-0.845	**Viable** lowest dose/BMDL ratio > 3.0
Unrestricted Models								
Logistic	5419.418	7406.273	10035.413	0.0701	75.579	-0.512	-0.595	**Questionable** Goodness of fit p-value < 0.1
LogProbit	4563.885	7552.269	11690.696	0.407	73.834	0.099	-0.308	**Viable**
Probit	5279.316	7029.519	9445.448	0.0525	76.644	-0.541	-0.689	**Questionable** Goodness of fit p-value < 0.1
Quantal Linear	1781.118	2359.101	3194.274	0.0701	77.268	0.374	0.374	**Questionable** lowest dose/BMDL ratio > 3.0 lowest dose/BMD ratio > 3.0 Goodness of fit p-value < 0.1

[a] BMDS recommended best fitting model
[b] The BMDLs of the viable models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected.

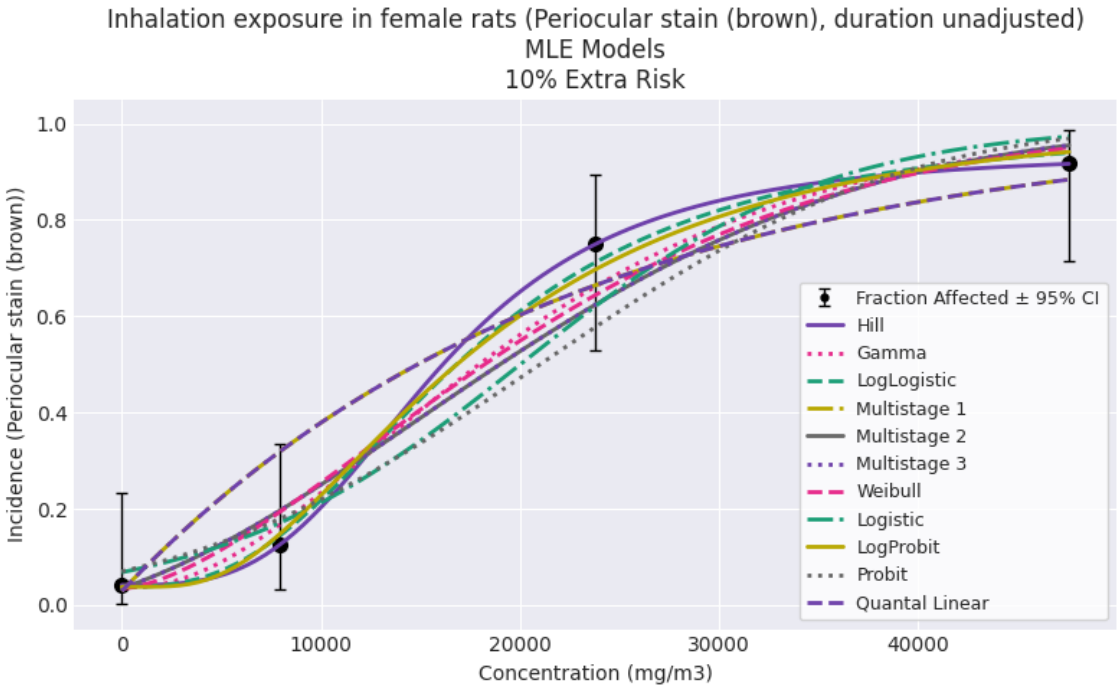

Figure 2-4. Summary Plot of Response by Concentration with Fitted Curves for Model Outputs for Periocular (Brown) Staining in Female Rats Exposed to *trans*-1,2-Dichloroethylene Via Inhalation for Six Hours and BMR of 10%ER (Hurtt et al., 1993)

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

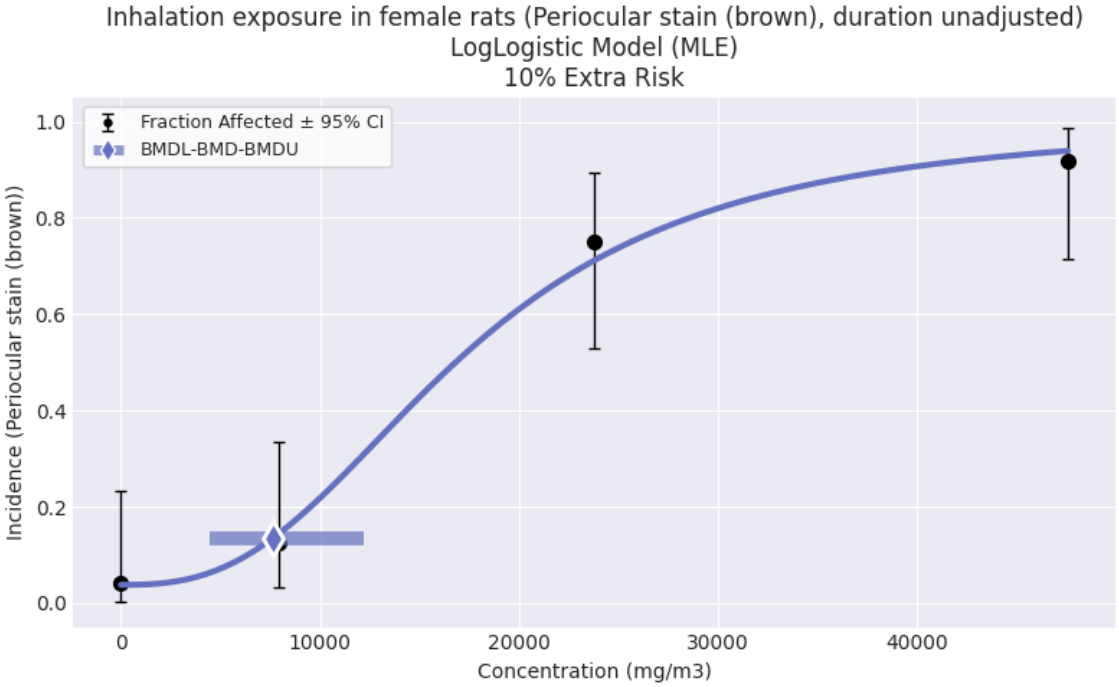

Figure 2-5. Plot of Response by Concentration with Fitted Curve for the Selected Model (Log Logistic) for Periocular (Brown) Staining in Female Rats Exposed to *trans*-1,2-Dichloroethylene Via Inhalation for Six Hours and BMR of 10%ER (Hurtt et al., 1993)

Model Results

Benchmark Dose	
BMD	7614.76
BMDL	4443.64
BMDU	12197.5
AIC	73.6142
Log-Likelihood	-33.8071
P-value	0.492851
Overall d.f.	1
Chi^2	0.470297

Model Parameters			
# of Parameters	3		
Variable	Estimate	On Bound	Std Error
g	0.0378058	no	0.0623906
a	-26.1036	no	6.27844
b	2.67474	no	0.62764

Goodness of Fit					
Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	24	1	0.90734	0.0378058	0.0991693
7930	24	3	3.45209	0.143837	-0.262971
23800	24	18	17.0897	0.712069	0.410384
47580	24	22	22.5509	0.939621	-0.472116

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P-Value
Full Model	-33.5795	4	–	–	–
Fitted Model	-33.8071	3	0.455186	1	0.499882
Reduced Model	-66.2084	1	65.2578	3	4.41869e-14

Figure 2-6. Details Regarding the Selected Model (Log Logistic) for Periocular (Brown) Staining in Female Rats Exposed to *trans*-1,2-Dichloroethylene Via Inhalation for Six Hours and BMR of 10%ER

2.2 Shopp et al., 1985

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Analysis URL: View
BMDS Online Version: 25.1 (pybmds 25.1; bmdscore 25.1)

Data sets identified for BMD modeling for immune effects in a 90-day drinking water study (Shopp et al., 1985) include changes in antibody-forming cells/10^6 cells in male mice.

Modeled results were not presented for the antibody-forming cells/spleen in male mice data (Shopp et al., 1985) because with the constant variance model applied, the goodness of fit test could not be calculated for the Exponential 5 model as the model was saturated (degree of freedom = 0), and of the remaining models, only the Hill model provided adequate fit to the means (test 4 p-value > 0.1). BMDs and BMDLs for the Hill model were 10 times lower than the lowest non-zero dose and the BMD/BMDL ratio was > 20, and therefore, the model was not considered viable. With the nonconstant variance model applied, results were similar to modeling with the constant variance model applied, and thus no model was selected.

2.2.1 Antibody Forming Cells (AFC)/10^6 in Male Mice – 90-Day Drinking Water Study

Antibody forming cells/10^6 cells were decreased in male mice exposed to *trans*-1,2-dichloroethylene administered via drinking water for 90 days (Shopp et al., 1985). The dose and response data used for the modeling are presented in Table 2-5. Continuous models were used to fit the dose-response data.

A BMR of one SD was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012).

Table 2-5. Antibody Forming Cells (AFC)/10^6 in Male Mice and Associated Doses Selected for Dose-Response Modeling for *trans*-1,2-Dichloroethylene from a 90-Day Oral Exposure Study (Shopp et al., 1985)

Dose (mg/kg-day) [a]	Number of Animals	Mean	SD
0	12	2200	433
2.21	8	2048	430
22.8	8	1625	385
50.3	8	1618	639

[a] TWA doses as reported in Shopp et al. (1985).

The BMD modeling results for decreased antibody forming cells/10^6 in male mice are summarized in Table 2-6 and a summary plot of model fits is presented in Figure 2-7. The constant variance model provided adequate fit to the variance data. With the constant variance model applied, the goodness-of-fit p-values for the means (test 4) could not be derived for the Exponential 5, Polynomial 3 and Hill models because the models were saturated (degrees of freedom = 0). The remaining models provided adequate fit to the means (test 4 p-value > 0.1). The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC (Exponential 3) was selected.

Table 2-6. Summary of BMD Modeling Results for Humoral Immune Response in Male Mice Administered *trans*-1,2-Dichloroethylene in Drinking Water (Shopp et al., 1985) Using the Constant Variance Model

Model	BMDL	BMD	BMDU	*P*-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD	Recommendation and Notes
Restricted Models								
Exponential 3[ab]	21.388	36.911	–	0.511	550.153	0.625	0.652	**Recommended - Lowest AIC**
Exponential 5	1.88	8.755	16.128	–	551.844	-1.36E–8	-1.38E–7	**Questionable** Zero degrees of freedom; saturated model BMD/BMDL ratio > 3.0
Hill	2.397	2.499	2.766	–	551.845	-1.02E–7	1.53E–8	**Questionable** Zero degrees of freedom; saturated model
Polynomial 2	25.353	40.197	96.534	0.261	550.531	0.721	0.595	**Viable**
Polynomial 3	24.84	47.122	48.098	–	554.935	0.942	0.291	**Questionable** Zero degrees of freedom; saturated model
Power	25.34	40.173	96.531	0.261	550.531	0.72	0.596	**Viable**
Unrestricted Models								
Linear	25.335	40.173	96.531	0.261	550.531	0.72	0.596	**Viable**

[a] BMDS recommended best fitting model
[b] User selected best fitting model

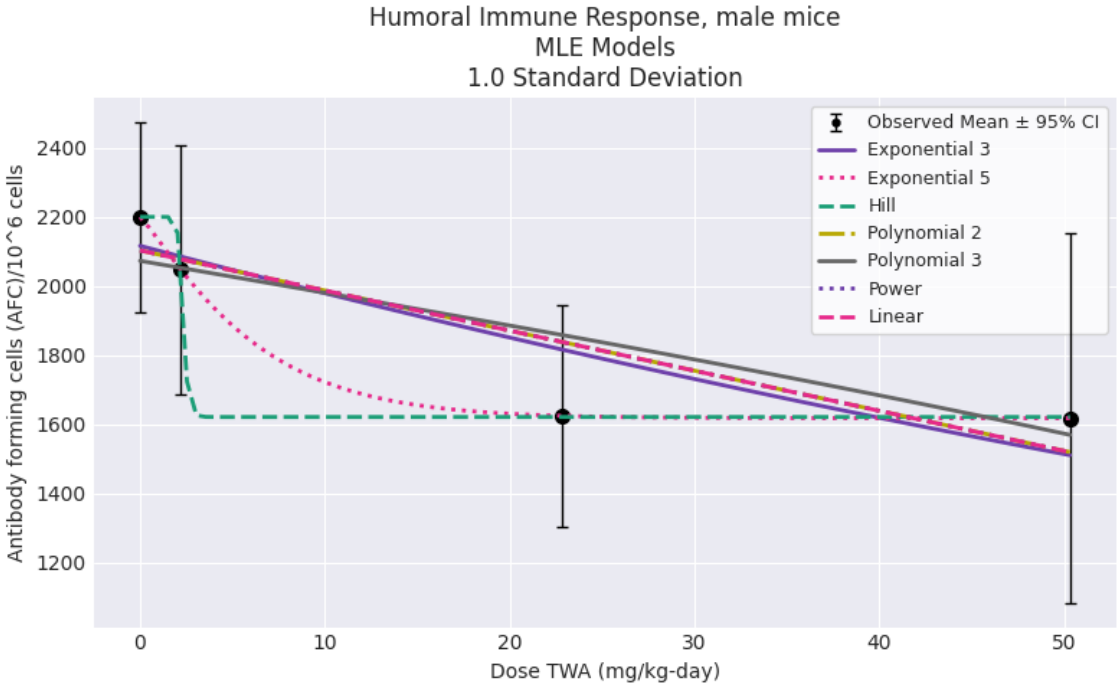

Figure 2-7. Summary Plot of Response by Concentration with Fitted Curves for Model Outputs for Humoral Immune Response in Male Mice Administered *trans*-1,2-Dichloroethylene in Drinking Water (Shopp et al., 1985)

A plot of the selected Exponential 3 model with a BMR of one SD is shown in Figure 2-8. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-9.

Figure 2-8. Plot of Response by Concentration with Fitted Curve for the Selected Model (Exponential 3) for Humoral Immune Response in Male Mice Administered *trans*-1,2-Dichloroethylene in Drinking Water (Shopp et al., 1985)

Model Results

Benchmark Dose	
BMD	36.9113
BMDL	21.3885
BMDU	-9999
AIC	550.153
Log-Likelihood	-272.077
P-value	0.510749
Model d.f.	3

Model Parameters			
# of Parameters	4		
Variable	Estimate	On Bound	Std Error
a	2116.44	no	71.9892
b	0.00669609	no	0.00213383
d	1	yes	Not reported
log-alpha	12.2775	no	0.235701

Goodness of Fit				
Dose	N	Sample Mean	Model Fitted Mean	Scaled Residual
0	12	2200	2116.44	0.624523
2.2	8	2048	2085.49	-0.228815
22.8	8	1625	1816.78	-1.17039
50.3	8	1618	1511.23	0.651587

Goodness of Fit			
Dose	N	Sample SD	Model Fitted SD

0	12	433	463.47
2.2	8	430	463.47
22.8	8	385	463.47
50.3	8	639	463.47

Likelihoods			
Model	Log Likelihood	# of Parameters	AIC
A1	-270.922	5	551.844
A2	-269.622	8	555.243
A3	-270.922	5	551.844
fitted	-272.077	2	548.153
reduced	-276.241	2	556.482

Tests of Mean and Variance Fits			
Name	-2 * Log(Likelihood Ratio)	Test d.f.	P-Value
Test 1	13.2386	6	0.0394
Test 2	2.60042	3	0.457415
Test 3	2.60042	3	0.457415
Test 4	2.30926	3	0.510749

Test 1: Test the null hypothesis that responses and variances don't differ among dose levels (A2 vs Reduced). If this test fails to reject the null hypothesis (p-value > 0.05), there may not be a dose-response.

Test 2: Test the null hypothesis that variances are homogenous (A1 vs A2). If this test fails to reject the null hypothesis (p-value > 0.05), the simpler constant variance model may be appropriate.

Test 3: Test the null hypothesis that the variances are adequately modeled (A3 vs A2). If this test fails to reject the null hypothesis (p-value > 0.05), it may be inferred that the variances have been modeled appropriately.

Test 4: Test the null hypothesis that the model for the mean fits the data (Fitted vs A3). If this test fails to reject the null hypothesis (p-value > 0.1), the user has support for use of the selected model.

Figure 2-9. Details Regarding the Selected Model (Exponential 3) for Humoral Immune Response in Male Mice Administered *trans*-1,2-Dichloroethylene in Drinking Water (Shopp et al., 1985)

2.2.2 Antibody Forming Cells (AFC)/10^6 in Male Mice – 90-Day Drinking Water Study (Highest Dose Excluded)

Antibody forming cells/10^6 cells were decreased in male mice exposed to *trans*-1,2-dichloroethylene administered via drinking water for 90 days (Shopp et al., 1985). Based on the poor visual fit for the BMD model on the full dataset and large residual near the BMD, for comparison, EPA additionally modeled the dataset with the highest dose dropped because the dose-response appeared to be flat between the two highest doses. These results are for comparison with the full dataset.

The dose and response data used for the modeling are presented in Table 2-7. Continuous models were used to fit the dose-response data.

A BMR of one SD was chosen according to EPA's *BMD Technical Guidance* (U.S. EPA, 2012).

Table 2-7. Antibody Forming Cells (AFC)/10^6 in Male Mice and Associated Doses Selected for Dose-Response Modeling for *trans*-1,2-Dichloroethylene from a 90-Day Oral Exposure Study (Shopp et al., 1985) (Highest Dose Excluded)

Dose (mg/kg-day) [a]	Number of Animals	Mean	SD
0	12	2200	433
2.21	8	2048	430
22.8	8	1625	385

[a] TWA doses as reported in Shopp et al. (1985).

The BMD modeling results for decreased antibody forming cells/10^6 in male mice are summarized in Table 2-8 and a summary plot of model fits is presented in . The constant variance model provided adequate fit to the variance data. With the constant variance model applied, the goodness-of-fit p-values for the means (test 4) could not be derived for the Exponential 5 and Hill models because the models were saturated (degrees of freedom = 0). The remaining models provided adequate fit to the means (test 4 p-value > 0.1). The BMDLs for the fit models were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC (Exponential 3) was selected. EPA determined that it was not appropriate to use BMD results for the truncated dataset because viable models were available using the full dataset.

Table 2-8. Summary of BMD Modeling Results for Humoral Immune Response in Male Mice Administered *trans*-1,2-Dichloroethylene in Drinking Water (Shopp et al., 1985) Using the Constant Variance Model (Highest Dose Excluded)

Model	BMDL	BMD	BMDU	*P*-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD	Recommendation and Notes
Restricted Models								
Exponential 3[ab]	9.326	15.858	39.896	0.61	420.702	0.295	0.052	**Recommended - Lowest AIC**
Exponential 5	2.727	2.942	3.331	–	424.441	1.05E–7	6.85E–8	**Questionable** Zero degrees of freedom; saturated model
Hill	6.28	9.051	8258	–	424.441	-1.01E–7	2.75E–7	**Questionable** Zero degrees of freedom; saturated model
Polynomial 2	10.808	16.746	28.281	0.581	420.746	0.329	0.036	**Viable**
Power	10.657	16.707	38.441	0.581	420.745	0.325	0.043	**Viable**
Unrestricted Models								

Model	BMDL	BMD	BMDU	*P*-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD	Recommendation and Notes
Linear	10.657	16.707	38.441	0.581	420.745	0.325	0.043	**Viable**

[a] BMDS recommended best fitting model
[b] User selected best fitting model

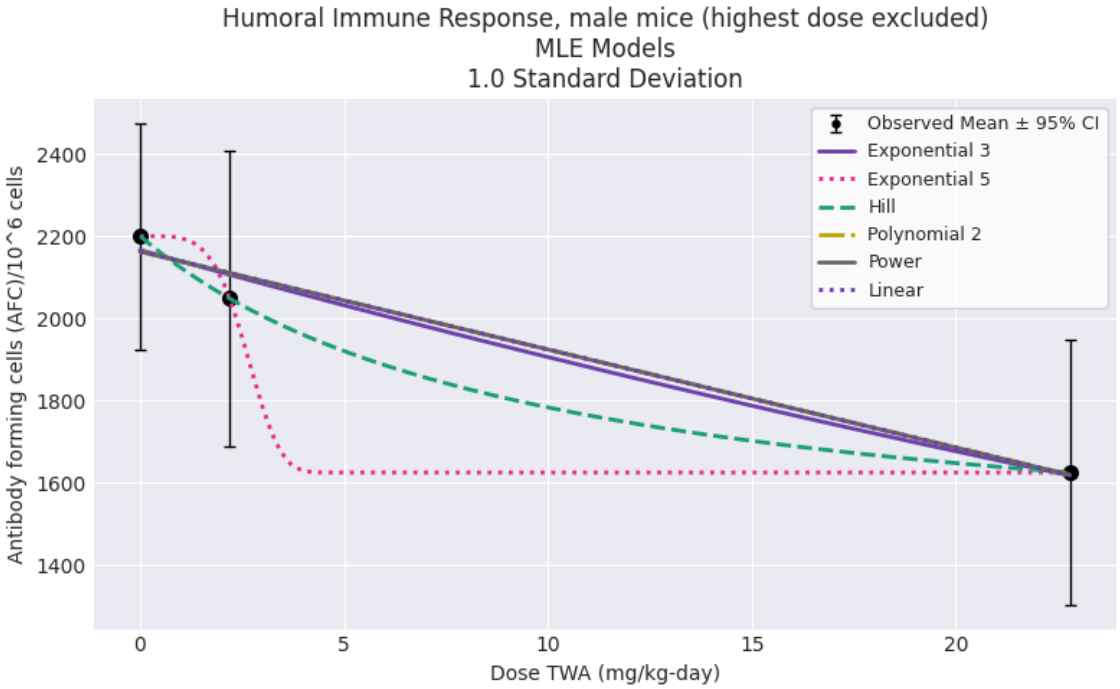

Figure 2-10. Summary Plot of Response by Concentration with Fitted Curves for Model Outputs for Humoral Immune Response in Male Mice Administered *trans*-1,2-Dichloroethylene in Drinking Water (Shopp et al., 1985) (Highest Dose Excluded)

A plot of the selected Exponential 3 model with a BMR of one SD is shown in Figure 2-11. Additional modeling details, including model parameters, goodness of fit at each dose, and log likelihood are shown in Figure 2-12.

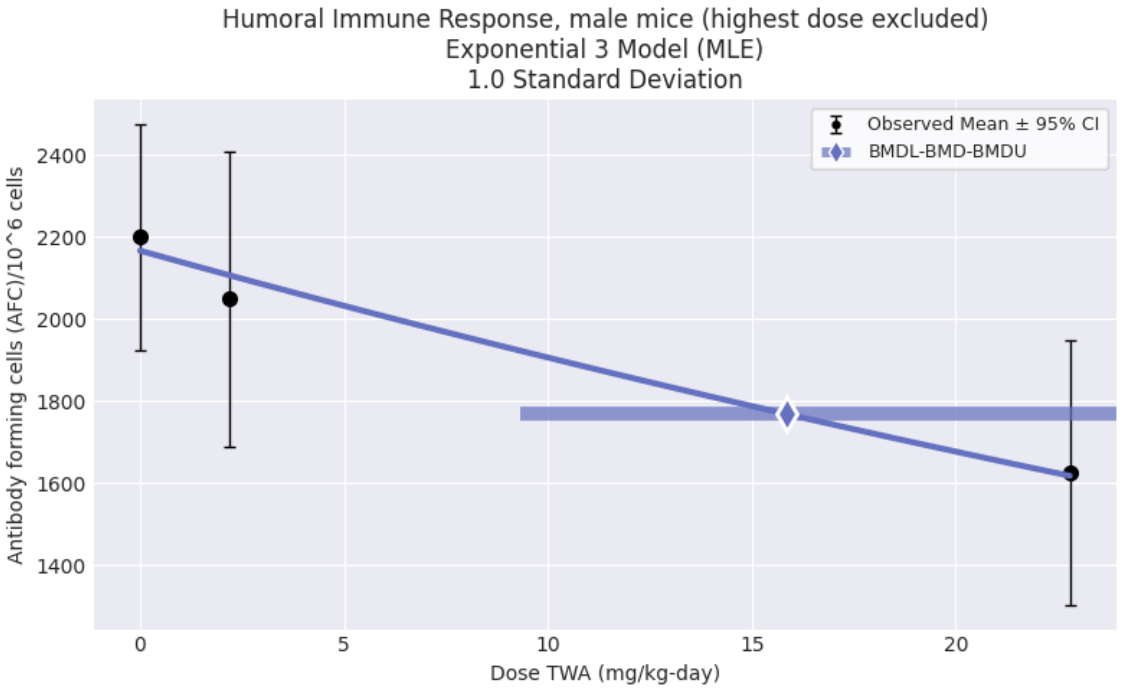

Figure 2-11. Plot of Response by Concentration with Fitted Curve for the Selected Model (Exponential 3) for Humoral Immune Response in Male Mice (Highest Dose Excluded)

Model Results

Benchmark Dose	
BMD	15.8582
BMDL	9.32629
BMDU	39.895
AIC	420.702
Log-Likelihood	-207.351
P-value	0.60979
Model d.f.	1

Model Parameters			
# of Parameters	4		
Variable	Estimate	On Bound	Std Error
a	2116.44	no	68.3638
b	0.0128026	no	0.00411356
d	1	yes	Not reported
log-alpha	11.9729	no	0.26726

Goodness of Fit				
Dose	N	Sample Mean	Model Fitted Mean	Scaled Residual
0	12	2200	2116.44	0.295231
2.2	8	2048	2085.49	-0.411629
22.8	8	1625	1816.78	0.0517048

Goodness of Fit			
Dose	N	Sample SD	Model Fitted SD
0	12	433	398.001

2.2	8	430	398.001
22.8	8	385	398.001

Likelihoods			
Model	Log Likelihood	# of Parameters	AIC
A1	-207.221	4	422.441
A2	-207.125	6	426.25
A3	-207.221	4	422.441
fitted	-207.351	3	420.702
reduced	-211.619	2	427.237

Tests of Mean and Variance Fits			
Name	-2 * Log(Likelihood Ratio)	Test d.f.	P-Value
Test 1	8.98697	4	0.061426
Test 2	0.191384	2	0.908744
Test 3	0.191384	2	0.908744
Test 4	0.260481	1	0.60979

Test 1: Test the null hypothesis that responses and variances don't differ among dose levels (A2 vs Reduced). If this test fails to reject the null hypothesis (p-value > 0.05), there may not be a dose-response.

Test 2: Test the null hypothesis that variances are homogenous (A1 vs A2). If this test fails to reject the null hypothesis (p-value > 0.05), the simpler constant variance model may be appropriate.

Test 3: Test the null hypothesis that the variances are adequately modeled (A3 vs A2). If this test fails to reject the null hypothesis (p-value > 0.05), it may be inferred that the variances have been modeled appropriately.

Test 4: Test the null hypothesis that the model for the mean fits the data (Fitted vs A3). If this test fails to reject the null hypothesis (p-value > 0.1), the user has support for use of the selected model.

Figure 2-12. Details Regarding the Selected Model (Exponential 3) for Humoral Immune Response in Male Mice Administered *trans*-1,2-Dichloroethylene in Drinking Water (Highest Dose Excluded)

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