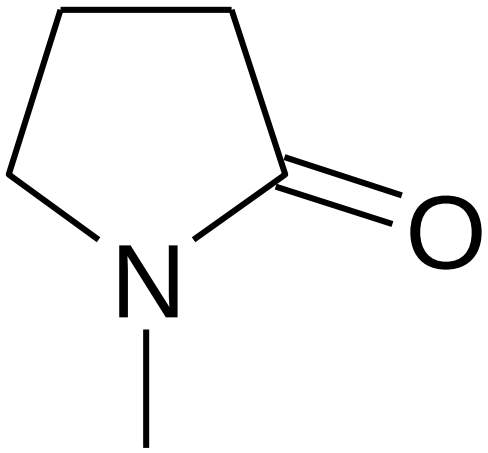
United States
Environmental Protection Agency

Office of Chemical Safety and
Pollution Prevention

Final Risk Evaluation for n-Methylpyrrolidone

Benchmark Dose Modeling Supplemental File

CASRN: 872-50-4



December 2020

Table of Contents

List of Figures

List of Tables

1 INTRODUCTION

This supplemental file describes benchmark dose (BMD) modeling approaches and results for all critical endpoints considered in the derivation of points of departure (PODs) for NMP. Reduced male fertility, reduced female fecundity, and reduced fetal body weights were all identified as sensitive reproductive and developmental endpoints associated with repeated dose exposures and were evaluated as the potential basis for chronic PODs. Post-implantation loss (resorptions and fetal mortality) and resorptions were identified as sensitive developmental endpoints that are relevant for single dose exposures and were evaluated as the potential basis for acute PODs.

In addition to the critical endpoints identified in the NMP risk evaluation, EPA performed dose-response analysis on several additional reproductive and developmental endpoints, including absolute testes weight, pup body weights, pup mortality, and stillbirth. These additional endpoints provide supporting evidence for POD selection, but contain uncertainties (*e.g.*, around exposure levels, or relevant exposure durations) that make them less suitable as the quantitative basis for PODs. For example, the relevance of stillbirths and pup mortality for acute versus chronic exposures is unclear. Stillbirths and pup mortality have been reported following repeated exposures throughout gestation, but could conceivably result from single exposures.

BMD modeling for post-implantation loss (resorptions and fetal mortality) and resorptions (Sections 2.1-2.10), fetal and pup body weight changes (Sections 3.1-3.3 and 5.5-5.6), male fertility and female fecundity (Sections 4.2-4.3), and absolute testes weight (Section 5.4) was performed using USEPA's BMD Software package version 3.1.1 (BMDS 3.1.1, released 07/31/2019), 3.1.2 (BMDS 3.1.2, released 11/ 8/2019) or 3.2 (BMDS 3.2, released 08/20/2020). Choice of BMD software was dictated by software availability at the time of BMD modeling for each endpoint. As each BMDS release provides updates, fixes, and enhancements to BMDS version 3, EPA chose to use the most up-to-date BMDS version available when conducting BMD modeling.[1] BMD modeling for stillbirths and pup death (Sections 4.4 and 5.7-5.8) was performed using USEPA's BMD Software package version 2.7 (BMDS 2.7, released 08/18/2017). The pup death and stillbirth endpoints were analyzed using BMDS 2.7 because it contains a larger suite of nested dichotomous models compared to BMDS version 3, and nested dichotomous models are preferred for these endpoints because they contain an intra-litter correlation coefficient for the assessment of litter-specific responses. All BMD modeling was conducted in a manner consistent with BMD technical guidance (U.S. EPA (2012)).

A peer-reviewed rat PBPK model for NMP (Poet et al. (2010)) modified by EPA (as described in Appendix I of the final NMP risk evaluation) was used to describe dose-response data for each endpoint in terms of internal doses (blood concentrations) in exposed rats. PODs based on internal doses in rats can be compared to blood concentrations in people predicted by human PBPK models for each condition of use. Internal dose metrics calculated with the rat PBPK model are in units of either AUC (hr mg/L) for chronic exposures or peak blood concentration (C_{max}, mg/L) for acute exposures.

[1] For a complete history of BMDS Version 3 software updates see: https://www.epa.gov/bmds/benchmark-dose-software-bmds-version-3-release-history

2 Benchmark Dose Modeling of Effects for Post-implantation Losses and Resorptions

The Saillenfait et al. (2003; 2002), Becci et al. (1982) and Sitarek et al. (2012) studies were selected for dose-response analysis of resorptions and post-implantation loss (resorptions and fetal mortality). Data available from the Sitarek et al. (2012) study did not allow for the analysis of post-implantation loss, as only fetal mortality data was reported. Fetal mortality is considered a less sensitive endpoint than the combined endpoint of post-implantation loss, which incorporates resorptions and fetal mortality. In the Sitarek et al. (2012) study, the mean percent dead fetuses across litters was significantly increased only in the highest dose group. Furthermore, the number of live pups in the highest exposure group was also significantly lower, and there were dam deaths and total litter loss in the highest exposure group. Benchmark dose (BMD) analysis of fetal mortality as a continuous response was not conducted for this data set, as study data were not consistent with this approach (*e.g.*, the mean and standard deviation was zero for some dose groups) (see Table 2-1). Thus, a NOAEL of 265 mg/L (based on C_{max}) was chosen as a POD for the Sitarek et al. (2012) study. Similarly, the dose-response data for resorptions in the Becci et al. (1982) dermal study was not amenable to BMD modeling, and a NOAEL of 662 mg/L (based on C_{max}) was chosen as a POD.

BMD modeling of resorptions and post-implantation loss (resorptions and fetal mortality) endpoints was performed for the Saillenfait et al. oral (2002) and inhalation (2003) studies using USEPA's BMD Software package version 3.1.2 (BMDS 3.1.2), in a manner consistent with BMD technical guidance (U.S. EPA (2012)). Dichotomous models were used to fit post-implantation loss incidence data and continuous models were used to fit dose-response data for mean number of resorptions. A BMR of 1% relative deviation (post-implantation loss) or 1% absolute deviation (resorptions) was used to address the relative severity of these endpoints (U.S. EPA (2012)). The peak NMP in maternal blood (C_{max}) and average area under the curve (AUC) blood concentration of NMP were used as dose metrics for these endpoints. The doses and response data used for the modeling post-implantation losses and resorptions are presented in Table 2-1 and Table 2-2, respectively. Model options and standard dichotomous and continuous BMDS 3.1.2 models applied to the post-implantation loss and the resorption endpoints are listed below.

Standard Dichotomous BMDS 3.1.2 Models Applied to Post-Implantation Loss Endpoint

- Gamma-restricted (Gam)
- Log-Logistic-restricted (Lnl)
- Multistage-restricted (Mst); from degree = 1 to degree = # dose groups - 1
- Weibull-restricted (Wei)
- Dichotomous Hill-unrestricted (Dhl)
- Logistic (Log)
- Log-Probit-unrestricted (Lnp)
- Probit (Pro)

Model Options Used for Dichotomous Response Modeling of Post-Implantation Loss

- Risk Type: Extra Risk
- Benchmark Response (BMR): 0.01 (1%)
- Confidence Level: 0.95
- Background: Estimated

Standard Continuous BMDS 3.1.2 Models Applied to Resorptions

- Exponential 2 (Exp2)-restricted
- Exponential 3 (Exp3)-restricted

- Exponential 4 (Exp4)-restricted
- Exponential 5 (Exp5)-restricted
- Hill (Hil)-restricted
- Polynomial Degree 4 (Ply4)-restricted
- Polynomial Degree 3 (Ply3)-restricted
- Polynomial Degree 2 (Ply2)-restricted
- Power (Pow)-restricted
- Linear (Lin)

Model Options Used for Continuous Response

- Benchmark Response (BMR): 1% Absolute Deviation
- Response Distribution-Variance Assumptions
    - Normal Distribution-Constant Variance
    - Normal Distribution-Non-Constant Variance
    - Lognormal Distribution, which assumes Constant Variance (if normal distribution models do not fit means)
- Confidence Level: 0.95
- Background: Estimated

Table 2-1 Resorptions (Mean % per litter) Data selected for Dose-Response Modeling for NMP

Reference and Endpoint	C_{max} (mg/L)	AUC (hr mg/L)	Number of Litters	Mean ± SD
Saillenfait et al. (2002) Resorptions	0	0	21	4.1 ± 6.1
	120	1,145	22	8.9 ± 21.2
	250	2,504	24	4.5 ± 6.6
	531	5,673	25	9.4 ± 8.9
	831	9,228	25	91 ± 16
Saillenfait et al. (2003) Resorptions	0	0	24	2.7 ± 3.7
	15	156.2	20	4.3 ± 4.1
	30	318.3	20	9.9 ± 22.3
	62	665.5	25	7 ± 9.4
Sitarek et al. (2012) Fetal Mortality	0	0	22	0.18 ± 0.85
	76	902	24	0 ± 0
	265	3,168	20	0.13 ± 0.34
	669	8,245	15	0.8 ± 1.1

Table 2-2 Post-implantation Loss Data Selected for Dose-Response Modeling for NMP

Reference and Endpoint	C_{max} (mg/L)	AUC (hr mg/L)	Litters w/ Implants	Mean Implants	Total Implants	Live Litters	Mean Live Fetuses	Total Live Fetuses	Total Lost Fetuses	Proportion Lost Fetuses	Design Effect	RS-Implants[a]	RS-Loss[a]
Saillenfait et al. (2002) Post-implant-ation loss	0	0	21	13.3	279.3	21	12.7	266.7	12.6	0.0451	2.0812	134.20	6.0541
	120	1145	22	13.6	299.2	21	13.1	275.1	24.1	0.0805	2.5498	117.34	9.4516
	250	2504	24	13.3	319.2	24	12.7	304.8	14.4	0.0451	2.0812	153.37	6.9190
	531	5673	25	14	350	25	12.4	310	40	0.1143	2.8824	121.42	13.877
	831	9228	25	13.8	345	8	2.4	19.2	325.8	0.9443	6.0479	57.044	53.870
Saillenfait et al. (2003) Post-implant-ation loss	0	0	24	14.3	343.2	24	13.9	333.6	9.6	0.0280	1.7605	194.94	5.4529
	15	156.2	20	13.4	268	20	12.6	252	16	0.0597	2.2958	116.73	6.9692
	30	318.3	20	14.1	282	19	14	266	16	0.0567	2.2552	125.04	7.0946
	62	665.5	25	12.9	322.5	25	12	300	22.5	0.0698	2.424	133.01	9.2798
Combined Saillenfait et al. (2003; 2002) Post-implant-ation loss	0 [b]	0 [b]	21	13.3	279.3	21	12.7	266.7	12.6	0.0451	2.0812	134.20	6.0541
	0 [b]	0 [b]	24	14.3	343.2	24	13.9	333.6	9.6	0.0280	1.7605	194.94	5.4529
	15	156.5	20	13.4	268	20	12.6	252	16	0.0597	2.2958	116.73	6.9692
	30	319	20	14.1	282	19	14	266	16	0.0567	2.2552	125.04	7.0946
	62	660.8	25	12.9	322.5	25	12	300	22.5	0.0698	2.424	133.01	9.2798
	120	1145	22	13.6	299.2	21	13.1	275.1	24.1	0.0805	2.5498	117.34	9.4516
	250	2504	24	13.3	319.2	24	12.7	304.8	14.4	0.0451	2.0812	153.37	6.9190
	531	5673	25	14	350	25	12.4	310	40	0.1143	2.8824	121.42	13.877
	831	9228	25	13.8	345	8	2.4	19.2	325.8	0.9443	6.0479	57.044	53.870

Data highlighted in gray was used for dose-response modeling for NMP.

[a] The Rao-Scott transformation (RS) entails dividing the total numbers of implantations and post-implantation loss by a design effect to approximate the true variance in the clustered data.

[b] Calculating the design effects separately for the control groups from each study is preferred as it captures possible differences between the groups.

Dose-response results from the Saillenfait et al. oral (2002) and inhalation (2003) studies were modeled separately and combined for the C_{max} and AUC dose metrics for the post-implantation loss dichotomous endpoint. The BMD analyses combining the oral and inhalation results are recommended for this endpoint, and this recommendation is supported by the following considerations:

- Saillenfait et al. (2003) reported that "mean numbers of implantation sites and of live fetuses and the incidences of non-live implants and resorptions were comparable across groups" up to and including their highest-exposure group, for which EPA's PBPK model estimates a 62 mg/L (C_{max}) internal dose (Table 2-1). Saillenfait et al. also point out that their findings are in agreement with the absence of teratogenic effects found in previous studies on the developmental toxic potential from similar inhalation exposures to NMP.

- A deviance test indicates no significant difference between dose-response relationships in the two Saillenfait et al. oral and inhalation studies, from combined and separate study results for doses at or below 530 mg/L C_{max} internal dose. Appendix B provides additional technical details on the statistical approach. Technically the statistical approach assumed that the dose-response in the region analyzed is sufficiently flat or otherwise linear for each study so that it can be approximated by a linear regression. Then the slopes and intercepts could be equal or unequal for the two Saillenfait studies. A useful null hypothesis is that both the slope and intercept are equal. This approach avoided complications of dependence on selecting a nonlinear model and technical issues of statistics with constrained parameter spaces (compared to Stiteler et al. (1993)). The assumption of a dose response curve with a flat or approximately linear portion at low doses is supported by graphical analysis and by tests for nonlinear trend (discussed further in the following bullet). The regression approach assumed that the response variable has a binomial distribution. The deviance test suggests that the data are consistent with equal intercepts and equal slopes in the dose range evaluated, which includes doses above the 62 mg/L C_{max} high dose blood concentration estimated for the Saillenfait et al. (2003) inhalation study. The analyses (as well as the trend analysis – next bullet) used Rao-Scott adjusted incidence values to account for possible litter effects.

- For the inhalation data, test for a trend in the relationship of incidence to C_{max} internal doses (further details provided in Appendix B) did not provide substantial evidence of an effect, thus did not support separate modeling. Modeling the combined data allows for an effect in the inhalation study, but attention is needed to the possibility of different dose-response curves for the inhalation study versus the oral gavage study. The trend analysis provided by the EPITOOLS software also provide a test of nonlinearity, which does not suggest any deviation from linearity at the lowest doses, providing some support for the deviance test (previous bullet) as a test for a difference in the dose-response relationship.

- Close similarity of strain, breed, source and housing helps alleviate uncertainties associated with combining control and test rat dose-response data from the two studies – The Saillenfait et al. (2003; 2002) oral and inhalation studies were conducted in the same laboratory within a year of each other, using the same strain of rats from the same source (Sprague–Dawley rats supplied by IFFA CREDO Breeding Laboratories, Saint-Germain-surl'Arbresle, France). Control rats of the oral study were not gavaged, making them more comparable to the inhalation study controls. Body weight on day 0, body weight gain and food consumption during the treatment period were nearly identical for control rats of both studies.

- Confidence in the PBPK estimates of internal doses helps alleviate uncertainties associated with combining control and test rat dose-response data from the two studies - EPA has confidence in

the NMP PBPK model used for this purpose as it has been thoroughly vetted through multiple reviews (further discussion of the NMP PBPK model is provided in Appendix I of the final NMP risk evaluation). An advantage that can come from use of a PBPK model with an appropriate internal dose metric is that it allows one to combine dose-response data from studies with different designs, such as inhalation studies with different daily exposure durations, oral exposure by gavage versus drinking water, and exposures by more than one route of exposure. Evaluation of whether the dose metric is appropriate is accomplished first by plotting the results of the health-effects studies together, using the PBPK-predicted dose metric as the measure of dose, and evaluating the overall congruence of the sets of results.[2] Statistical tests for consistency of dose-response relationships, as described in the above bullets, can then be performed for a rigorous analysis.

- Adding inhalation dose groups to the oral study increases confidence in the modeling results, particularly in the low dose region – Use of the post-implantation loss endpoint data from the Saillenfait et al. (2003) inhalation study alone is not recommended given the lack of a statistical or pharmacokinetic evidence for a dose-response trend. Use of the Saillenfait et al. (2002) oral study alone is not recommended for this endpoint given the lack of data in the low dose region of interest. The combination of two dose-response studies presumes that the data, including the endpoint incidence in control animals, are derived from the same overall population distribution (*i.e.*, the distribution of incidence versus exposure that would occur in the entire population of pregnant Sprague-Dawley rats), with differences only occurring because each study provides data on a different sample from that distribution. Given this assumption, the data for the two control groups can be combined, to provide a better estimate of the true response incidence among unexposed animals. While EPA recognizes the uncertainties associated with combining data from two studies, EPA does not think uncertainties outweigh the benefits associated with the increased statistical power that comes from combining the studies, which allows EPA to more confidently estimate low dose specific response levels (*i.e.*, the BMD and BMDL) for the post-implantation loss endpoint.

Analysis of Post-Implantation Loss as a Dichotomous Response:
Increases in post-implantation losses/implantations (Saillenfait et al. (2003; 2002)), which accounts for both resorptions and fetal/pup death, is evaluated as a dichotomous endpoint. To perform this analysis, incidences of post-implantation loss from the reported litter means[3] were modeled with standard BMDS 3.1.2 dichotomous models after adjusting for litter effects using a Rao-Scott transformation. Normally, individual animal data are necessary in order to account for intralitter correlation present in nested developmental toxicity data (*i.e.*, the observation that pups from one litter are more likely to respond alike one another compared to pups from another litter). But in this situation, study authors were unable to provide litter level data and instead an approximate approach was used. Briefly, the numbers of total implantations and total fetal loss (dead fetuses plus resorptions) were scaled by a design effect in order to approximate the true variance of the clustered data. This transformation is called the Rao-Scott transformation and has been shown to reasonably approximate the variance due to clustering and intralitter correlation in developmental toxicity data (Fox et al. (2016)). Details of the Rao-Scott transformation are shown in Table 2-2.

As discussed above, a two-sided test for trend indicates no significant trend in the Rao-Scott transformed Saillenfait et al. (2003) response data with increasing inhalation dose (Appendix B). Consequently, the

[2] A previous example of such an analysis was performed by Sasso et al. (2013) for chloroform-induced renal toxicity.
[3] Total post-implantation loss was calculated as follows: (mean implantations per litter x total litters) – mean live fetuses per litter x litter) = total number of post-implantation losses.

BMDLs derived from this dataset alone (Sections 2.7 and 2.8a) are not recommended for use and are not presented in the summary of BMD and BMDL results (Table 2-4).

The analysis of the eight dose groups associated with the combined dose response data from the two Saillenfait et al. (2003; 2002) studies presents a unique situation for the Multistage model that requires careful consideration. The default number of Multistage model degrees run in BMDS 3.1.2 is n-1, where n is the number of dose-groups in the dataset. Thus, in this case, the 1st degree through 7th degree Multistage models were run. Consideration needs to be given as to whether that many Multistage degrees are necessary and appropriate for the dataset being evaluated. Of the Multistage models, the 7th degree Multistage provides an adequate fit to the data that is similar to the model fit achieved by some non-Multistage models, but its BMDL estimate is nearly four-fold lower (Table 2-21 and Table 2-22 The Multistage degree 7 BMDL is lower because it contains several extra parameters (βeta coefficients for degrees 1 through 6). These parameters contribute to the BMDL estimation but are restricted at the 0 boundary criteria for the purposes of the maximum likelihood, BMD estimation. Thus, while the BMD estimates (377 mg/L C_{max}) of the 7th degree Multistage model are similar to adequately fitting non-Multistage models (423-472 mg/L C_{max}), its BMDL estimates are nearly four-fold lower (113 mg/L C_{max} versus 364-437 mg/L C_{max} for non-Multistage models). Hence, it appears that the extra parameters in the higher degree Multistage models are solely driving the derivation of the lower BMDLs for these models. In situations where BMDLs vary substantially (*i.e.*, by greater than three-fold), EPA BMD Technical Guidance (U.S. EPA (2012)) states that "expert statistical judgment may help at this point to judge whether model uncertainty is too great to rely on some or all of the results." In this case, given that trend tests of the combined dataset indicate a lack of linear dose-response trend in the low dose region up to and including 531 mg/L C_{max}, EPA's judgment is that the Multistage 7 model is not appropriate for the derivation of a BMDL from this dataset, despite its adequate statistical fit (p-value > 0.1) to the data. Because BMDLs from the remaining adequately fitting models are sufficiently close, the BMDL is derived from the model with the lowest AIC (U.S. EPA (2012)), which is the Log-Probit model (see Sections 2.9 and 2.10).

Analysis of Resorptions as a Continuous Response:
Summary statistics available from Saillenfait et al. (2003; 2002) do not allow for the preferred approach of evaluating of resorptions as dichotomous responses. Hence mean percent resorptions per litter reported by Saillenfait et al. (2003; 2002) were evaluated as continuous responses. As with the fetal weight data discussed in Section 3, because the Saillenfait et al. (2003; 2002) resorption datasets were obtained from a nested design, with fetus nested within litter, it is preferable to analyze the individual fetal data in order to incorporate variability across fetuses. However, fetal data were not available for this study; thus, the means and standard deviations (SDs) of litter mean percent resorption as well as number of litters in each dose group were modeled (see Method 2 in Appendix A for details).

Standard models gave adequate results for all endpoints, and thus non-standard models were not considered. Also, since adequate fits to the means were obtained using normal distribution models, lognormal models were not applied.

The variances for resorptions from Saillenfait et al. (2003; 2002) could not be fit using either the constant or nonconstant variance models available in BMDS. Therefore, a sensitivity analysis using the original, minimum and maximum SDs for the dataset, was conducted to determine the influence of the variances on the resorption results. Briefly, from the results of the modeling using the observed SDs, a model was selected from the models that fit the means adequately, assuming constant variance. Then the data were modeled by replacing the SDs in all the groups by the minimum SD across the groups, assuming constant variance and only fitting models that fit the means adequately for the observed SD

case, and a model was selected from these fits. This step was repeated with the SDs in all the groups replaced by the maximum SD across the groups. The results of the sensitivity analysis are summarized in Table 2-3 and the BMD modeling details are presented in Sections 2.1-2.4. For three datasets (Sections 2.1, 2.2 and 2.4), the lowest BMDL from an adequately fitting model would typically be recommended because the selected BMDLs for each of the three variance cases did not differ greatly (*i.e.*, BMDLs varied by less than three-fold). However, due to uncertainty caused by the lack of model fits (Test 4 P-value < 0.1) when SDs were set to the minimum SDs of the group, these BMDLs were compared to the NOAEL for the endpoint and the lowest of these BMDL and NOAEL values is recommended as the POD. For the other dataset (Section 2.3), the sensitivity analysis indicated the selected BMDLs for the three variance cases differ greatly (*i.e.*, BMDLs differed by more than three-fold). Thus, EPA does not regard the available model results as acceptable and hence the NOAEL for the endpoint is recommended as the POD. Table 2-3 summarizes the results for this variance sensitivity analysis, with the recommended POD values highlighted in gray and shown in bold font. Note that the "free-standing" C_{max} and AUC NOAELs from Saillenfait et al. (2003) are not bolded and not recommended due to the existence of higher C_{max} and AUC NOAELs from Saillenfait et al. (2002).

Table 2-3 BMD and BMDL Derivations from the Variance (SD) Sensitivity Analysis of Saillenfait et al. (2003; 2002) Resorption Data, with Corresponding NOAELs

Section	Response	Dose Metric	SD Case [a]	Selected Model	Test 4 P-value	BMD_{1AD}	$BMDL_{1AD}$
2.1	Resorption (Mean %) Saillenfait et al. (2002)	C_{max} (mg/L)	Observed	Hill	0.389	535	511
			Minimum	Hill [b]	0.015	535	522
			Maximum	Hill	0.696	535	502
			NOAEL	--	--	--	**250**
2.2		AUC (hr mg/L)	Observed	Hill	0.389	5,719	5,462
			Minimum	Power [b]	0.014	5,797	5,298
			Maximum	Poly 4	0.417	4,307	3,222
			NOAEL	--	--	--	**2504**
2.3	Resorption (Mean %) Saillenfait et al. (2003)	C_{max} (mg/L)	Observed	Linear	0.251	14.078	6.30
			Minimum	Hill [b]	0.00874	14.5	13.7
			Maximum	Linear	0.668	14.077	4.31
			NOAEL [c]	--	--	--	62
2.4		AUC (hr mg/L)	Observed	Linear	0.248	151	67.9
			Minimum	Exp5 [b]	0.00874	152	83.7
			Maximum	Poly 3	0.6664	151	46.4
			NOAEL [c]	--	--	--	666

[a] The lowest BMDL from an adequately fitting model is selected and bolded if all BMDLs are reasonably close (*i.e.*, withing threefold) and the BMDL is lower than the NOAEL. Otherwise, the NOAEL is selected and bolded.
[b] No model adequately fit the dataset means (Test 4 p-value <0.1); results for the model with the lowest AIC are shown.
[c] The "free-standing" C_{max} and AUC NOAELs from Saillenfait et al. (2003) are not bolded and are not recommended for use as PODs due to the existence of higher C_{max} and AUC NOAELs from Saillenfait et al. (2002) study.

For each dataset-specific BMD analysis, a single preferred model was chosen from the standard set of models and modeling options listed above. The modeling restrictions and the model selection criteria facilitated in BMDS 3.1.2 and defined in the BMDS 3.1.2 User Guide were applied in accordance with EPA BMD Technical Guidance (U.S. EPA (2012)). Briefly, for each dataset, BMDS models with standard restrictions were fitted to the data using the maximum likelihood method. For dichotomous

models, if the BMDLs from adequately fitting models (p-value < 0.1) were sufficiently close (within a threefold range), the model with the lowest AIC was selected as the best-fitting model, and its BMDL was used as the POD. Per BMD Technical Guidance "This criterion is intended to help arrive at a single BMDL value in an objective, reproducible manner." If the BMDLs are not sufficiently close (not within a threefold range), it was determined that the BMDLs were substantially model-dependent; thus, the BMDL from the adequately fitting model with the lowest BMDL was used as the POD. From continuous models applied to the resorptions endpoint, model fit was assessed by a series of tests as follows. For each model, first the homogeneity of the variances was tested using a likelihood ratio test (BMDS Test 2). If Test 2 was not rejected ($\chi 2$ p-value ≥ 0.05), the model was fitted to the data assuming constant variance. If Test 2 was rejected ($\chi 2$ p-value < 0.05), the variance was modeled as a power function of the mean, and the variance model was tested for adequacy of fit using a likelihood ratio test (BMDS Test 3). For fitting models using either constant variance or modeled variance, models for the mean response were tested for adequacy of fit using a likelihood ratio test (BMDS Test 4, with $\chi 2$ p-value < 0.10 indicating inadequate fit). From among the models that yielded an adequate fit, the model for POD determination was selected using the same procedure as for the dichotomous models. For both the dichotomous and continuous model analyses, other factors were also used to assess the model fit, such as scaled residuals, visual fit, and adequacy of fit in the low-dose region and in the vicinity of the BMR.

Comparisons of model fits obtained for post-implantation losses and resorptions are provided in Table 2-5 through Table 2-22. The best-fitting models, based on the criteria described above, are bolded and highlighted in gray. For each of the best fitting models in Sections 2.1-2.10, subsequent tables and figures show the model version number, model form, benchmark dose calculation, parameter estimates and estimated values.

PODs identified based on the best fit models for post-implantation loss and resorptions for the Saillenfait et al. (2003; 2002) studies are summarized in Table 2-4.

Table 2-4. Summary of PODs identified for C_{max} and AUC Dose Metrics for Post-Implantation Loss and Resorptions

Section	Response	Dose Metric	Selected Model [a]	BMD_{1ER} or NOAEL [b]	$BMDL_{1ER}$ or NOAEL [b]
2.5	Post-Implantation Losses/Implants (Saillenfait et al. (2002))	C_{max} (mg/L)	Log-Probit	474	437
2.6		AUC (hr mg/L)	Log-Probit	5,010	4,592
2.9	Post-Implantation Losses/Implants (Saillenfait et al. (2003; 2002) combined)	C_{max} (mg/L)	Log-Probit	470	437
2.10		AUC (hr mg/L)	Log-Probit	4,990	4,590
2.1	Resorption (Mean %) (Saillenfait et al. (2002))	C_{max} (mg/L)	NOAEL [c]	--	250
2.2		AUC (hr mg/L)	NOAEL [c]	--	2,500

[a] Since standard models gave adequate results for all endpoints, non-standard models were not considered. Since fits to the means of the mean % resorption data were obtained using normal distribution models, lognormal models were not applied.
[b] BMD and BMDL values are for BMR of 1% Extra Risk (1ER) for post-implantation losses/Implants and NOAELs for mean % resorptions (see Table 2-3).
[c] The NOAEL for this dataset is recommended for use over the BMDL values derived for this endpoint (see Table 2-3).

2.1 Resorptions: Results for Saillenfait et al. (2002) using C_{max}

Table 2-5 Model Predictions for Resorptions (Mean % per Litter) in Rats Exposed to NMP via Gavage Using C_{max} as the Dose Metric (Saillenfait et al. (2002))
BMR = 1% Absolute Deviation (AD)

Model [a]	Goodness of fit		BMD (mg/L)	BMDL (mg/L)	BMDU (mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.007044	947.069	393.2644	323.4513	4479.5071	Only Exponential 3, Hill and Power models provided an adequate fit (Test 4 p-value ≥ 0.10). Of these, the Hill model was selected based on lowest AIC.
Exponential 3	0.379373	938.906	548.3582	424.5308	723.8003	
Exponential 4	<0.0001	1084.78	51.9053	46.8503	58.0743	
Exponential 5	0.000125	953.690	481.7744	0	521.0350	
Hill [b]	**0.389268**	**938.855**	**535.1995**	**511.3336**	**704.9748**	
Polynomial 4°	0.007024	947.054	387.6039	351.9091	Infinity	
Polynomial 3°	<0.0001	968.580	300.8686	277.3312	Infinity	
Polynomial 2°	<0.0001	1011.52	183.1171	167.1364	Infinity	
Power	0.388006	938.861	541.5904	459.9201	574.7369	
Linear	<0.0001	1073.71	42.9383	38.2120	49.0001	

[a] No variance model fit this dataset using reported SD values (BMDS Test 2 and 3 p-values < 0.0001). Results for constant variance model are shown.
[b] Model selection based on lowest AIC from adequately fitting models.

Table 2-6 Model Predictions for Resorptions (Mean % per Litter) in Rats Exposed to NMP via Gavage Using C_{max} as the Dose Metric (Saillenfait et al. (2002))

BMR = 1% Absolute Deviation (AD); minimum SD among groups used for all groups in analysis

Model [a]	Goodness of fit		BMD (mg/L)	BMDL (mg/L)	BMDU (mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	<0.0001	803.718	393.2456	353.6334	437.6397	No model adequately fit the mean response data.
Exponential 3	0.012984	766.749	548.3653	483.8053	636.6293	
Exponential 4	<0.0001	1054.98	51.8658	47.6549	56.8808	
Exponential 5	0.003606	768.533	538.1709	509.8833	603.9132	
Hill	0.014526	766.525	535.1998	521.5652	561.5738	
Polynomial 4°	<0.0001	808.344	387.6039	376.5096	Infinity	
Polynomial 3°	<0.0001	867.713	300.8687	290.5825	Infinity	
Polynomial 2°	<0.0001	950.354	183.1170	173.1190	Infinity	
Power	0.014322	766.553	541.5890	498.5351	605.4818	
Linear	<0.0001	1041.71	42.9380	38.7557	48.1304	

[a] No model adequately fit the means of this dataset using the 6.1 minimum SD value for all dose groups (BMDS Test 4 < 0.1). No variance model fit this dataset using reported SD values (BMDS Test 2 and 3 p-values < 0.0001). Results for constant variance model are shown.

Table 2-7 Model Predictions for Resorptions (Mean % per Litter) in Rats Exposed to NMP via Gavage Using C_{max} as the Dose Metric (Saillenfait et al. (2002))

BMR = 1% Absolute Deviation (AD); maximum SD among groups used for all groups in analysis

Model [a]	Goodness of fit		BMD (mg/L)	BMDL (mg/L)	BMDU (mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.189295	1052.3296	393.2780	290.2496	539.9314	The Hill model was selected based on lowest AIC among adequately fitting models (Test 4 P-value > 0.1).
Exponential 3	0.689247	1050.3022	548.3492	363.5049	732.9579	
Exponential 4	<0.0001	1128.5692	51.8672	46.2820	58.9588	
Exponential 5	0.394674	1052.2824	537.0627	420.4268	708.2826	
Hill [b]	**0.696127**	**1050.2823**	**535.1428**	**502.2433**	**705.4570**	
Polynomial 4°	0.232517	1051.1411	387.6039	302.4135	Infinity	
Polynomial 3°	0.004892	1060.4678	300.8687	251.0415	Infinity	
Polynomial 2°	<0.0001	1082.9218	183.0936	155.4972	Infinity	
Power	0.694961	1050.2857	544.5289	420.2064	671.7613	
Linear	<0.0001	1120.6978	42.93835	37.2979	50.5875	

[a] Results for constant variance model are shown. SD set to maximum value of 21.2 for all dose groups.
[b] Model selection based on lowest AIC from adequately fitting models.

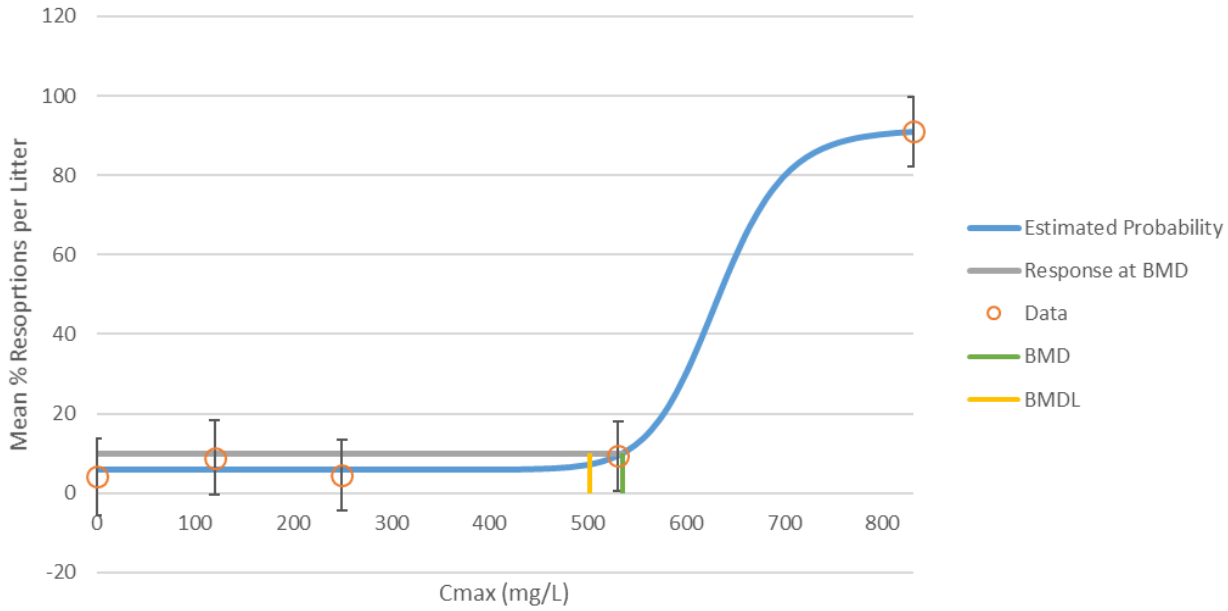


Figure 2.1-1 Plot of Response by Dose, with Fitted Curve for Selected Hill Model for Resorptions (Mean % per Litter) in Rats Exposed to NMP via Gavage (Saillenfait et al. (2002))
BMR = 1% AD; all SDs set to the maximum SD across the groups

USER INPUT

Info	
Model	frequentist Hill v1.1
Dose-Response Model	M[dose] = g + v*dose^n/(k^n + dose^n)
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Abs. Dev.
BMRF	1
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	C_{max} (mg/L)
Independent Variable	Mean% Resorptions per litter
Total # of Observations	5
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	535.1428123
BMDL	502.243266
BMDU	705.4569526
AIC	1050.282358
Test 4 P-value	0.696126859
D.O.F.	2

Model Parameters	
# of Parameters	5
Variable	Estimate
g	5.813844994
v	85.79623561
k	631.9163554
n	Bounded
alpha	432.9057039

Goodness of Fit

Dose	Size	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	21	4.1	20.80638613	21.2	21.2	-0.377471819
120	22	8.9	20.80638613	21.2	21.2	0.695716689
250	24	4.5	20.80638613	21.2	21.2	-0.309353259
531	25	9.4	20.80638613	21.2	21.2	-0.000237076
831	25	91	20.80638613	21.2	21.2	0.001359032

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-520.7789555	6	1053.557911
A2	-520.7786645	10	1061.557329
A3	-520.7789555	6	1053.557911
fitted	-521.1411788	4	1050.282358
R	-598.5686115	2	1201.137223

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	155.5798939	8	<0.0001
2	0.000581864	4	0.999999958
3	0.000581864	4	0.999999958
4	0.724446735	2	0.696126859

* Includes additive constant of -107.51581. This constant was not included in the LL derivation prior to BMDS 3.0.

2.2 Resorptions: Results for Saillenfait et al. (2002) using AUC

Table 2-8 Model Predictions for Resorptions (Mean % per Litter) in Rats Exposed to NMP via Gavage Using AUC as the Dose Metric (Saillenfait et al. (2002))

BMR = 1% Absolute Deviation (AD)

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.008986	946.544	4043.1086	3295.7539	5010.8819	Only Exponential 3, Hill and Power models provided an adequate fit (Test 4 p-value ≥ 0.10). Of these, the Hill model was selected based on lowest AIC.
Exponential 3	0.379432	938.906	5875.3609	4450.0672	8103.4619	
Exponential 4	<0.0001	1075.559	559.6636	507.9306	622.4397	
Exponential 5	0.000124	953.701	5263.5918	0	5585.7252	
Hill [b]	**0.389268**	**938.855**	**5718.8813**	**5462.4791**	**7838.6124**	
Polynomial 4°	0.040523	942.962	4306.9967	3852.5679	Infinity	
Polynomial 3°	<0.0001	961.304	3339.8312	3068.5732	Infinity	
Polynomial 2°	<0.0001	1000.875	2027.7227	1855.6345	Infinity	
Power	0.388006	938.861	5797.0548	4853.5551	6326.2892	
Linear	<0.0001	1067.162	472.3225	422.3903	535.6331	

[a] No variance model fit this dataset using reported SD values (BMDS Test 2 and 3 *p*-values < 0.0001). Results for constant variance model are shown.

[b] Model selection based on lowest AIC from adequately fitting models.

Table 2-9 Model Predictions for Resorptions (Mean % per Litter) in Rats Exposed to NMP via Gavage Using AUC as the Dose Metric (Saillenfait et al. (2002))

BMR = 1% Absolute Deviation (AD); minimum SD among groups used for all groups in analysis

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	<0.0001	801.920	4042.9257	3615.8068	4532.9584	No model adequately fit the mean response data.
Exponential 3	0.012993	766.748	5875.3642	5127.2682	6661.9635	
Exponential 4	<0.0001	1043.697	559.4295	515.9626	610.3890	
Exponential 5	0.003623	768.525	5734.7899	5504.3446	6241.6250	
Hill	0.003623	768.525	5718.9466	5571.8781	6000.1162	
Polynomial 4°	<0.0001	794.383	4306.9964	4175.4460	Infinity	
Polynomial 3°	<0.0001	849.688	3339.8310	3231.0905	Infinity	
Polynomial 2°	<0.0001	933.375	2027.7128	1925.1043	Infinity	
Power	0.014322	766.553	5797.0518	5298.1645	6543.8546	
Linear	<0.0001	1033.026	472.3283	428.5655	526.0557	

[a] No model adequately fit the means of this dataset using the 6.1 minimum SD value for all dose groups (BMDS Test 4 < 0.1). No variance model fit this dataset using reported SD values (BMDS Test 2 and 3 p-values < 0.0001). Results for constant variance model are shown.

Table 2-10 Model Predictions for Resorptions (Mean % per Litter) in Rats Exposed to NMP via Gavage Using AUC as the Dose Metric (Saillenfait et al. (2002))

BMR = 1% Absolute Deviation (AD); maximum SD among groups used for all groups in analysis

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.207145	1052.116	4043.0558	2952.3908	5709.1001	Exponential 2, 3, Hill, Power, and Polynomial 4 models provided an adequate fit (Test 4 p-value ≥ 0.10). Of these, the Polynomial 4 model was selected based on lowest AIC.
Exponential 3	0.689288	1050.302	5875.7504	3757.6576	8151.6558	
Exponential 4	<0.0001	1124.251	560.0255	496.0853	640.6819	
Exponential 5	0.015662	1057.398	5198.5546	3645.3150	5974.0792	
Hill	0.695791	1050.283	5710.8575	5360.7253	7835.6455	
Polynomial 4° [b,c]	**0.417028**	**1049.477**	**4306.9964**	**3221.5295**	**Infinity**	
Polynomial 3°	0.020166	1057.206	3339.8268	2748.7368	Infinity	
Polynomial 2°	<0.0001	1076.304	2027.7670	1720.5274	Infinity	
Power	0.695257	1050.284	5797.0501	4400.0709	7721.2377	
Linear	<0.0001	1116.355	472.29675	412.2081	552.9808	

[a] Results for constant variance model are shown. SD set to maximum value of 21.2 for all dose groups.
[b] Model selection based on lowest AIC from adequately fitting models.
[c] Scaled residuals for selected Poly 4 model for 0, 1144, 2503, 5674 and 9231 hr mg/L were 0.1170, 1.183, 0.1094, -1.543, and 0.2195, respectively.

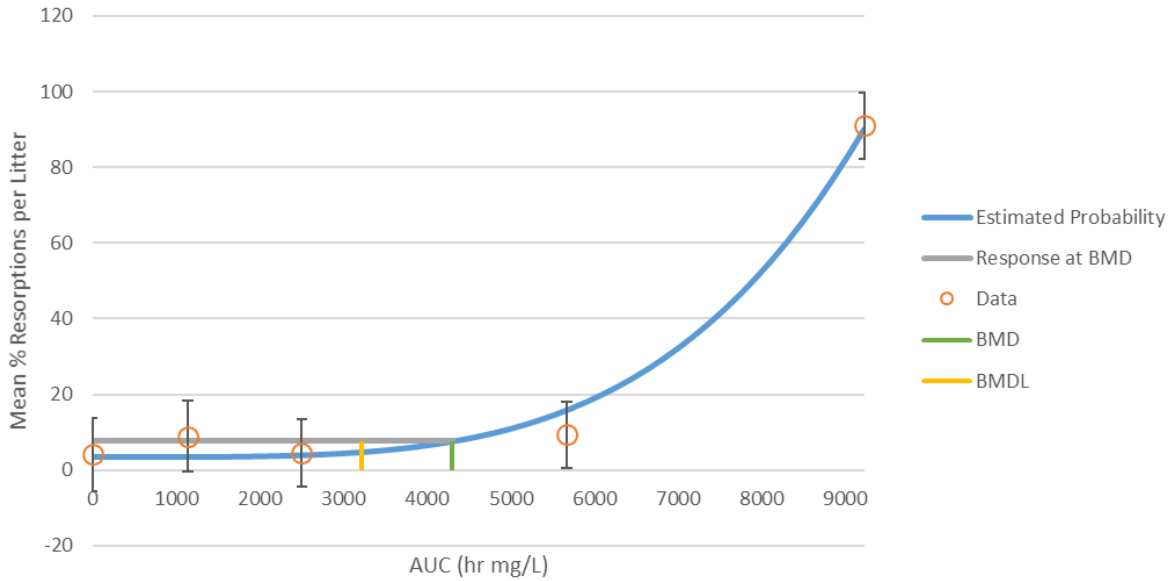


Figure 2.2-1 Plot of Response by Dose, with Fitted Curve for Selected Polynomial Degree 4 Model for Resorptions (Mean % per Litter) in Rats Exposed to NMP via Gavage (Saillenfait et al. (2002))
BMR = 1% AD for the BMD and 0.95 lower confident limit for the BMDL; all SDs set to the maximum SD across the groups

USER INPUT

Info	
Model	frequentist Polynomial degree 4 v1.1
Dose-Response Model	M[dose] = g + b1*dose + b2*dose^2 + ...
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Abs. Dev.
BMRF	1
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	AUC (hr mg/L)
Independent Variable	Mean % Resorptions per litter
Total # of Observations	5
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	4306.996436
BMDL	3221.529462
BMDU	Infinity
AIC	1049.477283
Test 4 P-value	0.417027552
D.O.F.	4

Model Parameters	
# of Parameters	6
Variable	Estimate
g	3.561301059
b1	Bounded
b2	Bounded
b3	Bounded
b4	Bounded
alpha	444.8896007

Goodness of Fit

Dose	Size	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	21	4.1	21.09240623	21.2	21.2	0.117038741
1144	22	8.9	21.09240623	21.2	21.2	1.182653022
2503	24	4.5	21.09240623	21.2	21.2	0.109405041
5674	25	9.4	21.09240623	21.2	21.2	-1.543357153
9231	25	91	21.09240623	21.2	21.2	0.219466033

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-520.7789555	6	1053.557911
A2	-520.7786645	10	1061.557329
A3	-520.7789555	6	1053.557911
fitted	-522.7386417	2	1049.477283
R	-598.5686115	2	1201.137223

* Includes additive constant of -107.51581. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	155.5798939	8	<0.0001
2	0.000581864	4	0.999999958
3	0.000581864	4	0.999999958
4	3.919372507	4	0.417027552

2.3 Resorptions: Results for Saillenfait et al. (2003) using C_{max}

Table 2-11 Model Predictions for Resorptions (Mean % per Litter) in Rats Exposed to NMP via Gavage Using C_{max} as the Dose Metric (Saillenfait et al. (2003))

BMR = 1% Absolute Deviation (AD)

Model [a]	Goodness of fit		BMD (mg/L)	BMDL (mg/L)	BMDU (mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.213813	699.611	21.11962	12.83895	Infinity	The Linear model was selected based on lowest AIC.
Exponential 3	0.213813	699.611	21.12014	12.83898	Infinity	
Exponential 4	0.209689	700.099	2.947766	0.432368[c]	Infinity	
Exponential 5	NA	701.204	13.80411	0	31.64662	
Hill	NA	701.204	14.48207	5.265227	41.21115	
Polynomial 4°	--	--	--	--	--	
Polynomial 3°	0.250824	699.291	13.97376	6.300609	Infinity	
Polynomial 2°	0.250824	699.291	13.9729	6.30061	Infinity	
Power	0.250824	699.291	13.97397	6.300571	Infinity	
Linear [b]	**0.250824**	**699.291**	**13.97378**	**6.300621**	**Infinity**	

[a] No variance model fit this dataset using reported SD values (BMDS Test 2 and 3 p-values < 0.0001). Results for constant variance model are shown.
[b] Model selection based on lowest AIC from adequately fitting models.
[c] Model is considered to be of questionable relevance as the estimated BMDL is substantially > 10 below lowest dose.

Table 2-12 Model Predictions for Resorptions (Mean % per Litter) in Rats Exposed to NMP via Gavage Using C_{max} as the Dose Metric (Saillenfait et al. (2003))

BMR = 1% Absolute Deviation (AD); minimum SD among groups used for all groups in analysis

Model [a]	Goodness of fit		BMD (mg/L)	BMDL (mg/L)	BMDU (mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	<0.0001	515.375	21.12172	16.46037	34.91679	No model adequately fit the mean response data.
Exponential 3	<0.0001	515.375	21.12172	16.46037	34.91678	
Exponential 4	<0.0001	504.624	2.948015	1.542205	6.039347	
Exponential 5	NA	498.236	13.73017	8.170257	24.87779	
Hill	0.008742	496.236	14.501	13.66569	22.98806	
Polynomial 4°	--	--	--	--	--	
Polynomial 3°	<0.0001	512.813	13.97417	9.791243	24.39673	
Polynomial 2°	<0.0001	512.813	13.97452	9.791353	24.39666	
Power	<0.0001	512.813	13.97453	9.791287	24.39600	
Linear	<0.0001	512.813	13.97459	9.791277	24.39678	

[a] No model adequately fit the means of this dataset using the 3.7 minimum SD value for all dose groups (BMDS Test 4 < 0.1). No variance model fit this dataset using reported SD values (BMDS Test 2 and 3 p-values < 0.0001). Results for constant variance model are shown.

Table 2-13 Model Predictions for Resorptions (Mean % per Litter) in Rats Exposed to NMP via Gavage Using C_{max} as the Dose Metric (Saillenfait et al. (2003))

BMR = 1% Absolute Deviation (AD); maximum SD among groups used for all groups in analysis

Model [a]	Goodness of fit		BMD (mg/L)	BMDL (mg/L)	BMDU (mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.637063	807.997	21.11877	10.41853	Infinity	The Linear model was selected based on lowest AIC.
Exponential 3	0.637063	807.997	21.11949	10.41858	Infinity	
Exponential 4	0.498954	809.552	2.947133	0.32408 [c]	Infinity	
Exponential 5	NA	811.292	13.61688	0	Infinity	
Hill	NA	811.291	14.50418	4.648527	Infinity	
Polynomial 4°	--	--	--	--	--	
Polynomial 3°	0.667837	807.902	13.97068	4.310606	Infinity	
Polynomial 2°	0.667837	807.902	13.95906	4.3106	Infinity	
Power	0.667837	807.902	13.97127	4.332837	Infinity	
Linear [b]	**0.667837**	**807.902**	**13.96877**	**4.310579 [d]**	**Infinity**	

[a] Results for constant variance model are shown. SD set to maximum value of 22.3 for all dose groups.
[b] Model selection based on lowest AIC from adequately fitting models.
[c] Model is considered to be of questionable relevance as the estimated BMDL is substantially > 10 below lowest dose.
[d] $BMDL1_{AD}$ selection for this dataset (bolded) based on lowest BMDL from selected models for each SD approach (Tables a-c) for this BMR type. Selected models in bold; scaled residuals for selected Linear model for doses 0, 15, 30, and 62 mg/L were -0.2719, -0.1407, 0.7839 and -0.3091, respectively.

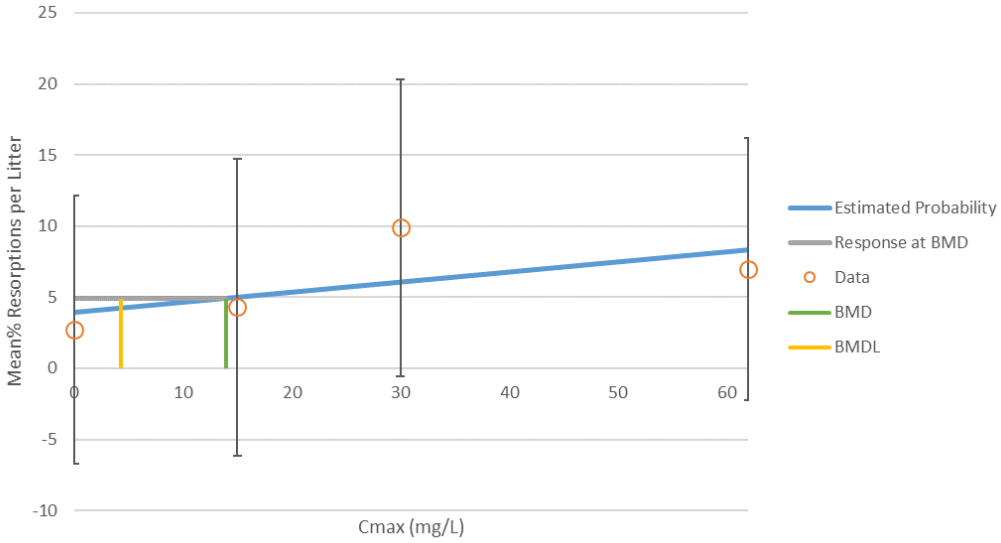


Figure 2.3-1 Plot of Response by Dose, with Fitted Curve for Selected Linear Model for Resorptions (Mean % per Litter) in Rats Exposed to NMP via inhalation (Saillenfait et al. (2003))
BMR = 1% AD; all SDs set to the maximum SD across the groups

USER INPUT

Info	
Model	frequentist Linear v1.1
Dose-Response Model	M[dose] = g + b1*dose
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Abs. Dev.
BMRF	1
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	C_{max} (mg/L)
Independent Variable	Mean% Resorptions per litter
Total # of Observations	4
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	13.96877456
BMDL	4.310579039
BMDU	Infinity
AIC	807.9022344
Test 4 P-value	0.667837175
D.O.F.	2

Model Parameters	
# of Parameters	4
Variable	Estimate
g	3.914947346
beta1	0.071588238
alpha	479.2687721

Goodness of Fit						
Dose	Size	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	24	2.7	21.892208	22.3	22.3	-0.271877653
15	20	4.3	21.892208	22.3	22.3	-0.140701988
30	20	9.9	21.892208	22.3	22.3	0.783904443
62	25	7	21.892208	22.3	22.3	-0.309109551

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-400.5474063	5	811.094813
A2	-400.5468877	8	817.093775
A3	-400.5474063	5	811.094813
fitted	-400.9511172	3	807.902234
R	-401.2235829	2	806.447166

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	1.353390341	6	0.96863225
2	0.001037257	3	0.99999112
3	0.001037257	3	0.99999112
4	0.807421769	2	0.66783718

2.4 Resorptions: Results for Saillenfait et al. (2003) using AUC

Table 2-14 Model Predictions for Resorptions (Mean % per Litter) in Rats Exposed to NMP via Gavage Using AUC as the Dose Metric (Saillenfait et al. (2003))

BMR = 1% Absolute Deviation (AD)

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.211980	699.6287	227.9498	137.8811	Infinity	The Linear model was selected based on lowest AIC.
Exponential 3	0.211980	699.628	227.9498	137.8820	Infinity	
Exponential 4	0.212197	700.082	30.916	4.641077[c]	Infinity	
Exponential 5	NA	701.204	151.6068	0	509.9996	
Hill	NA	701.205	149.9484	38.47086	519.3482	
Polynomial 4°	--	--	--	--	--	
Polynomial 3°	0.248246	699.312	151.1512	67.92561	Infinity	
Polynomial 2°	0.248246	699.312	151.2107	67.92571	Infinity	
Power	0.248246	699.312	151.2246	67.92488	Infinity	
Linear [b]	**0.248246**	**699.312**	**151.1247**	**67.92584**	**Infinity**	

[a] No variance model fit this dataset using reported SD values (BMDS Test 2 and 3 p-values < 0.0001). Results for constant variance model are shown.
[b] Model selection based on lowest AIC from adequately fitting models.
[c] Model is considered to be of questionable relevance as the estimated BMDL is substantially > 10 below lowest dose.

Table 2-15 Model Predictions for Resorptions (Mean % per Litter) in Rats Exposed to NMP via Gavage Using AUC as the Dose Metric (Saillenfait et al. (2003))

BMR = 1% Absolute Deviation (AD); minimum SD among groups used for all groups in analysis

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	<0.0001	515.511	227.8383	177.0871	379.0394	No model adequately fit the mean response data.
Exponential 3	<0.0001	515.511	227.8254	177.0872	379.0402	
Exponential 4	0.000102	504.469	30.91629	16.28533	63.04971	
Exponential 5	0.008743	496.236	151.6093	83.69496	274.3896	
Hill	0.008744	496.236	150.9994	140.9521	243.9417	
Polynomial 4°	--	--	--	--	--	
Polynomial 3°	<0.0001	512.980	151.1449	105.6824	265.1396	
Polynomial 2°	<0.0001	512.980	151.1439	105.6817	265.1420	
Power	<0.0001	512.980	151.1268	105.6816	265.1342	
Linear	<0.0001	512.980	151.1255	105.6819	265.1440	

[a] No model adequately fit the means of this dataset using the 3.7 minimum SD value for all dose groups (BMDS Test 4 < 0.1). No variance model fit this dataset using reported SD values (BMDS Test 2 and 3 p-values < 0.0001). Results for constant variance model are shown.

Table 2-16 Model Predictions for Resorptions (Mean % per Litter) in Rats Exposed to NMP via Gavage Using AUC as the Dose Metric (Saillenfait et al. (2003))

BMR = 1% Absolute Deviation (AD); maximum SD among groups used for all groups in analysis

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.635442	808.002	227.8262	111.7975	Infinity	The Polynomial 3 model was selected based on lowest AIC.
Exponential 3	0.635442	808.002	227.8273	111.7974	Infinity	
Exponential 4	0.501532	809.547	30.91004	3.47685 [c]	Infinity	
Exponential 5	NA	811.291	151.6049	0	Infinity	
Hill	NA	811.293	147.7947	0	Infinity	
Polynomial 4°	--	--	--	--	--	
Polynomial 3° [b]	**0.665804**	**807.908**	**151.1354**	**46.43517 [d]**	**Infinity**	
Polynomial 2°	0.665803	807.908	151.1375	46.43597	Infinity	
Power	0.665803	807.908	151.1461	46.62033	Infinity	
Linear	0.665803	807.908	151.1459	46.43533	Infinity	

[a] Results for constant variance model are shown. SD set to maximum value of 22.3 for all dose groups.
[b] Model selection based on lowest AIC from adequately fitting models.
[c] Model is considered to be of questionable relevance as the estimated BMDL is substantially > 10 below lowest dose.
[d] $BMDL1_{AD}$ selection for this dataset (bolded) based on lowest BMDL from selected models for each SD approach (Tables a-c) for this BMR type. Scaled residuals for selected Poly 3 model for doses 0, 156.5, 319 and 660.8 hr mg/L were -0.2781, -0.1382, 0.7866 and -0.3075, respectively.

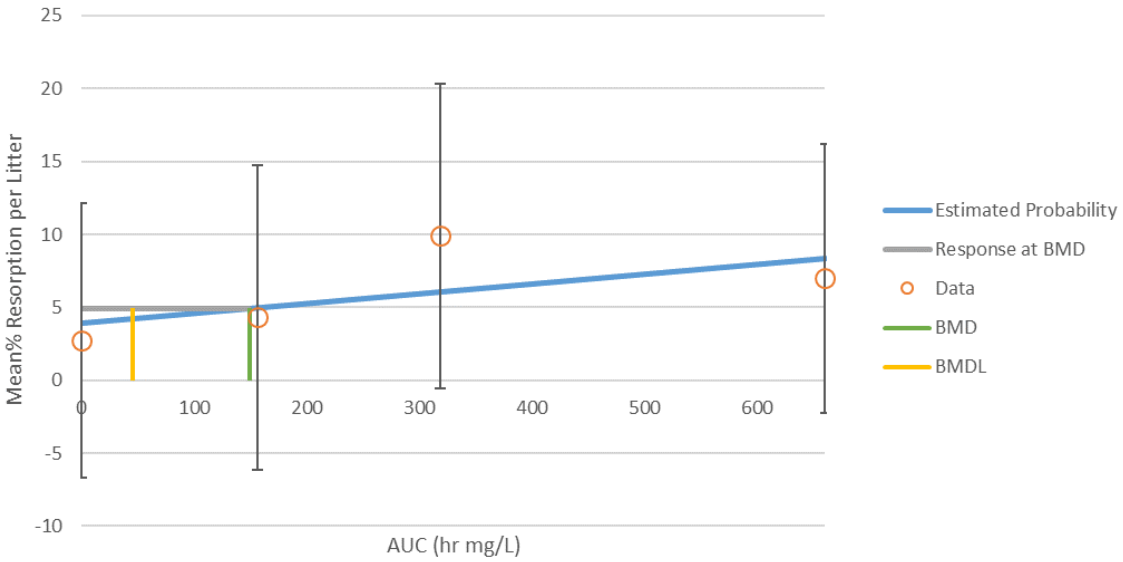


Figure 2.4-1 Plot of Response by Dose, with Fitted Curve for Polynomial Degree 3 Model for Resorptions (Mean % per Litter) in Rats Exposed to NMP via inhalation (Saillenfait et al. (2003))
BMR = 1% AD; all SDs set to the maximum SD across the groups

USER INPUT

Info	
Model	frequentist Polynomial degree 3 v1.1
Dose-Response Model	M[dose] = g + b1*dose + b2*dose^2 + ...
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Abs. Dev.
BMRF	1
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	AUC (hr mg/L)
Independent Variable	Mean% Resorptions per Litter
Total # of Observations	4
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	151.1354168
BMDL	46.43517436
BMDU	Infinity
AIC	807.9083341
Test 4 P-value	0.665803491
D.O.F.	2

Model Parameters	
# of Parameters	4
Variable	Estimate
g	3.942998221
b1	0.006616582
b2	Bounded
b3	Bounded
alpha	479.3001679

Goodness of Fit						
Dose	Size	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	24	2.7	21.8929251	22.3	22.3	-0.278145692
156.5	20	4.3	21.8929251	22.3	22.3	-0.138192477
319	20	9.9	21.8929251	22.3	22.3	0.786644232
660.8	25	7	21.8929251	22.3	22.3	-0.307481493

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-400.5474063	5	811.094813
A2	-400.5468877	8	817.093775
A3	-400.5474063	5	811.094813
fitted	-400.954167	3	807.9083341
R	-401.2235829	2	806.447166

* Includes additive constant of -81.78553. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	1.353390341	6	0.96863225
2	0.001037257	3	0.99999112
3	0.001037257	3	0.99999112
4	0.813521422	2	0.665803491

2.5 Post-implantation Losses: Results for Saillenfait et al. (2002) using C_{max}

Table 2-17 Model Predictions for Post-implantation Losses (Resorptions and Fetal Mortality) in Rats Exposed to NMP via Gavage Using C_{max} as the Dose Metric (Saillenfait et al. (2002))
BMR = 1% Relative Deviation (RD)

Model	Goodness of fit		BMD (mg/L)	BMDL (mg/L)	BMDU (mg/L)	Basis for model selection
	P-value	AIC				
Dichotomous Hill	0.1572321	292.17137	455.2478	410.9323	521.50995	The Log-Probit model is selected based on lowest AIC.
Gamma	0.0026842	302.78107	370.8095	351.7727	390.48307	
Log-Logistic	0.3677639	290.17137	455.2251	410.9016	521.51172	
Multistage 4°	<0.0001	315.70804	237.824	156.5285	252.46991	
Multistage 3°	<0.0001	334.71559	171.2772	123.605	184.79851	
Multistage 2°	<0.0001	361.93988	92.36062	71.96177	103.27055	
Multistage 1° (Quantal	<0.0001	405.75225	17.6278	14.49097	21.907659	
Weibull	0.3666823	290.17729	426.3443	365.4222	519.08535	
Logistic	<0.0001	339.80554	86.68156	65.90755	114.83487	
Log-Probit [a]	**0.367832**	**290.171**	**473.6389**	**437.3743**	**523.85736**	
Probit	<0.0001	351.11489	68.46759	52.41983	90.924229	

[a] Scaled residuals for selected Log-Probit model for doses 0, 120, 250, 531 and 831 mg/L were -0.5201, 1.192, -0.5560, 6.428E-08 and -6.292E-07, respectively.

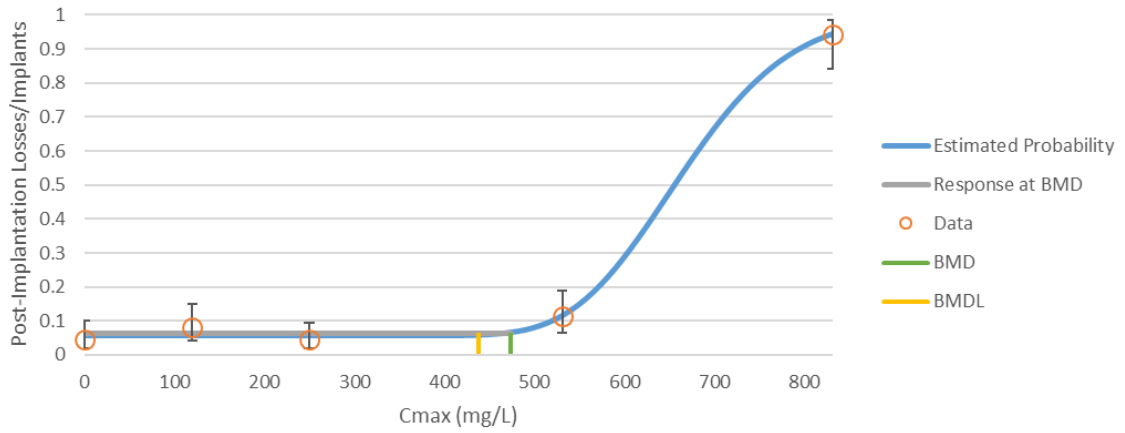


Figure 2.5-1 Plot of Response by Dose, with Fitted Curve for Selected Log-Probit Model for Post-implantation Loss in Rats Exposed to NMP via Gavage (Saillenfait et al. (2002))
BMR = 1% RD

USER INPUT

Info	
Model	frequentist Log-Probit v1.1
Dose-Response Model	P[dose] = g+(1-g) * CumNorm(a+b*Log(Dose))

Model Options	
Risk Type	Extra Risk
BMR	0.01
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	C_{max} (mg/L)
Independent Variable	Post-Implantation Loss
Total # of Observations	5

MODEL RESULTS

Benchmark Dose	
BMD	473.6389478
BMDL	437.3742789
BMDU	523.8573611
AIC	290.171
P-value	0.367832005
D.O.F.	2
Chi2	2.000257907

Model Parameters	
# of Parameters	4
Variable	Estimate
g	0.055381721
a	-44.95639542
b	6.919962006

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.055381721	7.432241273	6.05414704	134.2003	-0.520105
120	0.055381721	6.498562598	9.45162137	117.3413	1.1918875
250	0.055381721	8.493990027	6.91902519	153.3717	-0.556015
531	0.114285712	13.87709518	13.8770954	121.4246	6.428E-08
831	0.944347845	53.86959138	53.8695903	57.04423	-6.29E-07

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P-value
Full Model	-141.1497769	5	-	-	-
Fitted Model	-142.0855	3	1.87144618	2	0.3923021
Reduced Model	-251.1748556	1	220.050157	4	<0.0001

2.6 Post-implantation Losses: Results for Saillenfait et al. (2002) using AUC

Table 2-18 Model Predictions for Post-implantation Losses (Resorptions and Fetal Mortality) in Rats Exposed to NMP via Gavage Using AUC as the Dose Metric (Saillenfait et al. (2002))
BMR = 1% Relative Deviation (RD)

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	P-value	AIC				
Dichotomous Hill	0.157272	292.17101	5035.17	4290.223	Infinity	The Log-Probit model is selected based on lowest AIC.
Gamma	0.0117941	298.7412725	4025.695	3809.819	4246.349	
Log-Logistic	0.3677636	290.17138	4799.243	4292.557	5568.1149	
Multistage 4°	0.0001122	310.60220	2589.069	1673.568	2750.7374	
Multistage 3°	<0.0001	329.10985	1854.91	1328.066	2002.4376	
Multistage 2°	<0.0001	356.41697	991.3199	767.9789	1109.1373	
Multistage 1° (Quantal	<0.0001	400.78140	184.3376	151.5097	229.07485	
Weibull	0.3667049	290.17731	4468.994	3782.108	5537.3985	
Logistic	<0.0001	335.28734	892.2392	682.6192	1177.6672	
Log-Probit [a]	**0.3678321**	**290.171**	**5010.495**	**4592.073**	**5591.3344**	
Probit	<0.0001	346.05448	706.5968	544.8604	933.0203	

[a] Scaled residuals for selected Log-Probit model for doses 0, 1144, 2503, 5674 and 9231 hr mg/L were -0.5201, 1.192, -0.5560, 1.958E-05 and -1.140E-05, respectively.

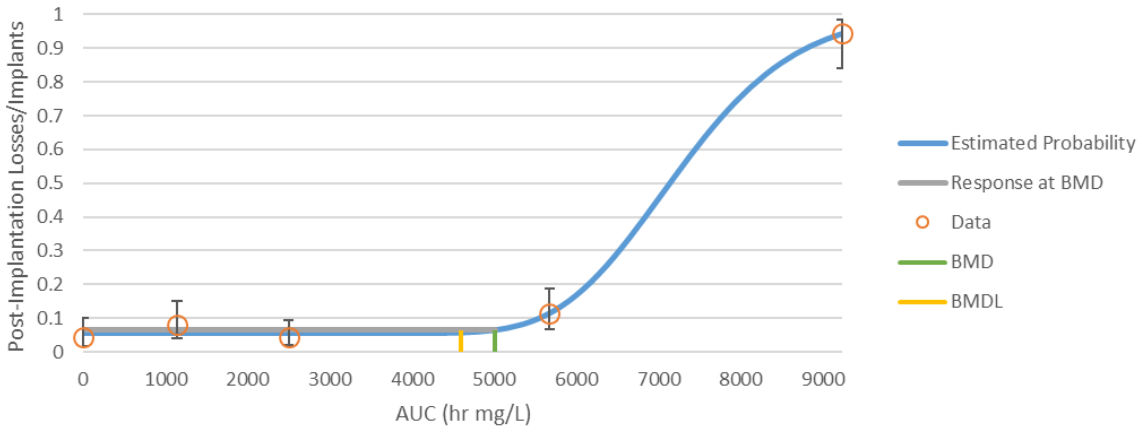


Figure 2.6-1 Plot of Response by Dose, with Fitted Curve for Selected Log-Probit Model for Post-implantation Loss in Rats Exposed to NMP via Gavage (Saillenfait et al. (2002))
BMR = 1% RD

USER INPUT

Info	
Model	frequentist Log-Probit v1.1
Dose-Response Model	P[dose] = g+(1-g) * CumNorm(a+b*Log(Dose))

Model Options	
Risk Type	Extra Risk
BMR	0.01
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	AUC (hr mg/L)
Independent Variable	Post-Implantation Loss
Total # of Observations	5

MODEL RESULTS

Benchmark Dose	
BMD	5010.494649
BMDL	4592.073168
BMDU	5591.334418
AIC	290.171
P-value	0.367832091
D.O.F.	2
Chi2	2.000257437

Model Parameters	
# of Parameters	4
Variable	Estimate
g	0.055381734
a	-56.59546142
b	6.370145171

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.055381734	7.432243129	6.05414704	134.2003	-0.520105
1145	0.055381734	6.498564221	9.45162137	117.3413	1.1918867
2504	0.055381734	8.493992148	6.91902519	153.3717	-0.556016
5673	0.114285641	13.87708647	13.8770954	121.4246	2.548E-06
9228	0.944348009	53.86960073	53.8695903	57.04423	-6.03E-06

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P-value
Full Model	-141.1497769	5	-	-	-
Fitted Model	-142.0855	3	1.87144618	2	0.3923021
Reduced Model	-251.1748556	1	220.050157	4	<0.0001

2.7 Post-implantation Losses: Results for Saillenfait et al. (2003) using C_{max}

Table 2-19 Model Predictions for Post-implantation Losses (Resorptions and Fetal Mortality) in Rats Exposed to NMP via Inhalation Using C_{max} as the Dose Metric (Saillenfait et al. (2003))
BMR = 1% Relative Deviation (RD)

Model [a]	Goodness of fit		BMD (mg/L)	BMDL (mg/L)	BMDU (mg/L)	Basis for model selection
	P-value	AIC				
Dichotomous Hill	0.7370213	230.47434	2.175642	0	85.665865	The Log-Logistic model is selected based on lowest AIC.
Gamma	0.6213002	229.26394	13.68791	6.54628	Infinity	
Log-Logistic [a]	**0.6269402**	**229.24610**	**13.37256**	**6.275856**	**Infinity**	
Multistage 3°	0.6213117	229.26394	13.68903	6.545976	Infinity	
Multistage 2°	0.6213117	229.26394	13.68903	6.545497	Infinity	
Multistage 1° (Quantal	0.6213133	229.26394	13.68924	6.545934	Infinity	
Weibull	0.6213117	229.26394	13.68904	6.546292	Infinity	
Logistic	0.5383909	229.56539	19.87295	12.25974	Infinity	
Log-Probit	0.774706	230.44280	0.192445	0	Infinity	
Probit	0.5484738	229.52492	18.94939	11.37275	Infinity	

[a] Scaled residuals for selected Log-Logistic model for doses 0, 15, 30 and 62 mg/L were -0.4312, 0.8051, 0.08788 and -0.3033, respectively.

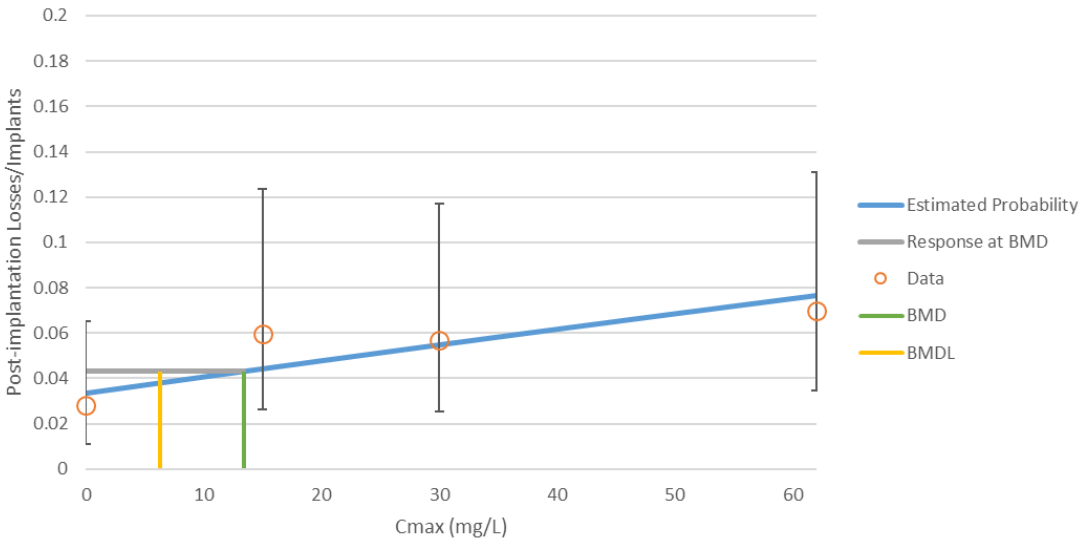


Figure 2.7-1 Post-Implantation Loss (Incidence) vs. C_{max} (Saillenfait et al. (2003)) - Log-Logistic Model with BMR of 1% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
BMR = 1% RD

USER INPUT

Info	
Model	frequentist Log-Logistic v1.1
Dose-Response Model	P[dose] = g+(1-g)/[1+exp(-a-b*Log(dose))]

Model Options	
Risk Type	Extra Risk
BMR	0.01
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	C_{max} (mg/L)
Independent Variable	Post-Implantation Loss
Total # of Observations	4

MODEL RESULTS

Benchmark Dose	
BMD	13.37255834
BMDL	6.275856421
BMDU	Infinity
AIC	229.2461007
P-value	0.626940156
D.O.F.	2
Chi2	0.933808377

Model Parameters	
# of Parameters	4
Variable	Estimate
g	0.033531344
a	-7.188324572
b	Bounded

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.033531344	6.536681453	5.45293497	194.9424	-0.431177
15	0.044359046	5.178190759	6.96916961	116.7336	0.8051078
30	0.054946823	6.870674643	7.09459598	125.0423	0.0878755
62	0.076768071	10.21092153	9.27976787	133.01	-0.303273

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P-value
Full Model	-112.1799236	4	-	-	-
Fitted Model	-112.6230503	2	0.88625345	2	0.6420258
Reduced Model	-114.0109142	1	3.66198111	3	0.3003533

2.8 Post-implantation Losses: Results for Saillenfait et al. (2003) using AUC

Table 2-20 Model Predictions for Post-implantation Losses (Resorptions and Fetal Mortality) in Rats Exposed to NMP via Inhalation Using AUC as the Dose Metric (Saillenfait et al. (2003))
BMR = 1% Relative Deviation (RD)

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	P-value	AIC				
Dichotomous Hill	0.735317008	230.4759003	22.2922271	0	921.8672575	The Log-Logistic model is selected based on lowest AIC.
Gamma	0.611906143	229.2931847	147.6424963	70.26024961	Infinity	
Log-Logistic [a]	**0.617393517**	**229.275429**	**144.2205252**	**67.33913159**	**Infinity**	
Multistage 3°	0.611906294	229.2931847	147.641914	70.25803339	Infinity	
Multistage 2°	0.611906294	229.2931847	147.6420727	70.25444987	Infinity	
Multistage 1° (Quantal	0.611916694	229.2931847	147.6569874	70.25519203	Infinity	
Weibull	0.611906298	229.2931847	147.6419509	70.25999005	Infinity	
Logistic	0.531714218	229.590634	214.0066138	131.5210445	Infinity	
Log-Probit	0.773895796	230.4434248	1.807927221	0	Infinity	
Probit	0.541437038	229.5508735	204.1141883	122.0150256	Infinity	

[a] Scaled residuals for selected Log-Logistic model for doses 0, 156.5, 319 and 660.8 mg/L were -0.445, 0.816, 0.0951 and -0.3031, respectively.

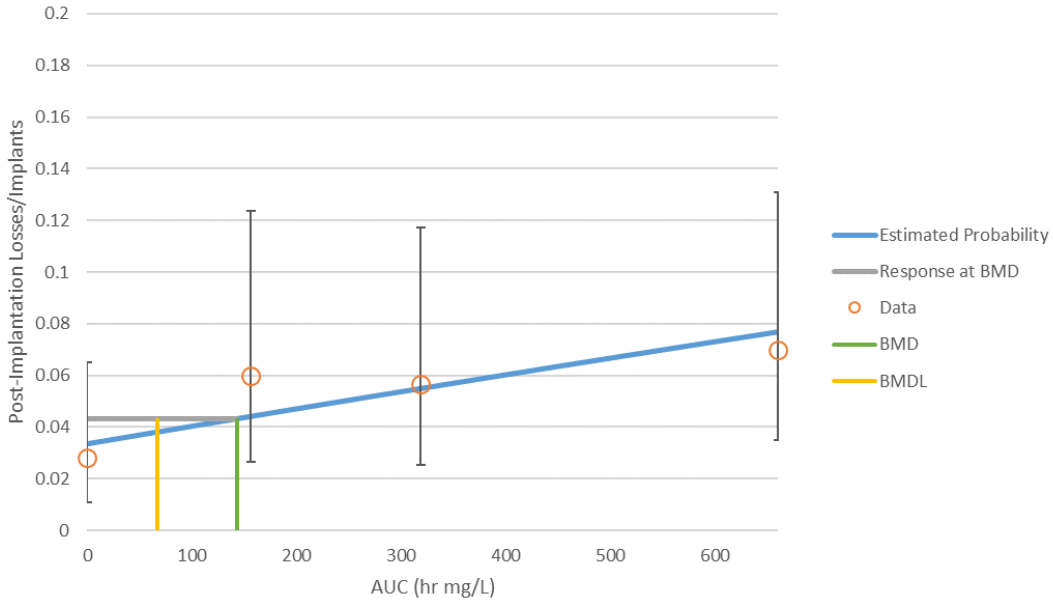


Figure 2.8-1 Post-Implantation Loss (Incidence) vs. AUC (Saillenfait et al. (2003)) - Log-Logistic Model with BMR of 1% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
BMR = 1% RD

USER INPUT

Info	
Model	frequentist Log-Logistic v1.1
Dose-Response Model	P[dose] = g+(1-g)/[1+exp(-a-b*Log(dose))]

Model Options	
Risk Type	Extra Risk
BMR	0.01
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	AUC (hr mg/L)
Independent Variable	Post-Implantation Loss
Total # of Observations	4

MODEL RESULTS

Benchmark Dose	
BMD	144.2205252
BMDL	67.33913159
BMDU	Infinity
AIC	229.275429
P-value	0.617393517
D.O.F.	2
Chi2	0.964497336

Model Parameters	
# of Parameters	4
Variable	Estimate
g	0.033730478
a	-9.566463403
b	Bounded

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.033730478	6.575501106	5.45293497	194.9424	-0.445347
156.5	0.044187105	5.158119485	6.96916961	116.7336	0.8156396
319	0.054802059	6.852573038	7.09459598	125.0423	0.0950973
660.8	0.076763207	10.21027468	9.27976787	133.01	-0.303071

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-112.1799236	4	-	-	-
Fitted Model	-112.6377145	2	0.915581768	2	0.632679766
Reduced Model	-114.0109142	1	3.66198111	3	0.3003533

2.9 Post-implantation Losses: Results for Saillenfait et al. (2003; 2002) combined using C_{max}

Table 2-21 Model Predictions for Post-implantation Losses (Resorptions and Fetal Mortality) in Rats Exposed to NMP via Gavage or Inhalation Using C_{max} as the Dose Metric (Saillenfait et al. (2003; 2002))

BMR = 1% Relative Deviation (RD)

Model [a]	Goodness of fit		BMD (mg/L)	BMDL (mg/L)	BMDU (mg/L)	Basis for model selection
	P-value	AIC				
Dichotomous Hill	0.2853	520.3039	453.0362	409.9375	507.9537	BMDL estimates from adequately fitting models are sufficiently close (within 3-fold). Per EPA BMD Technical Guidance endpoints (U.S. EPA (2012)), the Log-Probit model is selected based on it resulting in the lowest AIC from among appropriate and adequately fitting models.
Gamma	0.00901	530.8042	370.8499	351.8593	390.4129	
Log-Logistic	0.4135	518.3039	452.829	409.7989	507.9488	
Multistage Degree 7 [b]	0.3437	518.0253	377.3410	113.1514	393.1504	
Multistage Degree 6	0.09912	522.4614	338.3081	142.9029	353.8167	
Multistage Degree 5	0.00771	530.7404	292.7263	160.1728	307.7792	
Multistage Degree 4	0.0001	543.8711	238.1524	153.6198	252.7783	
Multistage Degree 3	<0.0001	563.1458	171.9726	122.7886	185.5231	
Multistage Degree 2	<0.0001	590.8305	93.54928	71.63636	104.6315	
Multistage Degree 1	<0.0001	631.9849	17.7798	14.59179	22.1200	
Weibull	0.4129	518.3090	422.892	364.4164	500.5706	
Logistic	<0.0001	576.8098	58.3057	49.52224	69.1827	
Log-Probit	**0.4136**	**518.3036**	**471.6574**	**436.584**	**514.4843**	
Probit	<0.0001	586.5139	47.8555	40.97493	56.2891	

[a] Scaled residuals for selected Log-Probit model for doses 0, 15, 30, 62, 120, 250, 531, and 831 mg/L were -1.43, 0.35, 0.21, 0.89, 1.36, -0.41, -0.003, and 0.003, respectively.

[b] The analysis of the eight dose groups associated with the combined dose response data from the two Saillenfait et al. studies (2003; 2002) presents a unique situation for the Multistage model that requires consideration. The default number of Multistage model degrees run in BMDS 3.1.2 is n-1, where n is the number of dose-groups in the dataset. Thus, in this case, the 1st degree through 7th degree Multistage models were run. Consideration needs to be given as to whether that many Multistage degrees are necessary and appropriate for the dataset being evaluated. Of the Multistage models, the 7th degree Multistage provides an adequate fit to the data that is similar to the model fit achieved by some non-Multistage models, but its BMDL estimate is nearly 4-fold lower. The Multistage degree 7 BMDL is lower because it contains several extra parameters (βeta coefficients for degrees 1 through 6). These parameters contribute to the BMDL estimation but are restricted at the 0 boundary criteria for the purposes of the maximum likelihood, BMD estimation. Thus, while the BMD estimates (377 mg/L C_{max}) of the 7th degree Multistage model are similar to adequately fitting non-Multistage models (423-472 mg/L C_{max}), its BMDL estimates are nearly 4-fold lower (113 mg/L C_{max} versus 364-437 mg/L C_{max} for non-Multistage models). Hence, it appears that the extra parameters in the higher degree Multistage models are solely driving the derivation of the lower BMDLs for these models. In situations where BMDLs vary substantially (*i.e.*, >3-fold), EPA BMD Technical Guidance (U.S. EPA (2012)) states that "expert statistical judgment may help at this point to judge whether model uncertainty is too great to rely on some or all of the results." In this case, given that trend tests of the combined dataset indicate a lack of linear dose-response trend in the low dose region up to and including 531 mg/L C_{max}, EPA's judgment is that the Multistage 7 model is not appropriate for the derivation of a BMDL from this dataset, despite its adequate statistical fit (p-value > 0.1) to the data.

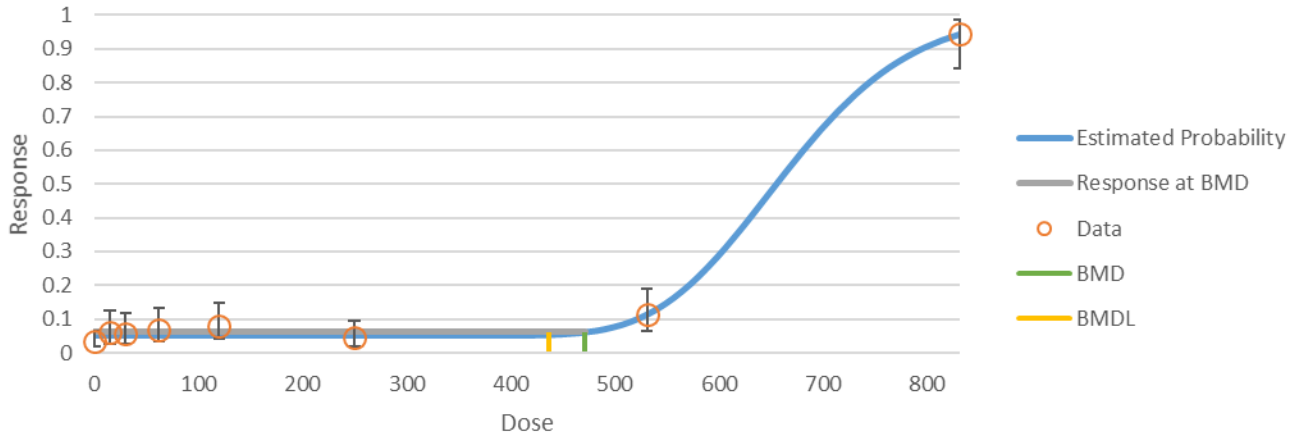


Figure 2.9-1 Plot of Response by Dose, with Fitted Curve for Selected Log-Probit Model for Post-implantation Loss in Rats Exposed to NMP via Gavage or Inhalation (Saillenfait et al. (2003; 2002))

BMR = 1% RD; Dose shown is C_{max} in units of mg/L

USER INPUT

Info	
Model	frequentist Log-Probit v1.1
Dose-Response Model	P[dose] = g+(1-g) * CumNorm(a+b*Log(Dose))

Model Options	
Risk Type	Extra Risk
BMR	0.01
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	C_{max} (mg/L)
Independent Variable	Post-Implantation Loss
Total # of Observations	8

MODEL RESULTS

Benchmark Dose	
BMD	471.6573999
BMDL	436.5840183
BMDU	514.484334
AIC	518.3035838
P-value	0.413581098
D.O.F.	5
Chi2	5.018874228

Model Parameters	
# of Parameters	3
Variable	Estimate
g	0.052551843
a	-44.61801666
b	6.869709488

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.052551843	17.29705468	11.50708201	329.1426844	-1.430252
15	0.052551843	6.134565349	6.96916961	116.7336	0.3461872
30	0.052551843	6.57120091	7.09459598	125.0423	0.2097633
62	0.052551843	6.989920959	9.27976787	133.01	0.8898004
120	0.052551843	6.166501106	9.45162137	117.3413	1.3591085
250	0.052551843	8.059966818	6.91902519	153.3717	-0.412875
531	0.11436183	13.88633778	13.8770954	121.4246	-0.002635
831	0.944242254	53.86356803	53.8695903	57.04423	0.003475

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-253.6691293	8	-	-	-
Fitted Model	-256.1517919	3	4.965325251	5	0.420126602
Reduced Model	-382.8277672	1	258.317276	8	<0.0001

2.10 Post-implantation Losses: Results for Saillenfait et al. (2003; 2002) combined using AUC

Table 2-22 Model Predictions for Post-implantation Losses (Resorptions and Fetal Mortality) in Rats Exposed to NMP via Gavage or Inhalation Using AUC as the Dose Metric (Saillenfait et al. (2003; 2002))

BMR = 1% Relative Deviation (RD)

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	P-value	AIC				
Dichotomous Hill	0.2853866	520.3036	4981.221	4279.555	Infinity	The Log-Probit model is selected based on it resulting in the lowest AIC from among appropriate and adequately fitting models.
Gamma	0.0306728	526.7632	4025.814	3810.557	4244.9365	
Log-Logistic	0.4134005	518.3039	4771.014	4283.133	5408.5029	
Multistage Degree 7 [b]	0.4748693	516.7767	4153.835	1001.527	4333.9282	
Multistage Degree 6	0.2155793	519.7480	3710.335	1364.709	3884.9435	
Multistage Degree 5	0.0280884	526.6318	3198.668	1634.376	3366.2372	
Multistage Degree 4	0.000571	538.7165114	2591.817	1622.292	2753.2022	
Multistage Degree 3	<0.0001	557.4245223	1860.889	1309.782	2008.5784	
Multistage Degree 2	<0.0001	585.0614255	1001.789	762.5566	1120.9533	
Multistage Degree 1	<0.0001	626.9736975	185.8796	152.5732	231.13825	
Weibull	0.4128887	518.3089987	4430.582	3768.154	5323.8529	
Logistic	<0.0001	571.0790154	621.6337	528.0541	737.29755	
Log-Probit	**0.4136068**	**518.3036**	**4988.572**	**4585.262**	**5483.0131**	
Probit	<0.0001	580.4845	509.6028	436.2995	599.34703	

[a] Scaled residuals for selected Log-Probit model for doses 0, 156.5, 319, 660.8, 1144, 2503, 5674, and 9231 mg/L were -1.43, 0.35, 0.21, 0.89, 1.36, -0.41, 1.7E-6, and -4.7E-6, respectively.

[b] The analysis of the eight dose groups associated with the combined dose response data from the two Saillenfait et al. studies (2003; 2002) presents a unique situation for the Multistage model that requires consideration. The default number of Multistage model degrees run in BMDS 3.1.2 is n-1, where n is the number of dose-groups in the dataset. Thus, in this case, the 1st degree through 7th degree Multistage models were run. Consideration needs to be given as to whether that many Multistage degrees are necessary and appropriate for the dataset being evaluated. Of the Multistage models, the 6th and 7th degree Multistage models provide an adequate fit to the data that is similar to the model fit achieved by some non-Multistage models, but BMDL estimates are 3- to 4-fold lower. The Multistage degree 6 and 7 BMDLs are lower because they contain several extra parameters (βeta coefficients for degrees 1 through 6). These parameters contribute to the BMDL estimation but are restricted at the 0 boundary criteria for the purposes of the maximum likelihood, BMD estimation. Thus, while the BMD estimates (3710 - 4154 hr mg/L AUC) of the 6th and 7th degree Multistage models are similar to adequately fitting non-Multistage models (4431 – 4989 hr mg/L AUC), BMDL estimates for Multistage models are 3- to 4-fold lower than non-Multistage models (1002 - 1365 hr mg/L AUC versus 3768 - 4585 mg/L AUC for non-Multistage models). Hence, it appears that the extra parameters in the higher degree Multistage models are solely driving the derivation of the lower BMDLs for these models. In situations where BMDLs vary substantially (*i.e.*, >3-fold), EPA BMD Technical Guidance (U.S. EPA (2012)) states that "expert statistical judgment may help at this point to judge whether model uncertainty is too great to rely on some or all of the results." In this case, given that trend tests of the combined dataset indicate a lack of linear dose-response trend in the low dose region, EPA's judgment is that the Multistage 6 and 7 models are not appropriate for the derivation of a BMDL from this dataset, despite the models adequate statistical fit (p-value > 0.1) to the data.

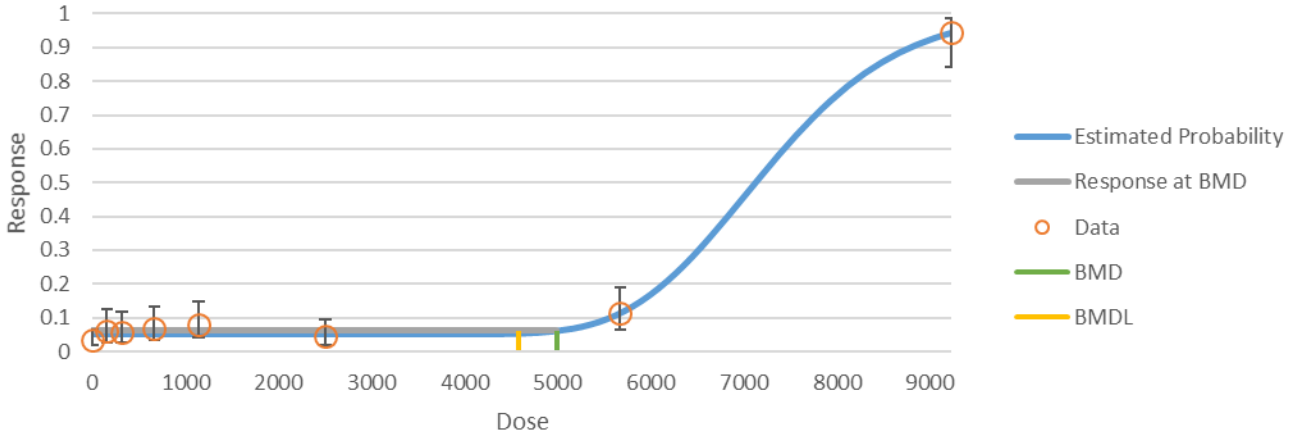


Figure 2.10-1 Plot of Response by Dose, with Fitted Curve for Selected Log-Probit Model for Post-implantation Loss in Rats Exposed to NMP via Gavage or Inhalation (Saillenfait et al. 2003; 2002))

BMR = 1% Relative Deviation; Dose shown is AUC in units of hr mg/L

USER INPUT

Info	
Model	frequentist Log-Probit v1.1
Dose-Response Model	P[dose] = g+(1-g) * CumNorm(a+b*Log(Dose))

Model Options	
Risk Type	Extra Risk
BMR	0.01
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	AUC (mg/L)
Independent Variable	Post-Implantation Loss
Total # of Observations	8

MODEL RESULTS

Benchmark Dose	
BMD	4988.571582
BMDL	4585.262231
BMDU	5483.013135
AIC	518.3035647
P-value	0.413606752
D.O.F.	5
Chi2	5.018663223

Model Parameters	
# of Parameters	8
Variable	Estimate
g	0.05255397
a	-56.20158759
b	6.327168701

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.05255397	17.29775491	11.50708201	329.1426844	-1.430398
156.5	0.05255397	6.134813689	6.96916961	116.7336	0.3460775
319	0.05255397	6.571466926	7.09459598	125.0423	0.2096527
660.8	0.05255397	6.990203926	9.27976787	133.01	0.8896734
1144	0.05255397	6.16675074	9.45162137	117.3413	1.3589793
2503	0.05255397	8.060293103	6.91902519	153.3717	-0.412986
5674	0.114285666	13.87708957	13.8770954	121.4246	1.666E-06
9231	0.944347968	53.86959837	53.8695903	57.04423	-4.67E-06

3 Benchmark Dose Modeling of Fetal and Pup Body Weight Changes

BMD modeling for fetal and pup body weight changes was performed using USEPA's BMD Software package version 3.1.2 (BMDS 3.1.2), in a manner consistent with BMD technical guidance (U.S. EPA (2012)).

The DuPont (1990), Becci et al. (1982), Saillenfait et al. (2002), and Saillenfait et al. (2003) studies were selected for dose-response analysis. Individual fetal and pup data were not available for these studies. Thus, the reported litter means and standard deviations (SDs) applying to the litter level data were modeled. The data tables in the source reports were not explicit about types of means presented for pup weight, however, the methods section of Saillenfait et al. (2003; 2002) indicated that analyses were performed on a per litter basis supporting modeling in this manner. Further details on the analysis method are provided in Appendix A.

The dose-response data for fetal weight change reported in the dermal study conducted by Becci et al. (1982) was not amenable to BMD modeling as mean body weight increased gradually from the control to the middle dose group and then decreased significantly at the high dose group (see Table 3-1). This dose-response pattern is essentially equivalent to one where only the highest dose has a response and thus the model estimates of the parameters and BMDs would not be reliable. Hence the NOAEL was used to derive a POD from the Becci et al. (1982) study.

EPA considered combing data from the Saillenfait et al. (2002) oral and Saillenfait et al. (2003) inhalation studies to provide a more extensive characterization of the dose-response curve across exposure routes. However, the Saillenfait et al. (2003) inhalation study observed a statistically significant decrease in fetal body weights at an internal dose that corresponds to an oral dose lower than the NOAEL in the Saillenfait et al. (2002) oral study. This implies that fetal body weights were more sensitive to inhalation exposures and this was not fully accounted for in the PBPK model. Therefore, datasets from the two studies were not combined for this endpoint.

Benchmark dose modeling was conducted using U.S. EPA BMD Software version 3.1.2 (BMDS 3.1.2) in accordance with EPA BMD Technical Guidance (U.S. EPA (2012)). Mean fetal and pup body weight was evaluated with standard continuous response models available in BMDS 3.1.2. Standard continuous models and model options used for evaluating mean fetal and pup body weight are listed below. Since adequate model fits to the mean were achieved for continuous models in all cases for the standard model suite, no non-standard modeling was conducted.

Standard Continuous BMDS 3.1.2 Models Applied to Mean Fetal Body Weight

- Exponential 2 (Exp2)-restricted
- Exponential 3 (Exp3)-restricted
- Exponential 4 (Exp4)-restricted
- Exponential 5 (Exp5)-restricted
- Hill (Hil)-restricted
- Polynomial Degree 4 (Ply4)-restricted
- Polynomial Degree 3 (Ply3)-restricted
- Polynomial Degree 2 (Ply2)-restricted
- Power (Pow)-restricted
- Linear (Lin)

Model Options Used for Continuous Response

- Benchmark Response (BMR): 5% Relative Deviation for Fetal Body Weight
- Response Distribution-Variance Assumptions
    - Normal Distribution-Constant Variance
    - Normal Distribution-Non-Constant Variance
    - Lognormal Distribution, which assumes Constant Variance (if normal distribution models do not fit means)
- Confidence Level: 0.95
- Background: Estimated

A BMR of 5% relative deviation (RD) from control mean was applied in modeling pup body weight changes under the assumption that it represents a minimal biologically significant response. In adults, a 10% decrease in body weight in animals is generally recognized as a biologically significant response associated with identifying a maximum tolerated dose. During development, however, identification of a smaller (5%) decrease in body weight is consistent with the assumptions that development represents a susceptible lifestage and that the developing animal is more adversely affected by a decrease in body weight than the adult. In humans, reduced birth weight is associated with numerous adverse health outcomes, including increased risk of infant mortality as well as heart disease and type II diabetes in adults (Barker (2007; Reyes and Mañalich (2005)). The selection of a 5% BMR is additionally supported by data from Kavlock et al. (1995), which found that a BMR of 5% RD for fetal weight reduction was statistically similar to several other BMR measurements as well as to statistically-derived NOAEL values. For these reasons, a BMR of 5% RD was selected for decreased pup weight.

Daily AUC for NMP in blood, averaged over the exposure period until the day of measurement (*e.g.*, GD 6-20 for Becci et al. (1982) or GD 5-21 for Saillenfait et al. (2002)), was used as the dose metric for this endpoint. The doses and response data from Saillenfait et al. (2003; 2002) and DuPont (1990) used for BMD modeling are presented in Table 3-1.

Table 3-1 Fetal Body Weight Data Selected for Dose-Response Modeling for NMP

Reference	Dose AUC (hr mg/L)	Number of litters	Fetal body weight (g) Mean ± SD
Saillenfait et al. (2003)	0	24	5.671 ± 0.37
	156.2	20	5.623 ± 0.36
	318.3	19	5.469 ± 0.25
	665.5	25	5.393 ± 0.45
Saillenfait et al. (2002)	0	21	5.73 ± 0.5
	1145	21	5.59 ± 0.22
	2504	24	5.18 ± 0.35
	5673	25	4.02 ± 0.21
	9228	8	3.01 ± 0.39
DuPont (1990)	0	39	7.48 ± 0.701
	51	16	7.03 ± 0.705
	268	15	7.13 ± 0.695
	633	22	6.66 ± 0.616
Becci et al. (1982)	0	24	3.45 ± 0.20
	561	22	3.49 ± 0.24
	2052	23	3.54 ± 0.29
	7986	22	2.83 ± 0.39

For each dataset-specific BMD analysis, a single preferred model was chosen from the standard set of models and modeling options listed above. The modeling restrictions and the model selection criteria facilitated in BMDS 3.1.2 and defined in the BMDS 3.1.2 User Guide were applied in accordance with EPA BMD Technical Guidance (U.S. EPA (2012)). Briefly, for each dataset, BMDS models with standard restrictions were fitted to the data using the maximum likelihood method. For continuous models applied to the fetal weight endpoint, model fit was assessed by a series of tests as follows. For each model, first the homogeneity of the variances was tested using a likelihood ratio test (BMDS Test 2). If Test 2 was not rejected ($\chi 2$ p-value ≥ 0.05), the model was fitted to the data assuming constant variance. If Test 2 was rejected ($\chi 2$ p-value < 0.05), the variance was modeled as a power function of the mean, and the variance model was tested for adequacy of fit using a likelihood ratio test (BMDS Test 3). For fitting models using either constant variance or modeled variance, models for the mean response were tested for adequacy of fit using a likelihood ratio test (BMDS Test 4, with $\chi 2$ p-value < 0.10 indicating inadequate fit). Additional factors were also used to assess the model fit, such as scaled residuals, visual fit, and adequacy of fit in the low-dose region and in the vicinity of the BMR.

With respect to the continuous model distribution-variance modeling options, responses were first assumed to be normally distributed with constant variance across dose groups. If no model achieved adequate fit to response means (BMDS Test 4 p>0.1) and response variances (BMDS Test 2 p>0.05) under those

assumptions, models that assume normal distribution with non-constant variance, variance modeled as a power function of the dose group mean were considered (U.S. EPA (2012)). If no normal distribution model achieved adequate fit to response means under the non-constant variance assumption (BMDS Test 3 p>0.05), models that assume lognormal distribution with constant variance were considered and the same approach for evaluating model fit for mean and variance used for the normal distribution data was applied.

A comparison of model fits obtained for each data set of fetal/pup body weight changes is provided in each section. The best-fitting models, based on the criteria described above, are indicated in bold. For each of the best fitting models in Sections 3.1-3.3, subsequent tables and figures show the model version number, model form, benchmark dose calculation, parameter estimates and estimated values.

PODs identified for fetal body weight in each of the studies evaluated here are summarized in Table 3-2.

Table 3-2. Summary of Recommended BMD and BMDL Values for Fetal Weight.

Section	Response	Selected Model [a]	BMD_{5Pct} (hr mg/L)	$BMDL_{5Pct}$ (hr mg/L)
3.1	Saillenfait et al. (2003)	Exp 3	654	414
3.2	Saillenfait et al. (2002)	Exp 3 [b]	1400	981
3.3	DuPont (1990)	Exp 3	315	223
N/A	Becci et al. (1982)	No model recommended. NOAEL = 2,052	N/A	N/A

[a] Since standard models gave adequate results for all endpoints, non-standard models were not considered. Since fits to the means were obtained using normal distribution models, lognormal models were not applied.

[b] For Saillenfait et al. (2002), the BMD and BMDL reported are from modeling the data with all the SDs equal to the maximum SD across the groups.

3.1 Results for Saillenfait et al. (2003) using AUC

Individual fetal data were not available for the Saillenfait et al. (2003) inhalation study. Thus, the reported litter means and standard deviations applying to the litter level data were modeled. The tables in the source report were not explicit about types of means presented for pup weight, however, the paper's methods section indicated that analyses were performed on a per litter basis supporting modeling in this manner. Additional details on the analysis method are provided in Appendix A (Method 2).

Table 3-3. Model Predictions for Fetal Body Weights in Rats Exposed to NMP by Inhalation Using Daily Average AUC as the Dose Metric (Saillenfait et al. (2003))

BMR = 5% Relative Deviation (RD)

Model [a,b]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.733	78.008	654	414	1543	Exponential model 3 was selected based on lowest AIC among adequately fitting models (Test 4 P-value > 0.1).
Exponential 3	**0.733**	**78.008**	**654**	**414**	**1543**	
Exponential 4	0.431	80.008	654	215	1543	
Polynomial 3°	0.726	78.028	657	422	1528	
Polynomial 2°	0.726	78.028	657	422	1528	
Power	0.726	78.028	657	422	1528	
Linear	0.726	78.028	657	422	1528	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.074), selected model in bold; scaled residuals for selected model for doses 0, 158, 323 and 668 hr mg/L were 0.08, 0.329, -0.68 and 0.22, respectively.

[b] Exponential 5 and Hill models were not fit to the dataset because these models are overparameterized according to model selection criteria (*i.e.*, same number of parameters as dose groups).

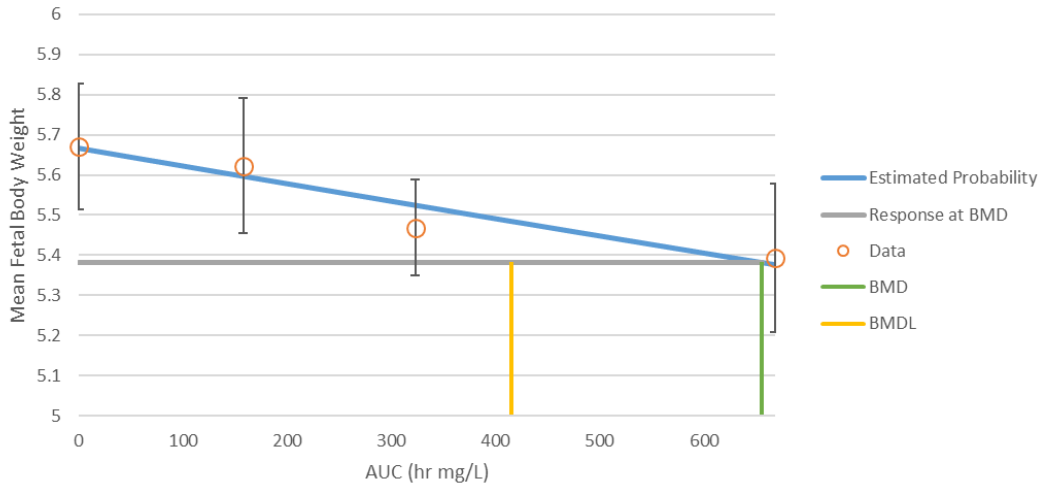


Figure 3.1-1 Plot of Mean Response by Dose, with Fitted Curve for Selected Exponential 3 Model for Fetal Body Weight in Rats Exposed to NMP via Inhalation (Saillenfait et al. (2003))

BMR = 5% Relative Deviation

USER INPUT

Info	
Model	frequentist Exponential degree 3 v1.1
Dose-Response Model	M[dose] = a * exp(±1 * (b * dose)^d)
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Rel. Dev.
BMRF	0.05
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	Dose
Independent Variable	Mean
Total # of Observations	4
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	654.2564991
BMDL	414.2823399
BMDU	1543.192782
AIC	78.00786013
Test 4 P-value	0.732911552
D.O.F.	2

Model Parameters	
# of Parameters	4
Variable	Estimate
a	5.665131549
b	7.83994E-05
d	Bounded
log-alpha	-2.019605929

Goodness of Fit						
Dose	Size	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	24	5.671	0.36429075	0.37	0.37	0.078918885
156	20	5.623	0.36429075	0.36	0.36	0.329255934
318	19	5.469	0.36429075	0.25	0.25	-0.676169981
666	25	5.393	0.36429075	0.45	0.45	0.217779171

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-35.69319981	5	81.3863996
A2	-32.2216643	8	80.4433286
A3	-35.69319981	5	81.3863996
fitted	-36.00393006	3	78.00786013
R	-39.97467922	2	83.9493584

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	15.50602984	6	0.01666578
2	6.943071035	3	0.0737346
3	6.943071035	3	0.0737346
4	0.621460501	2	0.732911552

3.2 Results for Saillenfait et al. (2002) using AUC

Individual fetal data were not available for the Saillenfait et al. (2002) oral study. Thus, the reported litter means and standard deviations applying to the litter level data were modeled. The tables in the source report were not explicit about types of means presented for pup weight, however, the paper's methods section indicated that analyses were performed on a per litter basis supporting modeling in this manner. Additional details on the analysis method are provided in Appendix A (Method 2).

Mean fetal body weight data reported in Saillenfait et al. (2002) was amenable to BMD modeling, however, neither constant nor non-constant variance models fit the variances adequately (*i.e.*, the p-value was <0.05 for Tests 2 and 3). To address the lack of fit of the variance models, a sensitivity analysis was conducted to determine the influence of the variances on the results. The variances change haphazardly with dose, with no discernible pattern, so the data were modeled as follows. First, assuming constant variance, models that adequately fit the means were selected (*i.e.*, Hill and Exponential models 3 and 5; see Table 3-5). Then, assuming constant variance, the data were modeled by replacing the SDs across all dose groups with the minimum SD observed across all dose groups (Table 3-6). This step was then repeated by replacing the SDs across all dose groups with the maximum SD observed across all dose groups (Table 3-7). Finally, the BMDLs were compared for the models selected across the three cases. BMDLs across the three scenarios did not differ greatly (*i.e.*, by more than threefold), so the lowest BMDL was selected for use as the POD for this endpoint. The lowest BMDL came from the maximum SD analysis (Table 3-7). The selected BMD and BMDL are 1402 and 981 hr mg/L, respectively.

Table 3-4 BMD and BMDL Estimates from the Sensitivity Analysis of Fetal Body Weights (Saillenfait et al. (2002))

Standard Deviation Case	Selected Model	Test 4 P-value	BMD (hr mg/L)	BMDL (hr mg/L)
Observed	Exp 3	0.386	1400	1100
Minimum	Hill	0.872	1680	1400
Maximum [a]	**Exp 3**	**0.641**	**1400**	**981**

[a] The standard deviation case with the lowest BMDL is bolded and highlighted in gray.

Table 3-5 Model Predictions for Fetal Body Weights in Rats Exposed to NMP by Gavage Using Daily Average AUC as the Dose Metric (Saillenfait et al. (2002)); Observed SD case

BMR = 5% Relative Deviation (RD)

Model [a,b]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for Model Selection
	Test 4 P-value	AIC				
Exponential 2	0.001	85.305	768	713	831	Only exponential models 3 and 5 and the Hill model provided an adequate fit to the means (Test 4 p-value ≥ 0.10). Of these, exponential model 3 was selected based on lowest AIC.
Exponential 3	**0.3856**	**72.505**	**1402**	**1105**	**1736**	
Exponential 4	0.001	85.305	768	713	831	
Exponential 5	0.849	72.635	1661	1227	2143	
Hill	0.921	72.608	1683	1236	2161	
Polynomial 4°	0.029	77.649	1027	897	1259	
Polynomial 3°	0.029	77.649	1027	897	1259	
Polynomial 2°	0.029	77.649	1027	897	1259	
Power	0.068	75.981	1198	922	1518	
Linear	0.051	76.363	940	890.2856	998	

[a] Constant variance case presented (BMDS Test 2 p-value < 0.001), selected model in bold; scaled residuals for selected model for doses 0, 1144, 2503, 5674 and 9231 hr mg/L were -0.54, 0.55, 0.43, -0.79 and 0.69, respectively.

[b] Model selection was conducted in the context of addressing lack of variance fit and thus ignores the inadequate fit of the constant variance model.

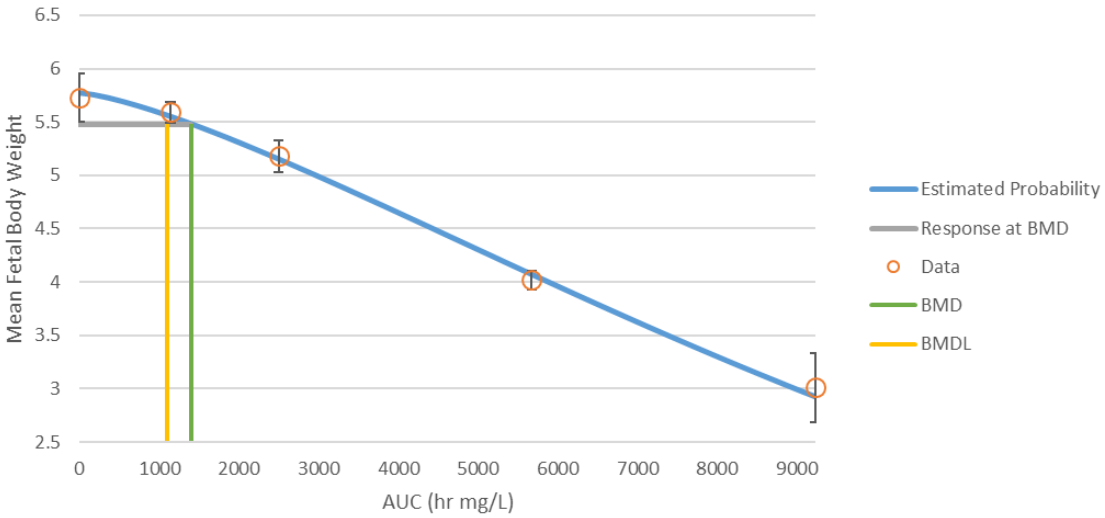


Figure 3.2-1 Plot of Mean Response by Dose, with Fitted Curve for Selected Exponential 3 Model for Fetal Body Weight in Rats Exposed to NMP via Gavage (Saillenfait et al. (2002))
BMR = 5% RD

USER INPUT

Info	
Model	frequentist Exponential degree 3 v1.1
Dataset Name	NMP: fetal weight in rats
Dose-Response Model	M[dose] = a * exp(±1 * (b * dose)^d)
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Rel. Dev.
BMRF	0.05
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	Dose
Independent Variable	Mean
Total # of Observations	5
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	1402.377226
BMDL	1104.917894
BMDU	1735.983131
AIC	72.5047725
Test 4 P-value	0.385541575
D.O.F.	2

Model Parameters	
# of Parameters	4
Variable	Estimate
a	5.76964136
b	8.16174E-05
d	1.370304417
log-alpha	-2.186350781

Goodness of Fit						
Dose	Size	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	21	5.73	0.335	0.50	0.50	-0.54
1145	21	5.59	0.335	0.22	0.22	0.55
2504	24	5.18	0.335	0.35	0.35	0.43
5673	25	4.02	0.335	0.21	0.21	-0.80
9228	8	3.01	0.335	0.39	0.39	0.69

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-31.29928	6	74.59856
A2	-19.79763928	10	59.5952786
A3	-31.29928	6	74.59856
fitted	-32.25238625	4	72.5047725
R	-133.0258433	2	270.051687

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	226.456408	8	<0.001
2	23.00328146	4	<0.001
3	23.00328146	4	<0.001
4	1.906212488	2	0.385541575

Table 3-6 Model Predictions for Fetal Body Weights in Rats Exposed to NMP by Gavage Using Daily Average AUC as the Dose Metric (Saillenfait et al. (2002)); Minimume SD Case.
BMR = 5% RD; minimum SD among groups used for all groups in analysis

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 3	0.085	-20.250	1402	1212	1607	The Hill model was selected based on lowest AIC.
Exponential 5	0.757	-23.094	1662	1389	1952	
Hill	**0.872**	**-23.163**	**1683**	**1407**	**1967**	

[a] Constant variance case presented, selected model in bold; only models that provided adequate fit in the observed SD case were modeled; scaled residuals for selected model for doses 0, 1144, 2503, 5674 and 9231 hr mg/L were -0.06, 0.12, -0.08, 0.03, and -0.02, respectively.

Table 3-7 Model Predictions for Fetal Body Weights in Rats Exposed to NMP by Gavage Using Daily Average AUC as the Dose Metric (Saillenfait et al. (2002)); Maximum SD Case.
BMR = 5% RD; maximum SD among groups used for all groups in analysis

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 3	**0.641**	**147.465**	**1402**	**981**	**1900**	Exponential model 3 was selected based on lowest AIC.
Exponential 5	0.897	148.593	1662	1050	2392	
Hill	0.946	148.581	1683	1052	2395	

[a] Constant variance case presented, selected model in bold; only models that provided adequate fit in the observed SD case were modeled; scaled residuals for selected model for doses 0, 1144, 2503, 5674 and 9231 hr mg/L were -0.06, 0.12, -0.08, 0.03, and -0.02, respectively.

3.3 Results for DuPont, 1990 using AUC

For the DuPont (1990) inhalation study, individual fetal data were not available, but the means and sizes of the individual litters were. Thus, in addition to modeling the means and standard deviations (SDs) of litter means, an alternative analysis was attempted in which SD values were adjusted to represent a pup-based (not litter based) model of fetal body weight. Additional details of this alternative analysis are provided in Appendix A (Method 1). This analysis should ostensibly yield approximately similar results as the analysis of the means and SDs of the litter means, provided the variability in the litter weight is not excessively high. However, in the alternative analysis, neither the constant nor the non-constant variance models fit the variances adequately (Test 2 and 3 p-value < 0.05), and none of the models fit the means adequately (Test 4 p-value < 0.10). By contrast, when modeling using the litter level means and SDs, both variance models fit adequately, and many models fit the means adequately. Modeling results using the litter level means and SDs are shown below. The BMDLs per model differed only slightly between the two analyses. Thus, the results from the modeling of means of litter means were used for DuPont (1990). Exponential model 5 or the Hill model were not fit to the dataset because these models are overparameterized (same number of parameters as dose groups). Also, the residual of the low dose group was rather high (-1.72) for all the models, including the selected model. The response at this dose group was low and appeared to be outside the pattern of the other three groups. Thus, it was considered an outlier and so was deemed not sufficiently significant to reject the model fit. The selected BMD and BMDL are 315 and 223 (hr mg/L) respectively.

Table 3-8 Model Predictions for Fetal Body Weights in Rats Exposed to NMP by Inhalation using Daily Average AUC as the Dose Metric (DuPont (1990))

BMR = 5% Relative Deviation (RD)

Model [a,b,c]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.139	196.355	315	223	528	Exponential model 3 was selected based on lowest AIC. (Exponential model 4 had a reported BMDL of zero, but this model was excluded because it did not fit the data adequately, Test 4 p-value < 0.10.).
Exponential 3	**0.139**	**196.355**	**315**	**223**	**528**	
Exponential 4	0.047	196.355	315	0	528	
Polynomial 3°	0.138	196.377	323	234	572	
Polynomial 2°	0.138	196.377	323	234	555	
Power	0.138	196.377	323	234	594	
Linear	0.138	196.377	323	234	532	

[a] Non-constant variance case presented (Test 2 p-value = 0.905), selected model in bold; scaled residuals for selected model for doses 0, 51, 268, and 633 hr mg/L were 0.88, -1.72, 0.35, and 0, respectively.

[b] Scaled residuals of the low dose group were high (1.72) for all the models, including the selected Exponential 3 model. The response at the low dose group was low and appeared to be outside the pattern of the other three dose groups. Thus, the low dose group was considered an outlier and the high scaled residual was deemed not sufficiently significant to reject the model fit.

[c] Exponential 5 and Hill models were not fit to the dataset because these models are overparameterized according to model selection criteria (*i.e.*, same number of parameters as dose groups).

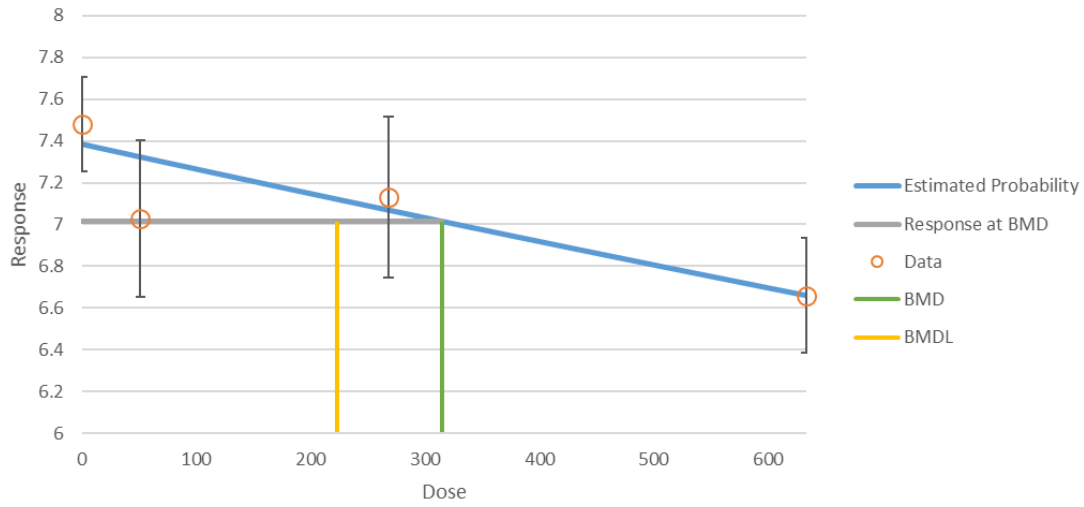


Figure 3.3-1 Plot of Mean Response by Dose, with Fitted Curve for Selected Exponential 3 Model for Fetal Body Weight in Rats Exposed to NMP via Inhalation (DuPont (1990))
BMR = 5% RD; Daily Average AUC as Dose Shown in hr mg/L

USER INPUT

Model	frequentist Power v1.1
Dataset Name	NMP: fetal weight in rats
Dose-Response Model	M[dose] = a * exp(±1 * (b * dose)^d)
Variance Model	Var[i] = alpha * mean[i] ^ rho

Model Options	
BMR Type	Rel. Dev.
BMRF	0.05
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Non-Constant

Model Data	
Dependent Variable	Dose
Independent Variable	Mean
Total # of Observations	4
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	314.8047273
BMDL	223.1325027
BMDU	528.274145
AIC	196.3549556
Test 4 P-value	0.139323996
D.O.F.	2

Model Parameters	
# of Parameters	4
Variable	Estimate
a	7.383675776
b	0.000162937
d	Bounded
log(alpha)	-0.76880135

Goodness of Fit

Dose	Size	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	39	7.48	0.68085857	0.701	0.701	0.883508874
51	16	7.03	0.68085857	0.705	0.705	-1.71884906
268	15	7.13	0.68085857	0.695	0.695	0.351596022
633	22	6.66	0.68085857	0.616	0.616	-0.00059944

Likelihoods of Interest

Model	Log Likelihood	# of Parameters	AIC
A1	-93.20652463	5	196.413049
A2	-92.92594586	8	201.851892
A3	-92.97423292	6	196.413049
fitted	-95.16107509	4	196.354956
R	-103.0646149	2	210.12923

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	20.27733814	6	0.00247147
2	0.561157542	3	0.90526397
3	0.561157542	2	0.90526397
4	3.941906304	2	0.139324

4 Benchmark Dose Modeling of Male Fertility, Female Fecundity, Litter Size and Pup Death in Exxon, 1991

BMD modeling for reduced male fertility, female fecundity, and reduced litter size described in a 2-generation reproductive study in rats exposed through diet (Exxon (1991b)) was performed using USEPA's BMD Software package version 3.1.1 (BMDS 3.1.1) or 2.7 (BMDS 2.7) in a manner consistent with Benchmark Dose Technical Guidance.

In the Exxon (1991b) study, two generations of both sexes were dosed daily for at least ten weeks prior to mating and throughout the mating period. Target doses for the exposed groups were 50, 160 and 500 mg/kg-day. Individual litter data reported in Appendices to the Exxon (1991b) report were used for the determination of dichotomous response incidence and continuous response means and standard deviations modeled in this report.

The strongest dose-responses for reproductive effects in the Exxon (1991b) study were observed for reduced Male Fertility Index and Female Fecundity Index in the first (P2/F2A; Table 73 of the Exxon report) and second (P2/F2B; Table 74 of the Exxon report) litters of the P2 (F1A) 2nd generation parents.

Overall BMD Modeling Approach for Exxon 1991 Data

Benchmark dose software version 3.1.1 (BMDS 3.1.1) was used to analyze male fertility, female fecundity and litter size. The pup death endpoint was analyzed using BMDS 2.7 because it contains the larger suite of nested dichotomous models.[4] Nested dichotomous models are preferred for this endpoint because they contain an intra-litter correlation coefficient for the assessment of litter-specific responses.

Only BMDS models that use likelihood optimization and profile likelihood-based confidence intervals were used in this analysis. All continuous models applied assume normal response distribution. Also, the benchmark response levels and dose metrics for the analysis are:

1. *Fertility and Fecundity for P2/F2A and P2/F2B parental rats* – estimate BMDs for 10% extra risk using PBPK estimates of average daily blood concentrations for young (50 g) rat as doses (four datasets), plus a sensitivity analysis using average daily blood concentrations for 250 g, 350 g and 450 g rats.
2. *Litter Size for P2/F2A and P2/F2B* – estimate BMDs for 1 SD change from control mean using PBPK estimates of average daily blood concentrations for young (50 g) rat and GD 6-21 dams as doses (four datasets)
3. *Pup death for P2/F2A and P2/F2B* - estimate BMDs for death at Day 0 and by day 4 for 10%. 5% and 1% extra risk using PBPK estimates of average daily blood concentrations for GD 6-21 dam as doses (four datasets)

Standard and non-standard forms of these models[5] (defined for each endpoint below) were run separately in BMDS 3.1.1, but EPA model selection procedures (U.S. EPA (2012)) were applied only to the results of the standard model runs when adequate fit was achieved with any standard model. Since adequate model fits were obtained in all cases for the standard model suites, no non-standard modeling results are shown or discussed in this report.

[4] BMDS 3.1.1 contains the same NLogistic model, which is preferred because it has received the more extensive QA testing and is deemed to be the most reliable nested model, but NCTR and RaiVR models are provided as alternatives in this report.
[5] The set of standard models are identified in accordance with EPA BMD technical guidance (U.S. EPA (2012)) and are the default models in BMDS 3.1.1. Non-standard models are the remaining (non-default) models available in BMDS 3.1.1.

Model Restrictions and Model Selection

Restrictions for BMDS 3.1.1 models are defined in the BMDS 3.1.1 User Guide and are applied in accordance with EPA BMD Technical Guidance (U.S. EPA (2012)). For each BMD analysis, a single preferred model was chosen from among the preferred standard set of models (noting instances where consideration of non-standard models may be justified) in accordance with EPA BMD Technical Guidance (U.S. EPA (2012)). For continuous responses, dose group response standard deviation (SD) was modeled assuming constant variance across dose groups. If adequate fit (p>0.1) was not achieved for this variance model a non-constant variance assumption that models SD as a power function of the mean was applied (U.S. EPA (2012)). Nested dichotomous models were run two ways, with intra-litter correlation (ILC) coefficients estimated and with ILC coefficients assumed to be zero. Because potential litter-specific covariates (LSCs) such as dam BW are affected by dose, no appropriate LSC could be determined and LSCs were not estimated in the BMDS nested dichotomous model runs.

PBPK Analysis for Exxon 1991 Data

Details of the PBPK models for rats and humans are provided in Appendix I of the NMP Risk Evaluation. The models were developed to describe dosimetry in adult females during pregnancy and so were slightly adapted to estimate dosimetry in juvenile (post-weaning) rats and adult men.

Because NMP has a relatively short half-life in both rats and humans, exposures only need to be simulated for several days to a week to determine the internal dosimetry from a consistent exposure pattern, such as occurs in an animal bioassay or in the workplace (5 day/week). Therefore, adult human single-day or workplace exposures outside of pregnancy were assumed to be adequately represented by running the model for the first day or week of pregnancy, when physiological changes are minimal. Also, physiological differences between men and women were assumed to have minimal impact on the predicted dosimetry, except that a male-specific body weight (BW) and hand surface area (SA) were used to estimate dosimetry in men. Changing the BW also affects cardiac output, respiration, and metabolism, which all scale as $BW^{0.75}$ in the model. Exposures were simulated for a single day (residential consumer use) or a week (workplace, with 5 d/w exposure) and the average daily area-under-the-curve (AUC) blood concentration[6] was calculated.

For the rat, where pregnancy only lasts 21 days, the model code was modified to allow a user-specified day for the start of gestation (GSTART), so results for non-pregnant animals could be obtained; *i.e.*, with time < GSTART. As for humans, physiological differences between males and females were assumed to not significantly impact internal dosimetry, hence the non-pregnant female model was used to simulate male dosimetry. Simulations for post-weaning juvenile animals in the Exxon (1991b) bioassay were conducted by setting the (initial) BW to 50 g (and for comparison, 250 g, 350 g and 450 g). Because metabolism is scaled as $BW^{0.75}$ in the rats (as well as humans) the internal dose decreases as BW decreases, so using this BW yields the lowest estimated internal dose for post-weaning rats (weaning presumed to occur at about this BW). Using this BW in dose-response analysis for fertility and fecundity provides a lower bound on the internal dose that could give rise to those effects, since they could result from toxicity at any point in development or during maturity. Target exposure levels (50, 160, and 500 mg/kg/d) were used as exposure levels, exposure was simulated for one-week to go beyond any initial accumulation and the average blood concentration (C_{avg}) in the last day of exposure used as

[6] Since the 24-hour AUC can vary from day to day, in particular for workplace scenarios, a time-averaged AUC is computed as AUC_{avg} = AUC(averaging time)*(24 h)/(averaging time), where "averaging time" is typically a week. The average blood concentration is simply C_{avg} = AUC(averaging time)/(averaging time). Hence $C_{avg} = AUC_{avg}/(24\ h)$.

internal dose. Food consumption was assumed to occur 12 h/d, at a constant rate over the 12 h to match the target exposure. Results are given in Table 4-1.

Table 4-1 PBPK-predicted average blood concentrations (C_{avg}, mg/L) in juvenile rats

Exposure rate (mg/kg/d)	C_{avg} (50 g rat)	C_{avg} (250 g rat)	C_{avg} (350 g rat)	C_{avg} (450 g rat)
0	0	0	0	0
50	13.9	21.1	23.1	24.6
160	48.4	75.2	82.6	88.6
500	181.4	292.6	324.0	349.8

The existing PBPK model does not describe lactational dosimetry, hence the analysis did not include exposure during that period.

Since effects on litter size and pup viability could result from exposure during gestation, for these endpoints C_{avg} in the rat dam over gestation days (GDs) 6-21 days of gestation was estimated. For simulation of gestation, group-specific mean BW on GD 0 from Table 53 (P2/F2A) and Table 56 (P2/F2B) of the Exxon (1991b) report were used to set the initial BW of the animals. The gestational BW gain simulated by the model depended on the number of fetuses (NUMFET), an input parameter. Since group-specific BW values were also given on GD 20 (Tables 53 and 56 of the Exxon report), a nominal NUMFET was selected for each group to match, as closely as possible, the GD 20 BW value, though the NUMFET did not necessarily match the average number actually born. This choice was made since the BW impacts the internal dose, so it was considered most important to match the BW increase. The dose rates for each exposure group were calculated as the average of measured doses for days 6-20 from Tables 67 (P2/F2A) and 69 (P2/F2B) of the Exxon (1991b) report. The resulting internal doses are given in Table 4-2 and 4-3.

Table 4-2 PBPK-predicted average blood concentrations (Cavg, mg/L) during gestation for P2/F2A

GD 0 BW (kg)	GD 6-20 Exposure rate (mg/kg/d)	Predicted GD 20 BW (kg) (# fetuses simulated)	GD 6-21 C_{avg} (mg/L)
0.3243	52.475	0.4505 (17)	26.12
0.3054	166.75	0.4394 (19)	92.55
0.2815	494.1	0.3872 (14)	326.1

Table 4-3 PBPK-predicted average blood concentrations (Cavg, mg/L) during gestation for P2/F2B

GD 0 BW (kg)	GD 6-20 Exposure rate (mg/kg/d)	Predicted GD 20 BW (kg) (# fetuses simulated)	GD 6-21 C_{avg} (mg/L)
0.3706	49.350	0.5075 (18)	25.25
0.3536	156.70	0.4935 (19)	89.03
0.3187	466.63	0.4188 (12)	311.9

For human workplace and residential exposures, input parameters were specified in Excel spreadsheets. For workplace exposures, estimated air concentrations were assumed to be constant over each period of use, but the air concentration, liquid concentration (weight fraction), and duration of use varied between scenarios. Internal average blood concentrations for varying levels of protective equipment (face mask and/or gloves with varying protection factors (PFs)) were estimated assuming a five-day work week in which the exposure was repeated each day followed by two days without exposure. Residential applications were assumed to occur for a single day and air-concentration time-courses estimated for each application, along with liquid weight fraction and dermal contact duration specific to each use scenario. These inputs were read by a model script from Excel spreadsheets. For the analysis of potential for effect on male fertility, BW and hand surface area (SA) were set to male-specific values. For the analysis of potential for gestational effect, BW and SA were set to female-specific values. Residential application evaluated exposure for both adult and teenage women. Model results are written back to the Excel spreadsheet from which exposure inputs were obtained.

Since human internal doses are calculated as 24-h average AUC values, these must be divided by 24 h before comparison to C_{avg} BMD(L) values, or the C_{avg} BMD(L) values multiplied by 24 h, prior to MOE calculation.

4.1 Summary of BMD Modeling for Exxon, 1991 Data

Table 4-4 BMD Modeling Summary for Exxon (1991b)

Sec.	Response	Basis for Internal Dose Calculations	Selected Model [b]	BMR	BMD [c] (mg/L)	BMDL [c] (mg/L)	BMDU [c] (mg/L)	BMD [d] 24hr AUC (h mg/L)	BMDL [d] 24hr AUC (h mg/L)
4.2.1	P2/F2A Male Rat Fertility	Young rat (50 g)	Log-Logistic	10% ER	20.5	10.9	81.7	492	262
4.2.2	P2/F2B Male Rat Fertility	Young rat (50 g)[1]	Log-Logistic	10% ER	14.2	7.64	65.1	341	183
4.2.3	P2/F2A Female Rat Fecundity	Young rat (50 g)	Log-Logistic	10% ER	35.9	16.7	179	862	401
4.2.4	P2/F2B Female Rat Fecundity	Young rat (50 g)	Log-Logistic	10% ER	17.5	8.40	58.4	420	202
4.3.1	P2/F2A Litter Size	Young rat (50 g)	Polynomial 3	1 SD	203	151	715	4872	3624
4.3.2	P2/F2B Litter Size	Young rat (50 g)	Linear	1 SD	153	99.6	332	3672	2390
4.3.3	P2/F2A Litter Size [e]	Dam (GD 6-21)	Polynomial 3	1 SD	364	274	1280	8736	6576
4.3.4	P2/F2B Litter Size [e]	Dam (GD 6-21)	Linear	1 SD	265	172	575	6360	4128
4.4.1	P2/F2A Pup Death at Day 0 (stillborn)	Dam (GD 6-21)	NLogistic - ILC	5% ER	327	205	NC	7848	4920
				1% ER	281	49.3	NC	6744	1183
4.4.2	P2/F2B Pup Death at Day 0 (stillborn)	Dam (GD 6-21)	No Model Selected	5% ER	NA	NA	NA	NA	NA
				1% ER	NA	NA	NA	NA	NA
4.4.3	P2/F2A Pup Death by Day 4	Dam (GD 6-21)	No Model Selected	5% ER	NA	NA	NA	NA	NA
				1% ER	NA	NA	NA	NA	NA
4.4.4	P2/F2B Pup Death by Day 4	Dam (GD 6-21)	No Model Selected	5% ER	NA	NA	NA	NA	NA
				1% ER	NA	NA	NA	NA	NA

[a] BMDL estimates from the selected model (Log-Logistic) for this most sensitive endpoint using internal doses based on 250 g, 350 g and 450 g rats, were 12.1, 13.4 and 14.4 mg/L, respectively.
[b] As described in Section 4.1, BMDs were derived from the standard set of models as defined in the EPA BMD technical guidance and as identified in BMDS 3.1.1 as defaults. Since the standard approach gave adequate results for all endpoints, non-standard models were not considered for BMD derivations.
[c] BMD, BMDL and BMDU values are in terms of average concentration over 24 hrs and are reported to more than 3 significant figures in the tables in Section 4.2, 4.3 and 4.4. This has been done to facilitate QC (i.e., replication of the results to a higher number of significant figures gives greater assurance that QA model runs have been performed using the same modeling options).
[d] Adjusted BMD and BMDL are in terms of 24-hour AUC blood concentration. These units are directly comparable with BMDLs previously calculated for the NMP risk evaluation.
[e] Effects on litter size during gestation are of interest for acute exposure and would therefore be most appropriately evaluated based on maximum concentrations as opposed to 24 hr average or AUC concentrations shown here.
NC = not calculated; NA = not applicable

4.2 Results of BMD Modeling of P2 Male and Female Fertility Indices (Exxon, 1991)

The strongest dose-responses for reproductive effects in the Exxon (1991b) study were observed for reduced Male Fertility Index and Female Fecundity Index in the first (P2/F2A; Table 73 of the Exxon report) and second (P2/F2B; Table 74 of the Exxon report) litters of the P2 (F1A) 2nd generation parents. Incidence data for these effects were obtained from Appendices AF (P2/F2A parents) and AG (P2/F2B parents) of the Exxon (1991b) report. Because BMDS models dichotomous data using dose-response curves that are increasing in dose-response, the results reported in Appendices AF and AG in terms of successful impregnations were inverted to obtain incidence data in terms of "number of males unsuccessful at impregnating any female" per "number of males used for mating" (Males Unsuccessful/ Males Used) and "number of females that did not get pregnant" per "number of females sperm positive (confirmed mated or confirmed pregnant)" (Females Unsuccessful/Females Mated). These ratios were derived slightly differently from the Male Fertility and Female Fecundity indices shown in Tables 73 and 74 of the Exxon (1991b) report in that a confirmed pregnancy was counted as "sperm positive" regardless of whether the mating was "confirmed" (cases where this occurred are identified with footnotes in the tabular results of this Section).

Because of the existing uncertainty regarding the lifestage "window of toxicity," and the possibility that reproductive effects of concern could have been associated with early life exposures, the BMD analyses of potential reproductive effects were performed using PBPK estimates of internal doses that assume an early lifestage rat body weight of 50 g. A sensitivity analysis was performed on the P2/F2B Male Rat Fertility to determine the impact of the body weight assumption. As indicated in Footnote 1 of the table in Section 4.3, BMDL estimates for this most sensitive endpoint increased by less than 2-fold for body weight assumptions at or below 450 g. The following standard and non-standard dichotomous models and general modeling options were used to fit fertility incidence data.

Standard Dichotomous Models Applied to Fertility and Fecundity Responses:

- Gamma-restricted
- Log-Logistic-restricted
- Multistage-restricted; from degree = 1 to degree = # dose groups - 1
- Weibull-restricted
- Dichotomous Hill-unrestricted
- Logistic
- Log-Probit-unrestricted
- Probit

Non-Standard Dichotomous Models Applied to Fertility and Fecundity Responses:

- Dichotomous Hill-restricted
- Log-Probit-restricted
- Gamma-unrestricted
- Log-Logistic-unrestricted
- Multistage-unrestricted
- Weibull-unrestricted

General Model Options Used for Fertility and Fecundity Dichotomous Responses:

- Benchmark Response (BMR): 0.1 (10%) Extra Risk
- Confidence Level: 0.95
- Background: Estimated

4.2.1 P2/F2A Male Fertility (Males Unsuccessful/Males Used; Exxon Appendix AF)

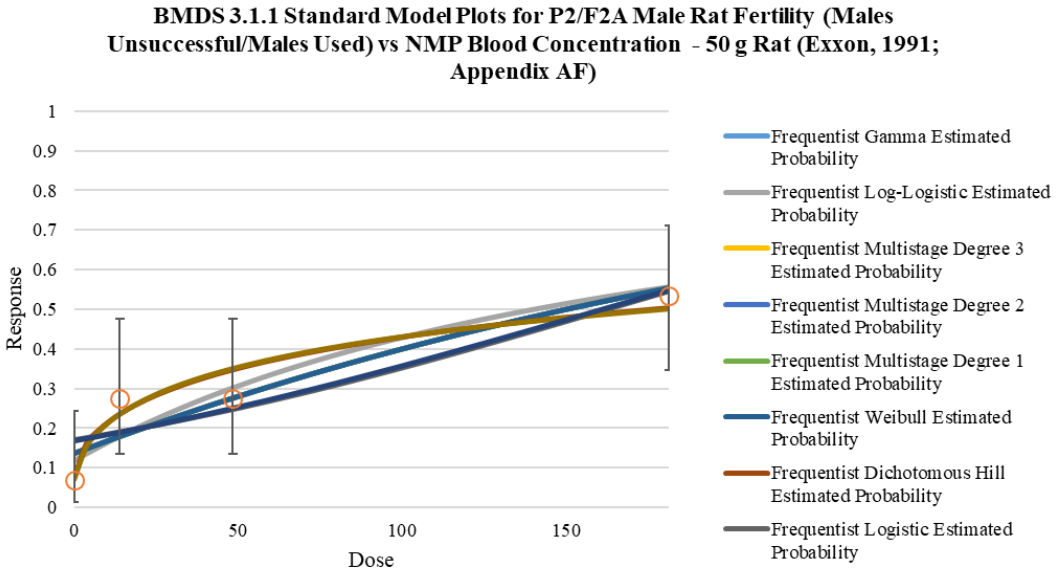
mg/L Blood - 50 g Rat	N	Incidence
0	29	2
13.9	29	8
48.4	29	8
181.4	30	16

Table 4-5 Model Predictions for Reduced Male Fertility in P2/F2A Male Rats (Exxon (1991b))

Standard Models	Restriction [b]	10% Extra Risk (mg/L blood – 50 g Rat)			P-value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL	BMDU				
Gamma	Restricted	28.8254	18.0677	106.5062	0.2212244	131.3647426	Viable - Alternate	
Log-Logistic [a]	**Restricted**	**20.4739**	**10.9376**	**81.73223**	**0.2674073**	**130.8745155**	**Recommended**	**Basis: Lowest BMDL In a > 3-Fold BMDL Range** Lowest AIC
Multistage Degree 3	Restricted	28.8254	18.0678	109.5157	0.221224	131.3647426	Viable - Alternate	
Multistage Degree 2	Restricted	28.8254	18.0675	91.60710	0.2212241	131.3647426	Viable - Alternate	
Multistage Degree 1	Restricted	28.8253	18.0676	56.96940	0.2212238	131.3647426	Viable - Alternate	
Weibull	Restricted	28.8254	18.0676	115.1404	0.2212239	131.3647426	Viable - Alternate	
Dichotomous Hill	Unrestricted	4.24566	0.00024	41.01537	0.3093156	131.3825536	Questionable	BMD/BMDL ratio > 2 BMD/BMDL ratio > 3 BMD 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose
Logistic	NA	51.4208	38.1985	79.82821	0.1620735	132.3326784	Viable - Alternate	
Log-Probit	Unrestricted	4.64211	0.00037	37.71069	0.2942246	131.4531168	Questionable	BMD/BMDL ratio > 20 BMD/BMDL ratio > 3 BMD 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose
Probit	NA	48.8614	36.4163	77.27841	0.1667614	132.2405329	Viable - Alternate	

[a] Selected Model (Gray); residuals for doses 0, 13.9, 48.4, and 181.4 were -0.811610042, 1.353899534, -0.296031585 and -0.242023672, respectively

[b] Restrictions defined in the BMDS 3.1.1 User Guide; NA = Not Applicable



Selected Model – Log-Logistic (Restricted) - Extra Risk, BMR = 0.1

USER INPUT

Info	
Model	Log-Logistic v1.0
Dataset Name	P2F2A Male Fertility

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

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

MODEL RESULTS

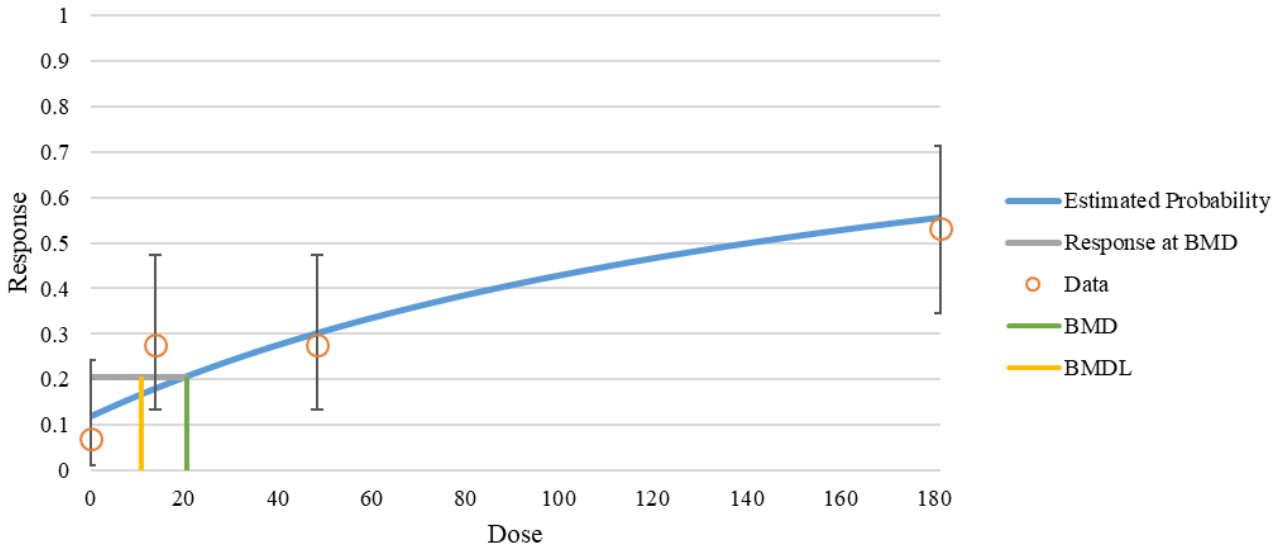
Benchmark Dose	
BMD	20.4738478
BMDL	10.93759459
BMDU	81.7322316
AIC	130.8745155
P-value	0.267407255
D.O.F.	2
Chi^2	2.637964966

Model Parameters	
# of Parameters	3
Variable	Estimate
g	0.117496501
a	-5.216372932
b	Bounded

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.117496501	3.407398541	2	29	-0.81161
13.9	0.17939856	5.202558252	8	29	1.3538995
48.4	0.301079065	8.731292894	8	29	-0.296032
181.4	0.555291468	16.65874405	16	30	-0.242024

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-62.1675397	4	-	-	-
Fitted Model	-63.43725776	2	2.53943612	2	0.2809108
Reduced Model	-70.51432209	1	16.6935648	3	0.0008171

P2/F2A Male Rat Fertility (Males Unsuccessful/Males Used) vs NMP Blood Concentration - 50 g Rat (Exxon, 1991; Appendix AF) - Log-Logistic Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL



4.2.2 P2/F2B Male Fertility (Males Unsuccessful/Males Used; Exxon Appendix AG)

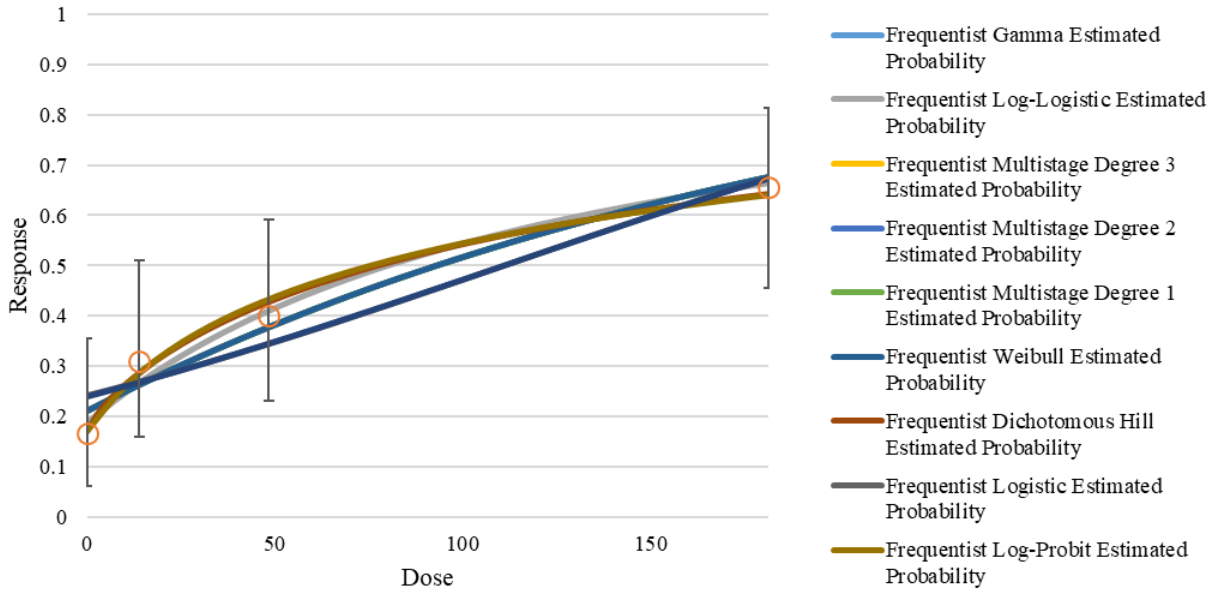
mg/L Blood - 50 g Rat	N	Incidence
0	30	5
13.9	29	9
48.4	30	12
181.4	29	19

Table 4-6 Model Predictions for Reduced Male Fertility in P2/F2B Male Rats (Exxon (1991b))

Standard Models	Restriction [b]	10% Extra Risk (mg/L blood – 50 g Rat)			P-value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL	BMDU				
Gamma	Restricted	21.4613	13.7489	76.52064	0.6666306	145.5183972	Viable - Alternate	
Log-Logistic [a]	**Restricted**	**14.2125**	**7.63824**	**65.11825**	**0.8248283**	**145.0806789**	**Recommended**	**Basis: Lowest BMDL In a > 3-Fold BMDL Range** Lowest AIC
Multistage Degree 3	Restricted	21.4613	13.7489	87.34237	0.6666306	145.5183972	Viable - Alternate	
Multistage Degree 2	Restricted	21.4613	13.7487	75.00523	0.6666309	145.5183972	Viable - Alternate	
Multistage Degree 1	Restricted	21.4613	13.7488	40.46712	0.6666306	145.5183972	Viable - Alternate	
Weibull	Restricted	21.4613	13.7489	80.30469	0.6666306	145.5183972	Viable - Alternate	
Dichotomous Hill	Unrestricted	8.67717	0.17104	60.82728	0.6564479	146.8984918	Questionable	BMD/BMDL ratio > 20 BMDL 10x lower than lowest non-zero dose
Logistic	NA	36.7271	27.0945	56.56066	0.4426321	146.3971535	Viable - Alternate	
Log-Probit	Unrestricted	9.26962	0.24178	59.56593	0.6161031	146.9522017	Questionable	BMD/BMDL ratio > 20 BMDL 10x lower than lowest non-zero dose
Probit	NA	35.7014	26.7157	55.32779	0.4533689	146.3437672	Viable - Alternate	

[a] Selected Model (Gray); residuals for doses 0, 13.9, 48.4 and 181.4 were -0.300662226, 0.518709072, -0.122358174 and -0.103594189, respectively.
[b] Restrictions defined in the BMDS 3.1.1 User Guide; NA = Not Applicable

BMDS 3.1.1 Standard Model Plots for P2/F2B Male Rat Fertility (Males Unsuccessful/Males Used; Appendix AG) vs NMP Blood Concentration - 50 g Rat (Exxon, 1991)



Selected Model - Log-Logistic (Restricted) - Extra Risk, BMR = 0.1

USER INPUT

Info	
Model	Log-Logistic v1.0
Dataset Name	P2F2B Male Fertility

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

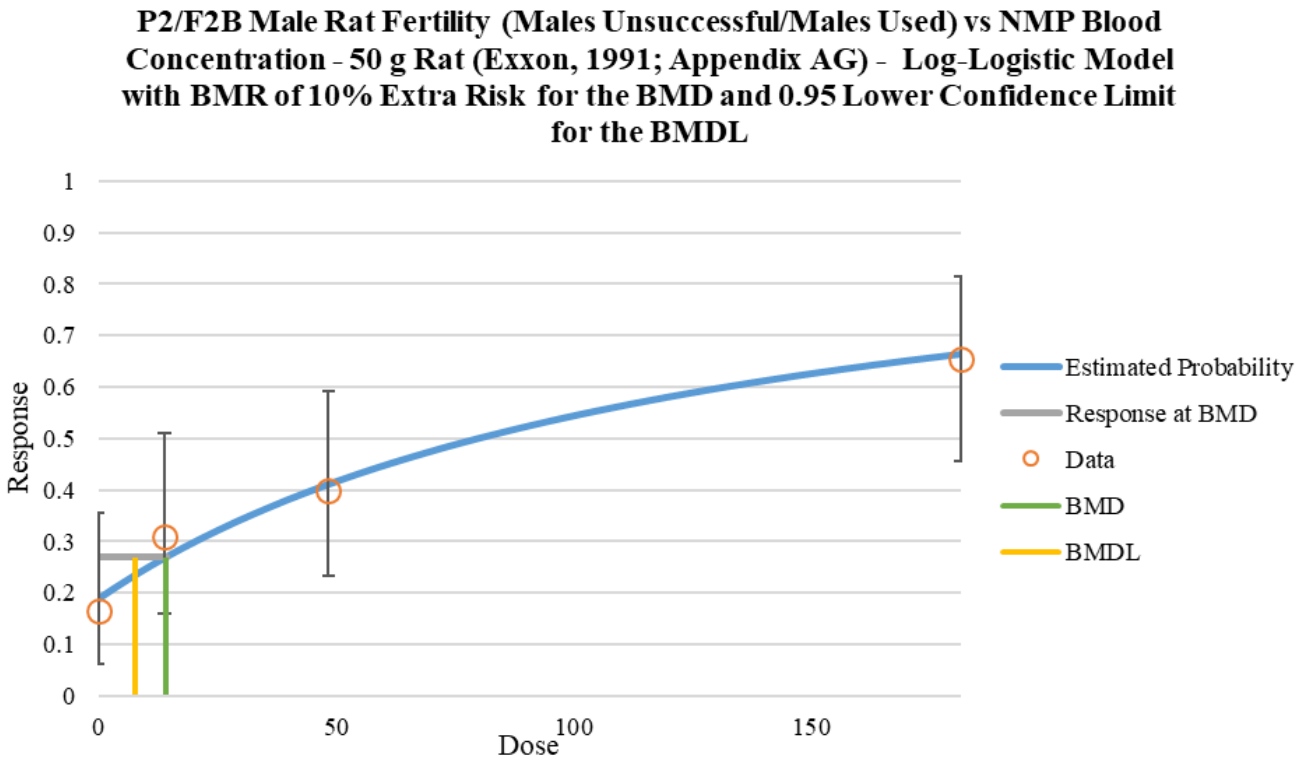
MODEL RESULTS

Benchmark Dose	
BMD	14.21245366
BMDL	7.638241538
BMDU	65.11824629
AIC	145.0806789
P-value	0.824828266
D.O.F.	2
Chi^2	0.385160154

Model Parameters	
# of Parameters	3
Variable	Estimate
g	0.188119322
a	-4.851343176
b	Bounded

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.188119322	5.643579645	5	30	-0.300662
13.9	0.267697459	7.763226311	9	29	0.5187091
48.4	0.410991312	12.32973936	12	30	-0.122358
181.4	0.664257058	19.26345469	19	29	-0.103594

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P-value
Full Model	-70.35048621	4	-	-	-
Fitted Model	-70.54033943	2	0.37970644	2	0.8270805
Reduced Model	-78.43743444	1	16.1738965	3	0.0010446



4.2.3 P2/F2A Female Fecundity (Females Unsuccessful/Females Mated; Exxon Appendix AF)

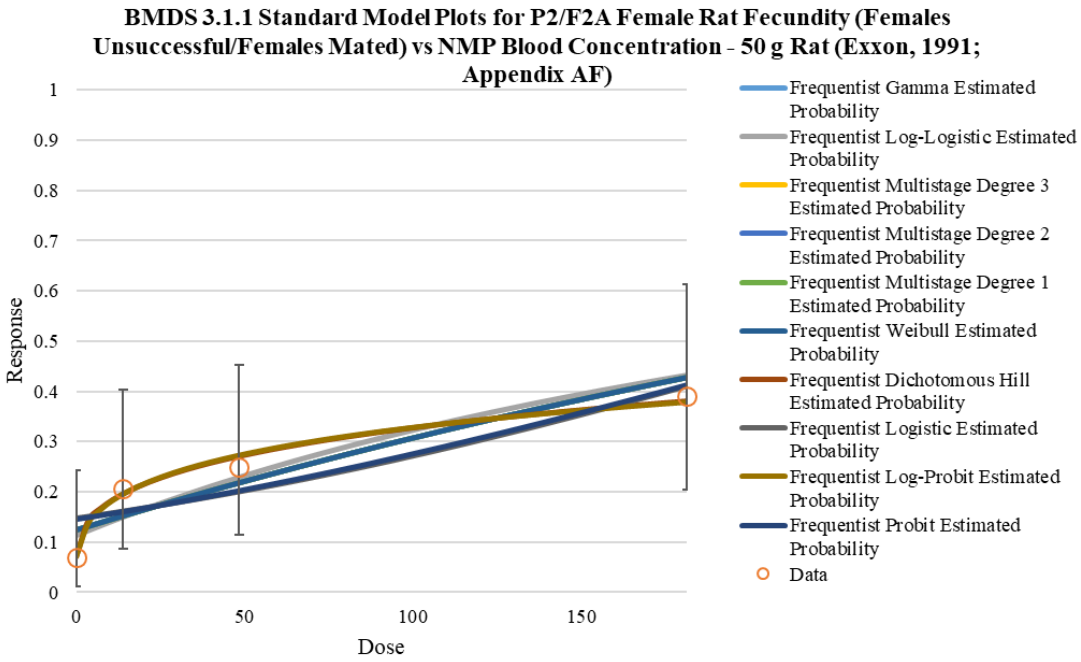
mg/L Blood - 50 g Rat	N	Incidence
0	29 [a]	2
13.9	29 [b]	6
48.4	28	7
181.4	23	9

[a] Includes 1 presumed mating (JAB149 with JAB273) that was not "Confirmed" but resulted in pregnancy of JAB273
[b] Includes 1 presumed mating (JAB008 with JAB105) that was not "Confirmed" but resulted in pregnancy of JAB105

Table 4-7 Model Predictions for Reduced Fecundity in P2/F2A Female Rats (Exxon (1991b))

Standard Models	Restriction [b]	10% Extra Risk (mg/L blood – 50 g Rat)			P-value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL	BMDU				
Gamma	Restricted	44.9690	24.2797	166.8743	0.4107328	112.2540963	Viable - Alternate	
Log-Logistic [a]	**Restricted**	**35.8500**	**16.7086**	**178.8394**	**0.4644837**	**111.9559685**	**Recommended**	**Basis: Lowest AIC**
Multistage Degree 3	Restricted	44.969	24.2793	152.7587	0.4107329	112.2540963	Viable - Alternate	
Multistage Degree 2	Restricted	44.9690	24.2797	145.5655	0.4107328	112.2540963	Viable - Alternate	
Multistage Degree 1	Restricted	44.9690	24.2794	139.9963	0.4107329	112.2540963	Viable - Alternate	
Weibull	Restricted	44.9690	24.2797	176.6268	0.4107328	112.2540963	Viable - Alternate	
Dichotomous Hill	Unrestricted	6.58476	0	78.86685	NA	114.5009914	Unusable	BMD computation failed; lower limit includes 0 BMDL not estimated d.f.=0 (Goodness of fit test cannot be calculated)
Logistic	NA	72.8142	49.2249	179.0743	0.3112546	112.9743842	Viable - Alternate	
Log-Probit	Unrestricted	7.04768	0	74.36506	0.7360008	112.5190346	Unusable	BMD computation failed; lower limit includes 0 BMDL not estimated
Probit	NA	69.2999	46.3835	174.6704	0.3207564	112.8954163	Viable - Alternate	

[a] Selected Model (Gray); residuals for doses 0, 13.9, 48.4 and 181.4 were -0.754747582, 0.857664083, 0.263750831 and -0.398574381, respectively.
[b] Restrictions defined in the BMDS 3.1.1 User Guide; NA = Not Applicable



Selected Model – Log-Logistic - Extra Risk, BMR = 0.1

USER INPUT

Info	
Model	Log-Logistic v1.0
Dataset Name	P2F2A Female Fecundity

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

Model Data	
Dependent Variable	mg/L Blood 50 g Rat
Independent Variable	Females Unsuccessful
Total # of Observations	4

MODEL RESULTS

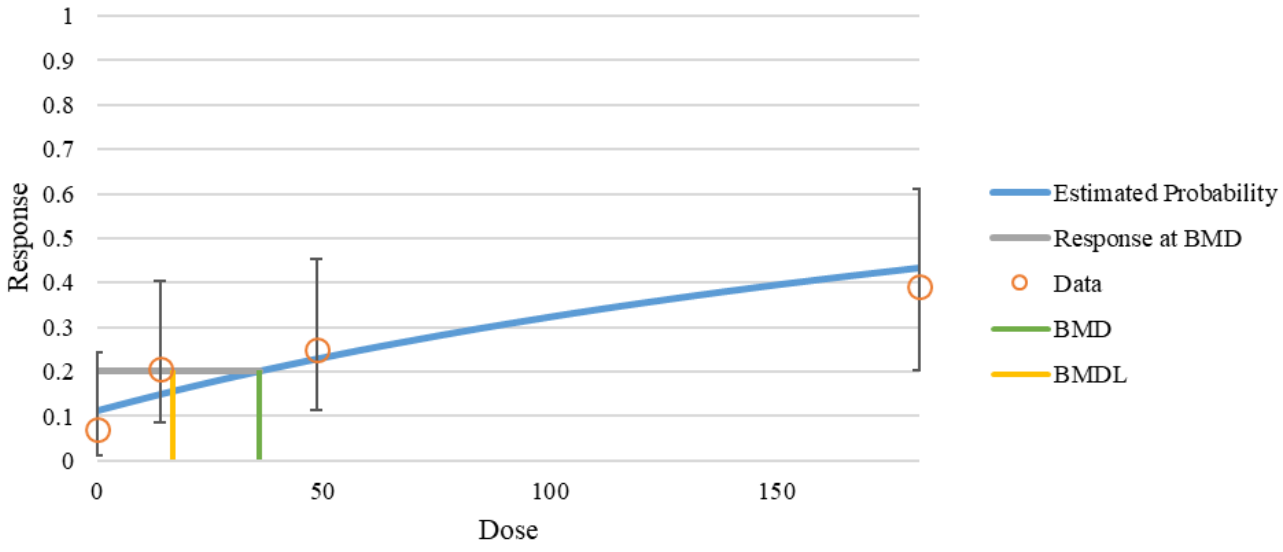
Benchmark Dose	
BMD	35.85003887
BMDL	16.70857886
BMDU	178.8394143
AIC	111.9559685
P-value	0.464483699
D.O.F.	2
Chi^2	1.53365763

Model Parameters	
# of Parameters	3
Variable	Estimate
g	0.11340654
a	-5.776569229
b	Bounded

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.11340654	3.288789653	2	29	-0.754748
13.9	0.150024089	4.350698589	6	29	0.8576641
48.4	0.22905425	6.41351901	7	28	0.2637508
181.4	0.432477945	9.946992746	9	23	-0.398574

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-53.20227182	4	-	-	-
Fitted Model	-53.97798425	2	1.55142486	2	0.4603757
Reduced Model	-57.45827043	1	8.51199723	3	0.0365346

P2/F2A Female Rat Fecundity (Females Unsuccessful/Females Mated) vs NMP Blood Concentration - 50 g Rat (Exxon, 1991; Appendix AF) - Log-Logistic Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL



4.2.4 P2/F2B Female Fecundity (Females Unsuccessful/Females Mated; Exxon Appendix AG)

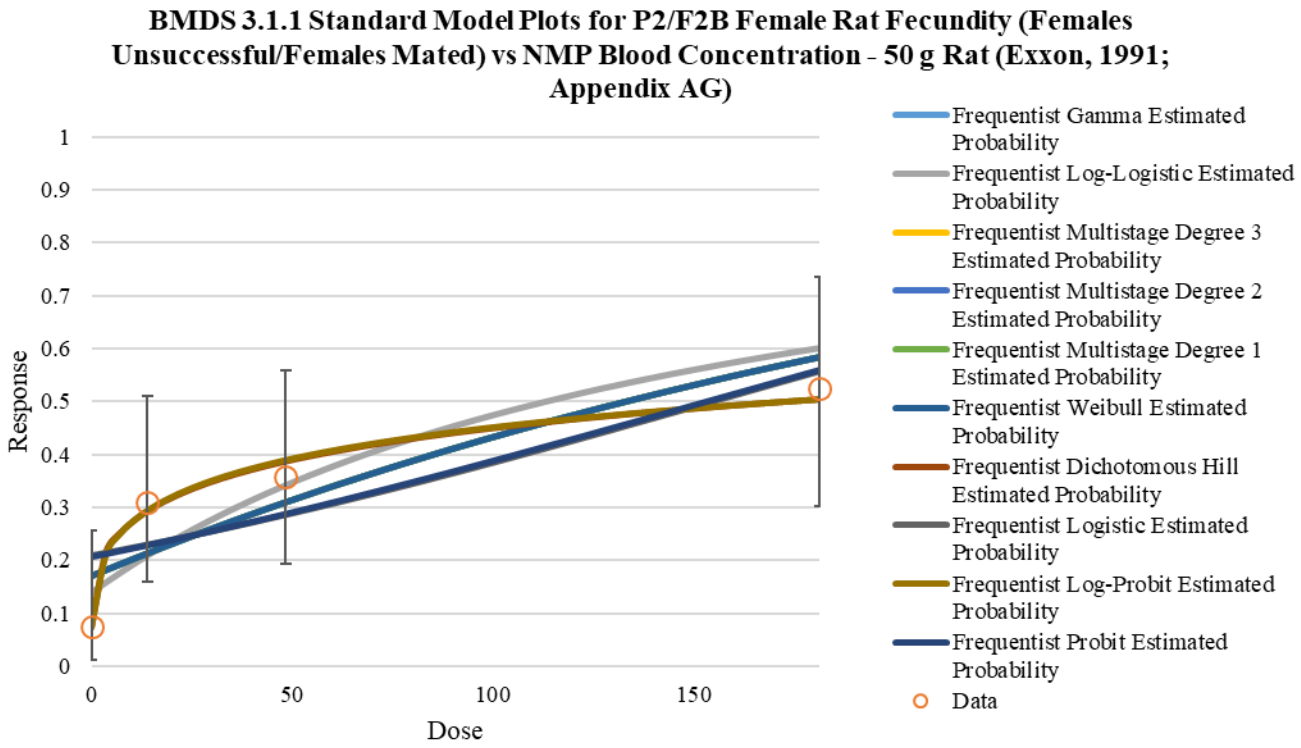
mg/L Blood - 50 g Rat	N	Incidence
0	27	2
13.9	29 [a]	9
48.4	28	10
181.4	21 [b]	11

[a] Includes 2 presumed matings (JAB194 with JAB279; JAB201 with JAB293) not "Confirmed" but resulting in pregnancies
[b] Includes 1 presumed mating (JAB022 with JAB134) that was not "Confirmed" but resulted in pregnancy of JAB134

Table 4-8 Model Predictions for Reduced Fecundity in P2/F2B Female Rats (Exxon (1991b))

Standard Models	Restriction [b]	10% Extra Risk (mg/L blood – 50 g Rat)			P-value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL	BMDU				
Gamma	Restricted	27.7596	15.9481	82.14200	0.1349299	123.9885415	Viable - Alternate	
Log-Logistic [a]	**Restricted**	**17.4528**	**8.39586**	**58.44882**	**0.1925123**	**123.0293723**	**Recommended**	**Basis: Lowest AIC**
Multistage Degree 3	Restricted	27.7598	15.9482	97.11740	0.1349306	123.9885415	Viable - Alternate	
Multistage Degree 2	Restricted	27.7598	15.9482	87.01075	0.1349306	123.9885415	Viable - Alternate	
Multistage Degree 1	Restricted	27.7619	15.9483	68.87117	0.134946	123.9885416	Viable - Alternate	
Weibull	Restricted	27.7600	15.9483	84.74789	0.1349318	123.9885415	Viable - Alternate	
Dichotomous Hill	Unrestricted	1.07172	0	18.13280	NA	123.9261336	Unusable	BMD computation failed; lower limit includes 0 BMDL not estimated BMD 10x lower than lowest non-zero dose d.f.=0 (Goodness of fit test cannot be calculated)
Logistic	NA	49.4825	34.0090	100.1899	0.0890178	125.2278017	Questionable	Goodness of fit p-value < 0.1
Log-Probit	Unrestricted	1.35920	0	18.12044	0.6604573	121.9394443	Unusable	BMD computation failed; lower limit includes 0 BMDL not estimated BMD 10x lower than lowest non-zero dose
Probit	NA	47.4459	32.8038	97.34369	0.0918383	125.1319918	Questionable	Goodness of fit p-value < 0.1

[a] Selected Model (Gray); residuals for doses 0, 13.9, 48.4 and 181.4 were -0.976071189, 1.341257654, 0.170425804 and -0.717257235, respectively.
[b] Restrictions defined in the BMDS 3.1.1 User Guide; NA = Not Applicable



Selected Model – Log-Logistic (Restricted) - Extra Risk, BMR = 0.1

USER INPUT

Info	
Model	Log-Logistic v1.0
Dataset Name	P2F2B Female Fecundity

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

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

MODEL RESULTS

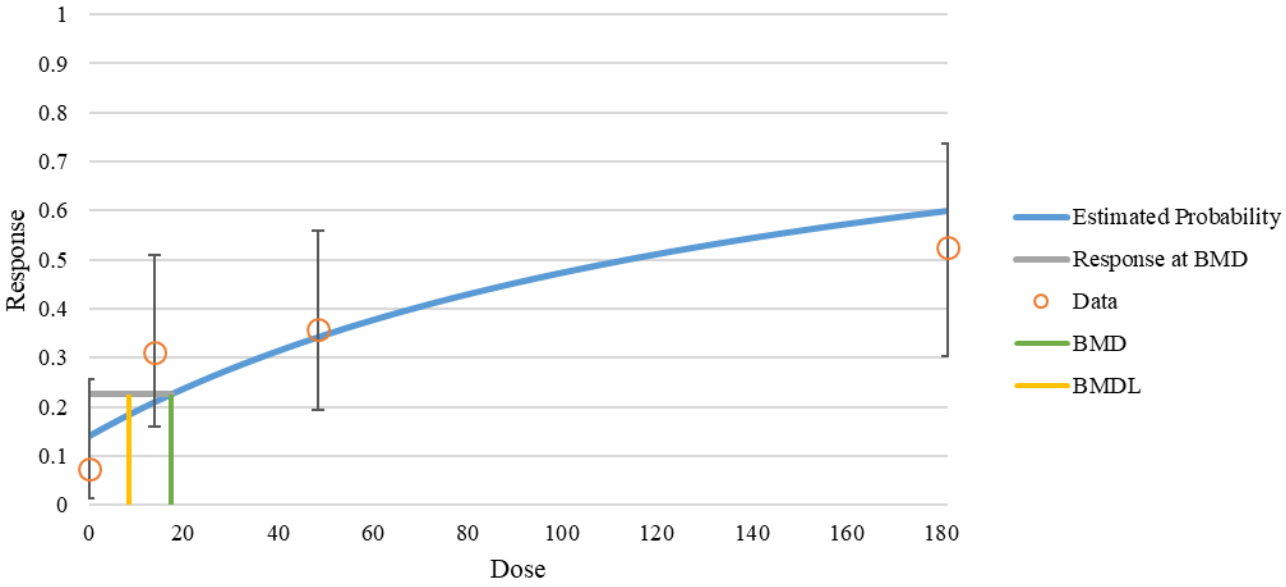
Benchmark Dose	
BMD	17.45276136
BMDL	8.395858147
BMDU	58.44881649
AIC	123.0293723
P-value	0.192512349
D.O.F.	2
Chi^2	3.295189957

Model Parameters	
# of Parameters	3
Variable	Estimate
g	0.139072629
a	-5.056722458
b	Bounded

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.139072629	3.754960985	2	27	-0.976071
13.9	0.209064738	6.062877397	9	29	1.3412577
48.4	0.341865741	9.572240753	10	28	0.1704258
181.4	0.600472417	12.60992076	11	21	-0.717257

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-57.87277378	4	-	-	-
Fitted Model	-59.51468613	2	3.2838247	2	0.1936094
Reduced Model	-64.55874867	1	13.3719498	3	0.0038975

P2/F2B Female Rat Fecundity (Females Unsuccessful/Females Mated) vs NMP Blood Concentration - 50 g Rat (Exxon, 1991; Appendix AG) - Log-Logistic Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL



4.3 Results of BMD Modeling of P2 Litter (Exxon (1991a))

The next most sensitive dose-related reproductive effect noted in the Exxon (1991b) study, other than the reduction in male fertility and female fecundity, was the reduction in litter size, which was most pronounced for the first (F2A) and 2nd (F2B) P2 rat litters. However, the Exxon (1991b) study also reported a dose-related increase in pup death by postnatal day 4 that was also most pronounced in the F2A and F2B litters of the P2 parental rats. Thus, the extent to which the reduction in litter size is due to reproductive effects on the parents or gestational effects on the fetus is not clear, and the Exxon (1991b) reproductive study design does not allow for a definitive investigation of that question (*e.g.*, the number of implantations and resorptions were not identified). For these reasons, the litter size reduction effect was analyzed three ways:

- Model litter size means and SD (live and stillborn pups) using BMDS continuous models against estimates of internal doses to young (50 g) parental rats (Sections 4.3.1 and 4.3.2).
- Model litter size means and SD (live and stillborn pups) using BMDS continuous models against estimates of internal doses to P2 maternal rats during GD 6-21 (Sections 4.3.3 and 4.3.4).
- Model pup death at day 0 (stillborn) and by postnatal day 4 per total pups born as incidence data using BMDS nested dichotomous models against estimates of internal doses to P2 maternal rats during GD 6-21 (Section 4.4).

Individual litter data that allows for the calculation of dose-specific means and standard deviations for litter size are available in Appendix AJ (for P2/F2A litters) and AK (for P2/FB litters) of the Exxon (1991b) report.

Standard and nonstandard continuous models (defined below) were used to fit litter size data. BMDs were estimated for 1 SD change from control mean. Internal doses used for BMD modeling were based on PBPK estimates of average daily blood concentrations for young (50 g) rat and GD 6-21 dams.

Standard Continuous Models Applied to Litter Size Response:

- Exponential 2-restricted
- Exponential 3-restricted
- Exponential 4-restricted
- Exponential 5-restricted
- Hill-restricted
- Polynomial Degree 3-restricted
- Polynomial Degree 2-restricted
- Power-restricted
- Linear

Non-Standard Continuous Models Applied to Litter Size Response:

- Hill-unrestricted
- Polynomial Degree 3-unrestricted
- Polynomial Degree 2-unrestricted
- Power-unrestricted

General Model Options Used for Litter Size Continuous Response:

- Benchmark Response (BMR): 1 Standard Deviation (SD) Change from Control Mean
- Confidence Level: 0.95
- Background: Estimated

4.3.1 P2/F2A Litter Size - 50 g Rat (Exxon Appendix AJ, "Total Pups Born")

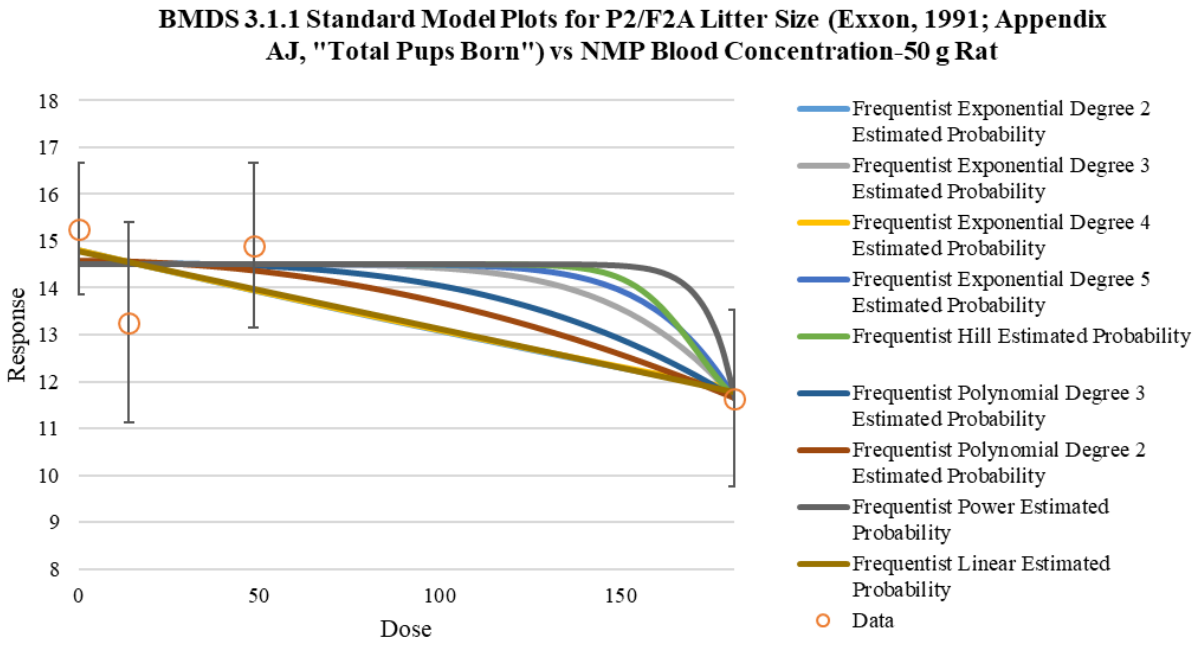
mg/L Blood – 50 g Rat	N	Mean	SD
0	27	15.2592593	3.558225
13.9	23	13.2608696	4.937955
48.4	21	14.9047619	3.871754
181.4	14	11.6428571	3.272429

Table 4-9 Model Predictions for Litter Size in P2/F2A Rats Based on Post-weaning Exposure (Exxon (1991b))

Standard Models	Restriction [b]	BMR = 1 Standard Deviation (mg/L blood – 50 g Rat)			P-value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL	BMDU				
Exponential 2 (CV)	Restricted	264.277	140.444	1032.840	0.1317861	483.4105957	Viable - Alternate	BMD higher than maximum dose
Exponential 3 (CV)	Restricted	190.060	149.059	788.7670	0.0625955	484.8246912	Questionable	Goodness of fit p-value < 0.1 BMD higher than maximum dose
Exponential 4 (CV)	Restricted	264.120	140.442	1032.835	0.1317865	483.4105902	Viable - Alternate	BMD higher than maximum dose
Exponential 5 (CV)	Restricted	190.171	149.060	788.7498	NA	486.8246961	Questionable	BMD higher than maximum dose d.f.=0 (Goodness of fit test cannot be calculated)
Hill (CV)	Restricted	-9999	0	Infinity	0.0625977	484.8246333	Unusable	BMD computation failed BMD not estimated BMDL not estimated Goodness of fit p-value < 0.1
Polynomial Degree 3 (CV) [a]	**Restricted**	**202.696**	**150.674**	**714.9564**	**0.1718518**	**482.8796917**	**Recommended**	**Basis: Lowest AIC** BMD higher than maximum dose
Polynomial Degree 2 (CV)	Restricted	214.035	148.914	757.4027	0.1605273	483.016028	Viable - Alternate	BMD higher than maximum dose
Power (CV)	Restricted	183.783	182.112	698.8191	0.0625983	484.824615	Questionable	Goodness of fit p-value < 0.1 BMD higher than maximum dose BMDL higher than maximum dose
Linear (CV)	NA	248.915	145.061	875.6812	0.1364343	483.34127	Viable - Alternate	BMD higher than maximum dose

[a] Selected Model (Gray); Constant variance case presented (Test 2 p-value = 0.24158); scaled residuals for doses 0, 13.9, 48.4 and 181.4 were 0.958706516, -1.509731959, 0.501737513 and -0.010801354, respectively.

[b] Restrictions defined in the BMDS 3.1.1 User Guide; NA = Not Applicable; CV = Constant Variance Model; NCV = Non-Constant Variance Model.



Selected Model – Polynomial Degree 3 (Restricted) - Extra Risk, BMR = 1 SD

USER INPUTS

Info	
Model	Polynomial degree 3 v1.1
Dataset Name	P2F2A Litter Size
Dose-Response Model	M[dose] = g + b1*dose + b2*dose^2 + ...

Model Options	
BMR Type	Std. Dev.
BMRF	1
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal

Model Data	
Dependent Variable	[Dose]
Independent Variable	[Response]
Total # of Observations	85
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	202.6960934
BMDL	150.6744181
BMDU	714.956421
AIC	482.8796917
Test 4 P-value	0.171851757
D.O.F.	2

Model Parameters	
# of Parameters	5
Variable	Estimate
g	14.52128961
b1	Bounded
b2	Bounded
b3	-4.80285E-07
alpha	15.99813687

Goodness of Fit

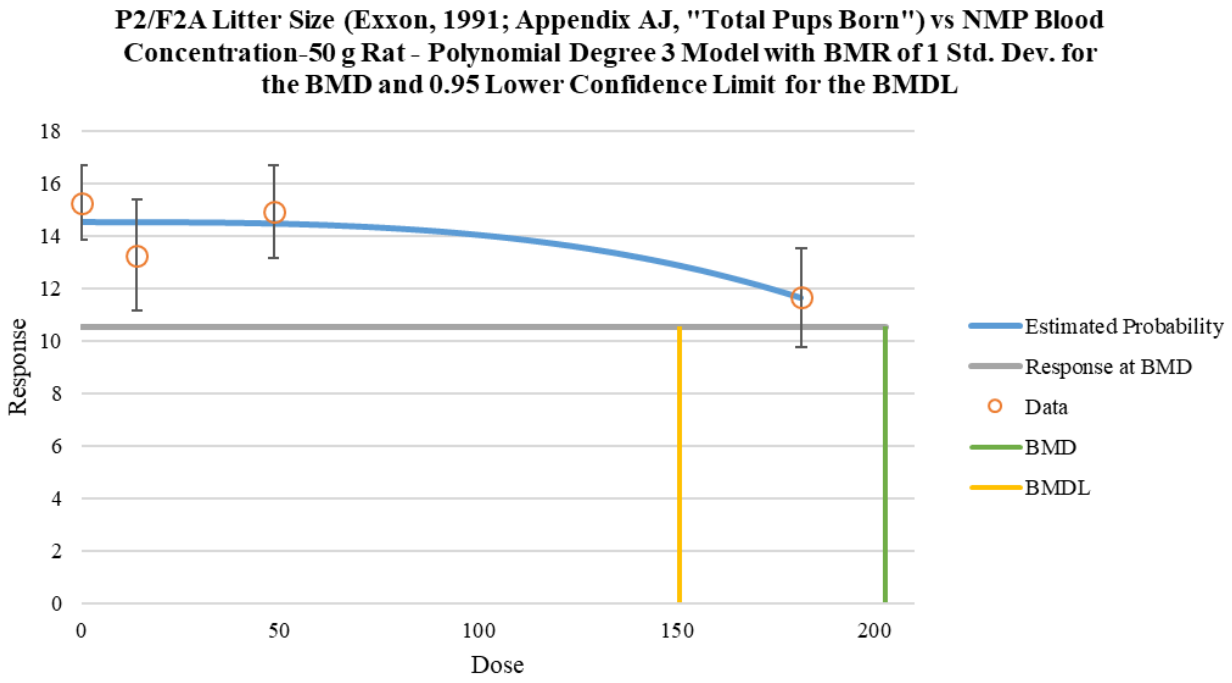
Dose	Size	Estimated Median	Calc'd Median	Observed Median	Estimated SD	Calc'd SD	Observed DS	Scaled Residual
0	27	14.52128961	15.2592593	15.2592593	3.9997671	3.558225	3.558225	0.958706516
13.9	23	14.51999975	13.2608696	13.2608696	3.9997671	4.937955	4.937955	-1.50973196
48.4	21	14.466835	14.9047619	14.9047619	3.9997671	3.871754	3.871754	0.501737513
181.4	14	11.6544036	11.6428571	11.6428571	3.9997671	3.272429	3.272429	-0.01080135

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-236.6787228	5	483.357446
A2	-234.583299	8	485.166598
A3	-236.6787228	5	483.357446
fitted	-238.4398459	3	482.879692
R	-241.3113542	2	486.622708

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	13.45611034	6	0.03633832
2	4.190847665	3	0.24157981
3	4.190847665	3	0.24157981
4	3.522246101	2	0.17185176


P2/F2A Litter Size (Exxon, 1991; Appendix AJ, "Total Pups Born") vs NMP Blood Concentration-50 g Rat - Polynomial Degree 3 Model with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
2
4
6
8
10
12
14
16
18
0
50
100
150
200
Estimated Probability
Response at BMD
Data
BMD
BMDL

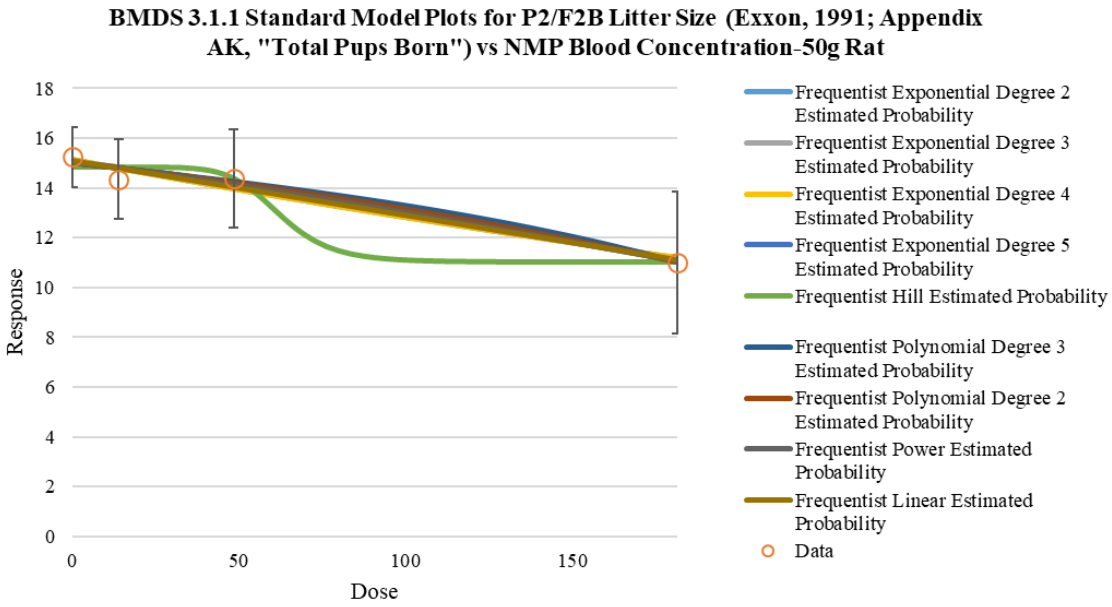
4.3.2 P2/F2B Litter Size - 50 g Rat (Exxon Appendix AK, "Total Pups Born")

mg/L Blood – 50 g Rat	N	Mean	SD
0	25	15.24	2.947881
13.9	20	14.35	3.422449
48.4	18	14.39	3.972536
181.4	9	11	3.708099

Table 4-10 Model Predictions for Litter Size in P2/F2B Rats Based on Post-weaning Exposure (Exxon (1991b))

Standard Models	Restriction [b]	BMR = 1 Standard Deviation (mg/L blood – 50 g Rat)			P-value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL	BMDU				
Exponential 2 (CV)	Restricted	151.211	90.0144	358.8807	0.710819 6	385.221887	Viable - Alternate	
Exponential 3 (CV)	Restricted	156.952	90.5626	352.6854	0.435551 2	387.147189	Viable - Alternate	
Exponential 4 (CV)	Restricted	151.178	90.0145	358.8685	0.710823 3	385.221876 5	Viable - Alternate	
Exponential 5 (CV)	Restricted	156.962	50.8164	352.691	NA	389.147203 2	Viable - Alternate	BMD/BMDL ratio > 3 d.f.=0 (Goodness of fit test cannot be calculated)
Hill (CV)	Restricted	79.4642	51.8612	Infinity	NA	389.317859	Questionable	d.f.=0 (Goodness of fit test cannot be calculated)
Polynomial Degree 3 (CV)	Restricted	162.787	100.264	324.5483	0.478185 6	387.042212	Viable - Alternate	
Polynomial Degree 2 (CV)	Restricted	159.731	100.102	326.2531	0.467703 9	387.066609 3	Viable - Alternate	
Power (CV)	Restricted	157.000	99.7630	329.8951	0.446602 9	387.118472 9	Viable - Alternate	
Linear (CV) [a]	NA	**153.231**	**99.6158**	**331.5177**	**0.740097 5**	**385.141160 3**	**Recommended**	**Basis: Lowest AIC**

[a] Selected Model (Gray); Constant variance case presented (Test 2 p-value = 0.60824); scaled residuals for doses 0, 13.9, 48.4 and 181.4 were 0.209483207, -0.589116734, 0.445351928 and -0.100787718, respectively.
[b] Restrictions defined in the BMDS 3.1.1 User Guide; NA = Not Applicable; CV = Constant Variance Model; NCV = Non-Constant Variance Model.



Selected Model – Linear - Extra Risk, BMR = 1 SD

USER INPUT

Info	
Model	Linear v1.1
Dataset Name	P2F2B Litter Size
User notes	[Add user notes here]
Dose-Response Model	M[dose] = g + b1*dose

Model Options	
BMR Type	Std. Dev.
BMRF	1
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal

Model Data	
Dependent Variable	[Dose]
Independent Variable	[Response]
Total # of Observations	72
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	153.2308251
BMDL	99.6158179
BMDU	331.5176516
AIC	385.1411603
Test 4 P-value	0.740097541
D.O.F.	2

Model Parameters	
# of Parameters	3
Variable	Estimate
g	15.09893919
beta1	-0.02197258
alpha	11.33585663

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	25	15.09893919	15.24	15.24	3.366876 39	2.947881	2.947881	0.209483207
13.9	20	14.79352033	14.35	14.35	3.366876 39	3.422449	3.422449	-0.5891167
48.4	18	14.03546634	14.38888 89	14.38888 89	3.366876 39	3.972536	3.972536	0.445351928
181.4	9	11.11311326	11	11	3.366876 39	3.708099	3.708099	-0.1007877

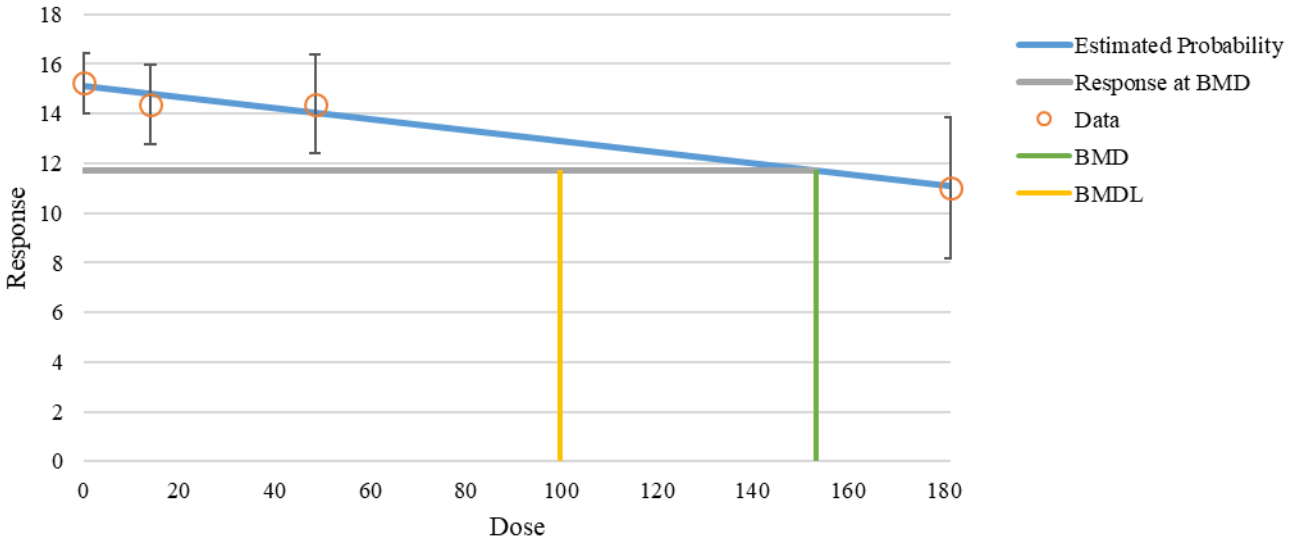
Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-189.2696069	5	388.539214
A2	-188.354168	8	392.708336
A3	-189.2696069	5	388.539214
fitted	-189.5705801	3	385.14116
R	-194.2508792	2	392.501758

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	11.79342232	6	0.06673919
2	1.830877708	3	0.60823876
3	1.830877708	3	0.60823876
4	0.601946577	2	0.74009754

P2/F2B Litter Size (Exxon, 1991; Appendix AK, "Total Pups Born") vs NMP Blood Concentration-50 g Rat - Linear Model with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL



4.3.3 P2/F2A Litter Size – GD 6-21 Rat (Exxon Appendix AJ, "Total Pups Born")

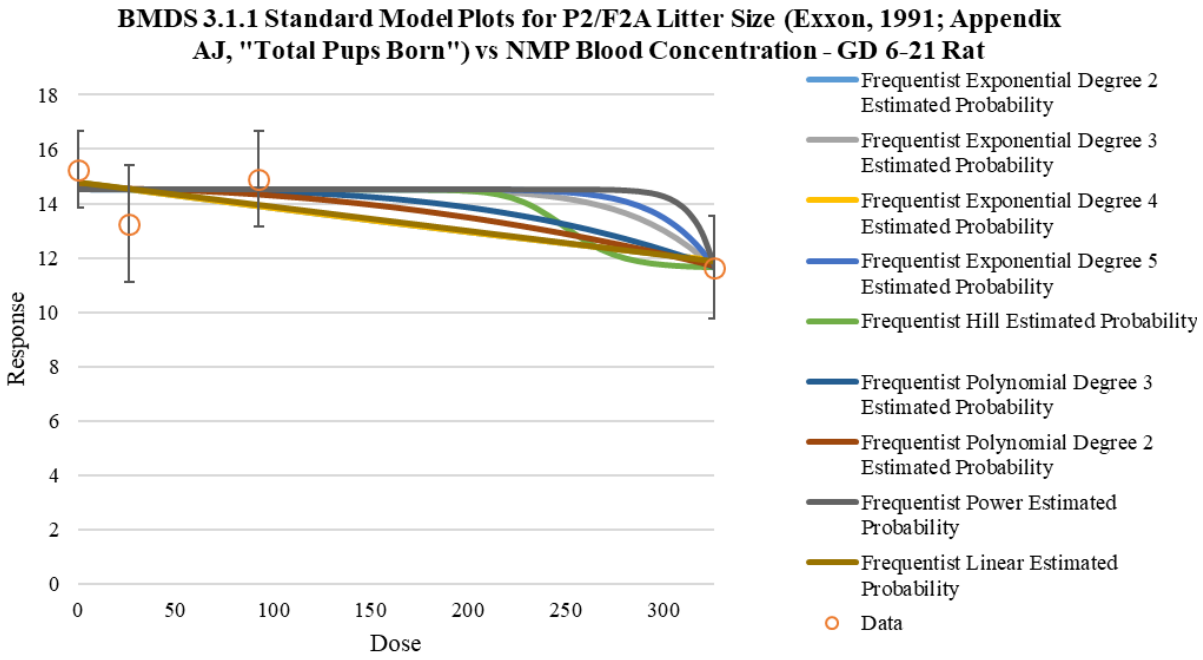
mg/L Blood – GD 6-21 Rat	N	Mean	SD
0	27	15.2592593	3.558225
26.1207	23	13.2608696	4.937955
92.5466	21	14.9047619	3.871754
326.1056	14	11.6428571	3.272429

Table 4-11 Model Predictions for Litter Size in P2/F2A Rats Based on Gestational Exposure (Exxon (1991b))

Standard Models	Restriction [b]	BMR = 1 Standard Deviation (mg/L Blood – GD 6-21 Rat)			P-value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL	BMDU				
Exponential 2 (CV)	Restricted	479.877	254.430	1919.152	0.1260017	483.5003647	Viable - Alternate	BMD higher than maximum dose
Exponential 3 (CV)	Restricted	341.070	272.816	1398.651	0.0625939	484.8247334	Questionable	Goodness of fit p-value < 0.1 BMD higher than maximum dose
Exponential 4 (CV)	Restricted	479.845	254.427	1919.011	0.041809	485.5003647	Viable - Alternate	Goodness of fit p-value < 0.1 BMD higher than maximum dose
Exponential 5 (CV)	Restricted	335.907	105.778	369.6251	NA	486.8246164	Questionable	BMD/BMDL ratio > 3 BMD higher than maximum dose d.f.=0 (Goodness of fit test cannot be calculated)
Hill (CV)	Restricted	-9999	0	Infinity	NA	486.8246156	Unusable	BMD computation failed BMD not estimated BMDL not estimated d.f.=0 (Goodness of fit test cannot be calculated)
Polynomial Degree 3 (CV) [a]	**Restricted**	**364.394**	**273.796**	**1275.735**	**0.170808**	**482.8918758**	**Recommended**	**Basis: Lowest AIC BMD higher than maximum dose**
Polynomial Degree 2 (CV)	Restricted	384.961	270.021	1364.628	0.1578744	483.0493569	Viable - Alternate	BMD higher than maximum dose
Power (CV)	Restricted	329.908	275.482	1240.389	0.0625983	484.824615	Questionable	Goodness of fit p-value < 0.1 BMD higher than maximum dose
Linear (CV)	NA	450.859	261.883	1618.656	0.1308827	483.4243533	Viable - Alternate	BMD higher than maximum dose

[a] Selected Model (Gray); Constant variance case presented (Test 2 p-value = 0.24158); scaled residuals for doses0, 26.1207, 92.5466 and 326.1056were 0.954993534, -1.512767309, 0.511175014 and -0.013313118, respectively.

[b] Restrictions defined in the BMDS 3.1.1 User Guide; NA = Not Applicable; CV = Constant Variance Model; NCV = Non-Constant Variance Model.



Selected Model – Polynomial Degree 3 (Restricted) - Extra Risk, BMR = 1

USER INPUT

Info	
Model	Polynomial degree 3 v1.1
Dataset Name	P2F2A Litter Size GD 6-21
Dose-Response Model	M[dose] = g + b1*dose + b2*dose^2 + ...

Model Options	
BMR Type	Std. Dev.
BMRF	1
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal

Model Data	
Dependent Variable	[Dose]
Independent Variable	[Response]
Total # of Observations	85
Adverse Direction	Automatic

MODEL RESULTS

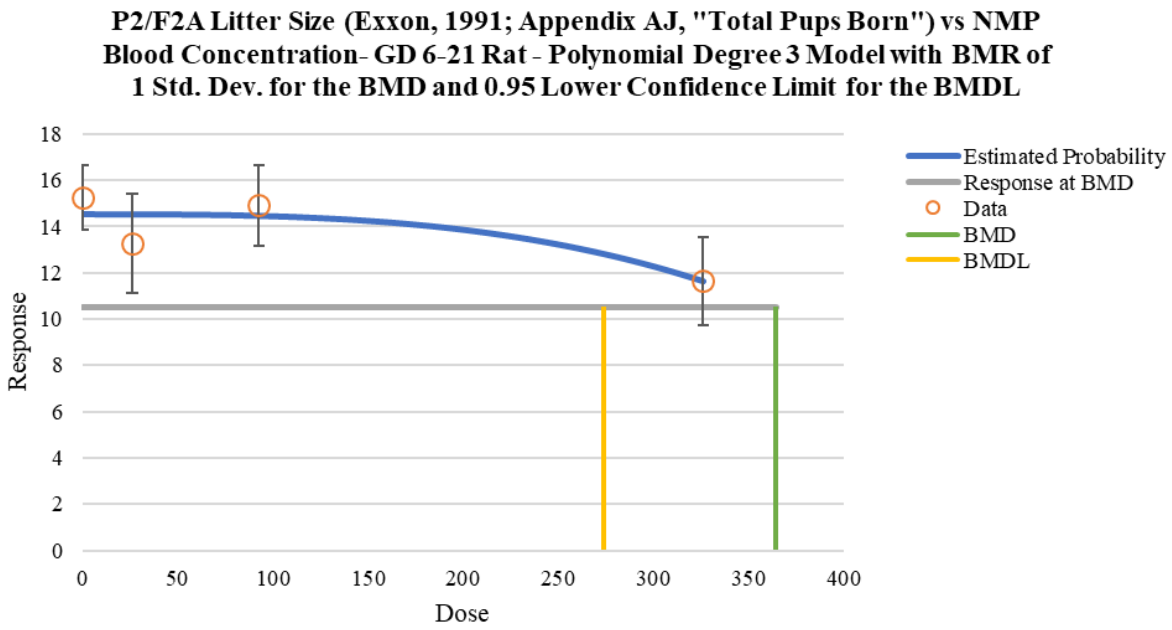
Benchmark Dose	
BMD	364.3935627
BMDL	273.7956247
BMDU	1275.734624
AIC	482.8918758
Test 4 P-value	0.170808016
D.O.F.	2

Model Parameters	
# of Parameters	5
Variable	Estimate
g	14.52409502
b1	Bounded
b2	Bounded
b3	-8.26711E-08
alpha	16.00042971

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	27	14.52409502	15.2592593	15.2592593	4.000053 71	3.558225	3.558225	0.954993534
26.1207	23	14.52262166	13.2608696	13.2608696	4.000053 71	4.937955	4.937955	-1.512767
92.5466	21	14.45856578	14.9047619	14.9047619	4.000053 71	3.871754	3.871754	0.511175014
326.1056	14	11.65708966	11.6428571	11.6428571	4.000053 71	3.272429	3.272429	-0.013313

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-236.6787228	5	483.357446
A2	-234.583299	8	485.166598
A3	-236.6787228	5	483.357446
fitted	-238.4459379	3	482.891876
R	-241.3113542	2	486.622708

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	13.45611034	6	0.03633832
2	4.190847665	3	0.24157981
3	4.190847665	3	0.24157981
4	3.534430134	2	0.17080802


P2/F2A Litter Size (Exxon, 1991; Appendix AJ, "Total Pups Born") vs NMP Blood Concentration- GD 6-21 Rat - Polynomial Degree 3 Model with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
2
4
6
8
10
12
14
16
18
0
50
100
150
200
250
300
350
400
Estimated Probability
Response at BMD
Data
BMD
BMDL

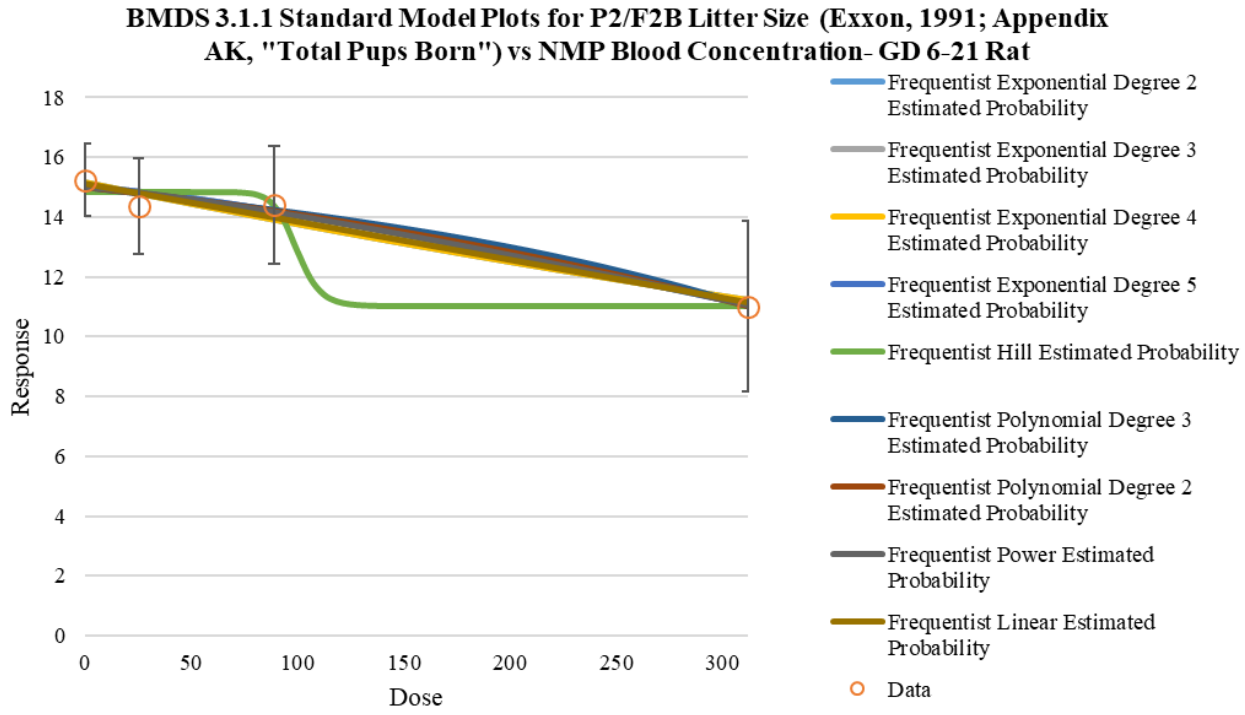
4.3.4 P2/F2B Litter Size – GD 6-21 Rat (Exxon Appendix AK, "Total Pups Born")

mg/L Blood – GD 6-21 Rat	N	Mean	SD
0	25	15.24	2.947881
25.25	20	14.35	3.422449
89.03	18	14.39	3.972536
311.9	9	11	3.708099

Table 4-12 Model Predictions for Litter Size in P2/F2B Rats Based on Gestational Exposure (Exxon (1991b))

Standard Models	Restriction [b]	BMR = 1 Standard Deviation (mg/L Blood – GD 6-21 Rat)			P-value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL	BMDU				
Exponential 2 (CV)	Restricted	262.367	156.209	625.5100	0.6820873	385.304409	Viable - Alternate	
Exponential 3 (CV)	Restricted	273.939	157.878	606.7505	0.4253036	387.1748276	Viable - Alternate	
Exponential 4 (CV)	Restricted	262.375	156.208	625.4980	0.6820873	385.304409	Viable - Alternate	
Exponential 5 (CV)	Restricted	273.909	157.876	606.7426	NA	389.1748274	Questionable	d.f.=0 (Goodness of fit test cannot be calculated)
Hill (CV)	Restricted	111.061	95.2881	Infinity	NA	389.3179007	Questionable	d.f.=0 (Goodness of fit test cannot be calculated)
Polynomial Degree 3 (CV)	Restricted	281.842	173.628	556.2398	0.4745885	387.0504862	Viable - Alternate	
Polynomial Degree 2 (CV)	Restricted	276.875	173.241	560.2511	0.4606428	387.0835461	Viable - Alternate	
Power (CV)	Restricted	273.907	172.502	568.1038	0.4351554	387.1482381	Viable - Alternate	
Linear (CV) [a]	**NA**	**264.704**	**171.883**	**574.9049**	**0.717494**	**385.203195**	**Recommended**	**Basis: Lowest AIC**

[a] Selected Model (Gray); Constant variance case presented (Test 2 p-value = 0.60824); scaled residuals for selected model for doses 0, 25.25, 89.0333, and 311.8896 were 0.180266075, -0.593822034, 0.507945167 and -0.133410146, respectively.
[b] Restrictions defined in the BMDS 3.1.1 User Guide; NA = Not Applicable; CV = Constant Variance Model; NCV = Non-Constant Variance Model.



Selected Model –Linear - Extra Risk, BMR = 1 SD

USER INPUT

Info	
Model	Linear v1.1
Dataset Name	P2F2B Litter Size GD 6-21
Dose-Response Model	M[dose] = g + b1*dose

Model Options	
BMR Type	Std. Dev.
BMRF	1
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal

Model Data	
Dependent Variable	Dose]
Independent Variable	Response]
Total # of Observations	72
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	264.7037947
BMDL	171.8830314
BMDU	574.9048606
AIC	385.203195
Test 4 P-value	0.717494025
D.O.F.	2

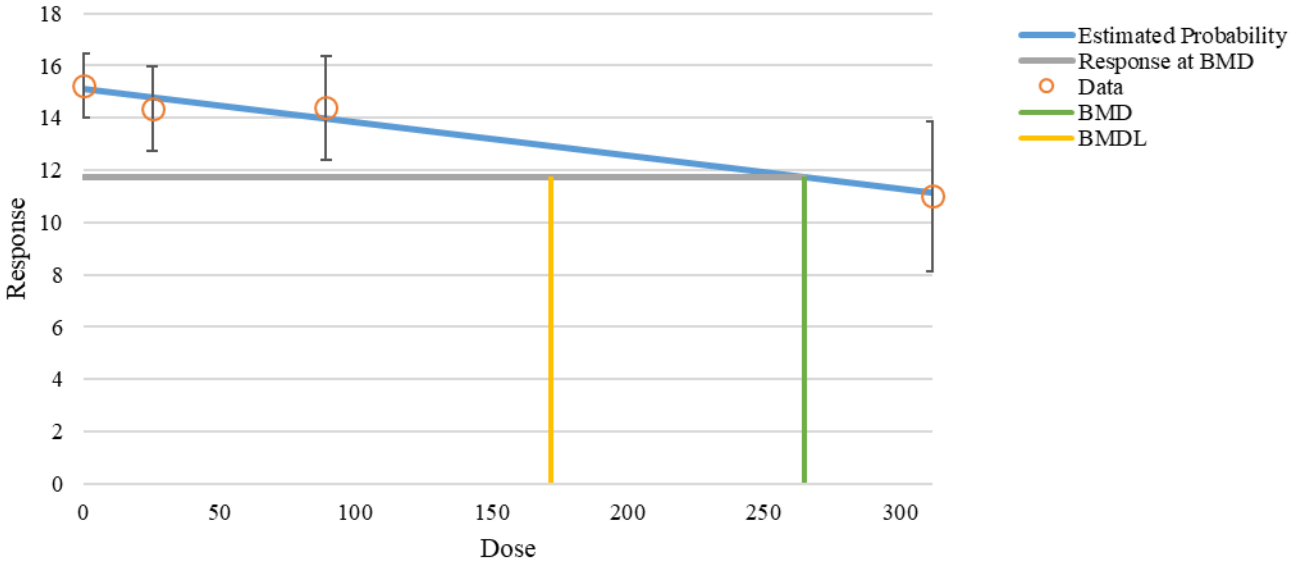
Model Parameters	
# of Parameters	3
Variable	Estimate
g	15.11856069
beta1	-0.012724921
alpha	11.34568072

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	25	15.11856069	15.24	15.24	3.368335 01	2.947881	2.947881	0.180266075
25.25	20	14.79725643	14.35	14.35	3.368335 01	3.422449	3.422449	-0.593822
89.0333	18	13.98561894	14.388889	14.388889	3.368335 01	3.972536	3.972536	0.507945167
311.8896	9	11.14979002	11	11	3.368335 01	3.708099	3.708099	-0.133410

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-189.2696069	5	388.539214
A2	-188.354168	8	392.708336
A3	-189.2696069	5	388.539214
fitted	-189.6015975	3	385.203195
R	-194.2508792	2	392.501758

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	11.79342232	6	0.06673919
2	1.830877708	3	0.60823876
3	1.830877708	3	0.60823876
4	0.663981316	2	0.71749403

P2/F2B Litter Size (Exxon, 1991; Appendix AK, "Total Pups Born") vs NMP Blood Concentration - GD 6-21 Rat - Linear Model with BMR of 1 SD for the BMD and 0.95 Lower Confidence Limit for the BMDL



4.4 Results of BMD Modeling of P2 Pup Death (Exxon (1991a))

Nested dichotomous models were applied to fit pup death for the P2/F2A and P2/F2B litters. Nested dichotomous models are preferred for this endpoint because they contain an intra-litter correlation coefficient for the assessment of litter-specific responses. Details regarding pup death at day 0 (stillborn) and by day 4 are available in Appendix AJ (for P2/F2A litters) and AK (for P2/FB litters) of the Exxon (1991b) report.

The pup death endpoint was analyzed using BMDS 2.7 because it contains the larger suite of nested dichotomous models. To assess intra-litter correlations (ILC) BMDS nested dichotomous models were run two ways, with ILC coefficients estimated and with ILC coefficients assumed to be zero. Because potential litter-specific covariates (LSCs) such as dam BW are affected by dose, LSCs were not assessed in the BMDS nested dichotomous model runs. The following nested dichotomous models and general modeling options were used to the pup death incidence data.

Nested Dichotomous Models Applied to Pup Death Response[7]:

- NLogistic – Nested Logistic model with ILC coefficients assumed to be 0
- NLogistic-ILC – Nested Logistic model with ILC coefficients estimated
- NCTR - National Center for Toxicological Research model with ILC coefficients assumed to be 0
- NCTR-ILC - NCTR model with ILC coefficients estimated
- RaiVR – Rai and Van Ryzin model with ILC coefficients assumed to be 0
- RaiVR-ILC - Rai and Van Ryzin model with ILC coefficients estimated

General Model Options Used for Pup Death Nested Dichotomous Response:

- Benchmark Response (BMR): 10% (not shown in report), 5% and 1% Extra Risk
- Confidence Level: 0.95
- Background: Estimated

[7] As indicated in the tables in 2.6, the NLogistic model is generally preferred because it has received the more extensive QA testing, but the NCTR and RaiVR models are provided as alternative models.

4.4.1 P2/F2A Pups Dead at Day 0 (Stillborn Day 0/Total Pups Born; Exxon 1991 Appendix AJ)

Control			26.1207 avg. mg/L blood GD 6-21			92.5466 avg. mg/L blood GD 6-21			326.1056 avg. mg/L blood GD 6-21		
Dam	N	Stillborn	Dam	N	Stillborn	Dam	N	Stillborn	Dam	N	Stillborn
JAB248	12	0	JAB029	17	0	JAB302	15	0	JAB325	13	0
JAB026	16	0	JAB032	17	0	JAB038	14	1	JAB327	12	0
JAB251	14	0	JAB279	14	2	JAB110	15	0	JAB041	13	8
JAB097	15	0	JAB104	13	1	JAB305	16	1	JAB135	7	0
JAB254	9	0	JAB282	13	0	JAB113	20	1	JAB136	4	0
JAB100	18	2	JAB285	16	1	JAB116	22	1	JAB045	14	0
JAB257	17	1	JAB288	17	0	JAB311	16	0	JAB050	12	0
JAB260	18	0	JAB035	14	1	JAB121	9	0	JAB336	11	0
JAB263	15	0	JAB107	19	0	JAB319	15	0	JAB329	11	0
JAB266	15	0	JAB292	1	1	JAB322	14	0	JAB330	8	2
JAB269	18	1	JAB295	7	0	JAB320	3	0	JAB046	14	0
JAB10	18	1	JAB347	16	0	JAB306	13	0	JAB328	14	0
JAB270	18	0	JAB298	5	0	JAB313	17	1	JAB134	16	1
JAB273	15	0	JAB348	19	1	JAB323	14	0	JAB341	14	1
JAB252	16	0	JAB293	5	0	JAB310	15	1			
JAB028	18	1	JAB037	14	1	JAB117	14	0			
JAB275	18	0	JAB349	16	0	JAB040	20	0			
JAB255	16	0	JAB278	16	1	JAB309	14	1			
JAB264	15	0	JAB105	14	0	JAB039	16	0			
JAB267	17	0	JAB297	15	0	JAB317	14	0			
JAB262	17	0	JAB106	17	0	JAB112	17	0			
JAB102	17	3	JAB281	6	0						
JAB246	2	1	JAB290	14	0						
JAB256	10	0									
JAB098	15	0									
JAB249	15	0									
JAB253	18	0									

Table 4-13 Model Predictions for Pup Death at Day 0 in P2/F2A Rats (Exxon (1991b))

Preferred Models [a]	5% Extra Risk		1% Extra Risk		P-value	AIC	BMDS Recommends [b]	BMDS Recommendation Notes
	BMD	BMDL	BMD	BMDL				
NLogistic	326.34	240.809	280.408	50.7883	0.0007	334.364	Questionable	BMD/BMDL ratio > 3 Goodness of fit p-value < 0.1
NLogistic-ILC	**327.095**	**205.186**	**281.145**	**49.3219**	**0.1017**	**313.315**	**Recommended**	**Basis: Lowest AIC BMD/BMDL ratio > 3 for 1% Extra Risk**
Alternative Models								
NCTR	326.327	271.939	282.34	235.284	0	332.364	Questionable	Goodness of fit p-value < 0.1
NCTR-ILC	327.114	0.633785	327.114	0.633785	0.1103	311.315	Questionable	BMD/BMDL ratio > 20
RaiVR	281.131	234.276	281.131	234.276	0	332.364	Questionable	Goodness of fit p-value < 0.1
RaiVR-ILC	327.118	0.633785	280.539	0.472244	0.0867	311.315	Questionable	BMD/BMDL ratio > 20

[a] NLogistic is preferred because it is the more rigorously tested nested model. All nested models were restricted. Restrictions are defined in the BMDS 3.1.1 User Guide; ILC = Intra-litter Correlation Coefficients estimated; Because potential litter-specific covariates (LSCs) such as dam BW are affected by dose, LSCs were not estimated.

[b] Selected Model (Gray); the average scaled residual for dose group nearest the BMD05 and BMD01 were -0.3523 and -0.3523, respectively.

Selected Model Results– NLogistic- ILC, BMR = 0.01 and 0.05 Extra Risk

```
================================================================
        NLogistic Model. (Version: 2.20; Date: 04/27/2015)
        Input Data File: C:/Users/jgift/BMDS2704/Data/NMP/P2F2A Dead Day 0/nln_P2F2A Day 0
Deaths_Nln-BMR01-Restrict-noLSC.(d)
                                                  Tue Jul 30 22:03:20 2019
================================================================
BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
The probability function is:

Prob. = alpha + theta1*Rij + [1 - alpha - theta1*Rij]/

            [1+exp(-beta-theta2*Rij-rho*log(Dose))],

     where Rij is the litter specific covariate.

Restrict Power rho >= 1.

Total number of observations = 85
Total number of records with missing values = 0
Total number of parameters in model = 9
Total number of specified parameters = 2

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
Number of Bootstrap Iterations per run: 1000
Bootstrap Seed:  1564538600

User specifies the following parameters:
     theta1 =         0
     theta2 =         0

          Default Initial Parameter Values
              alpha =      0.02553
               beta =     -66.0821
             theta1 =            0   Specified
             theta2 =            0   Specified
               rho =      10.9041
              phi1 =     0.0392728
              phi2 =             0
              phi3 =             0
              phi4 =      0.310565

                  Parameter Estimates

    Variable         Estimate          Std. Err.
      alpha           0.02553         0.00468854
       beta          -66.0821          0.792172
        rho           10.9041         0.0311563
       phi1         0.0392728                NA
```

phi2	0	Bounded
phi3	0	Bounded
phi4	0.310565	NA

Log-likelihood: -151.658 AIC: 313.315

Litter Data

Dose	Lit.-Spec. Cov.	Est._Prob.	Litter Size	Scaled Expected	Observed	Residual
0.0000	2.0000	0.026	2	0.051	1	4.1730
0.0000	9.0000	0.026	9	0.230	0	-0.4236
0.0000	10.0000	0.026	10	0.255	0	-0.4400
0.0000	12.0000	0.026	12	0.306	0	-0.4686
0.0000	14.0000	0.026	14	0.357	0	-0.4928
0.0000	15.0000	0.026	15	0.383	0	-0.5036
0.0000	15.0000	0.026	15	0.383	0	-0.5036
0.0000	15.0000	0.026	15	0.383	0	-0.5036
0.0000	15.0000	0.026	15	0.383	0	-0.5036
0.0000	15.0000	0.026	15	0.383	0	-0.5036
0.0000	15.0000	0.026	15	0.383	0	-0.5036
0.0000	15.0000	0.026	15	0.383	0	-0.5036
0.0000	16.0000	0.026	16	0.408	0	-0.5136
0.0000	16.0000	0.026	16	0.408	0	-0.5136
0.0000	16.0000	0.026	16	0.408	0	-0.5136
0.0000	17.0000	0.026	17	0.434	0	-0.5230
0.0000	17.0000	0.026	17	0.434	0	-0.5230
0.0000	17.0000	0.026	17	0.434	1	0.6820
0.0000	17.0000	0.026	17	0.434	3	3.0920
0.0000	18.0000	0.026	18	0.460	0	-0.5318
0.0000	18.0000	0.026	18	0.460	1	0.6254
0.0000	18.0000	0.026	18	0.460	1	0.6254
0.0000	18.0000	0.026	18	0.460	0	-0.5318
0.0000	18.0000	0.026	18	0.460	0	-0.5318
0.0000	18.0000	0.026	18	0.460	2	1.7826
0.0000	18.0000	0.026	18	0.460	1	0.6254
0.0000	18.0000	0.026	18	0.460	0	-0.5318
26.1207	1.0000	0.026	1	0.026	1	6.1782
26.1207	5.0000	0.026	5	0.128	0	-0.3619
26.1207	5.0000	0.026	5	0.128	0	-0.3619
26.1207	6.0000	0.026	6	0.153	0	-0.3965
26.1207	7.0000	0.026	7	0.179	0	-0.4282
26.1207	13.0000	0.026	13	0.332	1	1.1748
26.1207	13.0000	0.026	13	0.332	0	-0.5836
26.1207	14.0000	0.026	14	0.357	0	-0.6056
26.1207	14.0000	0.026	14	0.357	2	2.7833
26.1207	14.0000	0.026	14	0.357	0	-0.6056
26.1207	14.0000	0.026	14	0.357	1	1.0888
26.1207	14.0000	0.026	14	0.357	1	1.0888
26.1207	15.0000	0.026	15	0.383	0	-0.6269

26.1207	16.0000	0.026	16	0.408	1	0.9376
26.1207	16.0000	0.026	16	0.408	0	-0.6474
26.1207	16.0000	0.026	16	0.408	0	-0.6474
26.1207	16.0000	0.026	16	0.408	1	0.9376
26.1207	17.0000	0.026	17	0.434	0	-0.6674
26.1207	17.0000	0.026	17	0.434	0	-0.6674
26.1207	17.0000	0.026	17	0.434	0	-0.6674
26.1207	17.0000	0.026	17	0.434	0	-0.6674
26.1207	19.0000	0.026	19	0.485	1	0.7490
26.1207	19.0000	0.026	19	0.485	0	-0.7055
92.5466	3.0000	0.026	3	0.077	0	-0.2804
92.5466	9.0000	0.026	9	0.230	0	-0.4856
92.5466	13.0000	0.026	13	0.332	0	-0.5836
92.5466	14.0000	0.026	14	0.357	0	-0.6056
92.5466	14.0000	0.026	14	0.357	1	1.0888
92.5466	14.0000	0.026	14	0.357	0	-0.6056
92.5466	14.0000	0.026	14	0.357	1	1.0888
92.5466	14.0000	0.026	14	0.357	0	-0.6056
92.5466	14.0000	0.026	14	0.357	0	-0.6056
92.5466	15.0000	0.026	15	0.383	0	-0.6269
92.5466	15.0000	0.026	15	0.383	0	-0.6269
92.5466	15.0000	0.026	15	0.383	0	-0.6269
92.5466	15.0000	0.026	15	0.383	1	1.0101
92.5466	16.0000	0.026	16	0.408	0	-0.6474
92.5466	16.0000	0.026	16	0.408	1	0.9376
92.5466	16.0000	0.026	16	0.408	0	-0.6474
92.5466	17.0000	0.026	17	0.434	1	0.8703
92.5466	17.0000	0.026	17	0.434	0	-0.6674
92.5466	20.0000	0.026	20	0.511	1	0.6938
92.5466	20.0000	0.026	20	0.511	0	-0.7239
92.5466	22.0000	0.026	22	0.562	1	0.5925
326.1056	4.0000	0.073	4	0.291	0	-0.4031
326.1056	7.0000	0.073	7	0.509	0	-0.4379
326.1056	8.0000	0.073	8	0.582	2	1.0835
326.1056	11.0000	0.073	11	0.800	0	-0.4585
326.1056	11.0000	0.073	11	0.800	0	-0.4585
326.1056	12.0000	0.073	12	0.873	0	-0.4617
326.1056	12.0000	0.073	12	0.873	0	-0.4617
326.1056	13.0000	0.073	13	0.946	8	3.4649
326.1056	13.0000	0.073	13	0.946	0	-0.4645
326.1056	14.0000	0.073	14	1.018	1	-0.0085
326.1056	14.0000	0.073	14	1.018	0	-0.4669
326.1056	14.0000	0.073	14	1.018	0	-0.4669
326.1056	14.0000	0.073	14	1.018	0	-0.4669
326.1056	16.0000	0.073	16	1.164	1	-0.0663

Scaled Residual(s) for Dose Group Nearest the BMD

Minimum scaled residual for dose group nearest the BMD = -0.4669
Minimum ABS(scaled residual) for dose group nearest the BMD = 0.0085

Average scaled residual for dose group nearest the BMD = -0.3523
Average ABS(scaled residual) for dose group nearest the BMD = 0.3523
Maximum scaled residual for dose group nearest the BMD = -0.0085
Maximum ABS(scaled residual) for dose group nearest the BMD = 0.4669
Number of litters used for scaled residual for dose group nearest the BMD = 4

Observed Chi-square = 120.2685

Bootstrapping Results

Number of Bootstrap Iterations per run: 1000

Bootstrap Chi-square Percentiles

Bootstrap Run	P-value	50th	90th	95th	99th
1	0.1020	80.1651	120.8799	132.3672	165.0942
2	0.0930	81.2319	117.9970	132.3763	160.2242
3	0.1050	81.1876	121.5273	137.2496	166.6223
Combined	0.1000	80.9778	120.2642	133.6763	165.0942

The results for three separate runs are shown. If the estimated p-values are sufficiently stable (do not vary considerably from run to run), then then number of iterations is considered adequate. The p-value that should be reported is the one that combines the results of the three runs. If sufficient stability is not evident (and especially if the p-values are close to the critical level for determining adequate fit, *e.g.*, 0.05), then the user should consider increasing the number of iterations per run.

To calculate the BMD and BMDL, the litter specific covariate is fixed at the mean litter specific covariate of all the data: 14.035294

Benchmark Dose Computation

Specified effects = 0.01, 0.05

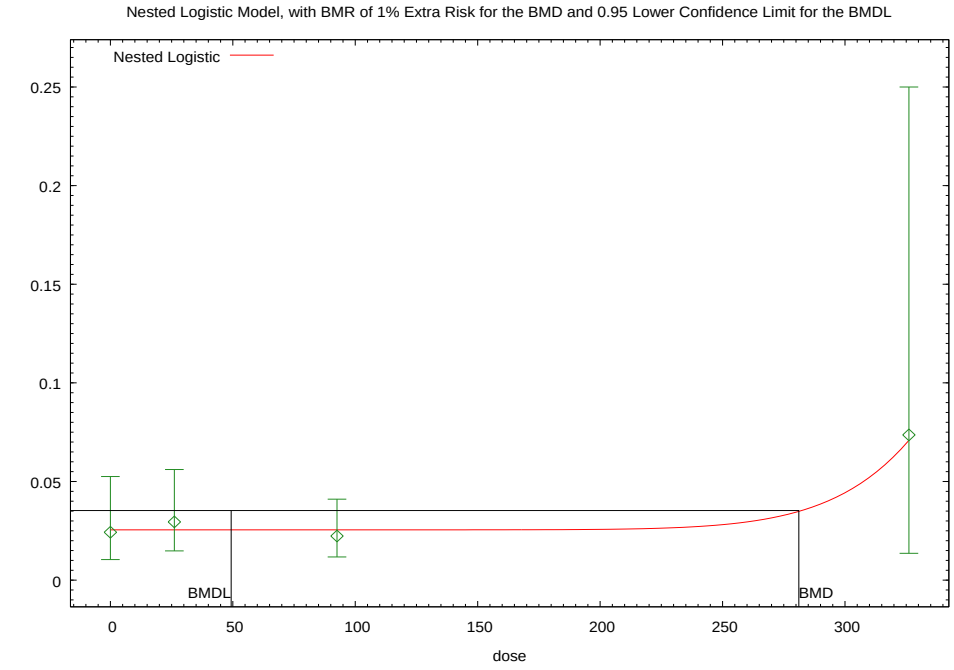
Risk Type = Extra risk

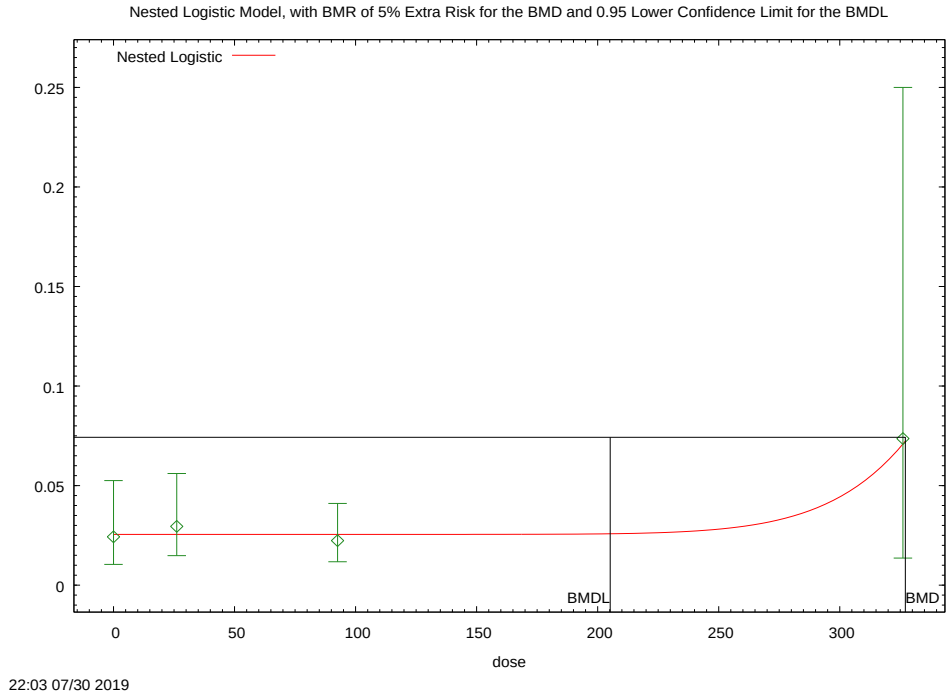
Confidence level = 0.95

BMDs = 281.145, 327.095

BMDLs = 49.3219, 205.186

Selected Model Plots– NLogistic- ILC, BMR = 0.01 and 0.05 Extra Risk





4.4.2 P2/F2B Pups Dead at Day 0 (Stillborn Day 0/Total Pups Born; Exxon 1991 Appendix AK)

Control			25.25 avg. mg/L blood GD 6-21			89.03 avg. mg/L blood GD 6-21			311.9 avg. mg/L blood GD 6-21		
Dam	N	Stillborn	Dam	N	Stillborn	Dam	N	Stillborn	Dam	N	Stillborn
JAB245	18	3	JAB029	15	0	JAB302	19	0	JAB327	14	0
JAB248	14	0	JAB032	15	0	JAB038	14	1	JAB045	15	0
JAB026	16	0	JAB279	14	0	JAB110	15	0	JAB339	4	0
JAB251	12	0	JAB104	18	7	JAB305	15	0	JAB329	14	13
JAB097	18	0	JAB288	15	0	JAB113	16	0	JAB330	13	0
JAB254	8	0	JAB035	15	0	JAB116	5	0	JAB343D	10	0
JAB100	16	0	JAB107	6	0	JAB308	6	0	JAB337	8	0
JAB257	16	2	JAB292	12	1	JAB311	17	0	JAB328	13	0
JAB260	18	0	JAB295	7	0	JAB121	13	0	JAB134	8	5
JAB266	11	0	JAB347	15	0	JAB127	14	1			
JAB269	14	0	JAB348	19	0	JAB130	17	0			
JAB101	15	0	JAB293	19	1	JAB319	18	0			
JAB270	20	0	JAB037	15	0	JAB320	17	0			
JAB273	18	0	JAB349	16	0	JAB313	11	0			
JAB252	11	1	JAB278	11	0	JAB040	18	1			
JAB028	16	0	JAB105	18	0	JAB309	15	0			
JAB275	15	0	JAB289	15	1	JAB039	11	0			
JAB255	20	0	JAB297	13	0	JAB112	18	0			
JAB264	14	0	JAB106	16	0						
JAB262	16	1	JAB290	13	0						
JAB102	17	1									
JAB256	14	0									
JAB098	11	1									
JAB249	16	0									
JAB253	17	0									

Table 4-14 Model Predictions for Pup Death at Day 0 in P2/F2B Rats (Exxon (1991b))

Standard Models [a]	5% Extra Risk		1% Extra Risk		P-value	AIC	BMDS Recommends [b]	BMDS Recommendation Notes
	BMD	BMDL	BMD	BMDL				
NLogistic	327.408	275.906	285.459	73.5614	0	246.193	Questionable	BMD/BMDL ratio > 3 Goodness of fit p-value < 0.1
NLogistic-ILC	CF	CF	CF	CF	CF	209.115	Unusable	BMD computation fail; Lower limit includes 0
Alternative Models								
NCTR	327.13	0.886689	285.638	0.237456	0	244.193	Questionable	BMD/BMDL ratio > 20 Goodness of fit p-value < 0.1
NCTR-ILC	324.07	0.659289	283.317	0.191833	0.256, 0.224	206.511	Questionable	BMD/BMDL ratio > 20
RaiVR	327.208	0.886689	285.513	0.514115	0	244.193	Questionable	BMD/BMDL ratio > 20 Goodness of fit p-value < 0.1
RaiVR-ILC	324.124	0.659289	283.199	0.517021	0.2407	206.511	Questionable	BMD/BMDL ratio > 20

[a] NLogistic is preferred because it is the more rigorously tested nested model. All nested models were restricted. Restrictions are defined in the BMDS 3.1.1 User Guide; ILC = Intra-litter Correlation Coefficients estimated; Because potential litter-specific covariates (LSCs) such as dam BW are affected by dose, LSCs were not estimated.

[b] No model selected as all models were questionable or unusable.

4.4.3 P2/F2A Pups Dead by Day 4 (Dead by Day 4/Total Pups Born; Exxon Appendix AJ)

Control			26.1207 avg. mg/L blood GD6-21			92.5466 avg. mg/L blood GD6-21			326.1056 avg. mg/L blood GD6-21		
Dam	N	Dead by Day 4	Dam	N	Dead by Day 4	Dam	N	Dead by Day 4	Dam	N	Dead by Day 4
JAB248	12	0	JAB029	17	4	JAB302	15	0	JAB325	13	9
JAB026	16	0	JAB032	17	0	JAB038	14	1	JAB327	12	12
JAB251	14	0	JAB279	14	3	JAB110	15	1	JAB041	13	13
JAB097	15	0	JAB104	13	1	JAB305	16	1	JAB135	7	0
JAB254	9	0	JAB282	13	5	JAB113	20	1	JAB136	4	0
JAB100	18	2	JAB285	16	1	JAB116	22	1	JAB045	14	2
JAB257	17	1	JAB288	17	0	JAB311	16	0	JAB050	12	12
JAB260	18	3	JAB035	14	1	JAB121	9	0	JAB336	11	11
JAB263	15	2	JAB107	19	2	JAB319	15	0	JAB329	11	1
JAB266	15	0	JAB292	1	1	JAB322	14	2	JAB330	8	8
JAB269	18	1	JAB295	7	0	JAB320	3	0	JAB046	14	0
JAB10	18	1	JAB347	16	0	JAB306	13	0	JAB328	14	14
JAB270	18	0	JAB298	5	0	JAB313	17	1	JAB134	16	16
JAB273	15	0	JAB348	19	3	JAB323	14	1	JAB341	14	14
JAB252	16	2	JAB293	5	0	JAB310	15	1			
JAB028	18	3	JAB037	14	1	JAB117	14	0			
JAB275	18	5	JAB349	16	0	JAB040	20	2			
JAB255	16	2	JAB278	16	3	JAB309	14	1			
JAB264	15	0	JAB105	14	0	JAB039	16	2			
JAB267	17	1	JAB297	15	1	JAB317	14	0			
JAB262	17	0	JAB106	17	0	JAB112	17	0			
JAB102	17	10	JAB281	6	3						
JAB246	2	2	JAB290	14	0						
JAB256	10	0									
JAB098	15	1									
JAB249	15	0									
JAB253	18	0									

Table 4-15 Model Predictions for Pup Death at Day 4 in P2/F2A Rats (Exxon (1991b))

Standard Models [a]	5% Extra Risk		1% Extra Risk		P-value	AIC	BMDS Recommends [b]	BMDS Recommendation Notes
	BMD	BMDL	BMD	BMDL				
NLogistic	253.849	136.252	226.386	91.5542	0	771.038	Questionable	Goodness of fit p-value < 0.1
NLogistic-ILC	257.878	132.515	231.394	88.2173	0.0317	608.697	Questionable	Goodness of fit p-value < 0.1
Alternative Models								
NCTR	261.47	217.891	232.338	193.615	0	769.038	Questionable	Goodness of fit p-value < 0.1
NCTR-ILC	267.663	223.052	240.654	200.545	0.0307, 0.0303	606.697	Questionable	Goodness of fit p-value < 0.1
RaiVR	261.996	218.33	233.057	194.214	0	769.038	Questionable	Goodness of fit p-value < 0.1
RaiVR-ILC	267.488	222.907	240.412	200.344	0.0333, 0.034	606.697	Questionable	Goodness of fit p-value < 0.1

[a] NLogistic is preferred because it is the more rigorously tested nested model. All nested models were restricted. Restrictions are defined in the BMDS 3.1.1 User Guide; ILC = Intra-litter Correlation Coefficients estimated; because potential litter-specific covariates (LSCs) such as dam BW are affected by dose, LSCs were not estimated.

[b] No model selected as all models were questionable or unusable.

4.4.4 P2/F2B Pups Dead by Day 4 (Dead by Day 4/Total Pups Born; Exxon Appendix AK)

Control			25.25 avg. mg/L blood GD6-21			89.03 avg. mg/L blood GD6-21			311.9 avg. mg/L blood GD6-21		
Dam	N	Dead by Day 4	Dam	N	Dead by Day 4	Dam	N	Dead by Day 4	Dam	N	Dead by Day 4
JAB245	18	18	JAB029	15	0	JAB302	19	1	JAB327	14	14
JAB248	14	0	JAB032	15	0	JAB038	14	1	JAB045	15	2
JAB026	16	0	JAB279	14	0	JAB110	15	1	JAB339	4	4
JAB251	12	0	JAB104	18	7	JAB305	15	0	JAB329	14	14
JAB097	18	0	JAB288	15	0	JAB113	16	0	JAB330	13	13
JAB254	8	0	JAB035	15	0	JAB116	5	0	JAB343D	10	10
JAB100	16	0	JAB107	6	0	JAB308	6	1	JAB337	8	8
JAB257	16	10	JAB292	12	1	JAB311	17	1	JAB328	13	13
JAB260	18	4	JAB295	7	1	JAB121	13	1	JAB134	8	8
JAB266	11	0	JAB347	15	0	JAB127	14	1			
JAB269	14	0	JAB348	19	0	JAB130	17	1			
JAB101	15	0	JAB293	19	2	JAB319	18	0			
JAB270	20	0	JAB037	15	2	JAB320	17	0			
JAB273	18	2	JAB349	16	0	JAB313	11	0			
JAB252	11	1	JAB278	11	1	JAB040	18	1			
JAB028	16	2	JAB105	18	2	JAB309	15	0			
JAB275	15	1	JAB289	15	6	JAB039	11	0			
JAB255	20	1	JAB297	13	0	JAB112	18	0			
JAB264	14	0	JAB106	16	0						
JAB262	16	3	JAB290	13	1						
JAB102	17	2									
JAB256	14	0									
JAB098	11	3									
JAB249	16	0									
JAB253	17	3									

Table 4-16 Model Predictions for Pup Death at Day 4 in P2/F2B Rats (Exxon (1991b))

Standard Models[a]	5% Extra Risk		1% Extra Risk		P-value	AIC	BMDS Recommends [b]	BMDS Recommendation Notes
	BMD	BMDL	BMD	BMDL				
NLogistic	229.655	126.176	206.373	92.1515	0	637.258	Questionable	BMD/BMDL ratio > 3 Goodness of fit p-value < 0.1
NLogistic-ILC	229.334	114.81	209.236	85.9385	0.065, 0.053	468.948	Questionable	Goodness of fit p-value < 0.1
Alternative Models								
NCTR	243.777	203.148	218.255	181.88	0	635.258	Questionable	Goodness of fit p-value < 0.1
NCTR-ILC	250.449	208.707	228.766	190.639	0.0623, 0.0687	466.948	Questionable	Goodness of fit p-value < 0.1
RaiVR	243.156	202.63	217.451	181.209	0	635.258	Questionable	Goodness of fit p-value < 0.1
RaiVR-ILC	250.449	208.707	228.766	190.639	0.059, 0.0603	466.948	Questionable	Goodness of fit p-value < 0.1

[a] NLogistic is preferred because it is the more rigorously tested nested model. All nested models were restricted. Restrictions are defined in the BMDS 3.1.1 User Guide; ILC = Intra-litter Correlation Coefficients estimated; Because potential litter-specific covariates (LSCs) such as dam BW are affected by dose, LSCs were not estimated.

[b] No model selected as all models were questionable or unusable

5 Benchmark Dose Modeling of Fetal and Pup Body Weight, Pup Death, Stillbirths, and Absolute Testes Weight in NMP Producers Group 1999a,b

BMD modeling for reduced fetal and pup bodyweight, increase pup death and stillbirths, and increased absolute testes weight described in two-generation reproductive studies in Sprague-Dawley rats (NMP Producers Group (1999a)) and Wistar rats (NMP Producers Group (1999b)) exposed to NMP through diet was performed using USEPA BMD Software package versions 2.7 (BMDS 2.7) or 3.2 (BMDS 3.2) in a manner consistent with Benchmark Dose Technical Guidance (U.S. EPA (2012)).

In both NMP Producers Group studies (NMP Producers Group (1999a, b)), male and female rats were exposed to NMP through diet for two generations (prior to mating through gestation, lactation, weaning, etc). Each parental generation produced two litters (A and B). In both studies, initial doses were 0, 50, 160 and 500 mg/kg-day and the high dose was reduced from 500 mg/kg-day to 350 mg/kg-day after the F1A litter due to a high level of mortality in dams exposed to 500 mg/kg-day. F1A litters were exposed to 500 mg/kg-day; F1B, F2A, and F2B litters were exposed to 350 mg/kg-day. The number of pregnant dams in each dose group was 20-25 in all of the rat strain and generation combinations except for the 500 mg/kg-day dose group, which had a range of 5-13 pregnant dams across the rat strain and generation combinations.

Due to uncertainties, several of the endpoints (*i.e.*, pup death, stillbirth, and absolute testes weight) significantly affected by NMP exposure in these studies were not the critical endpoints identified as the focus of dose-response analysis in the risk evaluation. For example, stillbirths were observed following repeated exposure to NMP throughout gestation; however, it is unknown whether stillbirths are the result of a single dose at a critical stage of development or are the result of repeated exposure to NMP. Thus, there is uncertainty around whether stillbirths should be considered most relevant for acute or chronic exposures. EPA performed BMD modeling on these additional reproductive and developmental endpoints (including pup death, stillbirth, and absolute testes weight) to provide information on a broader set of endpoints in support of POD selection.

In both NMP Producers Group studies (1999a, b), individual animal data was available for stillbirth and pup survival through PND4 and PND21 in both litters of both generations. However, pups were culled on PND4, so PND21 survival should not be compared to PND1 or pre-cull PND4 numbers. Individual animal data was not available for the fetal and pup body weight endpoints for either study, and therefore summary statistics for fetal and pup body weights from PND1-PND21 in both litters of both generations were used for BMD modeling. Additional details regarding modeled endpoints are provided in Table 5-1.

Table 5-1 Description of Endpoints from NMP Producers Group Studies (1999a, b) that were used for BMD Modeling

Species & Reference	Endpoint Description	Endpoints Modeled	Litter
Sprague-Dawley Rats (NMP Producers Group (1999a))	Individual animal data on stillbirth and pup survival through PND4 and PND21 in both litters of both generations; note pups are culled on PND4, so PND21 survival should not be compared to PND1 or pre-cull PND4 numbers	Percent stillborn	F1A
		Survival to PND4	F2B
		Survival to PND21	F2B
	Summary statistics for fetal and pup body weights on PND1-PND21 in both litters of both generations.	Fetal body weight PND1	F2B
		Pup body weight PND7	F2B
		Pup body weight PND21	F2B
Wistar Rats (NMP Producers Group (1999b))	Individual animal data on stillbirth and pup survival through PND4 and PND21 in both litters of both generations; note pups are culled on PND4, so PND21 survival should not be compared to PND1 or pre-cull PND4 numbers	Percent stillborn	F1A, F1B
		Survival to PND4	F1A, F2B
		Survival to PND21	F2B
	Summary statistics for fetal and pup body weights on PND1-PND21 in both litters of both generations.	Fetal body weight PND1	F1A
		Pup body weight PND7	F1A
		Pup body weight PND21	F1A
	Absolute testes weights	Absolute testes weights	P0 adult males

5.1 Overall BMD Modeling Approach for NMP Producers Group 1999a,b Data

Benchmark dose software was used and EPA BMD Technical Guidance (U.S. EPA (2012)) followed for the analysis of all endpoints. All endpoints were evaluated with preferred nested dichotomous models available in BMDS 2.7.0.4 and preferred continuous response models available in BMDS 3.2[8] using standard, restricted modeling options (listed below). No non-standard, unrestricted modeling results are shown or discussed in this section as they either were not needed to achieve adequate model fits or did not improve upon inadequate standard, restricted model fits.

Standard Nested Dichotomous BMDS 3.1.2 Models Applied to Stillbirth, PND4 and PND21 Pup Death Endpoints

- Nested Logistic (Nln)-restricted
- NCTR (Nct)-restricted

Model Options Used for Nested Dichotomous Response Modeling of Pup Death Endpoints

- Risk Type: Extra Risk
- Benchmark Response (BMR): 0.01 (1%), 0.05 (5%)
- Confidence Level: 0.95
- Background: Estimate
- Litter Specific Covariate (LSC): Dam weight at Lactation Day 1 (LND1)

Standard Continuous BMDS 3.2 Models Applied to Fetal and Pup Body Weight and Absolute Testes Weight Endpoints

- Exponential 2 (Exp2)-restricted
- Exponential 3 (Exp3)-restricted
- Exponential 4 (Exp4)-restricted
- Exponential 5 (Exp5)-restricted
- Hill (Hil)-restricted
- Polynomial Degree 4 (Ply4)-restricted
- Polynomial Degree 3 (Ply3)-restricted
- Polynomial Degree 2 (Ply2)-restricted
- Power (Pow)-restricted
- Linear (Lin)

Model Options Used for Continuous Response

- Benchmark Response (BMR): 5% Relative Deviation for Fetal Body Weight and 1% Absolute Deviation for Resorption
- Response Distribution-Variance Assumptions
- Normal Distribution-Constant Variance
- Normal Distribution-Non-Constant Variance
- Lognormal Distribution-Constant Variance (if normal distribution models do not fit means)
- Confidence Level: 0.95

[8] The nested dichotomous (pup death) modeling was performed using the nested logistic and NCTR models contained in BMDS 2.7.0.4 and the continuous response (body weight) modeling was performed using the standard (default) BMDS 3.2 continuous response models.

- Background: Estimated

Model Restrictions and Model Selection

Each nested dichotomous model analysis of the stillborn and pup death endpoints was performed four ways, with intra-litter correlation coefficients (ICCs) and LSC estimated, with only LSC estimated, with only ICCs estimated and with no ICC or LSC estimations. For both the nested dichotomous and continuous response analyses, each dataset-specific BMD analysis, a single preferred model was chosen from the standard set of models and modeling options listed above. The modeling restrictions and the model selection criteria facilitated in BMDS and defined in the BMDS 3.2 User Guide were applied in accordance with EPA BMD Technical Guidance (U.S. EPA (2012)). Briefly, for each dataset, BMDS models with standard restrictions were fit to the data using the maximum likelihood method. For nested dichotomous models applied to pup death endpoints, if the BMDLs from adequately fitting models (P-value < 0.1) were sufficiently close (within a threefold range), the model with the lowest AIC was selected as the best-fitting model, and its BMDL was used as the POD. Per BMD Technical Guidance "This criterion is intended to help arrive at a single BMDL value in an objective, reproducible manner." If the BMDLs are not sufficiently close (not within a threefold range), it was determined that the BMDLs were substantially model-dependent; thus, the BMDL from the adequately fitting model with the lowest BMDL was used as the POD.

For continuous models applied to the body and testes weight endpoints, model fit was assessed by a series of tests as follows. For each model, first the homogeneity of the variances was tested using a likelihood ratio test (BMDS Test 2). If Test 2 was not rejected ($\chi 2$ p-value ≥ 0.05), the model was fit to the data assuming constant variance. If Test 2 was rejected ($\chi 2$ p-value < 0.05), the variance was modeled as a power function of the mean, and the variance model was tested for adequacy of fit using a likelihood ratio test (BMDS Test 3). For fitting models using either constant variance or modeled (non-constant) variance, models for the mean response were tested for adequacy of fit using a likelihood ratio test (BMDS Test 4, with $\chi 2$ p-value < 0.10 indicating inadequate fit). From among the models that yielded an adequate fit, the model for POD determination was selected using the same procedure as for the nested dichotomous models. For both the dichotomous and continuous model analyses, other factors were also used to assess the model fit, such as scaled residuals, visual fit, and adequacy of fit in the low-dose region and in the vicinity of the BMR.

With respect to the continuous model distribution-variance modeling options, responses were first assumed to be normally distributed with constant variance across dose groups. If no model achieved adequate fit to response means and response variances under those assumptions, models that assume normal distribution with non-constant variance, variance modeled as a power function of the dose group mean were considered (U.S. EPA (2012)). If no normal distribution model achieved adequate fit to response means under the non-constant variance assumption (BMDS Test 3 $p>0.05$), models that assume lognormal distribution with constant variance were considered and the same approach for evaluating model fit for mean and variance used for the normal distribution data was applied. For each body weight endpoint, the mean and standard deviation (SD) of litter means per dose group was modeled, using the number of litters per group as the sample size.

For five endpoints, the constant variance model did not fit adequately when assuming normality, even though some models fit the means adequately assuming constant variance, and either the non-constant variance model did not fit adequately or did fit adequately but none of the models fit the means. For all these endpoints, the constant variance model did not fit adequately when assuming lognormality. Therefore, a sensitivity analysis was conducted to determine the influence of the variances on the results for these endpoints by re-modeling the data assuming a different set of SDs. First, the data were

modeled by replacing the SD in all the groups by the minimum SD among the groups, assuming constant variance and only fitting models that fit the means adequately in the observed SD case. This procedure was repeated with the SD in all the groups replaced by the maximum SD among the groups. For each case, a model was selected based on the procedure described above, provided all three cases yielded usable results, and if the BMDLs among the three cases differed by at most threefold, the lowest BMDL was selected as the POD. Table 5-2 provides the modeling results for the endpoints that underwent sensitivity analysis, in addition to the NOAELs for these endpoints. For Day 1 F1A male Wistar fetal weight (Section 5.6.2), the BMDLs differed by at most threefold, and the maximum SD case yielded the lowest BMDL. Thus, the BMDL from this case was selected as the POD for this endpoint. For Day 7 F2B female Sprague-Dawley pup weight (Section 5.5.3) and Day 21 F1A male Wistar pup weight (Section 5.6.6), the minimum SD case did not yield a model that fit the means adequately. For each of these endpoints, the lowest value from among the BMDL of the other two SD cases and the NOAEL was selected as the POD.

Table 5-2 BMD_{5Pct} and $BMDL_{5Pct}$ derivations from the variance (SD) sensitivity analysis of body and organ weight data, with corresponding NOAELs

Section	Response [a]	St Dev Case [b]	Selected Model	Test 4 P-value	BMD_{5Pct}	$BMDL_{5Pct}$
5.5.3	Sprague-Dawley Rat F2B Pup Body Weight at PND7 (Female)	Observed	Exp 3	0.116	1910	1230
		Minimum	Exp 3	0.013	1910	1370
		Maximum	**Exp 3**	**0.323**	**1910**	**1080**
		NOAEL	--	--	--	2050
5.5.4	Sprague-Dawley Rat F2B Pup Body Weight at PND7 (Male)	Observed	Exp 4	0.512	310	31.5
		Minimum	Exp 4	0.310	310	142
		Maximum	Exp 4	0.635	310	0
		NOAEL	**--**	**--**	**--**	**566**
5.5.6	Sprague-Dawley Rat F2B Pup Body Weight at PND21 (Male)	Observed	Exp 4	0.172	462	145
		Minimum	Exp 4	0.033	462	238
		Maximum	Exp 4	0.322	462	0
		NOAEL	**--**	**--**	**--**	**566**
5.6.2	Wistar Rat F1A Fetal Body Weight at PND1 (Male)	Observed	Poly 3	0.373	2380	1800
		Minimum	Poly 3	0.106	2610	2120
		Maximum	**Poly 3**	**0.652**	**2610**	**1760**
		NOAEL	--	--	--	1960
5.6.6	Wistar Rat F1A Pup Body Weight at PND21 (Male)	Observed	Poly 3	0.482	5960	3420
		Minimum	Poly 3	0.085	5960	4640
		Maximum	Poly 3	0.587	5960	2770
		NOAEL	**--**	**--**	**--**	**1960**

[a] For all endpoints listed, results assuming constant variance are presented. Entries in parentheses are from models that yielded unusable results, either because the model did not fit the means adequately (Test 4 p-value < 0.10; results for model selected in observed SD case presented) or the BMDL was zero.
[b] Case yielding the POD for each endpoint is shown in bold text and is highlighted in gray.

For Day 7 F2B male Sprague-Dawley pup weight and Day 21 F2B male Sprague-Dawley pup weight, the maximum SD cases yielded BMDLs equal to 0. Thus, it was determined that there was too much

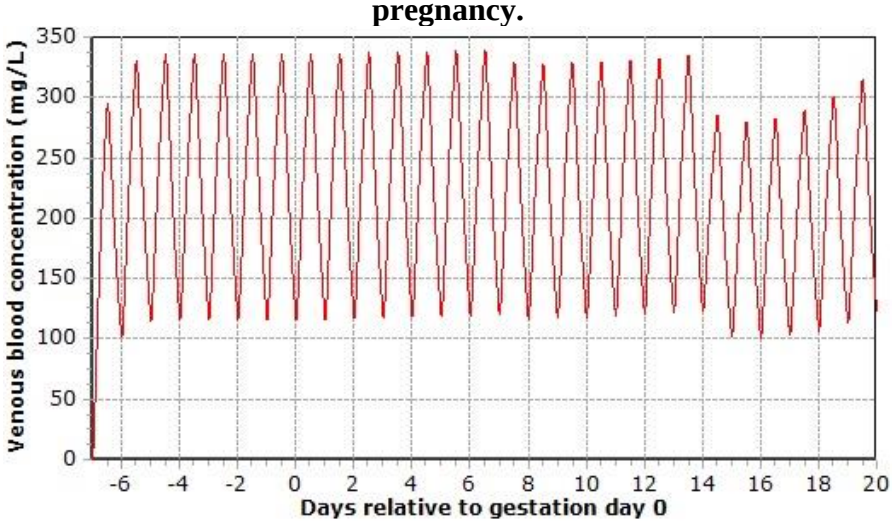
uncertainty in the BMD estimates across the three SD cases to rely on the modeling results for these endpoints, and the NOAEL was selected as the POD for each. For each of these, the NOAEL was more than three times higher than the BMDL based on the observed SD results. Furthermore, the mean weights at the NOAEL for these endpoints were 9% and 4% lower than the mean weight at the control, respectively, and thus their difference approximately corresponds to the BMR of 5% relative deviation from the control. In other words, these NOAELs approximately yield a minimum biological response.

5.2 PBPK Analysis for NMP Producers Group (1999a, b)

The dose-response analyses in Section 5 use AUC (hr mg/L) internal doses predicted using the U.S. EPA version of the NMP PBPK model, described in Appendix I of the risk evaluation for NMP. To conduct this analysis a table was created that listed the mean maternal body weight (BW) for each dose group/generation/pregnancy (*e.g.*, for the 160 mg/kg-day dose group, F0 females, F1B litter, the mean BW on GD 0 was 310.4 g) and the dose achieved for that group for GDs 0-7, 7-14, and 14-20. While the mean maternal BW of each group was reported for each week of gestation, because the model already predicts BW increase during pregnancy and the dose is specified as mg/kg-day (*i.e.*, is multiplied by the BW as predicted by the model, based on the measure GD 0 BW), these subsequent measured BW values were not used. However, the fact that group-specific initial BW values and group- and time-specific doses achieved were used, the model predictions are expected to reasonably incorporate the time-dependence in BW and dose.

PBPK modeling was conducted for 7 days of dosing prior to the start of gestation, during which time the maternal BW is treated as fixed at the GD 0 BW. Ingestion was assumed to occur at a constant rate for 12 hours per day (*i.e.*, evenly over the rat's active period, during which time the ingestion rate is twice the reported dose achieved, so the daily average dose matched what was reported). From testing with the model, a simulation of 7 days was found to be sufficient to achieve "periodicity," meaning that that the venous blood concentration was then predicted to repeat with the same pattern each day, given an ongoing constant dosing schedule. The dose achieved during GD 0-7 was used for each simulation up to GD 7. The dose was then set to the dose achieved for GD 7-14 and the simulation continued to GD 14. Finally, the dose was set to the dose achieved for GD 14-20 and the simulation continued to that time point. An example simulation is shown below. The result of a slight decrease in the dose achieved during GD 7-14 versus GD 0-7, and then a larger drop during GD 14-20, can be seen. After each simulation, the daily average venous blood AUC was calculated during pregnancy, simply as the AUC from GD 0 to GD 20 divided by 20.

Sample PBPK simulation of venous blood concentration in a rat dam prior to and during pregnancy.



For Wistar P0 male rats (testes weight endpoint), a time-weighted average achieved dose was calculated from the reported achieved doses for weeks 0-17 and 17-28 of dosing. The highest dose was reduced from a target of 500 mg/kg-day to 350 mg/kg-day after the first 17 weeks. Since animals grew throughout the exposure period, simulations were first conducted to evaluate the effect of BW on internal dose. These evaluation simulations were conducted with ingestion assumed to occur evenly over

12 hours of each day, as described above, for 7 days to achieve periodicity. The 24-hour AUC on the last day of exposure was used as the internal dose. For illustrative purposes, the table below provides estimated doses for exposures of exactly 50, 160 and 450 mg/kg-d in animals with BW set to 200-600 g.

NMP AUC values (hr mg/L) as a function of dose and BW predicted by PBPK modeling for non-pregnant rats

Dose (mg/kg-d)	Body weight (g)				
	200	**300**	**400**	**500**	**600**
50	478	531	573	608	637
160	1,700	1,900	2,060	2,190	2,310
450	5,770	6,520	7,110	7,610	8,050

These results demonstrate that a lower internal dose is estimated for younger/smaller rats, which occurs because, based on assumed $BW^{0.75}$ scaling, metabolism per BW is higher for smaller animals, but the difference between 200 and 500 g animals is only around 20-25%. The testes weight increase may be a developmental effect, determined primarily by exposure to younger animals, but data to define a window of vulnerability do not exist. Therefore, the average dose achieved and BW during exposure weeks 0-17 was used to estimate internal doses for this response. The corresponding BWs and doses achieved were 400.6, 399.2, and 403.7 g and 48.7, 155.8, and 487.0 mg/kg-day for the low, medium, and high doses, respectively.

5.3 Comparison of PODs for Critical Effects and for Effects Reported in the NMP Producers Group Studies

Table 5-3 provides a summary of acute PODs for effects reported in the NMP Producers Group Studies (1999a, b), including increased incidence of stillbirths (Sections 5.7 and 5.8). However, there is uncertainty around whether stillbirths should be considered most relevant for acute or chronic exposures and it is unknown whether this effect was the result of a single dose at a critical stage of development or a result of repeated exposure to NMP. Therefore, BMD modeling of the stillbirth endpoint was conducted using both C_{max} and AUC as dose metrics. Table 5-4 provides a summary of chronic PODs for critical effects reported in the NMP Producers Group Studies (1999a, b), including increased absolute testes weight (Section 5.4), decreased pup body weight (Sections 5.5 and 5.6), and increased incidence of stillbirths (Sections 5.7 and 5.8). Acute and chronic PODs derived for critical effects in the NMP risk evaluation are shown for comparison.

EPA selected a POD derived from post-implantation loss in a developmental study Saillenfait et al. (2003; 2002) as the basis for risk calculations for acute exposures to NMP. The selected POD (*i.e.*, a BMDL of 437 mg/L C_{max}) is not the lowest POD among those EPA modeled for acute endpoints. As demonstrated by Table 5-3, several studies were not amenable to BMD modeling, and for these studies NOAELs were selected as PODs, several of which were lower than the selected POD for post-implantation loss. For example, a NOAEL of 265 mg/L was selected as the POD for the fetal mortality endpoint (Sitarek et al. (2012)). However, fetal mortality in the study by Sitarek et al. occurred in a similar dose-range as post-implantation losses in the combined Saillenfait et al. oral and inhalation studies (*i.e.*, NOAELs for post-implantation losses and fetal mortality were 250 and 265 mg/L, respectively, and LOAELs were 669 and 531 mg/L, respectively). Further discussion regarding EPA's choice of acute POD is provided in Section 3.2.5.6 of the Final NMP Risk Evaluation.

EPA selected the POD derived from decreased male fertility (*i.e.*, a BMDL of 183 hr mg/L AUC) in a two-generation reproductive study (Exxon (1991a)) as the basis for risk calculations for chronic exposures to NMP. The selected POD is not the lowest POD among those EPA modeled for chronic endpoints. For example, BMD modeling of PND21 pup body weights in the NMP Producers Group (1999a) study identified a POD of 100 hr mg/L. Although reduced pup body weight is considered a sensitive endpoint, it is not the ideal basis for a chronic POD as there is uncertainty around actual internal serum levels achieved in rat pups during lactation. Further discussion regarding EPA's choice of chronic POD is provided in Section 3.2.5.6 of the Final NMP Risk Evaluation.

Table 5-3 Acute PODs: Comparison of PODs for critical effects and for effects reported in the NMP Producers Group Studies (1999a, b)

Endpoint and reference (exposure duration/route)	Dose Metric or NOAEL	Model	BMR	BMD	BMDL	POD	
						Internal dose [b]	Equivalent oral dose mg/kg/day [a]
Post-implantation Loss							
Saillenfait et al. (2002) (GD 6-20, oral, post-implantation loss)	C_{max} (mg/L blood)	Log-Probit	1% RD	474	437	**437**	418
	AUC (hr mg/L blood)	Log-Probit	1% RD	5010	4592	4592	419
Saillenfait et al. (2003; 2002) (GD 6-20, oral and inhalation)	C_{max} (mg/L blood)	Log-probit	1% RD	470	437	**437**	418
	AUC (hr mg/L blood)	Log-probit	1% RD	4990	4590	4590	419
Resorptions							
Saillenfait et al. (2002) (GD 6-20, oral, post-implantation loss)	NOAEL $C_{max,}$ (mg/L blood)	N/A	N/A	N/A	N/A	250 [c]	250
Becci et al. (1982) (GD 6-15, dermal)	NOAEL C_{max}, (mg/L blood)	N/A	N/A	N/A	N/A	662 [d]	612 (oral) 237 (dermal)
Fetal Mortality							
Sitarek et al. (2012) (GD1-PND1, oral)	NOAEL C_{max},(mg/L blood)	N/A	N/A	N/A	N/A	265 [e]	264
Stillbirths [f]							
NMP Producers Group (1999a) (Sprague-Dawley) (Dietary exposure throughout gestation, lactation, growth, pre-mating)	NOAEL C_{max} (mg/L blood	NA	NA	NA	NA	142	147
	NOAEL AUC (hr mg/L blood)	NA	NA	NA	NA	2,120	216
NMP Producers Group (1999b) (Wistar) (Dietary exposure throughout gestation, lactation, growth, pre-mating)	C_{max} (mg/L blood)	NLogistic-ICC	1% ER	429	58	58	62
	AUC (hr mg/L blood)	NLogistic-ICC	1% ER	6440	855	855	96
Exxon (1991a) (Sprague-Dawley) (Dietary exposure throughout gestation, lactation, growth, pre-mating)	AUC (hr mg/L blood)	NLogistic - ILC	1% ER	6744	1183	1183	129

Endpoint and reference (exposure duration/route)	Dose Metric or NOAEL	Model	BMR	BMD	BMDL	POD	
						Internal dose [b]	Equivalent oral dose mg/kg/day [a]

ER = extra risk; RD = relative deviation
The POD selected for calculating risk of acute NMP exposures is bolded and highlighted in gray.
[a] Assuming daily oral gavage and initial BW 0.259 kg (*i.e.*, the same experimental conditions as the Saillenfait et al. (2002) study) for the purposes of comparison across the studies.
[b] Internal doses refer to maternal blood concentrations (as opposed to fetal blood concentrations which are not predicted by the PBPK model).
[c] BMD models were considered unacceptable due to uncertainty caused by lack of model fit; the internal serum dose is based on a NOAEL of 250 mg/kg-bw/day.
[d] Dose-response data were not considered amenable to BMD modeling. The internal serum dose is based on a NOAEL of 237 mg/kg bw/day dermal exposure. An oral dose of 612 mg/kg bw/day, given on GD 6-20, is predicted to yield the same peak concentration (662 mg/L).
[e] BMD modeling failed to calculate an adequate BMD or BMDL value by either dose metric. The internal serum dose is based on a NOAEL of 450 mg/kg bw/day.
[f] The relevance of stillbirth for acute exposure is unclear, as these effects were only observed following exposure throughout gestation. In addition, the effect was reported in dietary studies in which exposure occurs throughout the day rather than through a single bolus (which would result in a greater peak exposure). PODs for the stillbirth endpoint are provided in terms of AUC and C_{max} for reference. BMD modeling was attempted for stillbirth data reported in the NMP Producers Group (1999a) study with Sprague-Dawley rats; however, no models adequately fit the dataset.

Table 5-4 Chronic PODs: Comparison of PODs for critical effects and for effects reported in the NMP Producers Group Studies (1999a, b)

Endpoint and reference (exposure duration/route)	Selected Model or NOAEL	BMR	BMD AUC (hr mg/L)	BMDL AUC (hr mg/L)	POD	
					AUC (hr mg/L blood) [a]	Equivalent oral dose [b] mg/kg/day
Fetal Body Weight						
Saillenfait et al. (2002) (oral exposure GD 6-20)	Exponential 3 [c,d]	5% RD	1400	981	981	109
Saillenfait et al. (2003) (inhalation exposure GD 6-20)	Exponential 3 [c]	5% RD	654	414	414	48
E. I. Dupont De Nemours & Co (1990) (inhalation exposure preconception and GD 1–20)	Exponential 3 [c]	5% RD	315	223	223	27
Becci et al. (1982) (dermal exposure GD 6-15)	NOAEL= 237 mg/kg/day [e]	NA	NA	NA	2052	210
Reduced Male Fertility						
Exxon (1991a) (Dietary exposure throughout gestation, lactation, growth, pre-mating)	Log-logistic	10% ER	492[f1] 341[f2]	262[f1] 183[f2]	**183**	28
Reduced Female Fecundity						
Exxon (1991a) (Dietary exposure throughout gestation, lactation, growth, pre-mating)	Log-logistic	10% ER	862 [f1] 420 [f2]	401 [f1] 202 [f2]	202	31

Endpoint and reference (exposure duration/route)	Selected Model or NOAEL	BMR	BMD AUC (hr mg/L)	BMDL AUC (hr mg/L)	POD	
					AUC (hr mg/L blood) [a]	Equivalent oral dose [b] mg/kg/day
Alternate NMP Producers Group 1999 and Exxon 1991 Endpoints						
Testes weights- absolute NMP Producers Group (1999b) (Wistar, dietary exposure throughout gestation, lactation, growth, pre-mating)	Exponential 4	5% RD	1,610	601	601	69
PND 21 Pup body weights- females NMP Producers Group (1999a) (Sprague-Dawley, dietary exposure throughout gestation, lactation, growth, pre-mating)	Exponential 4	5% RD	612	100	100	12
PND 21 Pup body weights- females NMP Producers Group (1999b) (Wistar, dietary exposure throughout gestation, lactation, growth, pre-mating)	Polynomial 3	5% RD	6,940	3,350	3,350	321
Stillbirth [g] NMP Producers Group (1999a) (Sprague-Dawley, dietary exposure throughout gestation, lactation, growth, pre-mating)	NOAEL= 160 mg/kg/day	NA	NA	NA	2,120	321
Stillbirth [g] NMP Producers Group (1999b) (Wistar, dietary exposure throughout gestation, lactation, growth, pre-mating)	NLogistic- ICC	1% ER	6,440	855	855	216
Stillbirth [g] Exxon (1991a) (Dietary exposure throughout gestation, lactation, growth, pre-mating)	NLogistic - ILC	1% ER	6,744	1,183	1,183	96

Endpoint and reference (exposure duration/route)	Selected Model or NOAEL	BMR	BMD AUC (hr mg/L)	BMDL AUC (hr mg/L)	POD	
					AUC (hr mg/L blood) [a]	Equivalent oral dose [b] mg/kg/day

RD = relative deviation; ER= extra risk

The POD selected for calculating risk of chronic NMP exposures is bolded and highlighted in gray.

[a] Internal doses for fetal body weight reflect maternal blood concentrations during gestation and internal doses for fertility reflect blood concentrations in pups post-weaning.

[b] Assuming daily oral gavage GDs 6-20 and initial BW 0.259 kg (*i.e.*, the same experimental conditions as the Saillenfait et al. (2002) study) for the purposes of comparison across the studies.

[c] Since standard models gave adequate results for all endpoints, non-standard models were not considered. Since fits to the means were obtained using normal distribution models, lognormal models were not applied

[d] For Saillenfait et al. (2002), the BMD and BMDL reported are from modeling the data with all the SDs equal to the maximum SD across the groups.

[e] The data in Becci (1982) were not amenable to BMD modeling. The mean weight increased gradually from the control to the middle dose group and then decreased significantly at the high dose group. This dose-response pattern is essentially equivalent to one where only the highest dose has a response and thus the model estimates of the parameters and BMDs would not be reliable. The internal serum dose is based on a NOAEL of 237 mg/kg bw/day dermal exposure.

[f] In the Exxon (1991a) study, each dam had two sets of mating periods. Each mating period was analyzed separately; d1 indicates results for the first mating period and d2 indicates results from the second mating period. PODs for male fertility and female fecundity in this study are calculated based on exposure levels in 50g rats immediately post-weaning.

[g] The relevance of stillbirth for acute vs. chronic exposure is unclear. These effects were observed following exposure throughout gestation. In addition, the effect was reported in dietary studies in which exposure occurs throughout the day rather than through a single bolus (which would result in a greater peak exposure). BMD modeling was attempted for stillbirth data reported in the NMP Producers Group (1999a) study with Sprague-Dawley rats; however, no models adequately fit the dataset.

5.4 Results for Benchmark Dose Modeling of Absolute Testes Weight in P0 Male Wistar Rats (NMP Producers Group (1999b))

Wistar Rat Absolute Testes Weight (P0 Adult Males) Data used for BMD Modeling.

AUC (hr mg/L)	N	Mean	Std. Dev.
0	25	3.59	0.2
557.5	25	3.634	0.246
1995	25	3.769	0.41
7862	25	3.782	0.277

Table 5-5 Model Predictions for AUC (hr mg/L) versus Wistar Rat Absolute Testes Weight (P0 Adult Males) (NMP Producers Group (1999b)).

BMR = 5% Relative Deviation (RD)

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.0003904	45.81758667	8544.569	4816.473	33594.218	Constant variance model did not fit adequately, but non-constant variance model did fit. Only exponential model 4 fit the means adequately assuming non-constant variance, so it was selected.
Exponential 3	0.0003904	45.81758466	8544.868	4816.477	34459.048	
Exponential 4	**0.1205979**	**34.35160178**	**1606.791**	**601.1339**	**10227.64**	
Polynomial 3°	0.0004012	45.76301492	8455.645	4680.749	34005.204	
Polynomial 2°	0.0004012	45.76301491	8455.675	4689.325	33533.859	
Power	0.0004012	45.76301831	8455.992	4681.267	33905.848	
Linear	0.0004012	45.76301472	8457.294	4682.196	33752.343	

[a] Results assuming non-constant variance presented (BMDS Test 2 p < 0.01, Test 3 p = 0.41); selected model in bold.

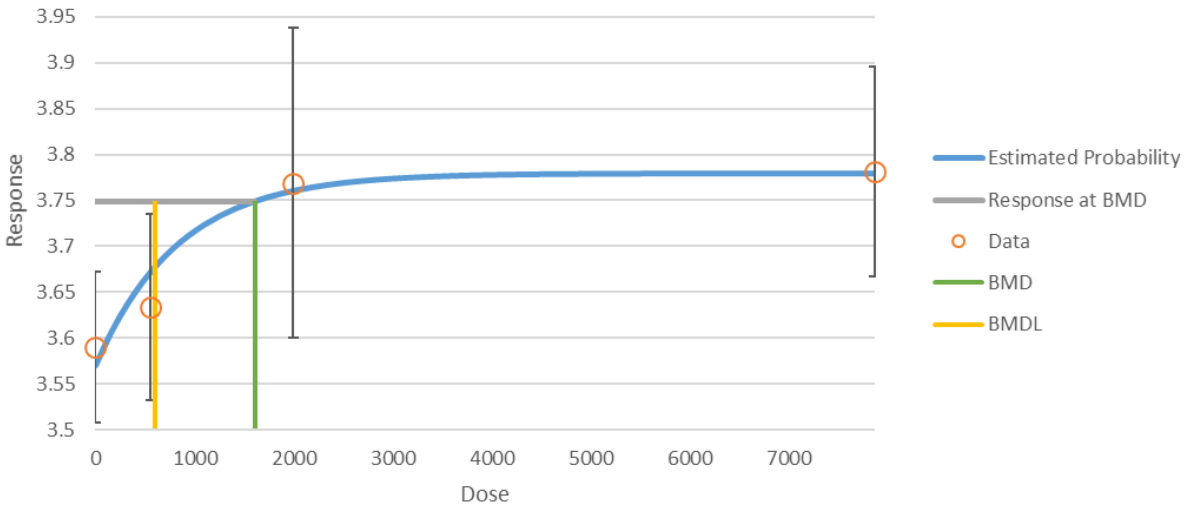


Figure 5.4-1 Plot of Mean Response by Dose, with Fitted Curve for Frequentist Exponential 4 Model for Absolute Testes Weight in Male Wistar Rats Exposed to NMP via Oral Gavage (NMP Producers Group (1999b))

BMR = 5% RD for the BMD and 0.95 lower confidence limit for the BMDL; daily average AUC as dose shown in hr mg/L

USER INPUT

Info	
Model	frequentist Exponential degree 4 v1.1
Dataset Name	Absolute testes weight in F0 male Wistar rats
Dose-Response Model	M[dose] = a * [c-(c-1) * exp(-b * dose)]
Variance Model	Var[i] = exp(log-alpha + log(mean[i]) * rho)

Model Options	
BMR Type	Rel. Dev.
BMRF	0.05
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Non-Constant

Model Data	
Dependent Variable	Dose
Independent Variable	Mean
Total # of Observations	4
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	1606.790852
BMDL	601.133903
BMDU	10227.64044
AIC	34.35160178
Test 4 P-value	0.120597877
d.f.	2

Model Parameters	
# of Parameters	5
Variable	Estimate
a	3.570619756
b	0.001200959
c	1.058492801
rho	Bounded
log-alpha	-26.09921678

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated GSD	Calc'd GSD	Observed SD	Scaled Residual
0	25	3.570619756	3.59	3.59	0.20291751	0.2	0.2	0.477539964
557.5	25	3.672552383	3.634	3.634	0.26142016	0.246	0.246	-0.737364388
1995	25	3.760450768	3.769	3.769	0.32343443	0.41	0.41	0.132163292
7862	25	3.77945874	3.782	3.782	0.33844925	0.277	0.277	0.037542698

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-17.37746746	5	44.7549349
A2	-10.17281491	8	36.3456298
A3	-11.06050729	6	34.1210146
fitted	-13.17580089	4	34.3516018
R	-21.40147557	2	46.8029511

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test d.f.	p-value
1	22.45732132	6	0.00100018
2	14.40930512	3	0.00239779
3	1.775384772	2	0.41160448
4	4.230587192	2	0.12059788

5.5 Results for BMD Modeling for Reduced Fetal and Pup Body Weight for Sprague-Dawley Rats (NMP Producers Group (1999a))

5.5.1 Sprague-Dawley Rat F2B Fetal Body Weight at PND1 (Females)

Sprague-Dawley Rat F2B Fetal Body Weight Data at PND1 (Females) used for BMD Modeling

AUC (hr mg/L)	N	Mean	Std. Dev.
0	25	6.9	0.66
566.5	26	6.5	1.04
2053	23	6.5	0.76
5235	23	6.2	0.82

Table 5-6 Model Predictions for AUC (hr mg/L) versus Sprague-Dawley Rat F2B Fetal Body Weight at PND1 (Females) Using Daily Average AUC as the Dose Metric

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.351778	250.5541583	3269.079	1953.617	9632.114	Assuming constant variance, exponential model 4 had a BMDL of zero, indicating that there is excessive uncertainty in the BMD estimate. No model was selected.
Exponential 3	0.351778	250.5541583	3269.139	1953.351	9632.2906	
Exponential 4	0.148401	252.5532581	3267.961	0	9631.5953	
Polynomial 3°	0.3461015	250.5866945	3339.144	2047.999	9628.0067	
Polynomial 2°	0.3461015	250.5866945	3339.144	2048.117	9623.9732	
Power	0.3461015	250.5866945	3339.143	2052.163	9563.3035	
Linear	0.3461015	250.5866945	3339.144	2048.046	9623.8352	

[a] Results assuming constant variance presented (BMDS Test 2 p = 0.07).

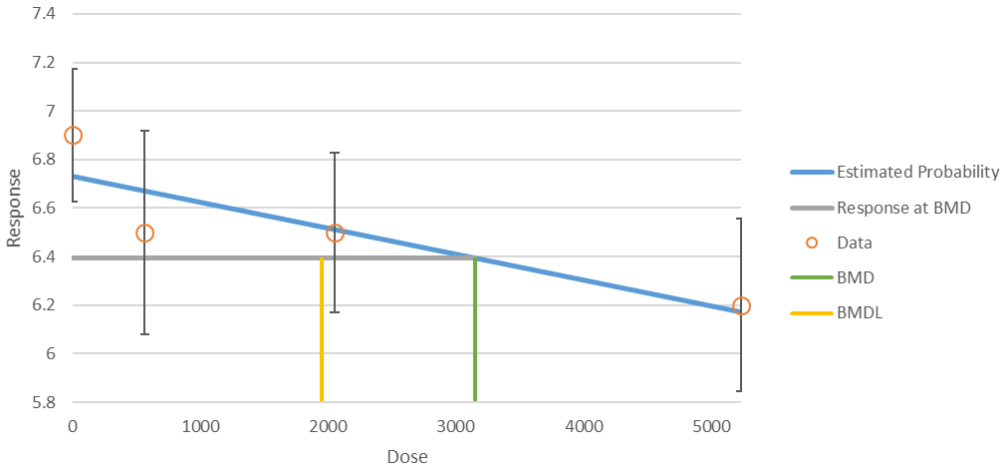


Figure 5.5-1 Plot of Mean Response by Dose, with Fitted Curve for Linear Model with Constant Variance for Sprague-Dawley Rat F2B Fetal Body Weight at PND1 (Females)
BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L

5.5.2 Sprague-Dawley Rat F2B Fetal Body Weight at PND1 (Males)

Sprague-Dawley Rat F2B Fetal Body Weight Data at PND1 (Males) used for BMD Modeling

AUC (hr mg/L)	N	Mean	Std. Dev.
0	25	7.3	0.66
566.5	26	6.9	1.04
2053	24	6.9	0.71
5235	23	6.6	0.93

Table 5-7 Model Predictions for AUC (hr mg/L) versus Sprague-Dawley Rat F2B Fetal Body Weight at PND1 (Males) Using Daily Average AUC as the Dose Metric

Model [a]	Goodness of Fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for Model Selection
	Test 4 P-value	AIC				
Exponential 2	0.351778	250.5541583	3269.079	1953.617	9632.114	Assuming constant variance, exponential model 4 had a BMDL of zero, indicating that there is excessive uncertainty in the BMD estimate. No model was selected.
Exponential 3	0.351778	250.5541583	3269.139	1953.351	9632.2906	
Exponential 4	0.148401	252.5532581	3267.961	0	9631.5953	
Polynomial 3°	0.3461015	250.5866945	3339.144	2047.999	9628.0067	
Polynomial 2°	0.3461015	250.5866945	3339.144	2048.117	9623.9732	
Power	0.3461015	250.5866945	3339.143	2052.163	9563.3035	
Linear	0.3461015	250.5866945	3339.144	2048.046	9623.8352	

[a] Results assuming constant variance presented (Test 2 p = 0.07).

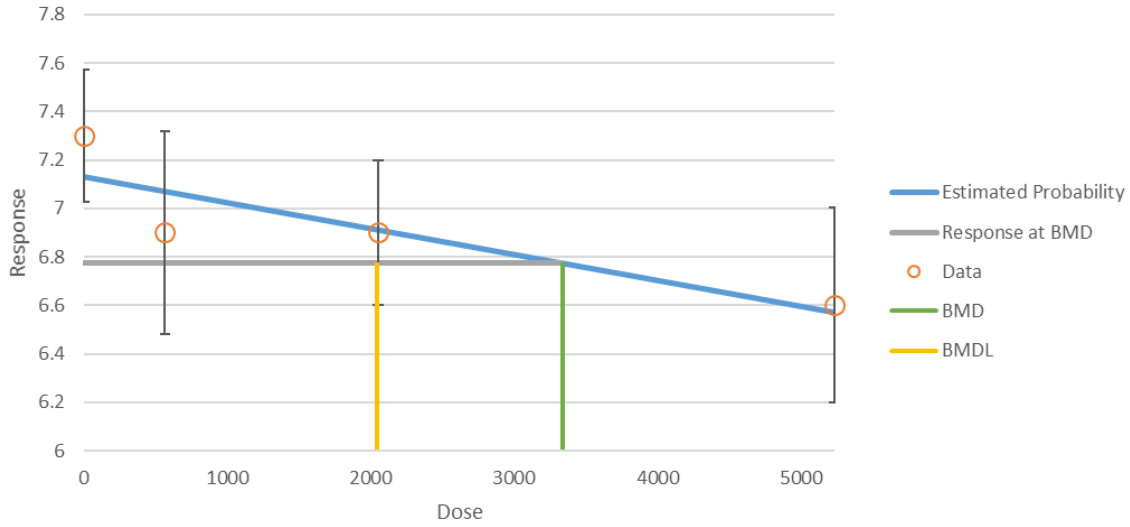


Figure 5.5-2 Plot of Mean Response by Dose, with Fitted Curve for Linear Model with Constant Variance for Sprague-Dawley Rat F2B Fetal Body Weight at PND1 (Males)
BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L

5.5.3 Sprague-Dawley Rat F2B Pup Body Weight at PND7 (Females)

Sprague-Dawley Rat F2B Pup Body Weight Data at PND7 (Females) used for BMD Modeling

AUC (hr mg/L)	N	Mean	Std. Dev.
0	25	16.2	1.72
566.5	26	14.6	2.6
2053	23	14.8	1.67
5235	21	13.6	3.32

Table 5-8 Model Predictions for AUC (hr mg/L) versus Sprague-Dawley Rat F2B Pup Body Weight at PND7 (Females) Using Daily Average AUC as the Dose Metric

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.1163921	441.7245971	1905.072	1225.905	4118.7554	The constant variance model did not fit adequately, and none of the models fit the means adequately assuming non-constant variance. In the context of a sensitivity analysis, exponential model 3 was selected from among the models that fit the means (Test 4 p-value ≥ 0.10), assuming constant variance.
Exponential 3	0.1163921	441.7245971	1905.072	1228.589	4118.7554	
Exponential 4	0.0938171	442.2306413	192.4316	0	2976.4058	
Polynomial 3°	0.1119924	441.8016643	2007.858	1339.323	4555.5464	
Polynomial 2°	0.1119924	441.8016643	2007.858	1339.409	4367.2799	
Power	0.1119924	441.8016643	2007.86	1339.381	4183.2379	
Linear	0.1119924	441.8016643	2007.863	1339.437	4201.9577	

[a] Results assuming constant variance presented (BMDS Test 2 p < 0.01).

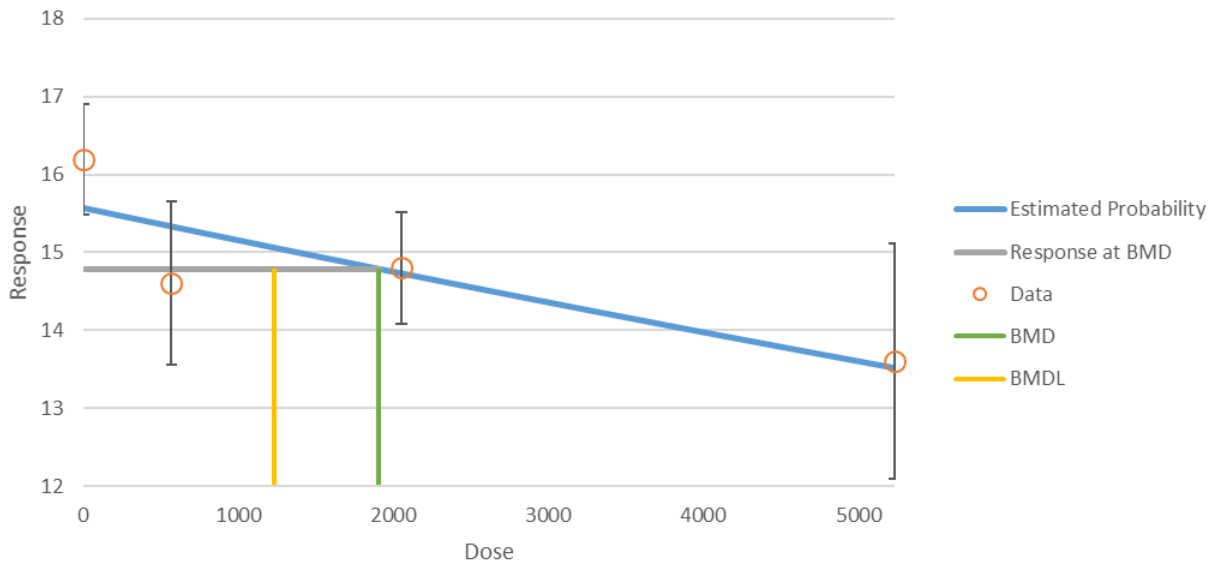


Figure 5.5-3 Plot of Mean Response by Dose, with Fitted Curve for Exponential 3 Model with Constant Variance for Sprague-Dawley Rat F2B Pup Body Weight at PND7 (Females)
BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L

USER INPUT

Info	
Model	frequentist Exponential degree 3 v1.1
Dataset Name	Day 7 pup body weight in F2B female Sprague-Dawley rats
Dose-Response Model	M[dose] = a * exp(±1 * (b * dose)^d)
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Rel. Dev.
BMRF	0.05
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	Dose
Independent Variable	Mean
Total # of Observations	4
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	1905.072384
BMDL	1228.588778
BMDU	4118.75535
AIC	441.7245971
Test 4 P-value	0.116392057
d.f.	2

Model Parameters	
# of Parameters	4
Variable	Estimate
a	15.56786252
b	2.69246E-05
d	Bounded
log-alpha	1.748697651

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	25	15.567863	16.2	16.2	2.3973137	1.72	1.72	1.318428778
566.5	26	15.332211	14.6	14.6	2.3973137	2.6	2.6	-1.557392921
2053	23	14.730682	14.8	14.8	2.3973137	1.67	1.67	0.138670184
5235	21	13.521197	13.6	13.6	2.3973137	3.32	3.32	0.150636477

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-215.7115076	5	441.423015
A2	-208.1511332	8	432.302266
A3	-215.7115076	5	441.423015
fitted	-217.8622986	3	441.724597
R	-222.4913993	2	448.982799

* Includes additive constant of -87.29916. This constant was not included in the LL derivation prior to BMDS 3.0

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test d.f.	p-value
1	28.68053237	6	<0.0001
2	15.12074884	3	0.00171631
3	15.12074884	3	0.00171631
4	4.301581969	2	0.11639206

Table 5-9 Model Predictions for AUC (hr mg/L) versus Sprague-Dawley Rat F2B Pup Body Weight at PND7 (Females) Using Daily Average AUC as the Dose Metric.

All SDs set to minimum SD across the group.

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.0132848	377.5904324	1905.072	1367.171	3097.7833	Assuming constant variance, no model fit the means adequately (Test 4 p-value < 0.10 for all models). No model was selected.
Exponential 3	0.0132848	377.5904324	1905.072	1371.022	3097.7833	
Polynomial 3°	0.0123167	377.7417503	2007.868	1477.946	3786.5275	
Polynomial 2°	0.0123167	377.7417503	2007.858	1478.013	3534.3112	
Power	0.0123167	377.7417503	2007.84	1480.133	3186.5526	
Linear	0.0123167	377.7417503	2007.858	1477.883	3188.3811	

[a] Results assuming constant variance presented (BMDS Test 2 p = 1.00).

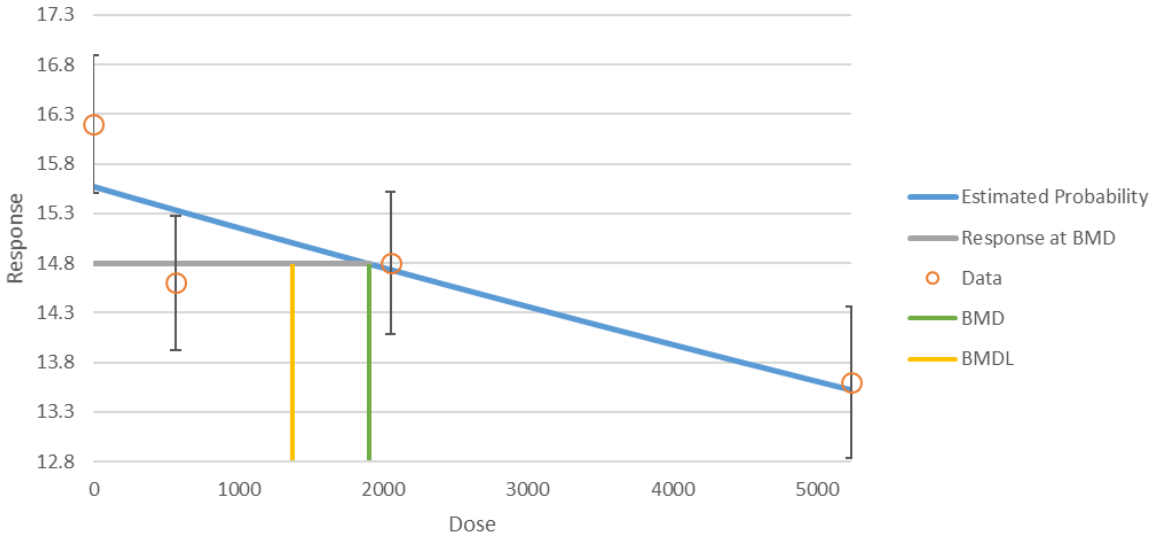


Figure 5.5-4 Plot of Mean Response by Dose, with Fitted Curve for Exponential 3 Model with Constant Variance for Sprague-Dawley Rat F2B Pup Body Weight at PND7 (Females)
BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L; with constant variance and all SDs set to the minimum SD across the group

Table 5-10 Model Predictions for AUC (hr mg/L) versus Sprague-Dawley Rat F2B Pup Body Weight at PND7 (Females) Using Daily Average AUC as the Dose Metric.
All SDs set to maximum SD across the group.

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.3226975	501.7670583	1904.883	1079.55	7149.0406	Assuming constant variance, exponential model 3 was selected based on lowest AIC.
Exponential 3	**0.3226976**	**501.767058**	**1905.072**	**1082.045**	**7149.0315**	
Polynomial 3°	0.3161543	501.8080281	2007.858	1195.667	7239.7544	
Polynomial 2°	0.3161543	501.8080281	2007.863	1195.548	7238.2775	
Power	0.3161543	501.8080281	2007.859	1195.81	7234.9478	
Linear	0.3161543	501.8080281	2007.858	1195.581	7242.2815	

[a] Results assuming constant variance presented (BMDS Test 2 p = 1.00); selected model in bold.

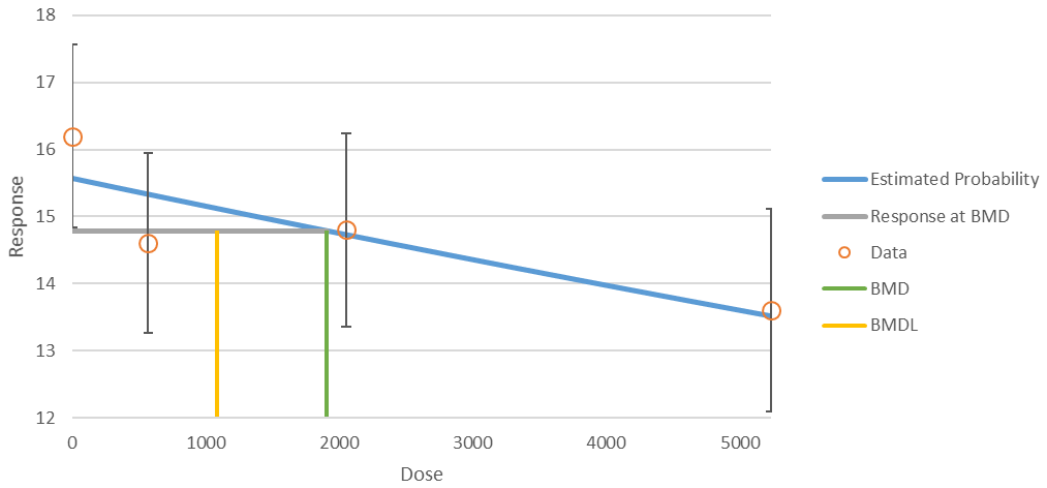


Figure 5.5-5 Plot of Mean Response by Dose, with Fitted Curve for Exponential 3 Model with Constant Variance for Sprague-Dawley Rat F2B Pup Body Weight at PND7 (Females)
BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L; all SDs set to the maximum SD across the group

USER INPUT

Info	
Model	frequentist Exponential degree 3 v1.1
Dataset Name	Day 7 pup body weight in F2B female Sprague-Dawley rats-max SD
Dose-Response Model	M[dose] = a * exp(±1 * (b * dose)^d)
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Rel. Dev.
BMRF	0.05
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	Dose
Independent Variable	Mean
Total # of Observations	4
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	1905.072384
BMDL	1082.044675
BMDU	7149.031453
AIC	501.767058
Test 4 P-value	0.322697556
d.f.	2

Model Parameters	
# of Parameters	4
Variable	Estimate
a	15.56786338
b	2.69246E-05
d	Bounded
log-alpha	2.380723761

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	25	15.56786338	16.2	16.2	3.28827095	3.32	3.32	0.961199104
566.5	26	15.33221177	14.6	14.6	3.28827095	3.32	3.32	-1.135418028
2053	23	14.73068203	14.8	14.8	3.28827095	3.32	3.32	0.101097904
5235	21	13.5211947	13.6	13.6	3.28827095	3.32	3.32	0.109824057

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-246.7524892	5	503.504978
A2	-246.7521789	8	509.504358
A3	-246.7524892	5	503.504978
fitted	-247.883529	3	501.767058
R	-250.3999906	2	504.799981

* Includes additive constant of -87.29916. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test d.f.	p-value
1	7.29562342	6	0.29437121
2	0.000620701	3	0.99999589
3	0.000620701	3	0.99999589
4	2.262079509	2	0.32269756

5.5.4 Sprague-Dawley Rat F2B Pup Body Weight at PND7 (Males)

Sprague-Dawley Rat F2B Pup Body Weight Data at PND7 (Males) used for BMD Modeling

AUC (hr mg/L)	N	Mean	Std. Dev.
0	25	17.2	1.82
566.5	26	15.7	2.73
2053	24	15	1.58
5235	21	14.4	3.39

Table 5-11 Model Predictions for AUC (hr mg/L) versus Sprague-Dawley Rat F2B Pup Body Weight at PND7 (Males) Using Daily Average AUC as the Dose Metric

Model	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.0973768	451.2052401	1709.332	1146.915	3260.3212	Neither variance model fit adequately. A sensitivity analysis indicated that there was too much uncertainty in the BMD estimate to use dose-response modeling results. No model was selected.
Exponential 3	0.0973768	451.2052401	1709.337	1149.303	3260.3231	
Exponential 4	0.5119478	448.9769894	310.3716	31.48148	1268.6804	
Polynomial 3°	0.0857581	451.4593557	1837.814	1274.571	3582.3314	
Polynomial 2°	0.0857581	451.4593557	1837.809	1274.531	3474.3836	
Power	0.0857581	451.4593557	1837.812	1274.512	3403.9466	
Linear	0.0857581	451.4593557	1837.814	1274.511	3415.2812	

[a] Results assuming constant variance presented (BMDS Test 2 p < 0.01).

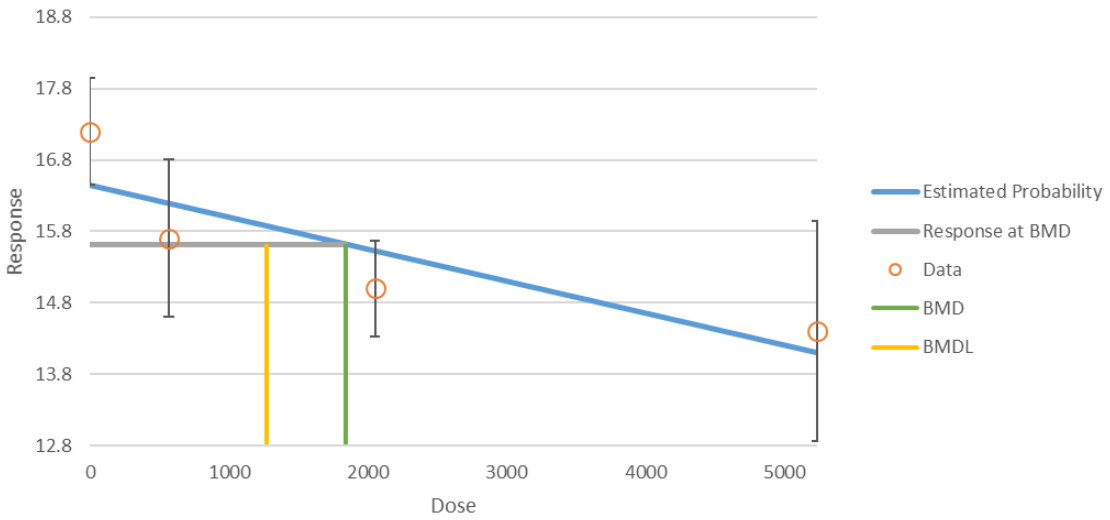


Figure 5.5-6 Plot of Mean Response by Dose, with Fitted Curve for Linear Model for Sprague-Dawley Rat F2B Pup Body Weight at PND7 (Males)

BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L

5.5.5 Sprague-Dawley Rat F2B Pup Body Weight at PND21 (Females)

Sprague-Dawley Rat F2B Pup Body Weight Data at PND21 (Females) used for BMD Modeling

AUC (hr mg/L)	N	Mean	Std. Dev.
0	25	51.7	4.35
566.5	26	49.1	5.87
2053	23	47.0	6.66
5235	20	46.1	7.04

Table 5-12 Model Predictions for AUC (hr mg/L) versus Sprague-Dawley Rat F2B Pup Body Weight at PND21 (Females) Using Daily Average AUC as the Dose Metric

Model	Test 4 P-value	AIC	BMD	BMDL	BMDU	Basis for model selection
Exponential 2	0.2091959	608.4509171	2567.306	1636.342	5782.4747	Exponential model 4 assuming constant variance was selected based on lowest BMDL (BMDLs differed by more than threefold). This model also had a much better visual fit and lower residuals than the other models.
Exponential 3	0.2091959	608.4509171	2567.306	1637.785	5782.4747	
Exponential 4	**0.8453858**	**607.3599775**	**611.6493**	**99.99824**	**2752.6331**	
Polynomial 3°	0.1957569	608.583712	2675.642	1749.609	5922.1867	
Polynomial 2°	0.1957569	608.583712	2675.652	1750.346	5912.9217	
Power	0.1957569	608.583712	2675.65	1753.461	5890.2517	
Linear	0.1957569	608.583712	2675.642	1749.831	5916.3703	

[a] Constant variance case presented (Test 2 p = 0.12); selected model in bold.

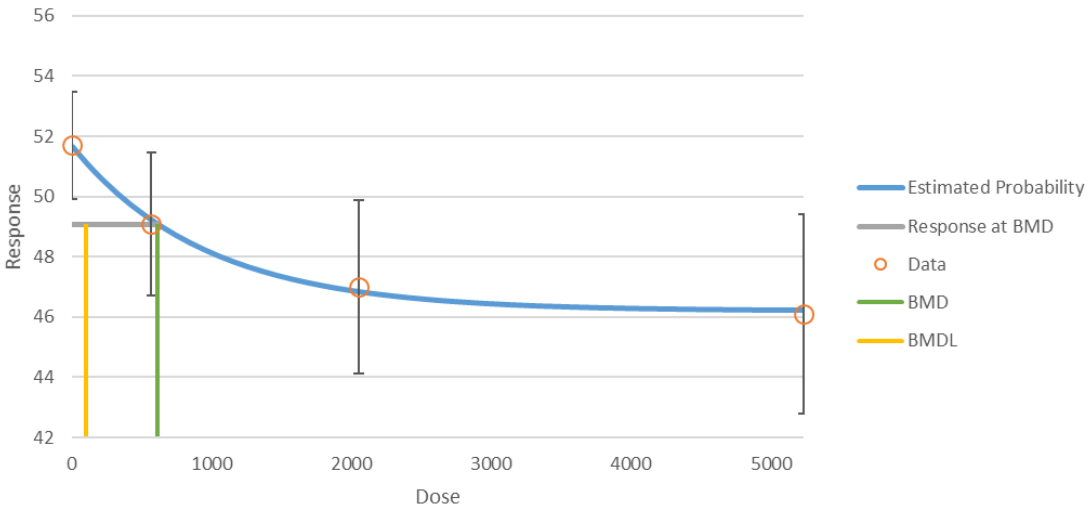


Figure 5.5-7 Plot of Mean Response by Dose, with Fitted Curve for Exponential 4 Model with Constant Variance for Sprague-Dawley Rat F2B Pup Body Weight at PND21 (Females)
BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L

USER INPUT

Info	
Model	frequentist Exponential degree 4 v1.1
Dataset Name	Day 21 pup body weight in F2B female Sprague-Dawley rats
Dose-Response Model	M[dose] = a * [c-(c-1) * exp(-b * dose)]
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Rel. Dev.
BMRF	0.05
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	[Custom]
Independent Variable	[Custom]
Total # of Observations	4
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	611.649313
BMDL	99.99824307
BMDU	2752.633086
AIC	607.3599775
Test 4 P-value	0.845385758
d.f.	1

Model Parameters	
# of Parameters	4
Variable	Estimate
a	51.65433514
b	0.001045796
c	0.894186168
log-alpha	3.538294035

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	25	51.65433514	51.7	51.7	5.86584776	4.35	4.35	0.038924347
566.5	26	49.2110082	49.1	49.1	5.86584776	5.87	5.87	-0.096496361
2053	23	46.82716494	47	47	5.86584776	6.66	6.66	0.141307424
5235	20	46.21150063	46.1	46.1	5.86584776	7.04	7.04	-0.085008337

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-299.6609745	5	609.321949
A2	-296.7494779	8	609.498956
A3	-299.6609745	5	609.321949
fitted	-299.6799888	4	607.359978
R	-305.5360764	2	615.072153

* Includes additive constant of -86.38022. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test d.f.	p-value
1	17.573197	6	0.00739219
2	5.822993199	3	0.12054684
3	5.822993199	3	0.12054684
4	0.038028582	1	0.84538576

5.5.6 Sprague-Dawley Rat F2B Pup Body Weight at PND21 (Males)

Sprague-Dawley Rat F2B Pup Body Weight Data at PND21 (Males) used for BMD Modeling

AUC (hr mg/L)	N	Mean	Std. Dev.
0	25	54	4.52
566.5	26	51.8	6.46
2053	24	47.2	9.82
5235	20	49.4	6.64

Table 5-13 Model Predictions for AUC (hr mg/L) versus Sprague-Dawley Rat F2B Pup Body Weight at PND21 (Males) Using Daily Average AUC as the Dose Metric

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.0223161	651.5750995	3026.784	1697.867	12736.279	Constant variance model did not fit adequately. Non-constant variance model fit adequately, but no model fit means adequately with this variance model. A sensitivity analysis indicated that there was too much uncertainty in the BMD estimate to use dose-response modeling results No model was selected.
Exponential 3	0.0223161	651.5750995	3026.784	1699.496	12736.279	
Exponential 4	0.1715587	647.8394728	461.9646	145.2656	1933.1638	
Polynomial 3°	0.0208586	651.7101835	3173.233	1828.495	13573.1	
Polynomial 2°	0.0208586	651.7101835	3173.233	1828.947	13562.995	
Power	0.0208586	651.7101835	3173.256	1833.186	13542.77	
Linear	0.0208586	651.7101835	3173.253	1828.535	13546.869	

[a] Results assuming constant variance presented (BMDS Test 2 p < 0.01).

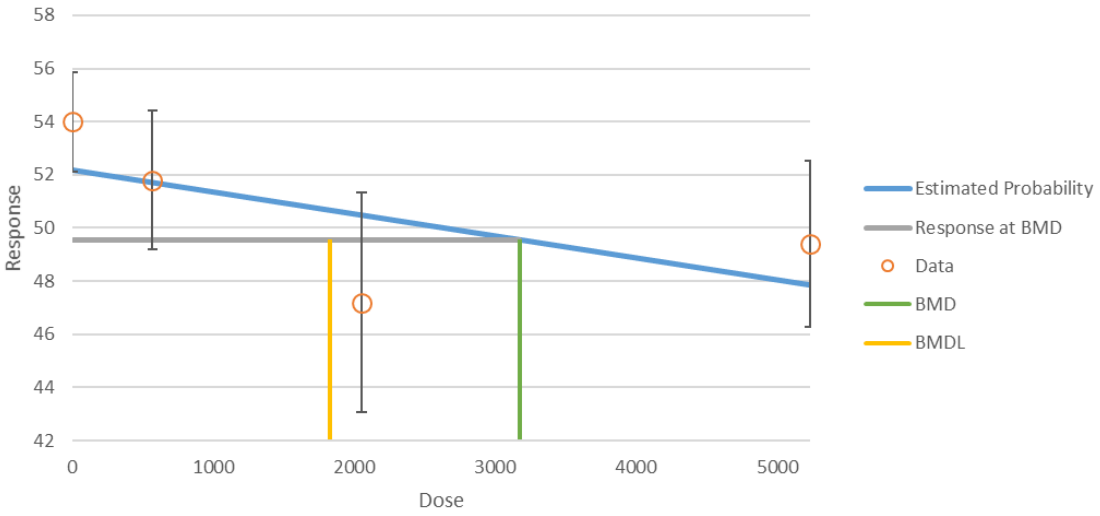


Figure 5.5-8 Plot of Mean Response by Dose, with Fitted Curve for Linear Model with Constant Variance for Sprague-Dawley Rat F2B Pup Body Weight at PND21 (Males)
BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L

5.6 Results for BMD Modeling for Reduced Fetal and Pup Body Weight for Wistar Rats (NMP Producers Group (1999b))

5.6.1 Wistar Rat F1A Fetal Body Weight at PND1 (Females)

Wistar Rat F1A Fetal Body Weight Data at PND1 (Females) used for BMD Modeling

AUC (hr mg/L)	N	Mean	Std. Dev.
0	25	6.2	0.46
538.0	25	6.0	0.55
1965	24	5.9	0.50
7793	13	5.1	0.85

Table 5-14 Model Predictions for AUC (hr mg/L) versus Wistar Rat F1A Fetal Body Weight at PND1 (Females) Using Daily Average AUC as the Dose Metric

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.7063237	151.0124763	2140.151	1640.755	3032.9951	Exponential model 3 assuming constant variance was selected based on lowest AIC.
Exponential 3	**0.7063237**	**151.0124763**	**2140.151**	**1645.211**	**3032.9951**	
Exponential 4	0.7063237	151.0124763	2140.151	1640.755	3032.9951	
Polynomial 3°	0.7042845	151.0182587	2288.456	1802.442	5406.6394	
Polynomial 2°	0.7042845	151.0182587	2288.456	1802.331	4750.7133	
Power	0.7042845	151.0182587	2288.418	1804.786	5426.4704	
Linear	0.7042845	151.0182587	2288.412	1802.472	3160.3402	

[a] Results assuming constant variance presented (Test 2 p = 0.05); selected model in bold.

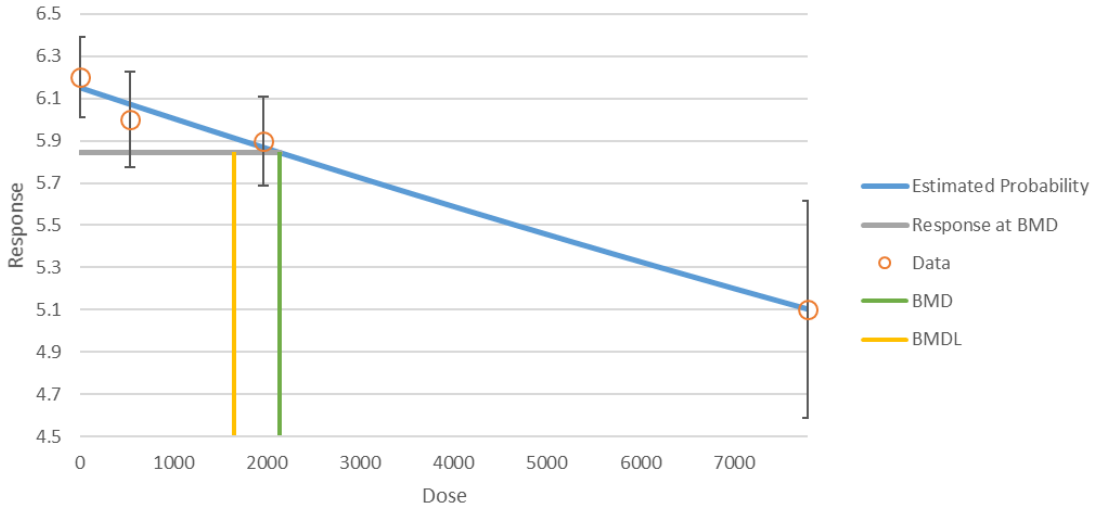


Figure 5.6-1 Plot of Mean Response by Dose, with Fitted Curve for Exponential 3 Model with Constant Variance for Wistar Rat F1A Fetal Body Weight at PND1 (Females)
BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L

USER INPUT

Info	
Model	frequentist Exponential degree 3 v1.1
Dataset Name	Day 1 fetal body weight in F1A female Wistar rats
Dose-Response Model	M[dose] = a * exp(±1 * (b * dose)^d)
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Std. Dev.
BMRF	0.5
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	Dose
Independent Variable	Mean
Total # of Observations	4
Adverse Direction	Automatic

MODEL OUTPUT

Benchmark Dose	
BMD	2140.151258
BMDL	1645.210527
BMDU	3032.995056
AIC	151.0124763
Test 4 P-value	0.706323686
d.f.	2

Model Parameters	
# of Parameters	4
Variable	Estimate
a	6.152774757
b	2.39671E-05
d	Bounded
log-alpha	-1.171066995

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	25	6.152774757	6.2	6.2	0.55680873	0.46	0.46	0.4240706
538	25	6.073948193	6	6	0.55680873	0.55	0.55	-0.664036
1965	24	5.86972465	5.9	5.9	0.55680873	0.5	0.5	0.2663721
7793	13	5.10452406	5.1	5.1	0.55680873	0.85	0.85	-0.0292950

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-72.15855649	5	154.317113
A2	-68.28868638	8	152.577373
A3	-72.15855649	5	154.317113
fitted	-72.50623816	3	151.012476
R	-86.92819994	2	177.8564

* Includes additive constant of -79.94765. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test d.f.	p-value
1	37.27902712	6	<0.0001
2	7.739740213	3	0.05170815
3	7.739740213	3	0.05170815
4	0.695363336	2	0.70632369

5.6.2 Wistar Rat F1A Fetal Body Weight at PND1 (Males)

Wistar Rat F1A Fetal Body Weight Data at PND1 (Males) used for BMD Modeling

AUC (hr mg/L)	N	Mean	Std. Dev.
0	25	6.6	0.41
538.0	25	6.3	0.67
1965	24	6.3	0.47
7793	16	5.5	0.95

Table 5-15 Model Predictions for AUC (hr mg/L) versus Wistar Rat F1A Fetal Body Weight at PND1 (Males) Using Daily Average AUC as the Dose Metric

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.3716029	174.2465268	2383.601	1804.475	3461.8727	Constant variance model did not fit adequately. Non-constant variance model fit adequately, but no model fit means adequately with this variance model. In the context of a sensitivity analysis, the polynomial 3° model was selected, assuming constant variance.
Exponential 3	0.3716029	174.2465268	2383.593	1807.673	3461.8886	
Exponential 4	0.3716029	174.2465268	2383.593	1804.471	3461.8886	
Polynomial 3°	0.3731475	174.2382308	2612.253	1963.694	5880.3753	
Polynomial 2°	0.3726155	174.2410841	2526.986	1963.472	5182.3553	
Power	0.3726155	174.2410842	2526.92	1966.249	7406.5677	
Linear	0.3726154	174.2410849	2527.32	1963.667	3577.1007	

[a] Results assuming constant variance presented (BMDS Test 2 p-value < 0.01, Test 3 p-value = 0.26).

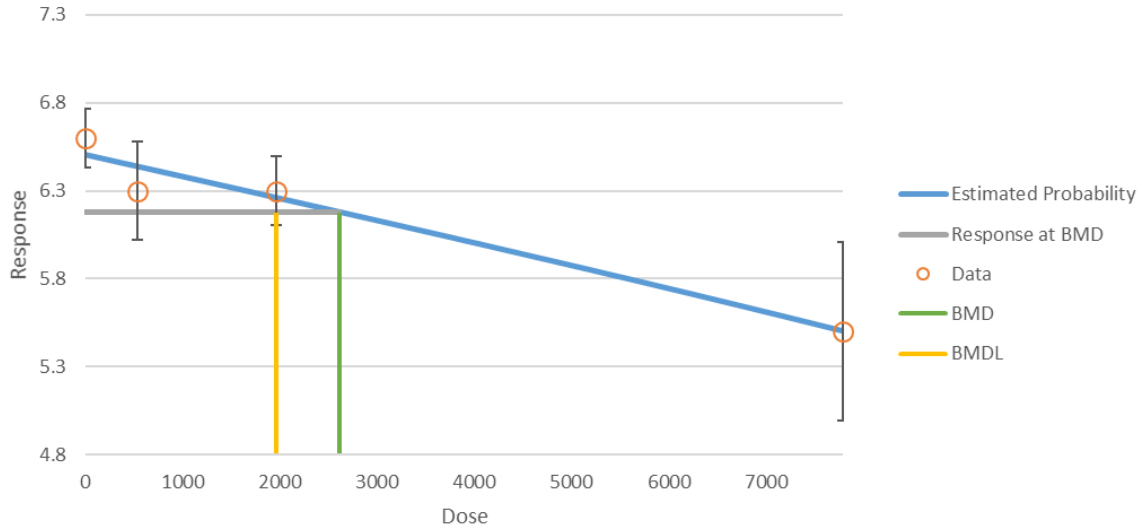


Figure 5.6-2 Plot of Mean Response by Dose, with Fitted Curve for Polynomial 3 Model with Constant Variance for Wistar Rat F1A Fetal Body Weight at PND1 (Males)
BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L

USER INPUT

Info	
Model	frequentist Polynomial degree 3 v1.1
Dataset Name	Day 1 fetal body weight in F1A male Wistar rats
Dose-Response Model	M[dose] = g + b1*dose + b2*dose^2 + ...
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Rel. Dev.
BMRF	0.05
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	Dose
Independent Variable	Mean
Total # of Observations	4
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	2612.253174
BMDL	1963.693651
BMDU	5880.375282
AIC	174.2382308
Test 4 P-value	0.373147505
d.f.	2

Model Parameters	
# of Parameters	5
Variable	Estimate
g	6.502864556
beta1	-0.00012395
beta2	Bounded
beta3	Bounded
alpha	0.379635268

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	25	6.502864556	6.6	6.6	0.616145	0.41	0.41	0.78825087
538	25	6.436167867	6.3	6.3	0.616145	0.67	0.67	-1.10499767
1965	24	6.258726554	6.3	6.3	0.616145	0.47	0.47	0.32816562
7793	16	5.500922185	5.5	5.5	0.616145	0.95	0.95	-0.00598680

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-83.1333339	5	176.266668
A2	-74.41376771	8	164.827535
A3	-83.1333339	5	176.266668
fitted	-84.11911538	3	174.238231
R	-97.11291497	2	198.22583

* Includes additive constant of -82.70447. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test d.f.	p-value
1	45.39829452	6	<0.0001
2	17.43913238	3	0.00057397
3	17.43913238	3	0.00057397
4	1.971562962	2	0.37314751

Table 5-16 Model Predictions for AUC (hr mg/L) versus Wistar Rat F1A Fetal Body Weight at PND1 (Males) Using Daily Average AUC as the Dose Metric.

All SDs set to Minimum SD Across the Group.

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.6511585	248.9425337	2383.593	1599.703	4482.8186	Assuming constant variance, the polynomial 3° model was selected based on lowest AIC.
Exponential 3	0.6511585	248.9425337	2383.593	1603.702	4482.8186	
Exponential 4	0.6511585	248.9425337	2383.593	1599.703	4482.8186	
Polynomial 3°	**0.6523374**	**248.9389161**	**2612.313**	**1764.59**	**6500.3761**	
Polynomial 2°	0.6519317	248.9401603	2526.993	1764.605	5959.5439	
Power	0.6519317	248.9401603	2526.98	1764.555	7541.4133	
Linear	0.6519317	248.9401603	2526.986	1764.597	4571.7527	

[a] Results assuming constant variance presented (BMDS Test 2 p-value = 1.00).

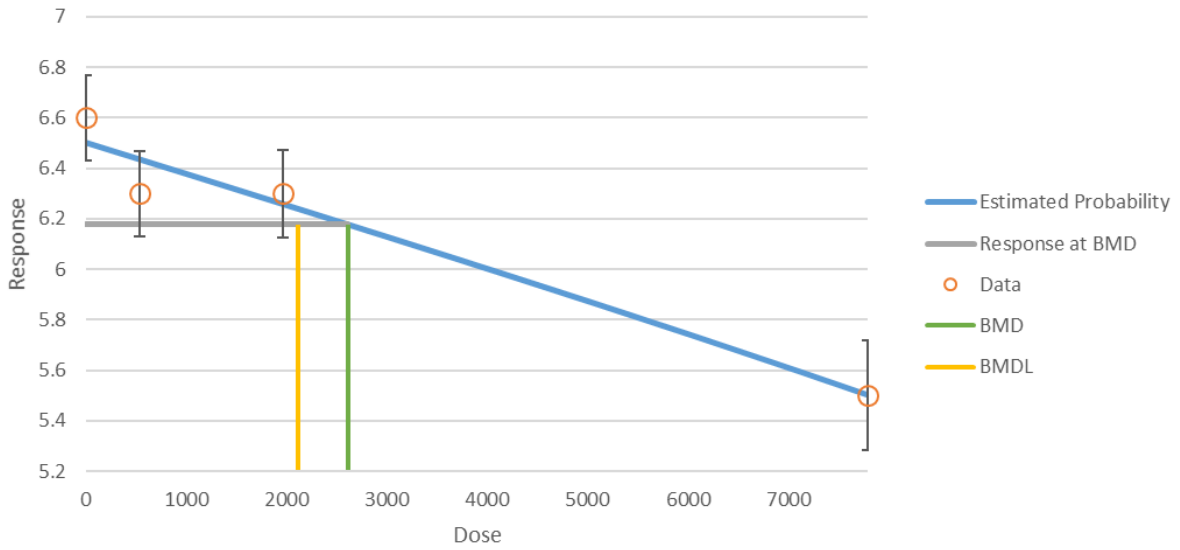


Figure 5.6-3 Plot of Mean Response by Dose, with Fitted Curve for Polynomial 3 Model with Constant Variance for Wistar Rat F1A Fetal Body Weight at PND1 (Males)
BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L; all SDs set to the minimum SD across the groups

USER INPUT

Info	
Model	frequentist Polynomial degree 3 v1.1
Dataset Name	Day 1 fetal body weight in F1A male Wistar rats
Dose-Response Model	M[dose] = g + b1*dose + b2*dose^2 + ...
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Rel. Dev.
BMRF	0.05
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	Dose
Independent Variable	Mean
Total # of Observations	4
Adverse Direction	Automatic

MODEL OUTPUT

Benchmark Dose	
BMD	2612.31263
BMDL	2120.291103
BMDU	5121.060892
AIC	101.324428
Test 4 P-value	0.105675358
d.f.	2

Model Parameters	
# of Parameters	5
Variable	Estimate
g	6.502860455
beta1	-0.000123946
beta2	Bounded
beta3	Bounded
alpha	0.168856677

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	25	6.502860455	6.6	6.6	0.41092174	0.41	0.41	1.18197136
538	25	6.436165633	6.3	6.3	0.41092174	0.41	0.41	-1.65683170
1965	24	6.258728964	6.3	6.3	0.41092174	0.41	0.41	0.49203033
7793	16	5.500924526	5.5	5.5	0.41092174	0.41	0.41	-0.0089995

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-45.41483043	5	100.829661
A2	-45.41306385	8	106.826128
A3	-45.41483043	5	100.829661
fitted	-47.66221398	3	101.324428
R	-72.91234561	2	149.824691

* Includes additive constant of -82.70447. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test d.f.	p-value
1	54.99856352	6	<0.0001
2	0.003533171	3	0.9999442
3	0.003533171	3	0.9999442
4	4.494767098	2	0.10567536

Table 5-17 Model Predictions for AUC (hr mg/L) versus Wistar Rat F1A Fetal Body Weight at PND1 (Males) Using Daily Average AUC as the Dose Metric. All SDs set to Maximum SD Across the Group.

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.6511585	248.9425337	2383.593	1599.703	4482.8186	Assuming constant variance, the polynomial 3° model was selected based on lowest AIC.
Exponential 3	0.6511585	248.9425337	2383.593	1603.702	4482.8186	
Exponential 4	0.6511585	248.9425337	2383.593	1599.703	4482.8186	
Polynomial 3°	**0.6523374**	**248.9389161**	**2612.313**	**1764.59**	**6500.3761**	
Polynomial 2°	0.6519317	248.9401603	2526.993	1764.605	5959.5439	
Power	0.6519317	248.9401603	2526.98	1764.555	7541.4133	
Linear	0.6519317	248.9401603	2526.986	1764.597	4571.7527	

[a] Results assuming constant variance presented (BMDS Test 2 p-value = 1.00).

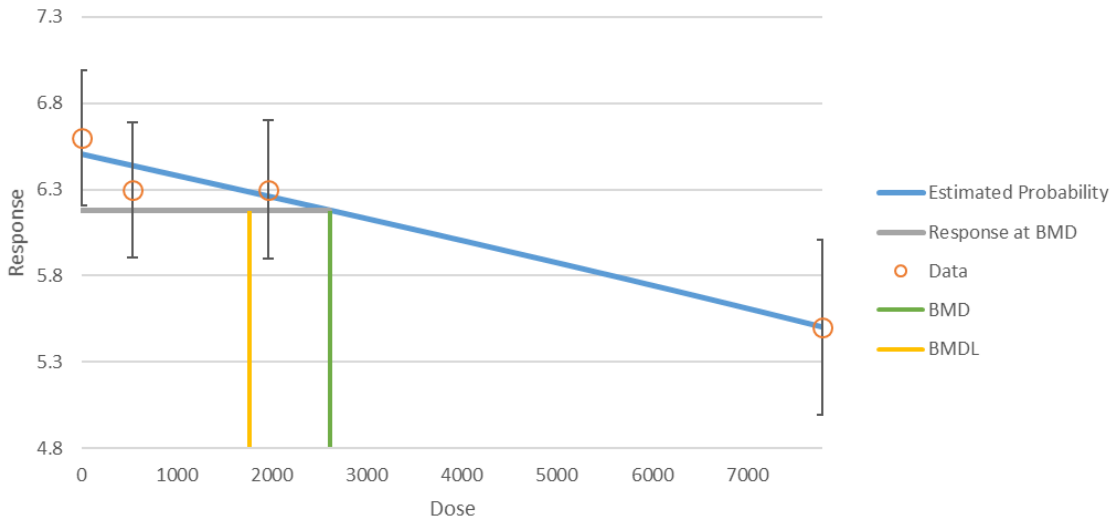


Figure 5.6-4 Plot of Mean Response by Dose, with Fitted Curve for Polynomial 3 Model with Constant Variance for Wistar Rat F1A Fetal Body Weight at PND1 (Males)
BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L; all SDs set to the maximum SD across the groups

USER INPUT

Info	
Model	frequentist Polynomial degree 3 v1.1
Dataset Name	Day 1 fetal body weight in F1A male Wistar rats
Dose-Response Model	M[dose] = g + b1*dose + b2*dose^2 + ...
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Rel. Dev.
BMRF	0.05
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	Dose
Independent Variable	Mean
Total # of Observations	4
Adverse Direction	Automatic

MODEL OUTPUT

Benchmark Dose	
BMD	2612.31263
BMDL	1764.589754
BMDU	6500.376091
AIC	248.9389161
Test 4 P-value	0.652337387
d.f.	2

Model Parameters	
# of Parameters	5
Variable	Estimate
g	6.502862348
beta1	-0.000123946
beta2	Bounded
beta3	Bounded
alpha	0.870621557

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	25	6.502862348	6.6	6.6	0.9330710	0.95	0.95	0.5205265
538	25	6.436167543	6.3	6.3	0.9330710	0.95	0.95	-0.7296740
1965	24	6.258730828	6.3	6.3	0.9330710	0.95	0.95	0.2166789
7793	16	5.500920556	5.5	5.5	0.9330710	0.95	0.95	-0.0039463

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-121.0422647	5	252.084529
A2	-121.0404981	8	258.080996
A3	-121.0422647	5	252.084529
fitted	-121.469458	3	248.938916
R	-127.6007931	2	259.201586

* Includes additive constant of -82.70447. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test d.f.	p-value
1	13.12059002	6	0.04116044
2	0.003533146	3	0.9999442
3	0.003533146	3	0.9999442
4	0.854386774	2	0.65233739

5.6.3 Wistar Rat F1A Pup Body Weight at PND7 (Females)

Wistar Rat F1A Pup Body Weight Data at PND7 (Females) used for BMD Modeling

AUC (hr mg/L)	N	Mean	Std. Dev.
0	25	14.3	1.36
538.0	25	13.4	1.56
1965	24	13.7	1.6
7793	6	11.1	4.23

Table 5-18 Model Predictions for AUC (hr mg/L) versus Wistar Rat F1A Pup Body Weight at PND7 (Females) Using Daily Average AUC as the Dose Metric

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.0975118	313.3363909	1971.475	1124.407	5002.8131	Assuming non-constant variance, of the models that fit the means adequately (Test 4 p-value ≥ 0.10), the polynomial 3° model was selected based on lowest AIC.
Exponential 3	0.0323356	315.2614419	2849.393	1132.245	6431.9847	
Exponential 4	0.0989096	313.307925	2113.589	1127.362	4987.7772	
Polynomial 3°	**0.1362271**	**312.667691**	**3045.909**	**1277.225**	**10384.373**	
Polynomial 2°	0.1243995	312.8493423	2784.37	1255.667	11080.809	
Power	0.0341136	315.1698264	2319.472	1220.992	7714.5917	
Linear	0.1058252	313.1727608	2158.999	1220.729	11324.451	

[a] Results assuming non-constant variance presented (BMDS Test 2 p < 0.01, Test 3 p = 0.85); selected model in bold.

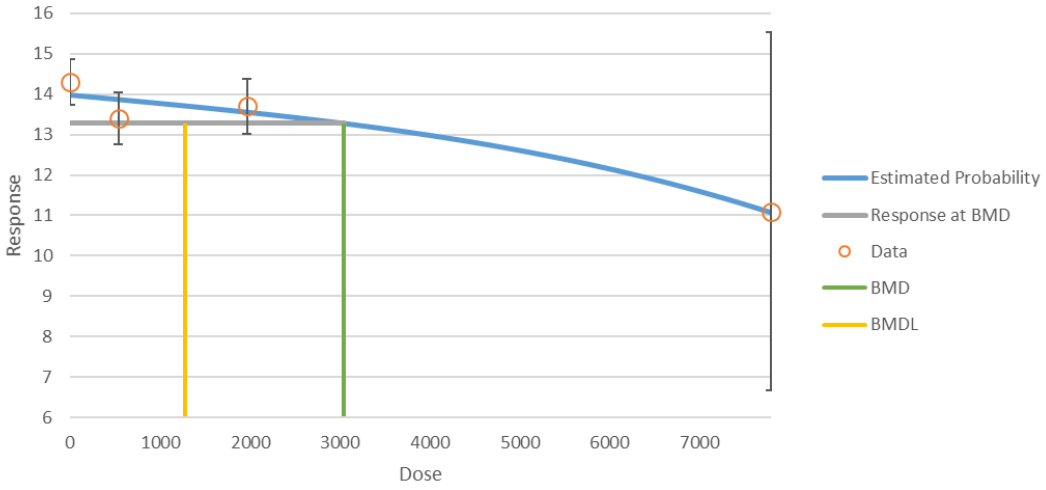


Figure 5.6-5 Plot of Mean Response by Dose, with Fitted Curve for Polynomial 3 Model with Non-constant Variance for Wistar Rat F1A Pup Body Weight at PND7 (Females)
BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L

USER INPUT

Info	
Model	frequentist Polynomial degree 3 v1.1
Dataset Name	Day 7 pup body weight in F1A female Wistar rats
Dose-Response Model	M[dose] = g + b1*dose + b2*dose^2 + ...
Variance Model	Var[i] = alpha * mean[i] ^ rho

Model Options	
BMR Type	Rel. Dev.
BMRF	0.05
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Non-Constant

Model Data	
Dependent Variable	Dose
Independent Variable	Mean
Total # of Observations	4
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	3045.909437
BMDL	1277.225416
BMDU	10384.37289
AIC	312.667691
Test 4 P-value	0.136227112
d.f.	2

Model Parameters	
# of Parameters	6
Variable	Estimate
g	13.97477502
beta1	-0.000203959
beta2	Bounded
beta3	Bounded
alpha	-8.483523005

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	25	13.97477502	14.3	14.3	1.43641314	1.36	1.36	1.1320733
538	25	13.86461787	13.4	13.4	1.48544976	1.56	1.56	-1.563896
1965	24	13.55318758	13.7	13.7	1.63572057	1.6	1.6	0.4397029
7793	6	11.0874095	11.1	11.1	3.83388349	4.23	4.23	0.0080441

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-159.2746464	5	328.549293
A2	-150.1744151	8	316.34883
A3	-150.3404137	6	312.680827
fitted	-152.3338455	4	312.667691
R	-166.6684684	2	337.336937

* Includes additive constant of -73.51508. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test d.f.	p-value
1	32.98810654	6	<0.0001
2	18.20046269	3	0.0003999
3	0.331997137	2	0.84704745
4	3.986863692	2	0.13622711

5.6.4 Wistar Rat F1A Pup Body Weight at PND7 (Males)

Wistar Rat F1A Pup Body Weight Data at PND7 (Males) used for BMD Modeling

AUC (hr mg/L)	N	Mean	Std. Dev.
0	25	15	1.2
538.0	25	13.7	2.03
1965	24	14.7	1.66
7793	7	12	4.24

Table 5-19 Model Predictions for AUC (hr mg/L) versus Wistar Rat F1A Pup Body Weight at PND7 (Males) Using Daily Average AUC as the Dose Metric

Model	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.0232561	350.7071703	2346.337	1424.574	5949.4775	Constant variance model did not fit adequately. Only polynomial 3° model fit the means adequately assuming constant variance, but its residual at the low dose group was high (1.9). Non-constant variance model fit adequately, but no model fit means adequately w/ this variance model. No model was selected.
Exponential 3	0.014954	351.1066788	7131.763	1668.443	7587.3348	
Exponential 4	0.0232561	350.7071703	2346.337	1424.574	5949.4775	
Polynomial 3°	0.1100963	347.2161199	5181.943	1739.039	6691.0253	
Polynomial 2°	0.0959664	347.5301189	4240.252	1686.923	6287.3627	
Power	0.014954	351.1066787	7443.559	7229.447	7773.2364	
Linear	0.0250331	350.5599121	2433.142	1557.746	5800.1603	

[a] Results assuming constant variance presented (BMDS Test 2 p < 0.01, Test 3 p = 0.66).

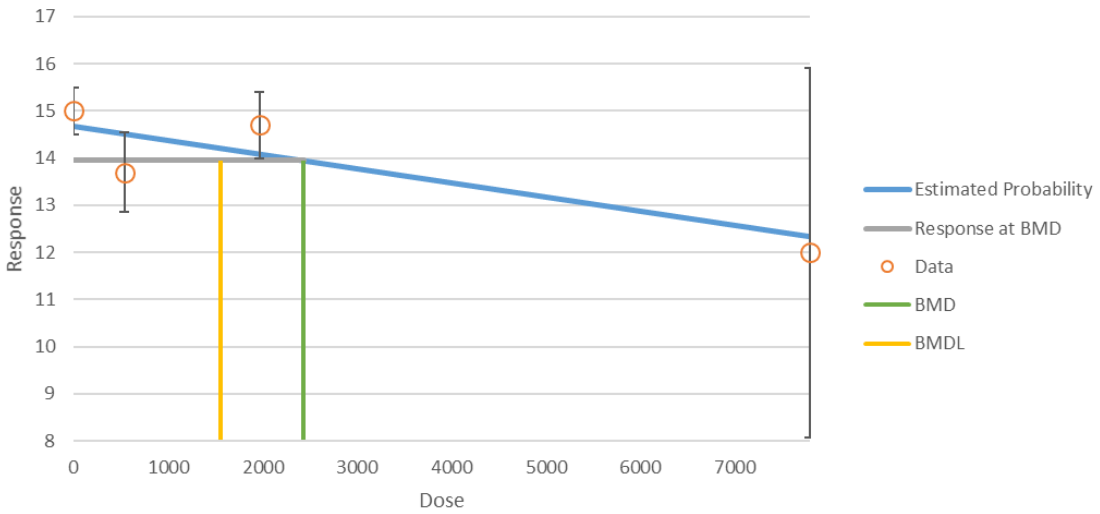


Figure 5.6-6 Plot of Mean Response by Dose, with Fitted Curve for Lines Model with Constant Variance for Wistar Rat F1A Pup Body Weight at PND7 (Females)
BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L

5.6.5 Wistar Rat F1A Pup Body Weight at PND21 (Females)

Wistar Rat F1A Pup Body Weight Data at PND21 (Females) used for BMD Modeling

AUC (hr mg/L)	N	Mean	Std. Dev.
0	25	47.9	3.09
538.0	25	46.6	4.24
1965	24	47.6	4.05
7793	5	44	3.71

Table 5-20 Model Predictions for AUC (hr mg/L) versus Wistar Rat F1A Pup Body Weight at PND21 (Females) Using Daily Average AUC as the Dose Metric

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.3004956	440.1433811	6106.267	3050.063	Infinity	Polynomial 3° model assuming constant variance was selected based on lowest AIC.
Exponential 3	0.198527	441.3919138	7456.866	3304.092	33820.167	
Exponential 4	0.3004956	440.1433808	6104.661	3050.074	Infinity	
Polynomial 3°	**0.6376365**	**437.4355767**	**6935.914**	**3353.844**	**34987.938**	
Polynomial 2°	0.6080195	437.5706289	6572.341	3304.633	41584.807	
Power	0.1985298	441.3918931	7690.254	6557.246	7918.5146	
Linear	0.304673	440.1157687	6078.114	3132.698	Infinity	

[a] Results assuming constant variance presented (BMDS Test 2 p = 0.42); selected model in bold.

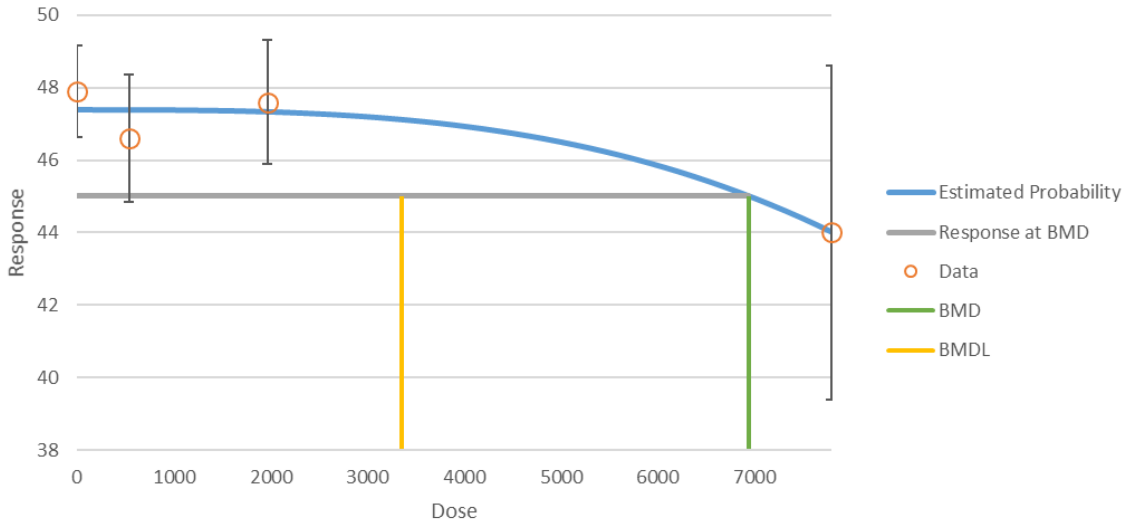


Figure 5.6-7 Plot of Mean Response by Dose, with Fitted Curve for Polynomial 3 Model with Constant Variance for Wistar Rat F1A Pup Body Weight at PND21 (Females)
BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L

USER INPUT

Info	
Model	frequentist Polynomial degree 3 v1.1
Dataset Name	Day 21 pup body weight in F1A female Wistar rats
Dose-Response Model	M[dose] = g + b1*dose + b2*dose^2 + ...
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Rel. Dev.
BMRF	0.05
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	Dose
Independent Variable	Mean
Total # of Observations	4
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	6935.913883
BMDL	3353.843846
BMDU	34987.93818
AIC	437.4355767
Test 4 P-value	0.637636501
d.f.	3

Model Parameters	
# of Parameters	5
Variable	Estimate
g	47.38002134
beta1	Bounded
beta2	Bounded
beta3	Bounded
alpha	14.13493282

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	25	47.38002134	47.9	47.9	3.75964531	3.09	3.09	0.6915262
538	25	47.37891573	46.6	46.6	3.75964531	4.24	4.24	-1.0358899
1965	24	47.3261519	47.6	47.6	3.75964531	4.05	4.05	0.35683585
7793	5	44.01979256	44	44	3.75964531	3.71	3.71	-0.0117717

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-215.8693682	5	441.738736
A2	-214.4497435	8	444.899487
A3	-215.8693682	5	441.738736
fitted	-216.7177884	2	437.435577
R	-218.5281122	2	441.056224

* Includes additive constant of -72.59614. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test d.f.	p-value
1	8.156737342	6	0.22684381
2	2.839249353	3	0.41707946
3	2.839249353	3	0.41707946
4	1.696840284	3	0.6376365

5.6.6 Wistar Rat F1A Pup Body Weight at PND21 (Males)

Wistar Rat F1A Pup Body Weight Data at PND21 (Males) used for BMD Modeling

AUC (hr mg/L)	N	Mean	Std. Dev.
0	25	50.5	2.58
538.0	25	49.1	5.34
1965	24	50.8	4.75
7793	6	44.5	2.59

Table 5-21 Model Predictions for AUC (hr mg/L) versus Wistar Rat F1A Pup Body Weight at PND21 (Males) Using Daily Average AUC as the Dose Metric

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 2	0.0733481	467.037135	4047.756	2406.045	11736.316	Constant variance model did not fit adequately. Non-constant variance model fit adequately, but no model fit means adequately with this variance model. In the context of a sensitivity analysis, the polynomial 3° model was selected, assuming constant variance.
Exponential 3	0.1294555	466.1110791	7067.155	3517.961	7766.675	
Exponential 4	0.0733481	467.037135	4047.756	2406.045	11736.316	
Polynomial 3°	0.4819038	462.2756656	5960.325	3423.292	7685.371	
Polynomial 2°	0.3956477	462.7860807	5257.935	3136.386	7838.2217	
Power	0.129462	466.1110017	7560.324	5771.249	7787.9527	
Linear	0.0782586	466.9075313	4053.597	2494.705	11188.116	

[a] Results assuming constant variance presented (BMDS Test 2 p < 0.01, Test 3 p < 0.01).

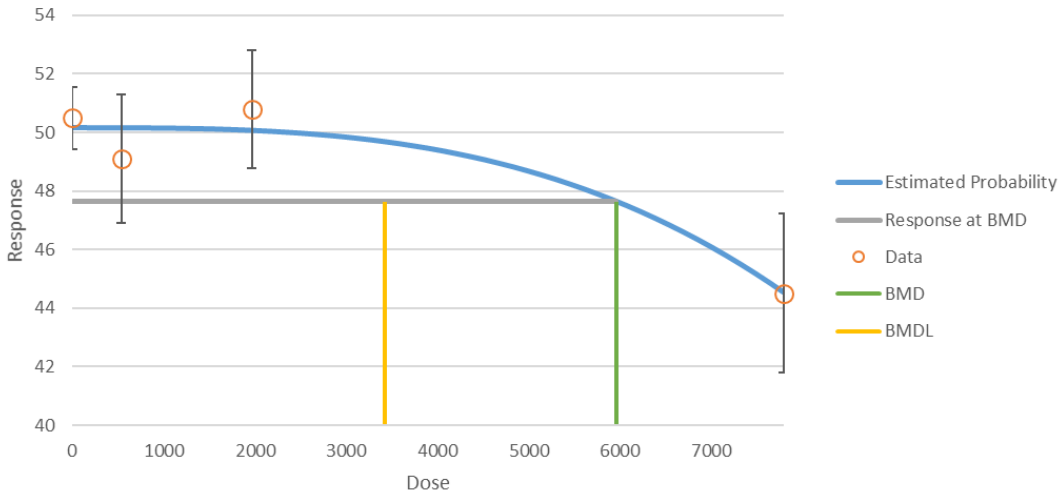


Figure 5.6-8 Plot of Mean Response by Dose, with Fitted Curve for Polynomial Degree 3 Model with Constant Variance for Wistar Rat F1A Pup Body Weight at PND21 (Males)
BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L

USER INPUT

Info	
Model	frequentist Polynomial degree 3 v1.1
Dataset Name	Day 21 pup body weight in F1A male Wistar rats
Dose-Response Model	M[dose] = g + b1*dose + b2*dose^2 + ...
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Rel. Dev.
BMRF	0.05
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	Dose
Independent Variable	Mean
Total # of Observations	4
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	5960.324782
BMDL	3423.29248
BMDU	7685.370953
AIC	462.2756656
Test 4 P-value	0.48190384
d.f.	3

Model Parameters	
# of Parameters	5
Variable	Estimate
g	50.15039221
beta1	Bounded
beta2	Bounded
beta3	Bounded
alpha	18.00362096

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	25	50.15039221	50.5	50.5	4.2430674	2.58	2.58	0.4119753
538	25	50.14854812	49.1	49.1	4.2430674	5.34	5.34	-1.2356015
1965	24	50.06054123	50.8	50.8	4.2430674	4.75	4.75	0.85376757
7793	6	44.54573298	44.5	44.5	4.2430674	2.59	2.59	-0.0264013

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-227.9060288	5	465.812058
A2	-220.1176472	8	456.235294
A3	-227.9060288	5	465.812058
fitted	-229.1378328	2	462.275666
R	-233.6652209	2	471.330442

* Includes additive constant of -73.51508. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test d.f.	p-value
1	27.09514741	6	0.00013898
2	15.5767632	3	0.00138457
3	15.5767632	3	0.00138457
4	2.463608041	3	0.48190384

Table 5-22 Model Predictions for AUC (hr mg/L) versus Wistar Rat F1A Pup Body Weight at PND21 (Males) Using Daily Average AUC as the Dose Metric.

All SDs set to Minimum SD Across the Group.

Model	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 3	0.012827	388.7658213	7412.757	4697.234	7599.4962	Assuming constant variance, no model fit the means adequately (Test 4 p-value < 0.10 for all models). No model was selected.
Polynomial 3°	0.0848587	385.1980681	5960.421	4635.693	6808.6243	
Polynomial 2°	0.0469322	386.5288966	5257.727	4201.064	6474.939	
Power	0.0128272	388.7657993	7579.644	4737.149	7726.4385	
[a] Results assuming constant variance presented (BMDS Test 2 p = 1.00).						

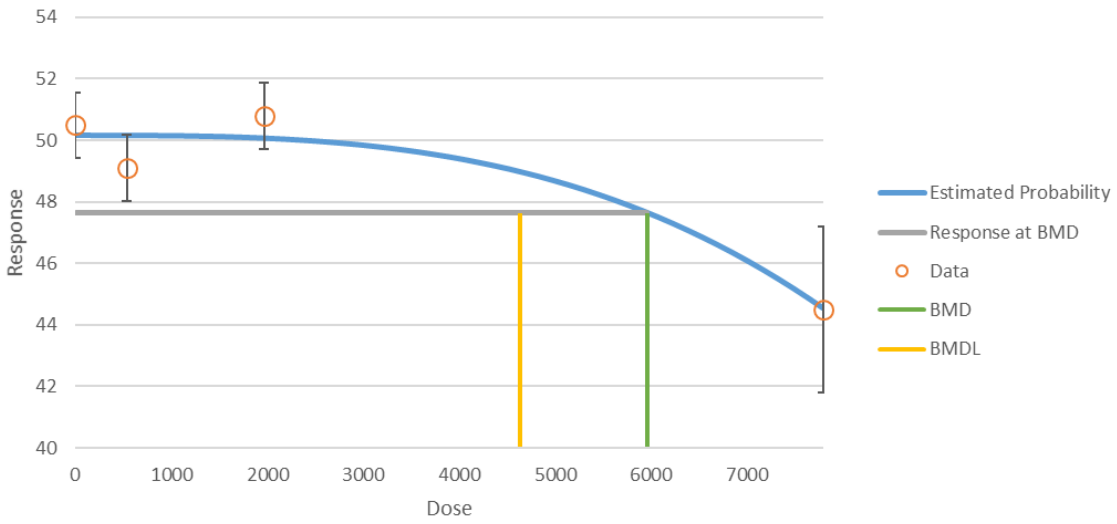


Figure 5.6-9 Plot of Mean Response by Dose, with Fitted Curve for Polynomial Degree 3 Model with Constant Variance for Wistar Rat F1A Pup Body Weight at PND21 (Males)
BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L; all SDs set to the minimum SD across the groups

Table 5-23 Model Predictions for AUC (hr mg/L) versus Wistar Rat F1A Pup Body Weight at PND21 (Males) Using Daily Average AUC as the Dose Metric.
All SDs set to Maximum SD Across the Group.

Model [a]	Goodness of fit		BMD (hr mg/L)	BMDL (hr mg/L)	BMDU (hr mg/L)	Basis for model selection
	Test 4 P-value	AIC				
Exponential 3	0.2223544	500.4519173	7071.418	2795.856	7908.6121	Assuming constant variance, the polynomial 3° model was selected based on lowest AIC.
Polynomial 3°	**0.6602299**	**496.5591027**	**5960.421**	**2772.076**	**8727.6197**	
Polynomial 2°	0.587235	496.8919861	5258.084	2640.539	9314.8981	
Power	0.2223618	500.4518697	7559.672	7419.501	7839.4866	

[a] Results assuming constant variance presented (BMDS Test 2 p = 1.00).

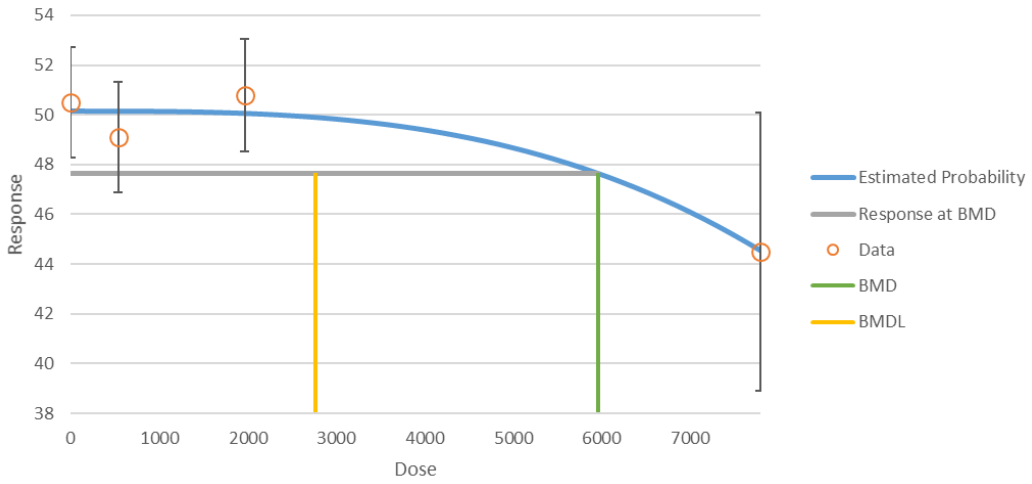


Figure 5.6-10 Plot of Mean Response by Dose, with Fitted Curve for Polynomial Degree 3 Model with Constant Variance for Wistar Rat F1A Pup Body Weight at PND21 (Males)
BMR = 5% relative deviation; daily average AUC as dose shown in hr mg/L; all SDs set to the maximum SD across the groups

USER INPUT

Info	
Model	frequentist Polynomial degree 3 v1.1
Dataset Name	Day 21 pup body weight in F1A male Wistar rats-max Sprague-Dawley
Dose-Response Model	M[dose] = g + b1*dose + b2*dose^2 + ...
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Rel. Dev.
BMRF	0.05
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	Dose
Independent Variable	Mean
Total # of Observations	4
Adverse Direction	Automatic

MODEL RESULTS

Benchmark Dose	
BMD	5960.421398
BMDL	2772.076153
BMDU	8727.619723
AIC	496.5591027
Test 4 P-value	0.660229866
d.f.	3

Model Parameters	
# of Parameters	4
Variable	Estimate
g	50.15035834
beta1	Bounded
beta2	Bounded
beta3	Bounded
alpha	27.63579123

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	25	50.15035834	50.5	50.5	5.25697548	5.34	5.34	0.332550213
538	25	50.14851434	49.1	49.1	5.25697548	5.34	5.34	-0.99726006
1965	24	50.0605119	50.8	50.8	5.25697548	5.34	5.34	0.689129526
7793	6	44.54598299	44.5	44.5	5.25697548	5.34	5.34	-0.02142579

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-245.4814031	5	500.962806
A2	-245.454905	8	506.90981
A3	-245.4814031	5	500.962806
fitted	-246.2795513	2	496.559103
R	-249.2864426	2	502.572885

* Includes additive constant of -73.51508. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test d.f.	p-value
1	7.663075137	6	0.2638408
2	0.052996268	3	0.99680631
3	0.052996268	3	0.99680631
4	1.596296449	3	0.66022987

5.7 Results for BMD Modeling for Stillbirths, and PND4 and PND21 Pup Deaths in Sprague-Dawley Rats (NMP Producers Group (1999a))

5.7.1 Sprague-Dawley Rat F1A stillborn/total delivered (NMP Producers Group (1999a))

Sprague-Dawley Rat F1A stillborn/total delivered (NMP Producers Group (1999a))

AUC (hr mg/L)	C_{max} (mg/L)	Total Delivered	Stillborn	Covariate (mg, LD1 Dam BW)
0	0	13	0	245
0	0	8	0	273
0	0	11	0	278
0	0	13	0	280
0	0	16	0	281
0	0	11	0	283
0	0	12	1	284
0	0	17	0	289
0	0	11	0	294
0	0	13	0	303
0	0	13	1	308
0	0	15	0	309
0	0	15	0	311
0	0	16	0	311
0	0	12	0	313
0	0	13	0	315
0	0	16	0	315
0	0	16	0	317
0	0	15	0	319
0	0	16	0	319
0	0	15	0	320
0	0	16	0	323
0	0	17	4	323
0	0	14	0	324
0	0	14	0	366
589.1	40.87	14	0	272
589.1	40.87	11	0	276
589.1	40.87	14	0	281
589.1	40.87	14	0	285
589.1	40.87	16	0	288
589.1	40.87	15	0	288
589.1	40.87	14	0	291
589.1	40.87	14	0	294
589.1	40.87	16	0	295
589.1	40.87	14	0	296
589.1	40.87	1	1	298
589.1	40.87	10	1	300
589.1	40.87	11	0	302
589.1	40.87	15	0	302
589.1	40.87	14	0	306
589.1	40.87	17	2	313
589.1	40.87	18	0	314

AUC (hr mg/L)	C_{max} (mg/L)	Total Delivered	Stillborn	Covariate (mg, LD1 Dam BW)
589.1	40.87	6	0	316
589.1	40.87	13	0	317
589.1	40.87	16	0	317
589.1	40.87	11	0	318
589.1	40.87	7	0	324
589.1	40.87	18	0	326
589.1	40.87	14	1	328
589.1	40.87	14	0	328
589.1	40.87	13	0	333
2117	142.35	11	0	231
2117	142.35	16	1	253
2117	142.35	16	0	260
2117	142.35	14	0	280
2117	142.35	14	0	288
2117	142.35	15	0	292
2117	142.35	12	0	294
2117	142.35	13	0	295
2117	142.35	14	0	299
2117	142.35	16	0	301
2117	142.35	15	0	302
2117	142.35	14	1	304
2117	142.35	14	0	309
2117	142.35	10	0	312
2117	142.35	14	0	314
2117	142.35	17	0	314
2117	142.35	14	0	315
2117	142.35	13	0	316
2117	142.35	16	0	321
2117	142.35	16	0	323
2117	142.35	16	0	324
2117	142.35	10	0	329
2117	142.35	14	0	331
2117	142.35	15	0	344
8511	557.5	14	0	243
8511	557.5	12	0	243
8511	557.5	9	0	250
8511	557.5	6	0	255
8511	557.5	11	4	256
8511	557.5	15	1	261
8511	557.5	11	0	266
8511	557.5	15	0	269
8511	557.5	11	0	274
8511	557.5	17	1	276
8511	557.5	13	1	280
8511	557.5	12	0	282
8511	557.5	13	0	282
8511	557.5	15	0	283
8511	557.5	15	0	287

AUC (hr mg/L)	C_{max} (mg/L)	Total Delivered	Stillborn	Covariate (mg, LD1 Dam BW)
8511	557.5	15	0	287
8511	557.5	14	1	288
8511	557.5	14	0	292
8511	557.5	13	0	293
8511	557.5	11	1	294
8511	557.5	15	1	299
8511	557.5	9	0	300
8511	557.5	13	0	300
8511	557.5	18	2	301
8511	557.5	4	0	306
8511	557.5	15	8	306
8511	557.5	15	0	318
8511	557.5	15	0	329
8511	557.5	9	0	336

Table 5-24 Summary of BMDS nested modeling results for AUC (hr mg/L) versus Sprague-Dawley Rat F1A stillborn/total delivered (NMP Producers Group (1999a)); BMR = 1% extra risk.

Model [a]	Goodness of fit		BMD_{01} (hr mg/L)	$BMDL_{01}$ (hr mg/L)	Basis for Model Selection
	P-value	AIC			
Litter-specific covariate = LD1 dam weight; intra-litter correlations estimated					No model is chosen because all model p-values are below 0.1.
Nlogistic (b. seed[b] = 1597161083)	0.0537	276.885	7445.74	1555.12	
NCTR (b. seed = 1597161085)	0.0483	274.881	7460.59	6217.16	
Litter-specific covariate = LD1 dam weight; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1597161079)	0	304.173	7349.34	2549.34	
NCTR (b. seed = 1597161080)	0	302.116	7369.93	6141.61	
Litter-specific covariate not used; intra-litter correlations estimated					
Nlogistic (b. seed = 1597161067)	0.051	272.956	7442.34	1546.16	
NCTR (b. seed = 1597161072)	0.0523	270.956	7465.2	6221	
Litter-specific covariate not used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1597161075)	0	300.939	7438.23	2810.64	
NCTR (b. seed = 1597161077)	0	298.939	7459.66	6216.39	

[a] Litter-specific data were fit using BMDS NLogistic and NCTR nested dichotomous models. Adequate model fit (p-value >0.1) was not achieved for either standard restricted (shown) and unrestricted (not shown) model forms.
[b] b. seed: bootstrap seed. The bootstrap seed shown must be entered into BMDS 2.7.0.4 nested model to replicate results.

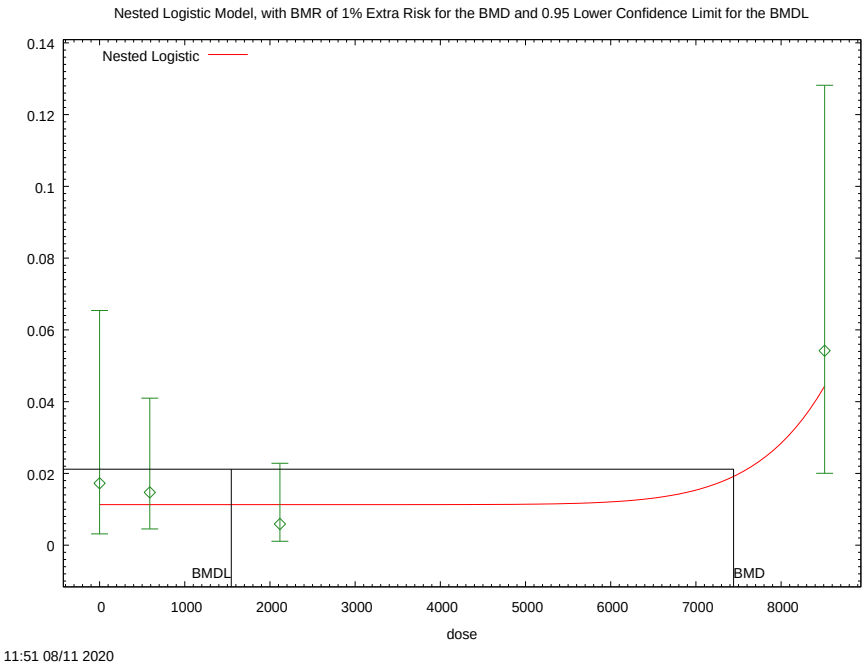


Figure 5.7-1 Plot of NLogistic (no LSC; ICC estimated) model for AUC (hr mg/L) versus Sprague-Dawley Rat F1A stillborn/total delivered.

Table 5-25 Summary of BMDS nested modeling results for C_{max} (mg/L) versus Sprague-Dawley Rat F1A stillborn/total delivered (NMP Producers Group (1999a)); BMR = 1% extra risk.

Model [a]	Goodness of fit		BMD_{01} (hr mg/L)	$BMDL_{01}$ (hr mg/L)	Basis for Model Selection
	P-value	AIC			
Litter-specific covariate = LD1 dam weight; intra-litter correlations estimated					No model is chosen because all model p-values are below 0.1.
Nlogistic (b. seed[b] = 1597185415)	0.0533	276.885	488.742	102.875	
NCTR (b. seed = 1597185417)	0.046	274.881	489.813	408.177	
Litter-specific covariate = LD1 dam weight; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1597185410)	0	304.173	482.277	170.785	
NCTR (b. seed = 1597185412)	0	302.116	483.956	403.297	
Litter-specific covariate not used; intra-litter correlations estimated					
Nlogistic (b. seed = 1597185401)	0.0537	272.956	488.56	102.333	
NCTR (b. seed = 1597185404)	0.0507	270.956	490.11	408.425	
Litter-specific covariate not used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1597185407)	0	300.939	488.285	187.934	
NCTR (b. seed = 1597185409)	0	298.939	489.746	408.122	

[a] Litter-specific data were fit using BMDS NLogistic and NCTR nested dichotomous models. Adequate model fit (p-value >0.1) was not achieved for either standard restricted (shown) and unrestricted (not shown) model forms.
[b] b. seed: bootstrap seed. The bootstrap seed shown must be entered into BMDS 2.7.0.4 nested model to replicate results.

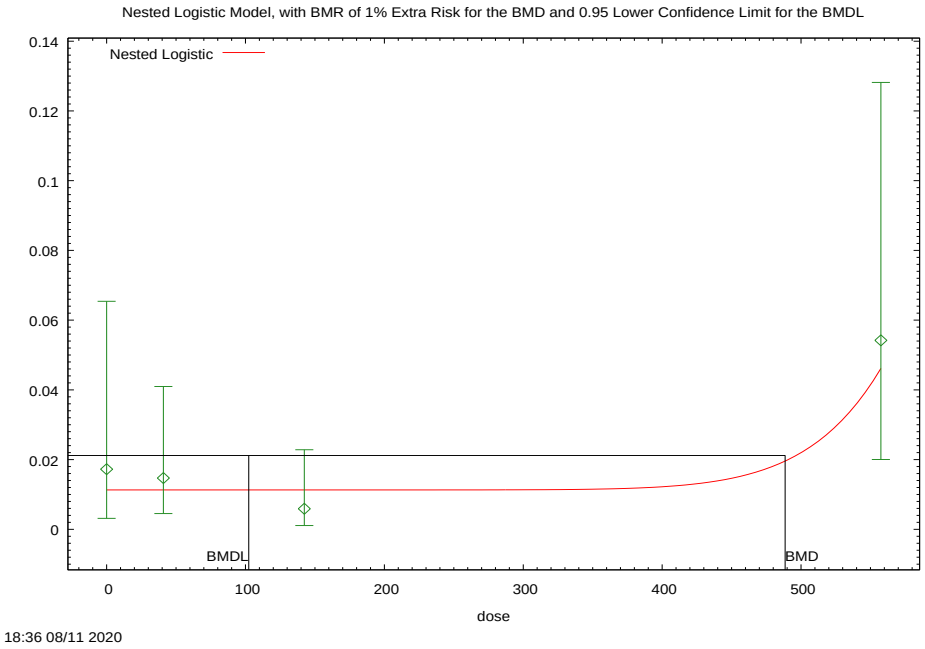


Figure 5.7-2 Plot of NLogistic (no LSC; ICC estimated) model for C_{max} (mg/L) versus Sprague-Dawley Rat F1A stillborn/total delivered.

5.7.2 Sprague-Dawley Rat F2B Pup death at PND4/total delivered (NMP Producers Group (1999a))

Sprague-Dawley Rat F2B Pup Death at PND4/total Delivered (NMP Producers Group (1999a))

AUC (hr mg/L)	Total Delivered	PND4 Pup Deaths	Covariate (mg, LD1 Dam BW)
0	17	6	342
0	18	0	346
0	11	0	355
0	17	0	356
0	16	0	358
0	16	1	358
0	14	0	358
0	17	0	365
0	12	1	368
0	12	0	369
0	14	3	369
0	19	3	373
0	18	0	377
0	19	1	378
0	17	0	381
0	10	0	384
0	16	0	385
0	12	1	386
0	13	0	387
0	15	1	387
0	18	4	389
0	17	2	394
0	16	0	394
0	18	0	417
0	18	2	421
566.5	16	8	279
566.5	13	0	321
566.5	8	0	324
566.5	16	0	330
566.5	14	1	334
566.5	12	0	338
566.5	15	0	342
566.5	15	0	345
566.5	19	1	347
566.5	13	4	348
566.5	17	0	349
566.5	17	0	359
566.5	18	0	372
566.5	20	1	372
566.5	15	0	381
566.5	8	2	385
566.5	14	0	386
566.5	17	0	390
566.5	9	0	394

AUC (hr mg/L)	Total Delivered	PND4 Pup Deaths	Covariate (mg, LD1 Dam BW)
566.5	19	2	403
566.5	19	0	413
566.5	10	0	413
566.5	19	7	419
566.5	20	1	427
566.5	19	1	447
566.5	14	0	456
2053	14	1	290
2053	12	1	308
2053	17	0	309
2053	13	0	318
2053	14	1	323
2053	12	0	324
2053	19	1	324
2053	18	0	325
2053	16	0	337
2053	17	0	340
2053	1	0	347
2053	16	0	358
2053	15	3	363
2053	17	0	369
2053	14	3	381
2053	14	0	381
2053	15	0	381
2053	15	0	388
2053	21	2	394
2053	18	0	401
2053	14	0	407
2053	2	0	409
2053	17	0	423
2053	19	1	433
5235	15	1	294
5235	14	12	306
5235	13	0	319
5235	19	19	326
5235	14	0	337
5235	16	1	337
5235	13	1	350
5235	18	0	359
5235	15	0	366
5235	16	2	367
5235	1	1	370
5235	13	0	371
5235	14	7	375
5235	3	0	378
5235	16	0	381
5235	12	0	381
5235	19	0	389

AUC (hr mg/L)	Total Delivered	PND4 Pup Deaths	Covariate (mg, LD1 Dam BW)
5235	10	0	389
5235	17	0	395
5235	16	4	395
5235	19	0	398
5235	15	1	423
5235	8	0	445
5235	15	0	456

Table 5-26 Summary of BMDS nested modeling results for AUC (hr mg/L) versus Sprague-Dawley Rat F2B Pup death at PND4 /total delivered (NMP Producers Group (1999a)); BMR = 1% extra risk.

Model [a]	Goodness of fit		BMD_{01} (hr mg/L)	$BMDL_{01}$ (hr mg/L)	Basis for Model Selection
	P-value	AIC			
Litter-specific covariate = LD1 dam weight; intra-litter correlations estimated					While some models met the p-value fit criteria (p-value > 0.1), no model was deemed to appropriate after visual inspection of model plots, which indicates considerable model uncertainty and a dose-response pattern analogous to having a positive response at only the highest dose.
Nlogistic (b. seed[b] = 1597167183)	0.2783	624.069	21778.9	212.473	
NCTR (b. seed = 1597167185)	0.469	612.588	4422.47	3685.39	
Litter-specific covariate = LD1 dam weight; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1597167179)	0	751.826	4733.93	3044.98	
NCTR (b. seed = 1597167181)	0	764.134	4501.04	3750.86	
Litter-specific covariate not used; intra-litter correlations estimated					
Nlogistic (b. seed = 1597167169)	0.1837	620.686	21779.5	201.176	
NCTR (b. seed = 1597167173)	0.3973	611.342	4450.73	3708.94	
Litter-specific covariate not used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1597167176)	0	787.278	4526.5	2061.5	
NCTR (b. seed = 1597167177)	0	785.278	4533.37	3777.81	

[a] Litter-specific data were fit using standard (restricted) BMDS NLogistic and NCTR nested dichotomous models. No model was chosen due the considerable model uncertainty indicated by visual inspection of model plots.

[b] b. seed: bootstrap seed. The bootstrap seed shown must be entered into BMDS 2.7.0.4 nested model to replicate results.

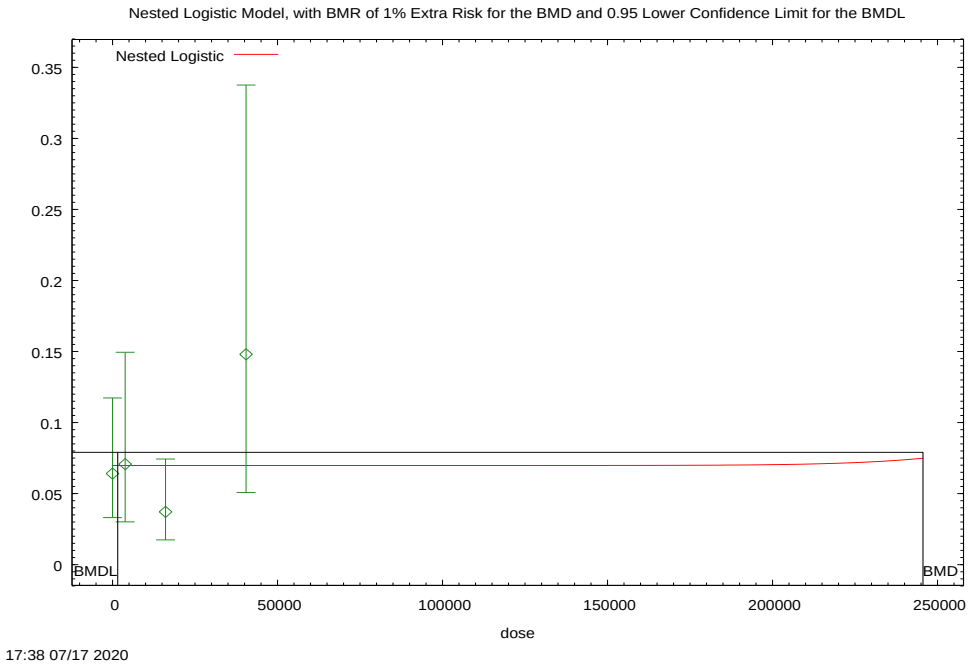


Figure 5.7-3 Plot of NLogistic (no LSC; ICC estimated) model for AUC (hr mg/L) versus Sprague-Dawley Rat F2B Pup Death at PND4/Total Delivered.

5.7.3 Sprague-Dawley Rat F2B Pup death at PND21/PND4 post-cull (NMP Producers Group (1999a))

Sprague-Dawley Rat F2B Pup Death at PND21/PND4 Post-cull (NMP Producers Group (1999a))

AUC (hr mg/L)	PND4 Live Post-cull	PND21 Pup Deaths	Covariate (mg, LD1 Dam BW)
0	10	0	342
0	10	0	346
0	10	0	355
0	10	0	356
0	10	0	358
0	10	0	358
0	10	0	358
0	10	0	365
0	10	0	368
0	10	0	369
0	10	0	369
0	10	1	373
0	10	0	377
0	10	0	378
0	10	0	381
0	10	0	384
0	10	0	385
0	10	0	386
0	10	0	387
0	10	0	387
0	10	0	389
0	10	0	394
0	10	0	394
0	10	0	417
0	10	0	421
566.5	8	0	279
566.5	10	0	321
566.5	8	0	324
566.5	10	3	330
566.5	10	0	334
566.5	10	0	338
566.5	10	0	342
566.5	10	0	345
566.5	10	0	347
566.5	9	0	348
566.5	10	0	349
566.5	10	0	359
566.5	10	0	372
566.5	10	0	372
566.5	10	0	381
566.5	6	0	385
566.5	10	0	386
566.5	10	0	390
566.5	9	0	394

AUC (hr mg/L)	PND4 Live Post-cull	PND21 Pup Deaths	Covariate (mg, LD1 Dam BW)
566.5	10	0	403
566.5	10	0	413
566.5	10	0	413
566.5	10	0	419
566.5	10	0	427
566.5	10	0	447
566.5	10	0	456
2053	10	0	290
2053	10	0	308
2053	10	1	309
2053	10	0	318
2053	10	0	323
2053	10	0	324
2053	10	0	324
2053	10	0	325
2053	10	0	337
2053	10	3	340
2053	1	0	347
2053	10	0	358
2053	10	0	363
2053	10	0	369
2053	10	0	381
2053	10	0	381
2053	10	0	381
2053	10	0	388
2053	10	0	394
2053	10	0	401
2053	10	0	407
2053	2	0	409
2053	10	0	423
2053	10	0	433
5235	10	0	294
5235	2	2	306
5235	10	10	319
5235	10	0	337
5235	10	0	337
5235	10	0	350
5235	10	0	359
5235	10	0	366
5235	10	0	367
5235	10	0	371
5235	7	2	375
5235	3	0	378
5235	10	0	381
5235	10	0	381
5235	10	0	389
5235	10	0	389
5235	10	0	395

AUC (hr mg/L)	PND4 Live Post-cull	PND21 Pup Deaths	Covariate (mg, LD1 Dam BW)
5235	10	0	395
5235	10	1	398
5235	10	1	423
5235	8	0	445
5235	10	0	456

Table 5-27 Summary of BMDS nested modeling results for AUC (hr mg/L) versus Sprague-Dawley Rat F2B Pup death at PND21/PND4 post-cull (NMP Producers Group (1999a)).
BMR = 1% extra risk.

Model [a]	Goodness of fit		BMD_{01} (hr mg/L)	$BMDL_{01}$ (hr mg/L)	Basis for Model Selection
	P-value	AIC			
Litter-specific covariate = LD1 dam weight; intra-litter correlations estimated					The NLogistic model that estimated intra-litter correlations but did not make use of a litter-specific covariate was selected based on estimating the lowest BMDL within a range of BMDLs from acceptable models (P-value > 0.1) that varied more than 3-fold.
Nlogistic (b. seed[b] = 1597171302)	0.4993	136.056	2190.56	407.944	
NCTR (b. seed = 1597171304)	0.4923	136.595	2063.58	1031.79	
Litter-specific covariate = LD1 dam weight; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1597171298)	0.0157	184.305	3227.07	1468.34	
NCTR (b. seed = 1597171299)	0.008	192.4	2157.95	1078.98	
Litter-specific covariate not used; intra-litter correlations estimated					
Nlogistic (b. seed = 1597171290)	**0.3293**	**135.305**	**1829.66**	**313.814**	
NCTR (b. seed = 1597171292)	0.3297	135.299	1816.24	908.119	
Litter-specific covariate not used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1597171294)	0	203.974	1697.58	555.973	
NCTR (b. seed = 1597171296)	0	203.961	1674.73	837.367	

[a] Litter-specific data were fit using standard (restricted) BMDS NLogistic and NCTR nested dichotomous models. Selected model is bolded.
[b] b. seed: bootstrap seed. The bootstrap seed shown must be entered into BMDS 2.7.0.4 nested model to replicate results.

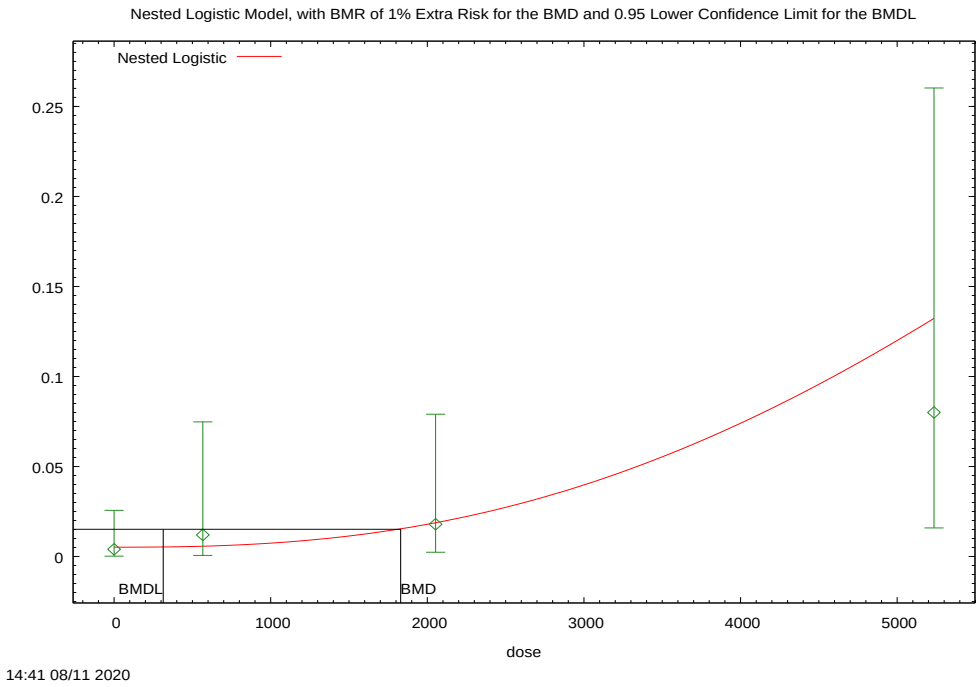


Figure 5.7-4 Plot of NLogistic model (LSC = LD1 dam weight; ICC estimated) for AUC (hr mg/L) versus Sprague-Dawley Rat F2B Pup Death at PND21/PND4 Live Post-cull.

==========

NLogistic Model. (Version: 2.20; Date: 04/27/2015)

Input Data File: C:/Users/jgift/BMDS2704/Data/SDF2b_Day21_p1563/Correct Doses/BMR01/nln_SDF2b_Day21_p1563_Nln-BMR1-Restrict-IC.(d)

Tue Aug 11 14:41:30 2020

==========

BMDS Model Run

~~~~~~~~~~

The probability function is:

Prob. = alpha + theta1*Rij + [1 - alpha - theta1*Rij]/

[1+exp(-beta-theta2*Rij-rho*log(Dose))],

where Rij is the litter specific covariate.

Restrict Power rho >= 1.

Total number of observations = 97
Total number of records with missing values = 0
Total number of parameters in model = 9
Total number of specified parameters = 2

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
~~~~~~~~~~

Number of Bootstrap Iterations per run: 1000
Bootstrap Seed: 1597171290

User specifies the following parameters:
theta1 = 0
theta2 = 0

Default Initial Parameter Values

alpha =	0.0051889	
beta =	-23.4938	
theta1 =	0	Specified
theta2 =	0	Specified
rho =	2.51584	
phi1 =	0	
phi2 =	0.274833	
phi3 =	0.205111	
phi4 =	0.730024	

Parameter Estimates

Variable	Estimate	Std. Err.
alpha	0.0051889	0.00385081
beta	-23.4939	0.509863
rho	2.51584	0.367021
phi1	0	Bounded
phi2	0.274833	0.534557
phi3	0.205111	NA
phi4	0.730024	NA

Log-likelihood: -61.6524 AIC: 135.305

Litter Data

Dose	Lit.-Spec. Cov.	Litter Est._Prob.	Size	Scaled Expected	Observed	Residual
0.0000	342.0000	0.005	10	0.052	0	-0.2284
0.0000	346.0000	0.005	10	0.052	0	-0.2284
0.0000	355.0000	0.005	10	0.052	0	-0.2284
0.0000	356.0000	0.005	10	0.052	0	-0.2284
0.0000	358.0000	0.005	10	0.052	0	-0.2284
0.0000	358.0000	0.005	10	0.052	0	-0.2284
0.0000	358.0000	0.005	10	0.052	0	-0.2284
0.0000	365.0000	0.005	10	0.052	0	-0.2284
0.0000	368.0000	0.005	10	0.052	0	-0.2284
0.0000	369.0000	0.005	10	0.052	0	-0.2284
0.0000	369.0000	0.005	10	0.052	0	-0.2284
0.0000	373.0000	0.005	10	0.052	1	4.1730

0.0000	377.0000	0.005	10	0.052	0	-0.2284
0.0000	378.0000	0.005	10	0.052	0	-0.2284
0.0000	381.0000	0.005	10	0.052	0	-0.2284
0.0000	384.0000	0.005	10	0.052	0	-0.2284
0.0000	385.0000	0.005	10	0.052	0	-0.2284
0.0000	386.0000	0.005	10	0.052	0	-0.2284
0.0000	387.0000	0.005	10	0.052	0	-0.2284
0.0000	387.0000	0.005	10	0.052	0	-0.2284
0.0000	389.0000	0.005	10	0.052	0	-0.2284
0.0000	394.0000	0.005	10	0.052	0	-0.2284
0.0000	394.0000	0.005	10	0.052	0	-0.2284
0.0000	417.0000	0.005	10	0.052	0	-0.2284
0.0000	421.0000	0.005	10	0.052	0	-0.2284

566.5000	279.0000	0.006	8	0.046	0	-0.1254
566.5000	321.0000	0.006	10	0.057	0	-0.1286
566.5000	324.0000	0.006	8	0.046	0	-0.1254
566.5000	330.0000	0.006	10	0.057	3	6.6241
566.5000	334.0000	0.006	10	0.057	0	-0.1286
566.5000	338.0000	0.006	10	0.057	0	-0.1286
566.5000	342.0000	0.006	10	0.057	0	-0.1286
566.5000	345.0000	0.006	10	0.057	0	-0.1286
566.5000	347.0000	0.006	10	0.057	0	-0.1286
566.5000	348.0000	0.006	9	0.051	0	-0.1272
566.5000	349.0000	0.006	10	0.057	0	-0.1286
566.5000	359.0000	0.006	10	0.057	0	-0.1286
566.5000	372.0000	0.006	10	0.057	0	-0.1286
566.5000	372.0000	0.006	10	0.057	0	-0.1286
566.5000	381.0000	0.006	10	0.057	0	-0.1286
566.5000	385.0000	0.006	6	0.034	0	-0.1205
566.5000	386.0000	0.006	10	0.057	0	-0.1286
566.5000	390.0000	0.006	10	0.057	0	-0.1286
566.5000	394.0000	0.006	9	0.051	0	-0.1272
566.5000	403.0000	0.006	10	0.057	0	-0.1286
566.5000	413.0000	0.006	10	0.057	0	-0.1286
566.5000	413.0000	0.006	10	0.057	0	-0.1286
566.5000	419.0000	0.006	10	0.057	0	-0.1286
566.5000	427.0000	0.006	10	0.057	0	-0.1286
566.5000	447.0000	0.006	10	0.057	0	-0.1286
566.5000	456.0000	0.006	10	0.057	0	-0.1286

2053.0000	290.0000	0.018	10	0.184	0	-0.2569
2053.0000	308.0000	0.018	10	0.184	0	-0.2569
2053.0000	309.0000	0.018	10	0.184	1	1.1366
2053.0000	318.0000	0.018	10	0.184	0	-0.2569
2053.0000	323.0000	0.018	10	0.184	0	-0.2569
2053.0000	324.0000	0.018	10	0.184	0	-0.2569
2053.0000	324.0000	0.018	10	0.184	0	-0.2569

2053.0000	325.0000	0.018	10	0.184	0	-0.2569
2053.0000	337.0000	0.018	10	0.184	0	-0.2569
2053.0000	340.0000	0.018	10	0.184	3	3.9234
2053.0000	347.0000	0.018	1	0.018	0	-0.1370
2053.0000	358.0000	0.018	10	0.184	0	-0.2569
2053.0000	363.0000	0.018	10	0.184	0	-0.2569
2053.0000	369.0000	0.018	10	0.184	0	-0.2569
2053.0000	381.0000	0.018	10	0.184	0	-0.2569
2053.0000	381.0000	0.018	10	0.184	0	-0.2569
2053.0000	381.0000	0.018	10	0.184	0	-0.2569
2053.0000	388.0000	0.018	10	0.184	0	-0.2569
2053.0000	394.0000	0.018	10	0.184	0	-0.2569
2053.0000	401.0000	0.018	10	0.184	0	-0.2569
2053.0000	407.0000	0.018	10	0.184	0	-0.2569
2053.0000	409.0000	0.018	2	0.037	0	-0.1766
2053.0000	423.0000	0.018	10	0.184	0	-0.2569
2053.0000	433.0000	0.018	10	0.184	0	-0.2569
5235.0000	294.0000	0.129	10	1.291	0	-0.4424
5235.0000	306.0000	0.129	2	0.258	2	2.7932
5235.0000	319.0000	0.129	10	1.291	10	2.9858
5235.0000	337.0000	0.129	10	1.291	0	-0.4424
5235.0000	337.0000	0.129	10	1.291	0	-0.4424
5235.0000	350.0000	0.129	10	1.291	0	-0.4424
5235.0000	359.0000	0.129	10	1.291	0	-0.4424
5235.0000	366.0000	0.129	10	1.291	0	-0.4424
5235.0000	367.0000	0.129	10	1.291	0	-0.4424
5235.0000	371.0000	0.129	10	1.291	0	-0.4424
5235.0000	375.0000	0.129	7	0.903	2	0.5330
5235.0000	378.0000	0.129	3	0.387	0	-0.4251
5235.0000	381.0000	0.129	10	1.291	0	-0.4424
5235.0000	381.0000	0.129	10	1.291	0	-0.4424
5235.0000	389.0000	0.129	10	1.291	0	-0.4424
5235.0000	389.0000	0.129	10	1.291	0	-0.4424
5235.0000	395.0000	0.129	10	1.291	0	-0.4424
5235.0000	395.0000	0.129	10	1.291	0	-0.4424
5235.0000	398.0000	0.129	10	1.291	1	-0.0996
5235.0000	423.0000	0.129	10	1.291	1	-0.0996
5235.0000	445.0000	0.129	8	1.032	0	-0.4405
5235.0000	456.0000	0.129	10	1.291	0	-0.4424

Scaled Residual(s) for Dose Group Nearest the BMD

Minimum scaled residual for dose group nearest the BMD = -0.2569
Minimum ABS(scaled residual) for dose group nearest the BMD = 0.2569
Average scaled residual for dose group nearest the BMD = -0.2569
Average ABS(scaled residual) for dose group nearest the BMD = 0.2569
Maximum scaled residual for dose group nearest the BMD = -0.2569

Maximum ABS(scaled residual) for dose group nearest the BMD = 0.2569
Number of litters used for scaled residual for dose group nearest the BMD = 1

Observed Chi-square = 101.3408

Bootstrapping Results

Number of Bootstrap Iterations per run: 1000

Bootstrap Chi-square Percentiles

Bootstrap Run	P-value	50th	90th	95th	99th
1	0.3340	78.0736	174.9388	219.4932	366.0397
2	0.3290	77.4467	186.1788	252.2181	403.7505
3	0.3250	76.9188	180.0700	253.0186	377.4700
Combined	0.3293	77.5709	182.1937	238.5844	383.6190

The results for three separate runs are shown. If the estimated p-values are sufficiently stable (do not vary considerably from run to run), then then number of iterations is considered adequate. The p-value that should be reported is the one that combines the results of the three runs. If sufficient stability is not evident (and especially if the p-values are close to the critical level for determining adequate fit, *e.g.*, 0.05), then the user should consider increasing the number of iterations per run.

To calculate the BMD and BMDL, the litter specific covariate is fixed at the mean litter specific covariate of all the data: 370.257732

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95
BMD = 1829.66
BMDL = 313.814

5.8 Results for BMD Modeling for Stillbirths, and PND4 and PND21 Pup Deaths in Wistar Rats (NMP Producers Group (1999b))

5.8.1 Wistar Rat F1A stillborn/total delivered (NMP Producers Group (1999b))

Wistar Rat F1A Stillborn/Total Delivered (NMP Producers Group (1999b))

AUC (hr mg/L)	C_{max} (mg/L)	Total Delivered	Stillborn	Covariate (mg, LD1 Dam BW)
0	0	12	0	294
0	0	15	0	295
0	0	14	1	299
0	0	15	0	300
0	0	14	0	303
0	0	14	0	304
0	0	9	0	308
0	0	11	0	308
0	0	13	0	314
0	0	9	0	314
0	0	16	0	315
0	0	16	0	315
0	0	16	0	321
0	0	10	0	322
0	0	13	1	322
0	0	12	0	326
0	0	7	0	327
0	0	11	0	327
0	0	9	0	328
0	0	11	1	329
0	0	15	1	332
0	0	19	0	336
0	0	15	2	339
0	0	14	0	343
0	0	17	1	344
538.0	37.49	8	0	264
538.0	37.49	17	3	281
538.0	37.49	16	0	287
538.0	37.49	13	3	290
538.0	37.49	17	0	294
538.0	37.49	12	0	296
538.0	37.49	14	0	302
538.0	37.49	13	0	303
538.0	37.49	14	0	304
538.0	37.49	15	0	306
538.0	37.49	15	0	307
538.0	37.49	17	0	307
538.0	37.49	12	1	308
538.0	37.49	13	0	308
538.0	37.49	5	1	308
538.0	37.49	17	0	314
538.0	37.49	16	2	315

AUC (hr mg/L)	C_{max} (mg/L)	Total Delivered	Stillborn	Covariate (mg, LD1 Dam BW)
538.0	37.49	10	1	315
538.0	37.49	13	0	316
538.0	37.49	15	0	316
538.0	37.49	5	0	330
538.0	37.49	13	0	334
538.0	37.49	13	0	336
538.0	37.49	13	0	339
538.0	37.49	14	0	339
1965	136.35	18	2	285
1965	136.35	14	0	288
1965	136.35	16	0	295
1965	136.35	15	0	295
1965	136.35	14	2	299
1965	136.35	8	0	301
1965	136.35	13	0	303
1965	136.35	16	0	303
1965	136.35	17	1	311
1965	136.35	5	0	311
1965	136.35	8	0	311
1965	136.35	13	0	313
1965	136.35	19	0	313
1965	136.35	15	0	318
1965	136.35	12	0	318
1965	136.35	8	0	323
1965	136.35	12	0	324
1965	136.35	14	0	326
1965	136.35	14	1	328
1965	136.35	13	0	329
1965	136.35	15	0	333
1965	136.35	12	1	341
1965	136.35	17	1	345
1965	136.35	18	0	354
7793	515.01	16	0	280
7793	515.01	13	1	283
7793	515.01	14	1	284
7793	515.01	10	0	286
7793	515.01	13	1	288
7793	515.01	16	0	288
7793	515.01	11	1	290
7793	515.01	15	1	292
7793	515.01	13	0	294
7793	515.01	12	4	295
7793	515.01	3	0	296
7793	515.01	16	1	301
7793	515.01	10	1	304
7793	515.01	13	0	305
7793	515.01	12	1	306
7793	515.01	17	0	308

AUC (hr mg/L)	C_{max} (mg/L)	Total Delivered	Stillborn	Covariate (mg, LD1 Dam BW)
7793	515.01	12	0	309
7793	515.01	11	2	318
7793	515.01	2	0	319
7793	515.01	14	1	320
7793	515.01	14	2	322
7793	515.01	14	2	333
7793	515.01	12	5	338
7793	515.01	13	0	338

Table 5-28 Summary of BMDS nested modeling results for AUC (hr mg/L) versus Wistar Rat F1A stillborn/total delivered (NMP Producers Group (1999b)); BMR = 1% extra risk.

Model [a]	Goodness of fit		BMD_{01} (hr mg/L)	$BMDL_{01}$ (hr mg/L)	Basis for Model Selection
	P-value	AIC			
Litter-specific covariate = LD1 dam weight; intra-litter correlations estimated					The NLogistic model that estimated intra-litter correlations and did not use a litter-specific covariate was selected based on estimating the lowest BMDL within a range of BMDLs from acceptable models (P-value >0.1) that varied more than 3-fold.
Nlogistic (b. seed[b] =1597172141)	0.457	410.726	6297.7	1276.04	
NCTR (b. seed =1597172143)	0.456	407.339	6320.06	5266.72	
Litter-specific covariate = LD1 dam weight; intra-litter correlations assumed to be zero					
Nlogistic (b. seed =1597172137)	0.095	410.058	6366.27	1944.49	
NCTR (b. seed =1597172139)	0.0637	409.736	6345.17	5287.64	
Litter-specific covariate not used; intra-litter correlations estimated					
Nlogistic (b. seed =1597172129)	**0.4443**	**407.919**	**6440.69**	**855.343**	
NCTR (b. seed =1597172131)	0.4547	405.919	6461.71	5384.76	
Litter-specific covariate not used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed =1597172134)	0.032	412.787	6477.21	960.487	
NCTR (b. seed =1597172135)	0.0287	410.787	6497.12	5414.26	

[a] Litter-specific data were fit using standard (restricted) BMDS NLogistic and NCTR nested dichotomous models. Selected model is bolded.

[b] b. seed: bootstrap seed. The bootstrap seed shown must be entered into BMDS 2.7.0.4 nested model to replicate results.

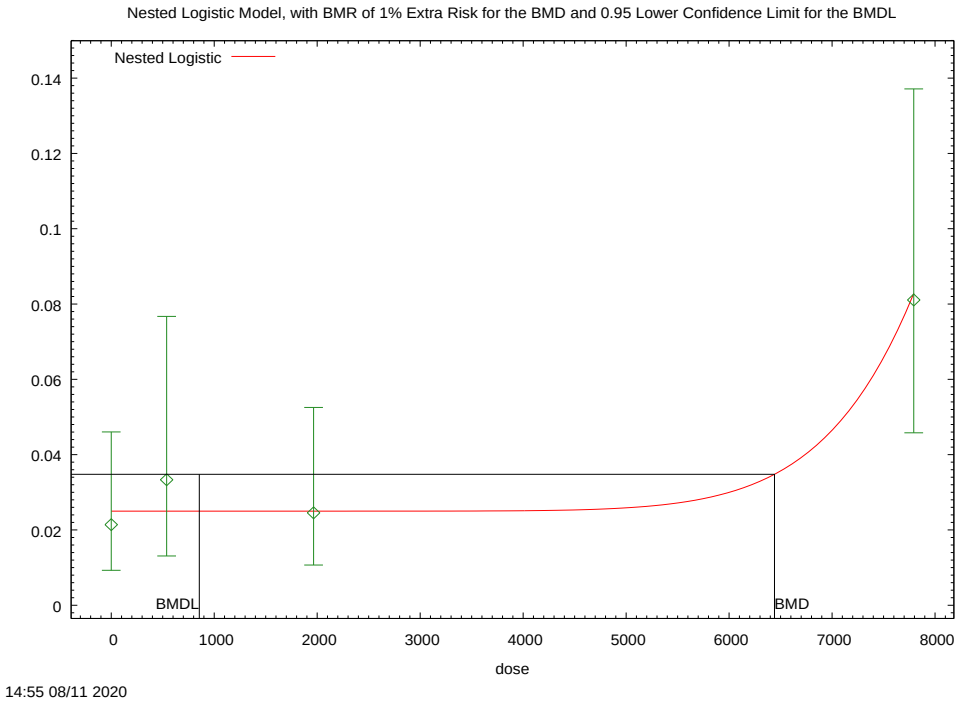


Figure 5.8-1 Plot of NLogistic (LSC = LD1 dam weight; ICC estimated) model for AUC (hr mg/L) versus Wistar Rat F1A Stillborn/Total Delivered.

==========

NLogistic Model. (Version: 2.20; Date: 04/27/2015)
Input Data File: C:/Users/jgift/BMDS2704/Data/WF1a_stillborn_p_558/Correct Doses/BMR01/nln_WF1a_stillborn_p_558_Nln-BMR1-Restrict-IC.(d)
Tue Aug 11 14:55:29 2020

==========

BMDS Model Run

~~~~~~~~~~

The probability function is:

Prob. = alpha + theta1*Rij + [1 - alpha - theta1*Rij]/

[1+exp(-beta-theta2*Rij-rho*log(Dose))],

where Rij is the litter specific covariate.

Restrict Power rho >= 1.

Total number of observations = 98
Total number of records with missing values = 0
Total number of parameters in model = 9
Total number of specified parameters = 2

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
~~~~~~~~~~

Parameter Convergence has been set to: 1e-008
Number of Bootstrap Iterations per run: 1000
Bootstrap Seed: 1597172129

User specifies the following parameters:
theta1 = 0
theta2 = 0

Default Initial Parameter Values
alpha = 0.0250345
beta = -88.7152
theta1 = 0 Specified
theta2 = 0 Specified
rho = 9.59136
phi1 = 0
phi2 = 0.0870947
phi3 = 0.011941
phi4 = 0.0521665

Parameter Estimates

Variable	Estimate	Std. Err.
alpha	0.0250345	0.00558747
beta	-88.7151	0.390723
rho	9.59137	0.0687291
phi1	0	Bounded
phi2	0.0870947	0.0426229
phi3	0.011941	NA
phi4	0.0521665	NA

Log-likelihood: -197.959 AIC: 407.919

Litter Data

Dose	Lit.-Spec. Cov.	Litter Est._Prob.	Size	Scaled Expected	Observed	Residual
0.0000	294.0000	0.025	12	0.300	0	-0.5551
0.0000	295.0000	0.025	15	0.376	0	-0.6206
0.0000	299.0000	0.025	14	0.350	1	1.1111
0.0000	300.0000	0.025	15	0.376	0	-0.6206
0.0000	303.0000	0.025	14	0.350	0	-0.5996
0.0000	304.0000	0.025	14	0.350	0	-0.5996
0.0000	308.0000	0.025	9	0.225	0	-0.4807
0.0000	308.0000	0.025	11	0.275	0	-0.5315
0.0000	314.0000	0.025	13	0.325	0	-0.5778
0.0000	314.0000	0.025	9	0.225	0	-0.4807
0.0000	315.0000	0.025	16	0.401	0	-0.6410

0.0000	315.0000	0.025	16	0.401	0	-0.6410
0.0000	321.0000	0.025	16	0.401	0	-0.6410
0.0000	322.0000	0.025	10	0.250	0	-0.5067
0.0000	322.0000	0.025	13	0.325	1	1.1975
0.0000	326.0000	0.025	12	0.300	0	-0.5551
0.0000	327.0000	0.025	7	0.175	0	-0.4240
0.0000	327.0000	0.025	11	0.275	0	-0.5315
0.0000	328.0000	0.025	9	0.225	0	-0.4807
0.0000	329.0000	0.025	11	0.275	1	1.3985
0.0000	332.0000	0.025	15	0.376	1	1.0321
0.0000	336.0000	0.025	19	0.476	0	-0.6985
0.0000	339.0000	0.025	15	0.376	2	2.6848
0.0000	343.0000	0.025	14	0.350	0	-0.5996
0.0000	344.0000	0.025	17	0.426	1	0.8917
538.0000	264.0000	0.025	8	0.200	0	-0.3572
538.0000	281.0000	0.025	17	0.426	3	2.5833
538.0000	287.0000	0.025	16	0.401	0	-0.4221
538.0000	290.0000	0.025	13	0.325	3	3.3201
538.0000	294.0000	0.025	17	0.426	0	-0.4271
538.0000	296.0000	0.025	12	0.300	0	-0.3967
538.0000	302.0000	0.025	14	0.350	0	-0.4106
538.0000	303.0000	0.025	13	0.325	0	-0.4040
538.0000	304.0000	0.025	14	0.350	0	-0.4106
538.0000	306.0000	0.025	15	0.376	0	-0.4166
538.0000	307.0000	0.025	15	0.376	0	-0.4166
538.0000	307.0000	0.025	17	0.426	0	-0.4271
538.0000	308.0000	0.025	12	0.300	1	0.9238
538.0000	308.0000	0.025	13	0.325	0	-0.4040
538.0000	308.0000	0.025	5	0.125	1	2.1566
538.0000	314.0000	0.025	17	0.426	0	-0.4271
538.0000	315.0000	0.025	16	0.401	2	1.6853
538.0000	315.0000	0.025	10	0.250	1	1.1361
538.0000	316.0000	0.025	13	0.325	0	-0.4040
538.0000	316.0000	0.025	15	0.376	0	-0.4166
538.0000	330.0000	0.025	5	0.125	0	-0.3086
538.0000	334.0000	0.025	13	0.325	0	-0.4040
538.0000	336.0000	0.025	13	0.325	0	-0.4040
538.0000	339.0000	0.025	13	0.325	0	-0.4040
538.0000	339.0000	0.025	14	0.350	0	-0.4106
1965.0000	285.0000	0.025	18	0.451	2	2.1312
1965.0000	288.0000	0.025	14	0.350	0	-0.5578
1965.0000	295.0000	0.025	16	0.401	0	-0.5903
1965.0000	295.0000	0.025	15	0.376	0	-0.5745
1965.0000	299.0000	0.025	14	0.350	2	2.6254
1965.0000	301.0000	0.025	8	0.200	0	-0.4354
1965.0000	303.0000	0.025	13	0.325	0	-0.5403

1965.0000	303.0000	0.025	16	0.401	0	-0.5903
1965.0000	311.0000	0.025	17	0.426	1	0.8171
1965.0000	311.0000	0.025	5	0.125	0	-0.3500
1965.0000	311.0000	0.025	8	0.200	0	-0.4354
1965.0000	313.0000	0.025	13	0.325	0	-0.5403
1965.0000	313.0000	0.025	19	0.476	0	-0.6337
1965.0000	318.0000	0.025	15	0.376	0	-0.5745
1965.0000	318.0000	0.025	12	0.300	0	-0.5219
1965.0000	323.0000	0.025	8	0.200	0	-0.4354
1965.0000	324.0000	0.025	12	0.300	0	-0.5219
1965.0000	326.0000	0.025	14	0.350	0	-0.5578
1965.0000	328.0000	0.025	14	0.350	1	1.0338
1965.0000	329.0000	0.025	13	0.325	0	-0.5403
1965.0000	333.0000	0.025	15	0.376	0	-0.5745
1965.0000	341.0000	0.025	12	0.300	1	1.2153
1965.0000	345.0000	0.025	17	0.426	1	0.8171
1965.0000	354.0000	0.025	18	0.451	0	-0.6198
7793.0000	280.0000	0.083	16	1.323	0	-0.8995
7793.0000	283.0000	0.083	13	1.075	1	-0.0591
7793.0000	284.0000	0.083	14	1.158	1	-0.1180
7793.0000	286.0000	0.083	10	0.827	0	-0.7832
7793.0000	288.0000	0.083	13	1.075	1	-0.0591
7793.0000	288.0000	0.083	16	1.323	0	-0.8995
7793.0000	290.0000	0.083	11	0.910	1	0.0803
7793.0000	292.0000	0.083	15	1.240	1	-0.1712
7793.0000	294.0000	0.083	13	1.075	0	-0.8489
7793.0000	295.0000	0.083	12	0.992	4	2.5131
7793.0000	296.0000	0.083	3	0.248	0	-0.4948
7793.0000	301.0000	0.083	16	1.323	1	-0.2196
7793.0000	304.0000	0.083	10	0.827	1	0.1640
7793.0000	305.0000	0.083	13	1.075	0	-0.8489
7793.0000	306.0000	0.083	12	0.992	1	0.0065
7793.0000	308.0000	0.083	17	1.406	0	-0.9139
7793.0000	309.0000	0.083	12	0.992	0	-0.8290
7793.0000	318.0000	0.083	11	0.910	2	0.9678
7793.0000	319.0000	0.083	2	0.165	0	-0.4139
7793.0000	320.0000	0.083	14	1.158	1	-0.1180
7793.0000	322.0000	0.083	14	1.158	2	0.6311
7793.0000	333.0000	0.083	14	1.158	2	0.6311
7793.0000	338.0000	0.083	12	0.992	5	3.3487
7793.0000	338.0000	0.083	13	1.075	0	-0.8489

Scaled Residual(s) for Dose Group Nearest the BMD

Minimum scaled residual for dose group nearest the BMD = -0.8290
Minimum ABS(scaled residual) for dose group nearest the BMD = 0.8290
Average scaled residual for dose group nearest the BMD = -0.8290

Average ABS(scaled residual) for dose group nearest the BMD = 0.8290
Maximum scaled residual for dose group nearest the BMD = -0.8290
Maximum ABS(scaled residual) for dose group nearest the BMD = 0.8290
Number of litters used for scaled residual for dose group nearest the BMD = 1

Observed Chi-square = 96.6123

Bootstrapping Results

Number of Bootstrap Iterations per run: 1000

Bootstrap Chi-square Percentiles

Bootstrap Run	P-value	50th	90th	95th	99th
1	0.4560	93.2688	135.9214	154.8401	208.1552
2	0.4400	93.4333	133.4073	152.3201	180.5382
3	0.4370	92.8919	134.4350	148.2379	177.4640
Combined	0.4443	93.1017	134.4672	152.1400	187.5065

The results for three separate runs are shown. If the estimated p-values are sufficiently stable (do not vary considerably from run to run), then then number of iterations is considered adequate. The p-value that should be reported is the one that combines the results of the three runs. If sufficient stability is not evident (and especially if the p-values are close to the critical level for determining adequate fit, *e.g.*, 0.05), then the user should consider increasing the number of iterations per run.

To calculate the BMD and BMDL, the litter specific covariate is fixed at the mean litter specific covariate of all the data: 311.714286

Benchmark Dose Computation
Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMD = 6440.69
BMDL = 855.343

Table 5-29 Summary of BMDS nesting modeling results for C_{max} (mg/L) versus Wistar Rat F1A stillborn/total delivered (NMP Producers Group (1999b)); BMR = 1% extra risk.

Model [a]	Goodness of fit		BMD_{01} (hr mg/L)	$BMDL_{01}$ (hr mg/L)	Basis for Model Selection
	P-value	AIC			
Litter-specific covariate = LD1 dam weight; intra-litter correlations estimated					The NLogistic model that estimated intra-litter correlations and did not use a litter-specific covariate was selected based on estimating the lowest BMDL within a range of BMDLs from acceptable models (P-value >0.1) that varied more than 3-fold.
Nlogistic (b. seed[b] =1597185893)	0.4783	410.726	418.119	90.2154	
NCTR (b. seed =1597185894)	0.4657	407.339	420.037	350.031	
Litter-specific covariate = LD1 dam weight; intra-litter correlations assumed to be zero					
Nlogistic (b. seed =1597185890)	0.0833	410.058	422.009	134.725	
NCTR (b. seed =1597185891)	0.0713	409.736	421.648	351.373	
Litter-specific covariate not used; intra-litter correlations estimated					
Nlogistic (b. seed =1597185882)	**0.453**	**407.919**	**429.396**	**57.6472**	
NCTR (b. seed =1597185885)	0.4447	405.919	429.188	357.657	
Litter-specific covariate not used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed =1597185887)	0.036	412.787	431.713	64.6766	
NCTR (b. seed =1597185888)	0.0267	410.787	431.47	359.558	

[a] Litter-specific data were fit using standard (restricted) BMDS NLogistic and NCTR nested dichotomous models. Selected model is bolded.
[b] b. seed: bootstrap seed. The bootstrap seed shown must be entered into BMDS 2.7.0.4 nested model to replicate results.

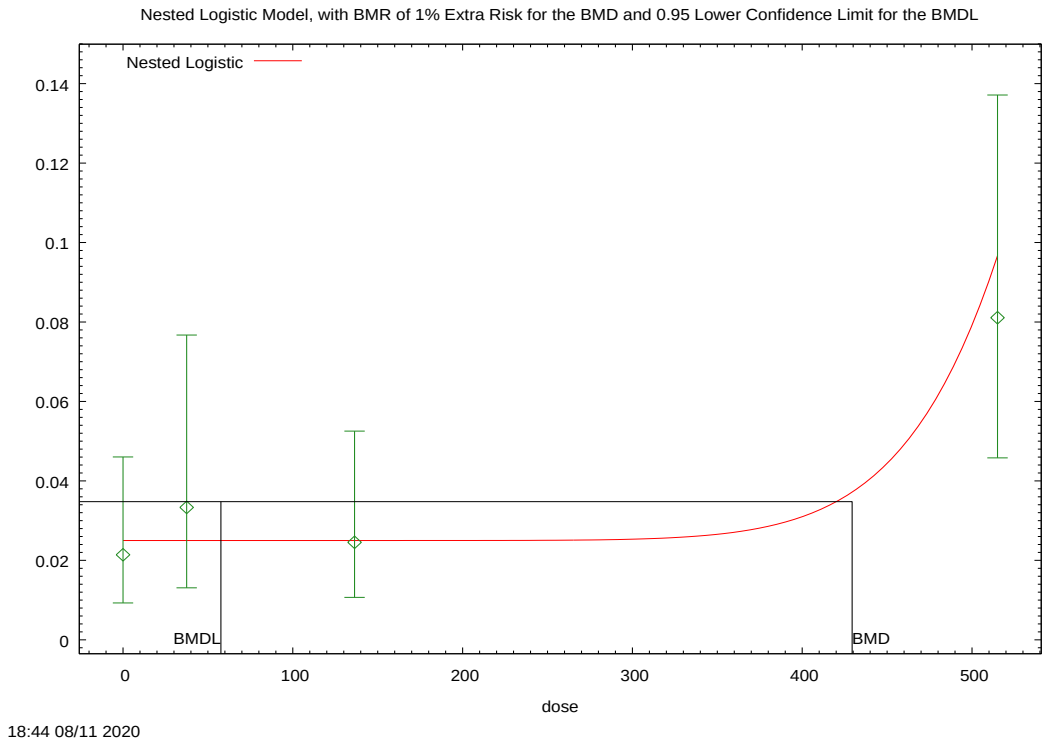


Figure 5.8-2 Plot of NLogistic (LSC = LD1 dam weight; ICC estimated) model for C_{max} (mg/L) versus Wistar Rat F1A Stillborn/Total Delivered.

```
================================================================================
        NLogistic Model. (Version: 2.20; Date: 04/27/2015)
        Input Data File: C:/Users/jgift/BMDS2704/Data/WF1a_stillborn_p_558/Correct
Doses/BMR01/Cmax/nln_WF1a_stillborn_p_558_Nln-BMR1-Restrict-IC.(d)
                                                  Tue Aug 11 18:44:42 2020
================================================================================
BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
The probability function is:

Prob. = alpha + theta1*Rij + [1 - alpha - theta1*Rij]/

                [1+exp(-beta-theta2*Rij-rho*log(Dose))],

      where Rij is the litter specific covariate.

Restrict Power rho >= 1.

Total number of observations = 98
Total number of records with missing values = 0
Total number of parameters in model = 9
Total number of specified parameters = 2

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
Number of Bootstrap Iterations per run: 1000
Bootstrap Seed:  1597185882

User specifies the following parameters:
      theta1 =         0
      theta2 =         0

            Default Initial Parameter Values
                  alpha =    0.0250345
                   beta =     -65.5512
                 theta1 =            0   Specified
                 theta2 =            0   Specified
                    rho =      10.0548
                   phi1 =            0
                   phi2 =    0.0870952
                   phi3 =    0.0119409
                   phi4 =    0.0521674

                        Parameter Estimates

    Variable         Estimate          Std. Err.
      alpha         0.0250345         0.00558747
```

beta	-65.5512	0.390724
rho	10.0548	0.0687296
phi1	0	Bounded
phi2	0.0870952	0.0426236
phi3	0.0119409	NA
phi4	0.0521674	NA

Log-likelihood: -197.959 AIC: 407.919

Litter Data

Dose	Lit.-Spec. Cov.	Litter Est._Prob.	Size	Scaled Expected	Observed	Residual
0.0000	294.0000	0.025	12	0.300	0	-0.5551
0.0000	295.0000	0.025	15	0.376	0	-0.6206
0.0000	299.0000	0.025	14	0.350	1	1.1111
0.0000	300.0000	0.025	15	0.376	0	-0.6206
0.0000	303.0000	0.025	14	0.350	0	-0.5996
0.0000	304.0000	0.025	14	0.350	0	-0.5996
0.0000	308.0000	0.025	9	0.225	0	-0.4807
0.0000	308.0000	0.025	11	0.275	0	-0.5315
0.0000	314.0000	0.025	13	0.325	0	-0.5778
0.0000	314.0000	0.025	9	0.225	0	-0.4807
0.0000	315.0000	0.025	16	0.401	0	-0.6410
0.0000	315.0000	0.025	16	0.401	0	-0.6410
0.0000	321.0000	0.025	16	0.401	0	-0.6410
0.0000	322.0000	0.025	10	0.250	0	-0.5067
0.0000	322.0000	0.025	13	0.325	1	1.1975
0.0000	326.0000	0.025	12	0.300	0	-0.5551
0.0000	327.0000	0.025	7	0.175	0	-0.4240
0.0000	327.0000	0.025	11	0.275	0	-0.5315
0.0000	328.0000	0.025	9	0.225	0	-0.4807
0.0000	329.0000	0.025	11	0.275	1	1.3985
0.0000	332.0000	0.025	15	0.376	1	1.0321
0.0000	336.0000	0.025	19	0.476	0	-0.6985
0.0000	339.0000	0.025	15	0.376	2	2.6848
0.0000	343.0000	0.025	14	0.350	0	-0.5996
0.0000	344.0000	0.025	17	0.426	1	0.8917
37.4900	264.0000	0.025	8	0.200	0	-0.3572
37.4900	281.0000	0.025	17	0.426	3	2.5833
37.4900	287.0000	0.025	16	0.401	0	-0.4221
37.4900	290.0000	0.025	13	0.325	3	3.3201
37.4900	294.0000	0.025	17	0.426	0	-0.4271
37.4900	296.0000	0.025	12	0.300	0	-0.3967
37.4900	302.0000	0.025	14	0.350	0	-0.4106
37.4900	303.0000	0.025	13	0.325	0	-0.4040

37.4900	304.0000	0.025	14	0.350	0	-0.4106
37.4900	306.0000	0.025	15	0.376	0	-0.4166
37.4900	307.0000	0.025	15	0.376	0	-0.4166
37.4900	307.0000	0.025	17	0.426	0	-0.4271
37.4900	308.0000	0.025	12	0.300	1	0.9238
37.4900	308.0000	0.025	13	0.325	0	-0.4040
37.4900	308.0000	0.025	5	0.125	1	2.1566
37.4900	314.0000	0.025	17	0.426	0	-0.4271
37.4900	315.0000	0.025	16	0.401	2	1.6853
37.4900	315.0000	0.025	10	0.250	1	1.1361
37.4900	316.0000	0.025	13	0.325	0	-0.4040
37.4900	316.0000	0.025	15	0.376	0	-0.4166
37.4900	330.0000	0.025	5	0.125	0	-0.3086
37.4900	334.0000	0.025	13	0.325	0	-0.4040
37.4900	336.0000	0.025	13	0.325	0	-0.4040
37.4900	339.0000	0.025	13	0.325	0	-0.4040
37.4900	339.0000	0.025	14	0.350	0	-0.4106
136.3500	285.0000	0.025	18	0.451	2	2.1312
136.3500	288.0000	0.025	14	0.350	0	-0.5578
136.3500	295.0000	0.025	16	0.401	0	-0.5903
136.3500	295.0000	0.025	15	0.376	0	-0.5745
136.3500	299.0000	0.025	14	0.350	2	2.6254
136.3500	301.0000	0.025	8	0.200	0	-0.4354
136.3500	303.0000	0.025	13	0.325	0	-0.5403
136.3500	303.0000	0.025	16	0.401	0	-0.5903
136.3500	311.0000	0.025	17	0.426	1	0.8171
136.3500	311.0000	0.025	5	0.125	0	-0.3500
136.3500	311.0000	0.025	8	0.200	0	-0.4354
136.3500	313.0000	0.025	13	0.325	0	-0.5403
136.3500	313.0000	0.025	19	0.476	0	-0.6337
136.3500	318.0000	0.025	15	0.376	0	-0.5745
136.3500	318.0000	0.025	12	0.300	0	-0.5219
136.3500	323.0000	0.025	8	0.200	0	-0.4354
136.3500	324.0000	0.025	12	0.300	0	-0.5219
136.3500	326.0000	0.025	14	0.350	0	-0.5578
136.3500	328.0000	0.025	14	0.350	1	1.0338
136.3500	329.0000	0.025	13	0.325	0	-0.5403
136.3500	333.0000	0.025	15	0.376	0	-0.5745
136.3500	341.0000	0.025	12	0.300	1	1.2153
136.3500	345.0000	0.025	17	0.426	1	0.8171
136.3500	354.0000	0.025	18	0.451	0	-0.6198
515.0100	280.0000	0.083	16	1.323	0	-0.8995
515.0100	283.0000	0.083	13	1.075	1	-0.0591
515.0100	284.0000	0.083	14	1.158	1	-0.1180
515.0100	286.0000	0.083	10	0.827	0	-0.7832
515.0100	288.0000	0.083	13	1.075	1	-0.0591

515.0100	288.0000	0.083	16	1.323	0	-0.8995
515.0100	290.0000	0.083	11	0.910	1	0.0803
515.0100	292.0000	0.083	15	1.240	1	-0.1712
515.0100	294.0000	0.083	13	1.075	0	-0.8489
515.0100	295.0000	0.083	12	0.992	4	2.5131
515.0100	296.0000	0.083	3	0.248	0	-0.4948
515.0100	301.0000	0.083	16	1.323	1	-0.2196
515.0100	304.0000	0.083	10	0.827	1	0.1640
515.0100	305.0000	0.083	13	1.075	0	-0.8489
515.0100	306.0000	0.083	12	0.992	1	0.0065
515.0100	308.0000	0.083	17	1.406	0	-0.9139
515.0100	309.0000	0.083	12	0.992	0	-0.8290
515.0100	318.0000	0.083	11	0.910	2	0.9678
515.0100	319.0000	0.083	2	0.165	0	-0.4139
515.0100	320.0000	0.083	14	1.158	1	-0.1180
515.0100	322.0000	0.083	14	1.158	2	0.6311
515.0100	333.0000	0.083	14	1.158	2	0.6311
515.0100	338.0000	0.083	12	0.992	5	3.3486
515.0100	338.0000	0.083	13	1.075	0	-0.8489

Scaled Residual(s) for Dose Group Nearest the BMD

Minimum scaled residual for dose group nearest the BMD = -0.8290
Minimum ABS(scaled residual) for dose group nearest the BMD = 0.8290
Average scaled residual for dose group nearest the BMD = -0.8290
Average ABS(scaled residual) for dose group nearest the BMD = 0.8290
Maximum scaled residual for dose group nearest the BMD = -0.8290
Maximum ABS(scaled residual) for dose group nearest the BMD = 0.8290
Number of litters used for scaled residual for dose group nearest the BMD = 1

Observed Chi-square = 96.6120

Bootstrapping Results

Number of Bootstrap Iterations per run: 1000

Bootstrap Chi-square Percentiles

Bootstrap Run	P-value	50th	90th	95th	99th
1	0.4500	92.5235	133.3830	146.8070	182.9345
2	0.4400	92.4527	133.6012	148.2521	188.2813
3	0.4690	94.4295	138.5229	155.0223	183.1285
Combined	0.4530	93.0302	135.0792	149.8451	186.4510

The results for three separate runs are shown. If the estimated p-values are sufficiently stable (do not vary considerably from run to run), then then number of iterations is

considered adequate. The p-value that should be reported is the one that combines the results of the three runs. If sufficient stability is not evident (and especially if the p-values are close to the critical level for determining adequate fit, *e.g.*, 0.05), then the user should consider increasing the number of iterations per run.

To calculate the BMD and BMDL, the litter specific covariate is fixed at the mean litter specific covariate of all the data: 311.714286

Benchmark Dose Computation
Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMD = 429.396
BMDL = 57.6472

5.8.2 Wistar Rat F1A Pup death at PND4/total delivered (NMP Producers Group (1999b))

Wistar Rat F1A Pup Death/Total Delivered (NMP Producers Group (1999b))

AUC (hr mg/L)	Total Delivered	Stillborn	Covariate (mg, LD1 Dam BW)
0	12	0	294
0	15	0	295
0	14	1	299
0	15	0	300
0	14	0	303
0	14	1	304
0	9	0	308
0	11	1	308
0	13	0	314
0	9	0	314
0	16	1	315
0	16	2	315
0	16	4	321
0	10	0	322
0	13	1	322
0	12	1	326
0	7	1	327
0	11	0	327
0	9	0	328
0	11	1	329
0	15	1	332
0	19	0	336
0	15	2	339
0	14	1	343
0	17	1	344
538	8	0	264
538	17	6	281
538	16	1	287
538	13	4	290
538	17	2	294
538	12	0	296
538	14	1	302
538	13	4	303
538	14	0	304
538	15	2	306
538	15	0	307
538	17	1	307
538	12	2	308
538	13	1	308
538	5	1	308
538	17	0	314
538	16	3	315
538	10	1	315
538	13	0	316
538	15	0	316

AUC (hr mg/L)	Total Delivered	Stillborn	Covariate (mg, LD1 Dam BW)
538	5	0	330
538	13	3	334
538	13	0	336
538	13	2	339
538	14	2	339
1965	18	2	285
1965	14	0	288
1965	16	0	295
1965	15	2	295
1965	14	3	299
1965	8	0	301
1965	13	0	303
1965	16	1	303
1965	17	2	311
1965	5	1	311
1965	8	0	311
1965	13	0	313
1965	19	1	313
1965	15	1	318
1965	12	1	318
1965	8	0	323
1965	12	0	324
1965	14	1	326
1965	14	1	328
1965	13	0	329
1965	15	0	333
1965	12	1	341
1965	17	1	345
1965	18	0	354
7793	16	16	280
7793	13	13	283
7793	14	14	284
7793	10	10	286
7793	13	13	288
7793	16	16	288
7793	11	11	290
7793	15	15	292
7793	13	3	294
7793	12	12	295
7793	3	0	296
7793	16	16	301
7793	10	5	304
7793	13	13	305
7793	12	12	306
7793	17	17	308
7793	12	12	309
7793	11	5	318
7793	2	0	319

AUC (hr mg/L)	Total Delivered	Stillborn	Covariate (mg, LD1 Dam BW)
7793	14	14	320
7793	14	14	322
7793	14	3	333
7793	12	12	338
7793	13	2	338

Table 5-30 Summary of BMDS nested modeling results for AUC (hr mg/L) versus Wistar Rat F1A Pup death at PND4/total delivered (NMP Producers Group (1999b)); BMR = 1% extra risk.

Model [a]	Goodness of fit		BMD_{01} (hr mg/L)	$BMDL_{01}$ (hr mg/L)	Basis for Model Selection
	P-value	AIC			
Litter-specific covariate = LD1 dam weight; intra-litter correlations estimated					The NCTR model that estimated intra-litter correlations and used LD1 dam weight as a litter-specific covariate was selected based on lowest AIC. BMDLs from acceptable models (P-value >0.1) did not vary more than 3-fold.
Nlogistic (b. seed[b] = 1597171727)	0.3343	641.926	5193.6	1707.85	
NCTR (b. seed = 1597171729)	**0.3203**	**640.119**	**5262.12**	**4385.1**	
Litter-specific covariate = LD1 dam weight; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1597171723)	0	751.242	5143.03	1888.53	
NCTR (b. seed = 1597171725)	0	749.195	5179.67	4316.39	
Litter-specific covariate not used; intra-litter correlations estimated					
Nlogistic (b. seed = 1597171713)	0.2783	642.357	5019.1	1731.28	
NCTR (b. seed = 1597171715)	0.274	640.357	5250.64	4375.54	
Litter-specific covariate not used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1597171719)	0	788.458	4927.89	1820.82	
NCTR (b. seed = 1597171721)	0	786.458	5168.83	4307.36	

[a] Litter-specific data were fit using standard (restricted) BMDS NLogistic and NCTR nested dichotomous models. Selected model is bolded.

[b] b. seed: bootstrap seed. The bootstrap seed must be entered into BMDS 2.7.0.4 nested model to replicate results.

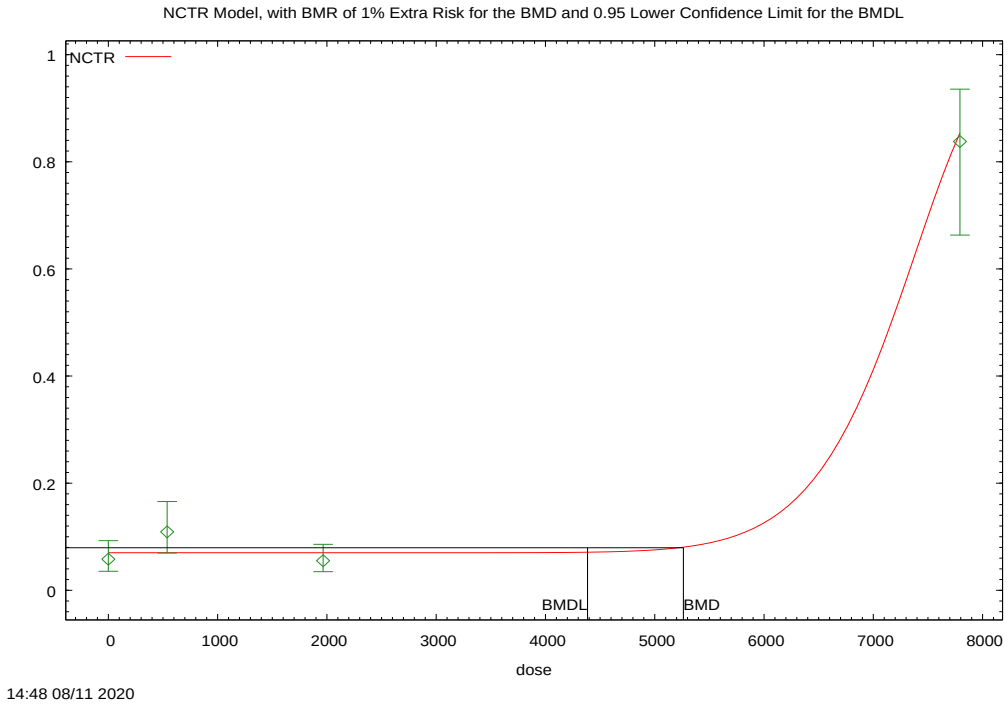


Figure 5.8-3 Plot of NCTR model (LSC = LD1 dam weight; ICC estimated) for AUC (hr mg/L) versus Wistar Rat F1A Pup Death at PND4/Total Delivered.

==========

NCTR Model. (Version: 2.13; Date: 04/27/2015)
Input Data File: C:/Users/jgift/BMDS2704/Data/WF1a_PND4_p_558/Correct Doses/BMR01/nct_WF1a_PND4_p_558_Nct-BMR1-Restrict-IC-LSC.(d)
Gnuplot Plotting File: C:/Users/jgift/BMDS2704/Data/WF1a_PND4_p_558/Correct Doses/BMR01/nct_WF1a_PND4_p_558_Nct-BMR1-Restrict-IC-LSC.plt
Tue Aug 11 14:48:49 2020

==========

BMDS Model Run

~~~~~~~~~~

The probability function is:

Prob. = 1 - exp[-(alpha + th1*Rij) - (beta + th2*Rij)*Dose^rho],

where Rij is the centralized litter specific covariate.

Restrict Power rho >= 1.

Total number of observations = 98
Total number of records with missing values = 0
Total number of parameters in model = 9
Total number of specified parameters = 0

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
~~~~~~~~~~

Parameter Convergence has been set to: 1e-008

Number of Bootstrap Iterations per run: 1000
Bootstrap Seed: 1597171729

Default Initial Parameter Values
alpha = 0.0708532
beta = 5.40955e-051
theta1 = -0.00167557
theta2 = 1e-008
rho = 12.9748
phi1 = 0.00383523
phi2 = 0.0578419
phi3 = 0
phi4 = 0.732024

Parameter Estimates

Variable	Estimate	Std. Err.
alpha	0.0726995	0.00999493
beta	4.73061e-051	Bounded
theta1	-0.000459225	0.000552295
theta2	-9.93029e-053	NA
rho	12.9871	1.51715e-024
phi1	0.00471897	0.0227674
phi2	0.0554074	0.0350542
phi3	0	Bounded
phi4	0.688877	0.600172

Log-likelihood: -313.059 AIC: 640.119

Litter Data

Dose	Lit.-Spec. Cov.	Litter Est._Prob.	Size	Scaled Expected	Observed	Residual
0.0000	294.0000	0.078	12	0.932	0	-0.9800
0.0000	295.0000	0.077	15	1.158	0	-1.0852
0.0000	299.0000	0.076	14	1.057	1	-0.0564
0.0000	300.0000	0.075	15	1.127	0	-1.0689
0.0000	303.0000	0.074	14	1.034	0	-1.0255
0.0000	304.0000	0.073	14	1.028	1	-0.0276
0.0000	308.0000	0.072	9	0.645	0	-0.8185
0.0000	308.0000	0.072	11	0.789	1	0.2413
0.0000	314.0000	0.069	13	0.899	0	-0.9560
0.0000	314.0000	0.069	9	0.622	0	-0.8026
0.0000	315.0000	0.069	16	1.099	1	-0.0950
0.0000	315.0000	0.069	16	1.099	2	0.8601

0.0000	321.0000	0.066	16	1.058	4	2.8595
0.0000	322.0000	0.066	10	0.657	0	-0.8214
0.0000	322.0000	0.066	13	0.854	1	0.1586
0.0000	326.0000	0.064	12	0.768	1	0.2668
0.0000	327.0000	0.064	7	0.445	1	0.8479
0.0000	327.0000	0.064	11	0.699	0	-0.8444
0.0000	328.0000	0.063	9	0.568	0	-0.7645
0.0000	329.0000	0.063	11	0.690	1	0.3770
0.0000	332.0000	0.061	15	0.921	1	0.0820
0.0000	336.0000	0.060	19	1.134	0	-1.0544
0.0000	339.0000	0.058	15	0.876	2	1.1988
0.0000	343.0000	0.057	14	0.793	1	0.2319
0.0000	344.0000	0.056	17	0.956	1	0.0448

538.0000	264.0000	0.090	8	0.722	0	-0.7563
538.0000	281.0000	0.083	17	1.413	6	2.9334
538.0000	287.0000	0.081	16	1.290	1	-0.1967
538.0000	290.0000	0.079	13	1.032	4	2.3608
538.0000	294.0000	0.078	17	1.320	2	0.4486
538.0000	296.0000	0.077	12	0.922	0	-0.7876
538.0000	302.0000	0.074	14	1.040	1	-0.0308
538.0000	303.0000	0.074	13	0.960	4	2.4990
538.0000	304.0000	0.073	14	1.028	0	-0.8030
538.0000	306.0000	0.073	15	1.088	2	0.6809
538.0000	307.0000	0.072	15	1.082	0	-0.8104
538.0000	307.0000	0.072	17	1.226	1	-0.1544
538.0000	308.0000	0.072	12	0.860	2	1.0050
538.0000	308.0000	0.072	13	0.932	1	0.0565
538.0000	308.0000	0.072	5	0.359	1	1.0060
538.0000	314.0000	0.069	17	1.175	0	-0.8181
538.0000	315.0000	0.069	16	1.099	3	1.3880
538.0000	315.0000	0.069	10	0.687	1	0.3195
538.0000	316.0000	0.068	13	0.888	0	-0.7565
538.0000	316.0000	0.068	15	1.024	0	-0.7868
538.0000	330.0000	0.062	5	0.311	0	-0.5214
538.0000	334.0000	0.061	13	0.787	3	1.9942
538.0000	336.0000	0.060	13	0.776	0	-0.7040
538.0000	339.0000	0.058	13	0.759	2	1.1375
538.0000	339.0000	0.058	14	0.818	2	1.0276

1965.0000	285.0000	0.081	18	1.466	2	0.4599
1965.0000	288.0000	0.080	14	1.123	0	-1.1048
1965.0000	295.0000	0.077	16	1.236	0	-1.1572
1965.0000	295.0000	0.077	15	1.158	2	0.8139
1965.0000	299.0000	0.076	14	1.057	3	1.9647
1965.0000	301.0000	0.075	8	0.597	0	-0.8036
1965.0000	303.0000	0.074	13	0.960	0	-1.0180
1965.0000	303.0000	0.074	16	1.181	1	-0.1734

1965.0000	311.0000	0.070	17	1.197	2	0.7610
1965.0000	311.0000	0.070	5	0.352	1	1.1324
1965.0000	311.0000	0.070	8	0.563	0	-0.7785
1965.0000	313.0000	0.070	13	0.904	0	-0.9859
1965.0000	313.0000	0.070	19	1.322	1	-0.2902
1965.0000	318.0000	0.067	15	1.011	1	-0.0118
1965.0000	318.0000	0.067	12	0.809	1	0.2197
1965.0000	323.0000	0.065	8	0.522	0	-0.7475
1965.0000	324.0000	0.065	12	0.778	0	-0.9123
1965.0000	326.0000	0.064	14	0.896	1	0.1136
1965.0000	328.0000	0.063	14	0.884	1	0.1275
1965.0000	329.0000	0.063	13	0.815	0	-0.9326
1965.0000	333.0000	0.061	15	0.915	0	-0.9870
1965.0000	341.0000	0.058	12	0.690	1	0.3839
1965.0000	345.0000	0.056	17	0.949	1	0.0544
1965.0000	354.0000	0.052	18	0.934	0	-0.9925
7793.0000	280.0000	0.941	16	15.059	16	0.2971
7793.0000	283.0000	0.935	13	12.150	13	0.3132
7793.0000	284.0000	0.932	14	13.052	14	0.3195
7793.0000	286.0000	0.927	10	9.274	10	0.3298
7793.0000	288.0000	0.922	13	11.988	13	0.3442
7793.0000	288.0000	0.922	16	14.754	16	0.3453
7793.0000	290.0000	0.916	11	10.081	11	0.3565
7793.0000	292.0000	0.910	15	13.656	15	0.3724
7793.0000	294.0000	0.904	13	11.750	3	-2.7048
7793.0000	295.0000	0.900	12	10.805	12	0.3933
7793.0000	296.0000	0.897	3	2.691	0	-3.3130
7793.0000	301.0000	0.877	16	14.034	16	0.4447
7793.0000	304.0000	0.864	10	8.635	5	-1.2479
7793.0000	305.0000	0.859	13	11.162	13	0.4806
7793.0000	306.0000	0.854	12	10.243	12	0.4898
7793.0000	308.0000	0.843	17	14.330	17	0.5132
7793.0000	309.0000	0.837	12	10.048	12	0.5213
7793.0000	318.0000	0.777	11	8.547	5	-0.9149
7793.0000	319.0000	0.769	2	1.538	0	-1.9859
7793.0000	320.0000	0.761	14	10.652	14	0.6649
7793.0000	322.0000	0.743	14	10.408	14	0.6966
7793.0000	333.0000	0.623	14	8.718	3	-0.9993
7793.0000	338.0000	0.550	12	6.605	12	1.0689
7793.0000	338.0000	0.550	13	7.156	2	-0.9443

Scaled Residual(s) for Dose Group Nearest the BMD

Minimum scaled residual for dose group nearest the BMD = 0.5213
Minimum ABS(scaled residual) for dose group nearest the BMD = 0.5213
Average scaled residual for dose group nearest the BMD = 0.5213
Average ABS(scaled residual) for dose group nearest the BMD = 0.5213

Maximum scaled residual for dose group nearest the BMD = 0.5213
Maximum ABS(scaled residual) for dose group nearest the BMD = 0.5213
Number of litters used for scaled residual for dose group nearest the BMD = 1

Observed Chi-square = 105.5696

Bootstrapping Results

Number of Bootstrap Iterations per run: 1000

Bootstrap Chi-square Percentiles

Bootstrap Run	P-value	50th	90th	95th	99th
1	0.3160	94.4716	124.7141	132.5897	155.1097
2	0.3360	96.3317	125.7066	136.8936	155.4666
3	0.3090	95.3719	122.8344	132.9378	153.6561
Combined	0.3203	95.6022	124.4557	134.0383	155.2218

The results for three separate runs are shown. If the estimated p-values are sufficiently stable (do not vary considerably from run to run), then then number of iterations is considered adequate. The p-value that should be reported is the one that combines the results of the three runs. If sufficient stability is not evident (and especially if the p-values are close to the critical level for determining adequate fit, *e.g.*, 0.05), then the user should consider increasing the number of iterations per run.

To calculate the BMD and BMDL, the litter specific covariate is fixed at the overall mean of the litter specific covariates: 311.714286

Benchmark Dose Computation
Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMD = 5262.12
BMDL = 4385.1

5.8.3 Wistar Rat F1B stillborn/total delivered (NMP Producers Group (1999b))

Wistar Rat F1B Stillborn/Total Delivered (NMP Producers Group (1999b))

AUC (hr mg/L)	C_{max} (mg/L)	Total Delivered	PND4 Pup Death	Covariate (mg, LD1 Dam BW)
0	0	18	0	311
0	0	14	0	319
0	0	12	0	321
0	0	12	0	322
0	0	6	0	324
0	0	13	0	327
0	0	13	0	332
0	0	14	0	340
0	0	16	0	343
0	0	17	0	347
0	0	17	0	347
0	0	10	0	347
0	0	14	0	347
0	0	18	0	350
0	0	12	0	351
0	0	11	0	351
0	0	12	0	352
0	0	18	0	354
0	0	15	0	355
0	0	13	0	356
0	0	15	0	359
0	0	14	0	364
0	0	16	0	370
0	0	16	0	382
549.8	38.25	17	0	289
549.8	38.25	12	0	309
549.8	38.25	15	0	314
549.8	38.25	8	1	320
549.8	38.25	13	0	323
549.8	38.25	13	0	324
549.8	38.25	16	0	327
549.8	38.25	8	2	327
549.8	38.25	14	1	328
549.8	38.25	18	0	330
549.8	38.25	15	0	331
549.8	38.25	14	0	332
549.8	38.25	13	0	332
549.8	38.25	12	0	335
549.8	38.25	15	0	339
549.8	38.25	6	1	342
549.8	38.25	14	0	343
549.8	38.25	12	0	343
549.8	38.25	21	5	343
549.8	38.25	13	0	344
549.8	38.25	11	0	344

AUC (hr mg/L)	C_{max} (mg/L)	Total Delivered	PND4 Pup Death	Covariate (mg, LD1 Dam BW)
549.8	38.25	7	0	362
549.8	38.25	14	0	363
549.8	38.25	18	0	365
549.8	38.25	20	0	365
2006	135.21	13	0	317
2006	135.21	14	0	321
2006	135.21	15	0	323
2006	135.21	19	0	324
2006	135.21	19	0	324
2006	135.21	17	1	324
2006	135.21	10	0	325
2006	135.21	15	0	332
2006	135.21	18	0	334
2006	135.21	17	0	335
2006	135.21	9	0	341
2006	135.21	12	0	342
2006	135.21	14	0	344
2006	135.21	3	0	347
2006	135.21	4	0	347
2006	135.21	14	0	348
2006	135.21	12	0	349
2006	135.21	15	4	350
2006	135.21	13	0	352
2006	135.21	13	0	352
2006	135.21	3	0	354
2006	135.21	14	1	363
2006	135.21	13	0	382
2006	135.21	14	0	383
2006	135.21	17	0	385
6589	357.69	14	0	307
6589	357.69	14	0	315
6589	357.69	13	0	318
6589	357.69	15	0	321
6589	357.69	14	0	325
6589	357.69	8	0	325
6589	357.69	10	0	327
6589	357.69	12	1	329
6589	357.69	11	0	329
6589	357.69	10	0	340
6589	357.69	8	0	342
6589	357.69	10	0	345
6589	357.69	8	0	347
6589	357.69	9	0	350
6589	357.69	14	0	350
6589	357.69	15	0	352
6589	357.69	11	0	353
6589	357.69	9	0	353
6589	357.69	3	1	355

AUC (hr mg/L)	C_{max} (mg/L)	Total Delivered	PND4 Pup Death	Covariate (mg, LD1 Dam BW)
6589	357.69	8	0	359
6589	357.69	10	0	366
6589	357.69	13	0	366
6589	357.69	7	0	373
6589	357.69	14	1	379
6589	357.69	15	2	390

Table 5-31 Summary of BMDS nested modeling results for AUC (hr mg/L) versus Wistar Rat F1B stillborn/total delivered (NMP Producers Group (1999b)); BMR = 1% extra risk

Model [a]	Goodness of fit		BMD_{01} (hr mg/L)	$BMDL_{01}$ (hr mg/L)	Basis for Model Selection
	P-value	AIC			
Litter-specific covariate = LD1 dam weight; intra-litter correlations estimated					In all cases, models either failed to compute BMD values or reported p-values that are below 0.1. Thus, no model is chosen.
Nlogistic (b. seed[b] = 1595011547)	0.5787	196.62	CF	CF	
NCTR (b. seed = 1595011553)	CF	195.195	CF	CF	
Litter-specific covariate = LD1 dam weight; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1595011544)	0	217.921	67525.6	47680	
NCTR (b. seed = 1595011546)	0	219.656	428161	1.10038	
Litter-specific covariate not used; intra-litter correlations estimated					
Nlogistic (b. seed = 1595011532)	0.583	192.62	CF	CF	
NCTR (b. seed = 1595011538)	CF	192.538	CF	CF	
Litter-specific covariate not used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1595011540)	0.0003	217.679	584759	45650.7	
NCTR (b. seed = 1595011542)	0.0007	217.681	559444	1.10161	

[a] Litter-specific data were fit using standard (restricted) BMDS NLogistic and NCTR nested dichotomous models.
[b]. seed: bootstrap seed. The bootstrap seed shown must be entered into BMDS 2.7.0.4 nested model to replicate results.
CF = Benchmark dose computation failed. Lower limit includes zero.

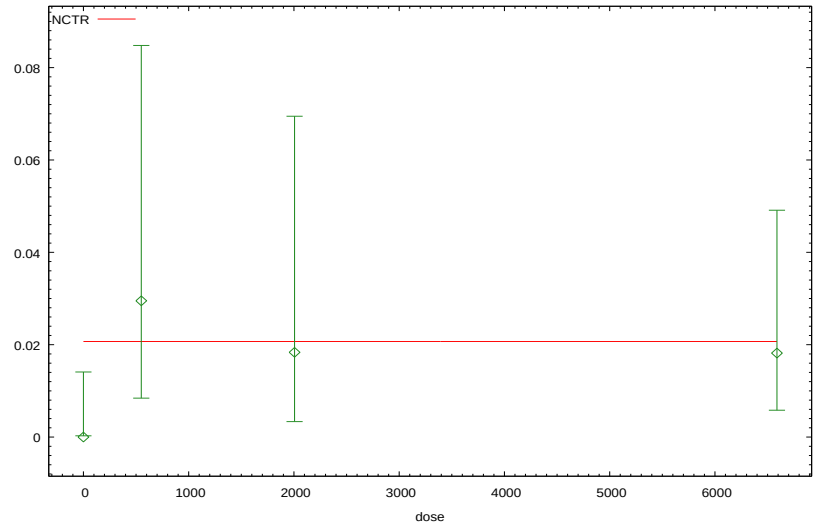


Figure 5.8-4 Plot of NCTR model (LSC = LD1 dam weight; ICC estimated) for AUC (hr mg/L) versus Wistar Rat F1B stillborn/total delivered.

Table 5-32 Summary of BMDS nested modeling results for C_{max} (mg/L) versus Wistar Rat F1B stillborn/total delivered (NMP Producers Group (1999b)); BMR = 1% extra risk.

Model [a]	Goodness of fit		BMD_{01} (hr mg/L)	$BMDL_{01}$ (hr mg/L)	Basis for Model Selection
	P-value	AIC			
Litter-specific covariate = LD1 dam weight; intra-litter correlations estimated					In all cases, models either failed to compute BMD values or reported p-values that are below 0.1. Thus, no model is chosen.
Nlogistic (b. seed[b] = 1597186626)	0.571	196.635	CF	CF	
NCTR (b. seed = 1597186632)	CF	195.195	CF	CF	
Litter-specific covariate = LD1 dam weight; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1597186623)	0	217.921	492.387	244.904	
NCTR (b. seed = 1597186624)	0.0003	219.512	307.326	0.272837	
Litter-specific covariate not used; intra-litter correlations estimated					
Nlogistic (b. seed = 1597186610)	0.5783	192.635	CF	CF	
NCTR (b. seed = 1597186619)	CF	192.538	CF	CF	
Litter-specific covariate not used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed = 1597186620)	0.0007	217.574	403.516	111.323	
NCTR (b. seed = 1597186621)	0	217.577	405.879	0.316558	

[a] Litter-specific data were fit using standard (restricted) BMDS NLogistic and NCTR nested dichotomous models.
[b] b. seed: bootstrap seed. The bootstrap seed shown must be entered into BMDS 2.7.0.4 nested model to replicate results.
CF = Benchmark dose computation failed. Lower limit includes zero.

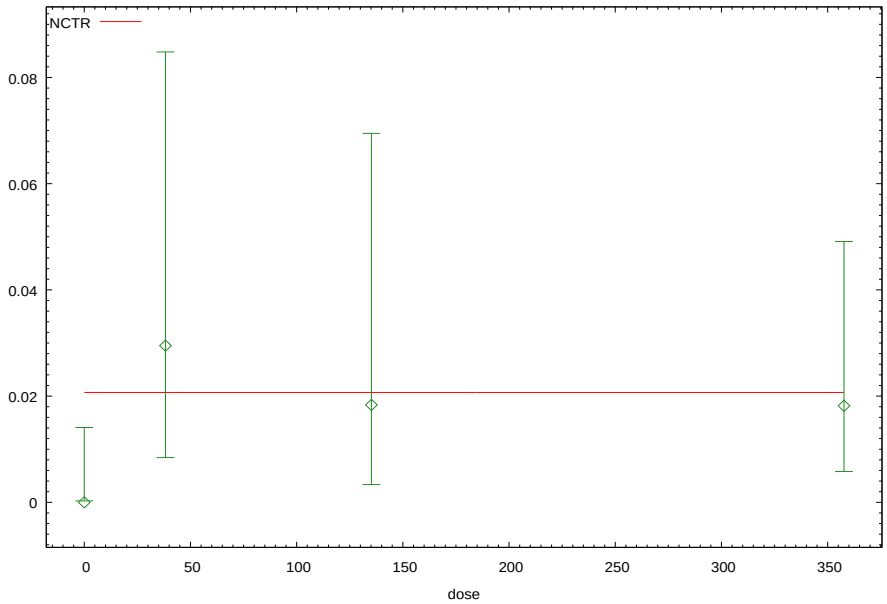


Figure 5.8-5 Plot of NCTR model (LSC = LD1 dam weight; ICC estimated) for C_{max} (mg/L) versus Wistar Rat F1B stillborn/total delivered.

5.8.4 Wistar Rat F2B Pup death at PND4/total delivered (NMP Producers Group (1999b))

Wistar Rat F2B Pup Death at PND4/Total Delivered (NMP Producers Group (1999b))

AUC (hr mg/L)	Total Delivered	PND4 Pup Death	Covariate (mg, LD1 Dam BW)
0	11	0	292
0	15	2	293
0	17	1	303
0	5	0	304
0	15	1	312
0	16	1	312
0	11	0	316
0	18	1	318
0	17	2	323
0	13	0	326
0	14	0	333
0	13	0	335
0	20	2	341
0	17	1	342
0	13	1	343
0	13	2	344
0	15	1	351
0	15	0	353
0	10	0	361
0	14	1	366
0	11	1	369
0	15	0	371
0	18	2	374
0	6	2	375
0	16	3	379
576.7	3	1	277
576.7	15	1	280
576.7	15	0	295
576.7	8	0	300
576.7	11	0	302
576.7	14	0	305
576.7	15	0	308
576.7	14	0	310
576.7	17	2	312
576.7	12	0	315
576.7	12	1	315
576.7	13	1	322
576.7	13	0	324
576.7	21	4	326
576.7	17	0	330
576.7	15	3	335
576.7	7	0	336
576.7	11	2	337
576.7	12	2	339
576.7	18	0	348

AUC (hr mg/L)	Total Delivered	PND4 Pup Death	Covariate (mg, LD1 Dam BW)
576.7	9	0	351
576.7	16	0	352
576.7	18	4	357
576.7	12	2	370
576.7	15	0	380
2024	5	0	282
2024	13	0	298
2024	13	0	298
2024	14	0	304
2024	12	1	308
2024	14	0	311
2024	14	0	315
2024	15	1	316
2024	18	0	316
2024	16	0	317
2024	19	2	318
2024	11	0	320
2024	16	3	322
2024	14	0	323
2024	14	1	323
2024	13	0	324
2024	12	0	325
2024	16	0	327
2024	9	0	331
2024	12	0	335
2024	9	0	336
2024	17	0	345
2024	11	0	347
2024	18	3	363
2024	15	0	392
5243	13	0	268
5243	13	0	294
5243	13	1	300
5243	17	0	301
5243	8	0	302
5243	6	0	309
5243	16	3	309
5243	13	1	314
5243	12	5	319
5243	12	10	320
5243	10	0	328
5243	14	1	335
5243	18	4	337
5243	12	0	340
5243	16	0	342
5243	14	0	345
5243	13	0	347
5243	11	3	349

AUC (hr mg/L)	Total Delivered	PND4 Pup Death	Covariate (mg, LD1 Dam BW)
5243	17	3	349
5243	15	5	350
5243	12	1	359
5243	10	0	361
5243	16	1	366
5243	19	2	385

Table 5-33 Summary of BMDS nested modeling results for AUC (hr mg/L) versus Wistar Rat F2B Pup death at PND4/total delivered (NMP Producers Group (1999b)); BMR = 1% extra risk.

Model [a]	Goodness of fit		BMD_{01} (hr mg/L)	$BMDL_{01}$ (hr mg/L)	Basis for Model Selection
	P-value	AIC			
Litter-specific covariate = LD1 dam weight; intra-litter correlations estimated					While some models met the p-value fit criteria (p-value > 0.1), no model was deemed to appropriate after visual inspection of model plots, which indicates considerable model uncertainty and a dose-response pattern analogous to having a positive response at only the highest dose.
Nlogistic (b. seed[b] =1597174507)	0.701	656.055	4632.85	695.198	
NCTR (b. seed =1597174509)	0.7017	653.707	4632.34	3860.28	
Litter-specific covariate = LD1 dam weight; intra-litter correlations assumed to be zero					
Nlogistic (b. seed =1597174503)	0	691.894	4619.65	2103.54	
NCTR (b. seed =1597174505)	0	689.888	4625.05	3854.21	
Litter-specific covariate not used; intra-litter correlations estimated					
Nlogistic (b. seed =1597174495)	0.7573	654.87	4624.92	726.435	
NCTR (b. seed =1597174497)	0.7313	652.87	4631.62	3859.68	
Litter-specific covariate not used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed =1597174499)	0	692.473	4613.99	2138.4	
NCTR (b. seed =1597174501)	0	690.473	4618.69	3848.91	

[a] Litter-specific data were fit using standard (restricted) BMDS NLogistic and NCTR nested dichotomous models. No model was chosen due to considerable model uncertainty indicated by visual inspection of model plots.

[b] b. seed: bootstrap seed. The bootstrap seed shown must be entered into BMDS 2.7.0.4 nested model to replicate results.

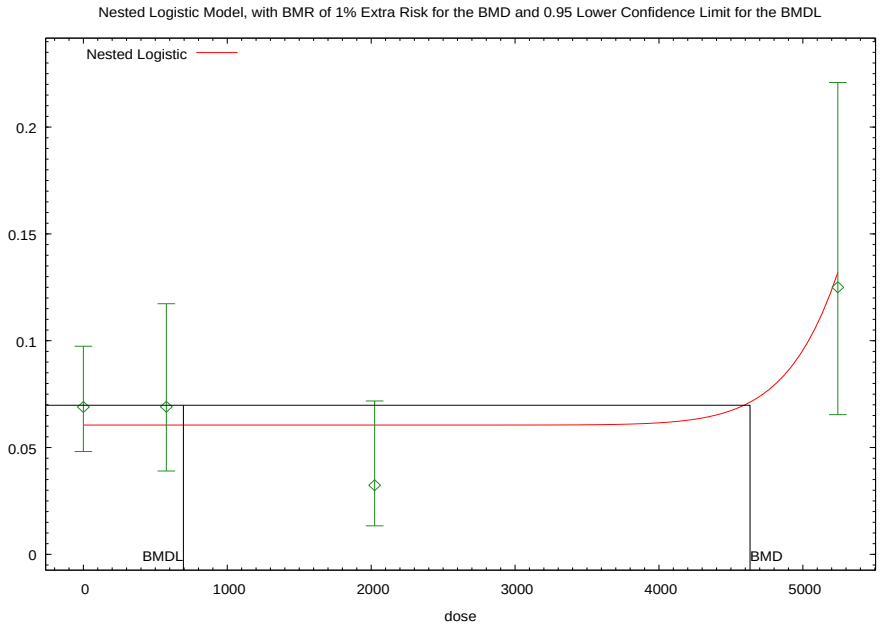


Figure 5.8-6 Plot of NCTR model (LSC = LD1 dam body weight; ICC estimated) for AUC (hr mg/L) versus Wistar Rat F2B Pup Death at PND4/Total Delivered.

5.8.5 Wistar Rat F2B Pup death at PND21/PND4 post-cull (NMP Producers Group (1999b))

Wistar Rat F2B Pup Death at PND21/PND4 Post-cull (NMP Producers Group (1999b))

AUC (hr mg/L)	PND4 Live Post-cull	PND21 Pup Death	Covariate (mg, LD1 Dam BW)
0	10	0	292
0	10	0	293
0	10	0	303
0	5	0	304
0	10	0	312
0	10	1	312
0	10	0	316
0	10	0	318
0	10	0	323
0	10	0	326
0	10	0	333
0	10	0	335
0	10	0	341
0	10	0	342
0	10	0	343
0	10	0	344
0	10	0	351
0	10	0	353
0	10	0	361
0	10	0	366
0	10	0	369
0	10	0	371
0	10	0	374
0	4	0	375
0	10	0	379
576.7	2	0	277
576.7	10	0	280
576.7	10	0	295
576.7	8	0	300
576.7	10	0	302
576.7	10	0	305
576.7	10	0	308
576.7	10	0	310
576.7	10	0	312
576.7	10	0	315
576.7	10	0	315
576.7	10	0	322
576.7	10	0	324
576.7	10	0	326
576.7	10	0	330
576.7	10	0	335
576.7	7	0	336
576.7	9	0	337
576.7	10	0	339

AUC (hr mg/L)	PND4 Live Post-cull	PND21 Pup Death	Covariate (mg, LD1 Dam BW)
576.7	10	0	348
576.7	9	0	351
576.7	10	0	352
576.7	10	1	357
576.7	10	0	370
576.7	10	0	380
2024	5	0	282
2024	10	0	298
2024	10	0	298
2024	10	0	304
2024	10	0	308
2024	10	0	311
2024	10	0	315
2024	10	0	316
2024	10	0	316
2024	10	0	317
2024	10	2	318
2024	10	0	320
2024	10	0	322
2024	10	0	323
2024	10	1	323
2024	10	0	324
2024	10	0	325
2024	10	0	327
2024	9	0	331
2024	10	0	335
2024	9	0	336
2024	10	0	345
2024	10	0	347
2024	10	0	363
2024	10	0	392
5243	10	0	268
5243	10	0	294
5243	10	0	300
5243	10	0	301
5243	8	0	302
5243	6	0	309
5243	9	3	309
5243	10	1	314
5243	7	0	319
5243	2	0	320
5243	10	0	328
5243	10	0	335
5243	10	6	337
5243	10	0	340
5243	10	1	342
5243	10	0	345
5243	10	0	347

AUC (hr mg/L)	PND4 Live Post-cull	PND21 Pup Death	Covariate (mg, LD1 Dam BW)
5243	8	0	349
5243	10	0	349
5243	10	1	350
5243	10	0	359
5243	10	0	361
5243	10	0	366
5243	10	1	385

Table 5-34 Summary of BMDS nested modeling results for AUC (hr mg/L) versus Wistar Rat F2B Pup death at PND21 /PND4 post-cull (NMP Producers Group (1999b)); BMR = 1% extra risk.

Model [a]	Goodness of fit		BMD_{01} (hr mg/L)	$BMDL_{01}$ (hr mg/L)	Basis for Model Selection
	P-value	AIC			
Litter-specific covariate = LD1 dam weight; intra-litter correlations estimated					The NLogistic model that estimated intra-litter correlations but did not make use of a litter-specific covariate was selected based on lowest AIC and BMDL. BMDLs from acceptable models (P-value >0.1) did not vary more than 3-fold.
Nlogistic (b. seed[b] =1597184767)	0.4807	151.165	2068.11	649.506	
NCTR (b. seed =1597184769)	0.4857	150.805	1633.38	816.692	
Litter-specific covariate = LD1 dam weight; intra-litter correlations assumed to be zero					
Nlogistic (b. seed =1597184764)	0.0877	166.9	2193.49	843.599	
NCTR (b. seed =1597184765)	0.0753	166.819	2140.17	1070.08	
Litter-specific covariate not used; intra-litter correlations estimated					
Nlogistic (b. seed =1597184753)	**0.4777**	**147.545**	**2266.39**	**723.867**	
NCTR (b. seed =1597184758)	0.4793	147.546	2269.33	1134.67	
Litter-specific covariate not used; intra-litter correlations assumed to be zero					
Nlogistic (b. seed =1597184761)	0.08	162.964	2221.61	910.752	
NCTR (b. seed =1597184762)	0.0857	162.965	2223.59	1111.79	

[a] Litter-specific data were fit using standard (restricted) BMDS NLogistic and NCTR nested dichotomous models. Selected model is bolded.

[b] b. seed: bootstrap seed. The bootstrap seed shown must be entered into BMDS 2.7.0.4 nested model to replicate results.

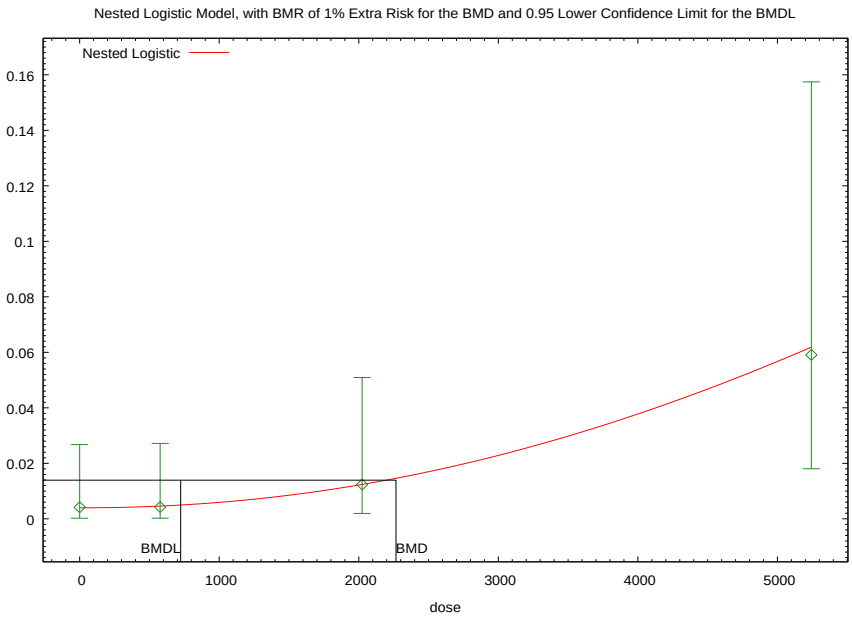


Figure 5.8-7 Plot of NLogistic model (no LSC; ICC estimated) for AUC (hr mg/L) versus Wistar Rat F2B Pup Death at PND21/Live PND4 Post-cull.

==========

NLogistic Model. (Version: 2.20; Date: 04/27/2015)
Input Data File: C:/Users/jgift/BMDS2704/Data/WF2b_PND21_p_942/Correct Doses/BMR01/nln_WF2b_PND21_p_942_Nln-BMR1-Restrict-IC.(d)
Tue Aug 11 18:25:53 2020

==========

BMDS Model Run

~~~~~~~~~~

The probability function is:

Prob. = alpha + theta1*Rij + [1 - alpha - theta1*Rij]/

[1+exp(-beta-theta2*Rij-rho*log(Dose))],

where Rij is the litter specific covariate.

Restrict Power rho >= 1.

Total number of observations = 99
Total number of records with missing values = 0
Total number of parameters in model = 9
Total number of specified parameters = 2
Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
Number of Bootstrap Iterations per run: 1000
Bootstrap Seed: 1597184753
~~~~~~~~~~

User specifies the following parameters:
theta1 = 0
theta2 = 0

Default Initial Parameter Values
alpha = 0.00396861
beta = -20.6474
theta1 = 0 Specified
theta2 = 0 Specified
rho = 2.0777
phi1 = 0
phi2 = 0
phi3 = 0.0926644
phi4 = 0.227904

Parameter Estimates

Variable	Estimate	Std. Err.
alpha	0.00396861	0.00249283
beta	-20.6474	0.42836
rho	2.0777	NA
phi1	0	Bounded
phi2	0	Bounded
phi3	0.0926644	NA
phi4	0.227904	NA

Log-likelihood: -68.7726 AIC: 147.545

Litter Data

Dose	Lit.-Spec. Cov.	Litter Est._Prob.	Litter Size	Scaled Expected	Scaled Observed	Scaled Residual
0.0000	292.0000	0.004	10	0.040	0	-0.1996
0.0000	293.0000	0.004	10	0.040	0	-0.1996
0.0000	303.0000	0.004	10	0.040	0	-0.1996
0.0000	304.0000	0.004	5	0.020	0	-0.1411
0.0000	312.0000	0.004	10	0.040	0	-0.1996
0.0000	312.0000	0.004	10	0.040	1	4.8301
0.0000	316.0000	0.004	10	0.040	0	-0.1996
0.0000	318.0000	0.004	10	0.040	0	-0.1996
0.0000	323.0000	0.004	10	0.040	0	-0.1996
0.0000	326.0000	0.004	10	0.040	0	-0.1996
0.0000	333.0000	0.004	10	0.040	0	-0.1996
0.0000	335.0000	0.004	10	0.040	0	-0.1996
0.0000	341.0000	0.004	10	0.040	0	-0.1996
0.0000	342.0000	0.004	10	0.040	0	-0.1996
0.0000	343.0000	0.004	10	0.040	0	-0.1996

0.0000	344.0000	0.004	10	0.040	0	-0.1996
0.0000	351.0000	0.004	10	0.040	0	-0.1996
0.0000	353.0000	0.004	10	0.040	0	-0.1996
0.0000	361.0000	0.004	10	0.040	0	-0.1996
0.0000	366.0000	0.004	10	0.040	0	-0.1996
0.0000	369.0000	0.004	10	0.040	0	-0.1996
0.0000	371.0000	0.004	10	0.040	0	-0.1996
0.0000	374.0000	0.004	10	0.040	0	-0.1996
0.0000	375.0000	0.004	4	0.016	0	-0.1262
0.0000	379.0000	0.004	10	0.040	0	-0.1996
576.7000	277.0000	0.005	2	0.009	0	-0.0957
576.7000	280.0000	0.005	10	0.046	0	-0.2139
576.7000	295.0000	0.005	10	0.046	0	-0.2139
576.7000	300.0000	0.005	8	0.036	0	-0.1913
576.7000	302.0000	0.005	10	0.046	0	-0.2139
576.7000	305.0000	0.005	10	0.046	0	-0.2139
576.7000	308.0000	0.005	10	0.046	0	-0.2139
576.7000	310.0000	0.005	10	0.046	0	-0.2139
576.7000	312.0000	0.005	10	0.046	0	-0.2139
576.7000	315.0000	0.005	10	0.046	0	-0.2139
576.7000	315.0000	0.005	10	0.046	0	-0.2139
576.7000	322.0000	0.005	10	0.046	0	-0.2139
576.7000	324.0000	0.005	10	0.046	0	-0.2139
576.7000	326.0000	0.005	10	0.046	0	-0.2139
576.7000	330.0000	0.005	10	0.046	0	-0.2139
576.7000	335.0000	0.005	10	0.046	0	-0.2139
576.7000	336.0000	0.005	7	0.032	0	-0.1790
576.7000	337.0000	0.005	9	0.041	0	-0.2029
576.7000	339.0000	0.005	10	0.046	0	-0.2139
576.7000	348.0000	0.005	10	0.046	0	-0.2139
576.7000	351.0000	0.005	9	0.041	0	-0.2029
576.7000	352.0000	0.005	10	0.046	0	-0.2139
576.7000	357.0000	0.005	10	0.046	1	4.4828
576.7000	370.0000	0.005	10	0.046	0	-0.2139
576.7000	380.0000	0.005	10	0.046	0	-0.2139
2024.0000	282.0000	0.012	5	0.059	0	-0.2092
2024.0000	298.0000	0.012	10	0.119	0	-0.2558
2024.0000	298.0000	0.012	10	0.119	0	-0.2558
2024.0000	304.0000	0.012	10	0.119	0	-0.2558
2024.0000	308.0000	0.012	10	0.119	0	-0.2558
2024.0000	311.0000	0.012	10	0.119	0	-0.2558
2024.0000	315.0000	0.012	10	0.119	0	-0.2558
2024.0000	316.0000	0.012	10	0.119	0	-0.2558
2024.0000	316.0000	0.012	10	0.119	0	-0.2558
2024.0000	317.0000	0.012	10	0.119	0	-0.2558
2024.0000	318.0000	0.012	10	0.119	2	4.0583

2024.0000	320.0000	0.012	10	0.119	0	-0.2558
2024.0000	322.0000	0.012	10	0.119	0	-0.2558
2024.0000	323.0000	0.012	10	0.119	0	-0.2558
2024.0000	323.0000	0.012	10	0.119	1	1.9013
2024.0000	324.0000	0.012	10	0.119	0	-0.2558
2024.0000	325.0000	0.012	10	0.119	0	-0.2558
2024.0000	327.0000	0.012	10	0.119	0	-0.2558
2024.0000	331.0000	0.012	9	0.107	0	-0.2491
2024.0000	335.0000	0.012	10	0.119	0	-0.2558
2024.0000	336.0000	0.012	9	0.107	0	-0.2491
2024.0000	345.0000	0.012	10	0.119	0	-0.2558
2024.0000	347.0000	0.012	10	0.119	0	-0.2558
2024.0000	363.0000	0.012	10	0.119	0	-0.2558
2024.0000	392.0000	0.012	10	0.119	0	-0.2558
5243.0000	268.0000	0.058	10	0.583	0	-0.4505
5243.0000	294.0000	0.058	10	0.583	0	-0.4505
5243.0000	300.0000	0.058	10	0.583	0	-0.4505
5243.0000	301.0000	0.058	10	0.583	0	-0.4505
5243.0000	302.0000	0.058	8	0.466	0	-0.4369
5243.0000	309.0000	0.058	6	0.350	0	-0.4167
5243.0000	309.0000	0.058	9	0.525	3	2.0957
5243.0000	314.0000	0.058	10	0.583	1	0.3222
5243.0000	319.0000	0.058	7	0.408	0	-0.4279
5243.0000	320.0000	0.058	2	0.117	0	-0.3176
5243.0000	328.0000	0.058	10	0.583	0	-0.4505
5243.0000	335.0000	0.058	10	0.583	0	-0.4505
5243.0000	337.0000	0.058	10	0.583	6	4.1853
5243.0000	340.0000	0.058	10	0.583	0	-0.4505
5243.0000	342.0000	0.058	10	0.583	1	0.3222
5243.0000	345.0000	0.058	10	0.583	0	-0.4505
5243.0000	347.0000	0.058	10	0.583	0	-0.4505
5243.0000	349.0000	0.058	8	0.466	0	-0.4369
5243.0000	349.0000	0.058	10	0.583	0	-0.4505
5243.0000	350.0000	0.058	10	0.583	1	0.3222
5243.0000	359.0000	0.058	10	0.583	0	-0.4505
5243.0000	361.0000	0.058	10	0.583	0	-0.4505
5243.0000	366.0000	0.058	10	0.583	0	-0.4505
5243.0000	385.0000	0.058	10	0.583	1	0.3222

Scaled Residual(s) for Dose Group Nearest the BMD

Minimum scaled residual for dose group nearest the BMD = -0.2491
Minimum ABS(scaled residual) for dose group nearest the BMD = 0.2491
Average scaled residual for dose group nearest the BMD = -0.2491
Average ABS(scaled residual) for dose group nearest the BMD = 0.2491
Maximum scaled residual for dose group nearest the BMD = -0.2491
Maximum ABS(scaled residual) for dose group nearest the BMD = 0.2491

Number of litters used for scaled residual for dose group nearest the BMD = 1

Observed Chi-square = 92.7301

Bootstrapping Results

Number of Bootstrap Iterations per run: 1000

Bootstrap Chi-square Percentiles

Bootstrap Run	P-value	50th	90th	95th	99th
1	0.4810	90.8819	170.6668	205.2285	260.8940
2	0.4710	90.1158	163.9175	188.5821	255.2733
3	0.4810	90.1495	168.9837	190.0508	267.9728
Combined	0.4777	90.3560	167.8649	194.2301	267.9728

The results for three separate runs are shown. If the estimated p-values are sufficiently stable (do not vary considerably from run to run), then then number of iterations is considered adequate. The p-value that should be reported is the one that combines the results of the three runs. If sufficient stability is not evident (and especially if the p-values are close to the critical level for determining adequate fit, *e.g.*, 0.05), then the user should consider increasing the number of iterations per run.

To calculate the BMD and BMDL, the litter specific covariate is fixed at the mean litter specific covariate of all the data: 329.161616

Benchmark Dose Computation
Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMD = 2266.39
BMDL = 723.867

6 References

Agresti, A. (1990). Categorical data analysis: Wiley. https://books.google.com/books?id=MCnvAAAAMAAJ.

Barker, DJP. (2007). The origins of the developmental origins theory. J Intern Med 261: 412-417. http://dx.doi.org/10.1111/j.1365-2796.2007.01809.x.

Becci, PJ; Knickerbocker, MJ; Reagan, EL; Parent, RA; Burnette, LW. (1982). Teratogenicity study of N-methylpyrrolidone after dermal application to Sprague-Dawley rats. Fundam Appl Toxicol 2: 73-76. http://dx.doi.org/10.1016/s0272-0590(82)80117-6.

Cochran, WG. (1977). Sampling Techniques (3 ed.). New York: John Wiley & Sons. https://www.wiley.com/en-us/Sampling+Techniques%2C+3rd+Edition-p-9780471162407.

DuPont. (1990). Letter from E I DuPont de Nemours & Company to USEPA submitting comments concerning the proposed test rule on n-methylpyrrolidone with attachment. (40-90107098). E I Dupont De Nemours & Co.

E. I. Dupont De Nemours & Co. (1990). Initial submission: reproductive and developmental toxicity of 1-methyl-2-pyrrolidinone in the rat with cover letter dated 10/01/92. (OTS: OTS0555618; 8EHQ Num: 8EHQ-1092-11957; DCN: 88-920010214; TSCATS RefID: 440618; CIS: NA).

Exxon, B. (1991a). Multigeneration Rat Reproduction Study with N-Methylpyrrolidone, Project Number 236535 [TSCA Submission]. (OTS#: 0532510; New Doc ID: 40-91107125; Old Doc ID: 42114 F1-2). Wayne, USA: GAF Corp.

Exxon, B. (1991b). Project No. 236535, 26 Nov 1991. ((sponsored by GAF Corp., Wayne, USA). (as cited in OECD, 2007)). Wayne, USA: GAF Corp.

Fox, JR; Hogan, KA; Davis, A. (2016). Dose-response modeling with summary data from developmental toxicity studies. Risk Anal 37: 905-917. http://dx.doi.org/10.1111/risa.12667.

Hothorn, LA. (2016). Statistics in Toxicology Using R. Boca Raton, Florida: CRC Press.

Kavlock, RJ; Allen, BC; Faustman, EM; Kimmel, CA. (1995). Dose-response assessments for developmental toxicity .4. Benchmark doses for fetal weight changes. Toxicol Sci 26: 211-222. http://dx.doi.org/10.1006/faat.1995.1092.

NMP Producers Group. (1999a). Two generation reproduction toxicity study with n-methylpyrrolidone (NMP) in sprague dawley rats: Administration in the diet. (Project No. 97-4106). Millestone, NJ: Huntingdon Life Science.

NMP Producers Group. (1999b). Two Generation Reproduction Toxicity Study with N-Mythylpyrrolidone (NMP) in Wistar Rats - Administration in the Diet. (Project No. 70R0056/97008). Ludwigshafen, Germany: Department of Toxicology of BASF Aktiengesellschaft.

Poet, TS; Kirman, CR; Bader, M; van Thriel, C; Gargas, ML; Hinderliter, PM. (2010). Quantitative risk analysis for N-methyl pyrrolidone using physiologically based pharmacokinetic and benchmark dose modeling. Toxicol Sci 113: 468-482. http://dx.doi.org/10.1093/toxsci/kfp264.

Reyes, L; Mañalich, R. (2005). Long-term consequences of low birth weight [Review]. Kidney Int Suppl 68: S107-S111. http://dx.doi.org/10.1111/j.1523-1755.2005.09718.x.

Saillenfait, AM; Gallissot, F; Langonné, I; Sabaté, JP. (2002). Developmental toxicity of N-methyl-2-pyrrolidone administered orally to rats. Food Chem Toxicol 40: 1705-1712. http://dx.doi.org/10.1016/S0278-6915(02)00115-1.

Saillenfait, AM; Gallissot, F; Morel, G. (2003). Developmental toxicity of N-methyl-2-pyrrolidone in rats following inhalation exposure. Food Chem Toxicol 41: 583-588. http://dx.doi.org/10.1016/S0278-6915(02)00300-9.

Sasso, AF; Schlosser, PM; Kedderis, GL; Genter, MB; Snawder, JE; Li, Z; Rieth, S; Lipscomb, JC. (2013). Application of an updated physiologically based pharmacokinetic model for chloroform to evaluate CYP2E1-mediated renal toxicity in rats and mice. Toxicol Sci 131: 360-374. http://dx.doi.org/10.1093/toxsci/kfs320.https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6834307Shoukri, MM; Chaudhary, MA. (2018). Analysis of correlated data with SAS and R. New York: R. Chapman and Hall. http://dx.doi.org/https://doi.org/10.1201/9781315277738.

Sitarek, K; Stetkiewicz, J; Wąsowicz, W. (2012). Evaluation of reproductive disorders in female rats exposed to N-methyl-2-pyrrolidone. Birth Defects Res B Dev Reprod Toxicol 95: 195-201. http://dx.doi.org/10.1002/bdrb.21001.

Stiteler, WM; Knauf, LA; Hertzberg, RC; Schoeny, RS. (1993). A statistical test of compatibility of data sets to a common dose-response model. Regul Toxicol Pharmacol 18: 392-402. http://dx.doi.org/10.1006/rtph.1993.1065.

U.S. EPA. (2012). Benchmark dose technical guidance. (EPA/100/R-12/001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. https://www.epa.gov/risk/benchmark-dose-technical-guidance.

APPENDICES

Appendix A Analysis of Continuous Response Summary Data Subject to Litter Effects

No individual fetal data were available for the studies analyzed here. For reference, when individual fetal data are available, the preferable approach to determining the data to model is to apply a nested analysis of variance to each dose group separately, with litter as main effect and offspring nested within litters representing the individual replicates, and allowing for unequal litter sizes. In this case, to determine the data to enter into BMDS, define the following:

$n =$ number of litters in group
$m_i =$ size of ith litter
$N = \sum_{i=1}^{n} m_i =$ total number of offspring in group
$\bar{Y}_i =$ mean response in ith litter

To allow for an effect of the nesting of fetuses within litters on observed variance in the overall mean, the following approach to BMDS analysis may be considered (applied separately for each group).

Sample size: N, total number of offspring
Mean: $\bar{\bar{Y}} = \frac{1}{N}\sum_{i=1}^{n} m_i \bar{Y}_i$, grand mean response of all offspring within the group
SD: $\sqrt{MS_A}$, the square root of the litter mean square (Cochran (1977)), where

$$MS_A = \sum_{i=1}^{n} m_i \left(\bar{Y}_i - \bar{\bar{Y}}\right)^2.$$

The last two quantities are the estimate of the mean among offspring and standard deviation of the mean per offspring.

In cases where the individual fetal data are not available, other methods are necessary to approximate the preferred analysis. Below are two methods applied here.

Method 1: Litter sizes and litter means are available. In this case, the litter sizes m_i and litter means $\bar{Y}_i$ are available, so the quantities to enter into BMDS for the analysis of individual fetal data can be calculated using these data as described above for the case where individual fetal data are available. This approach was used as an alternate approach for some of the analyses presented in Section 3.3; however, it was not utilized in the recommended modeling results.

Method 2: Means and SDs of litter means are available. When using any non-SD-based BMR, a reasonable approximation of the preferred analysis can be made. In addition to the quantities defined above, define the following:

$\bar{Y}_L = \frac{1}{n}\sum_{i=1}^{n} \bar{Y}_i =$ mean of litter means
$S_L^2 = \frac{1}{n-1}\sum_{i=1}^{n} (\bar{Y}_i - \bar{Y}_L)^2 =$ variance of litter means

The data to enter into BMDS for each group are as follows.

Sample size: n
Mean: $\bar{Y}_L$

SD: $S_L = S_L^2$

$\bar{Y}_L$ is generally similar to $\bar{\bar{Y}}$. S_L is smaller than $\sqrt{MS_A}$ by approximately a factor equal to the average litter size (the difference is exactly equal to the individual litter size when all the litter sizes are equal). However, the sample size n is also smaller than N by approximately the same factor, so these differences cancel each other out. Therefore, in most cases the analysis of the means and SDs of litter means provides a reasonable approximation of an analysis based on individual fetal data; however, high inter-litter variability may result in poorer approximations.

Appendix B Tests for Differences and Trends in Saillenfait et al. (2003; 2002) Post-Implantation Dose-Response Data

B.1 Background and Objectives

The purpose of this appendix is to document statistical analyses of trend and trend difference for two studies of the toxicity of NMP (Saillenfait et al. (2002) and (2003)). Saillenfait et al. (2002) is an oral exposure study, while Saillenfait et al. (2003) is an inhalation exposure study. The data used in the statistical analysis shown in this appendix is presented in Table_Apx B-1 in Appendix B.2.

Two related, complementary analyses are reported in this Appendix. First is a deviance test for a difference in dose-response relationships in the Saillenfait et al. (2002) and (2003) studies, restricted to doses at which the dose-response curve was considered to be approximately linear, if not flat. Restriction to a linear or flat dose range was based on graphical interpretation suggesting that the nonlinear part of the combined curve was limited to higher doses, which were evaluated only in the oral exposure study (Saillenfait et al. (2002)). Second is an analysis of trend based on a breakdown of the Pearson chi-square, into chi-square statistics that represents a two-sided Cochran-Armitage test for linear trend, and a chi-square test of nonlinearity (Agresti (1990)) as implemented in the software EPITOOLS. According to the test of nonlinearity there were no significant deviations from linearity in the dose range for which approximate linearity was assumed, in the deviance test.

The approach for modeling data from the Saillenfait et al. (2002) and (2003) studies was to combine the two studies by fitting a single exposure-response curve, substituting a single internal dose metric that can be estimated using a PBPK model for both oral and inhalation exposure routes, in place of the external exposure concentrations. This analysis focused on dead fetuses expressed as a proportion of implantations, "proportion dead fetuses" in Table_Apx B-1 below. The internal dose metric considered in the analysis is C_{max} (mg/l), as post-implantation loss is viewed as an acute response, and a statistical test of the equivalence of the dose-response relationship in the lower dose range of the dose-response curve was performed.

For purposes of testing for a statistical difference between the Saillenfait et al. (2002) and (2003) studies, a very simple situation would be that the same set of doses has been evaluated in each study. A conclusion on the role of study could then be made without a dose-response model. For a continuous response, the analysis could be based on a two-way ANOVA, with dose and study as the two factors. Absence of a main effect of dose, plus absence of a study-dose interaction, would together suggest that response depends in no way on study, and might or might not depend on dose. One could then proceed with some confidence to a dose-response model for the combined data. As an additional precaution, the fit of such a model should still be examined separately for the two studies. An analogous approach may in principle be developed for a dichotomous response (*i.e.*, post-implantation losses). For the Saillenfait et al. (2002) and (2003) studies, the controls were the only group that could be directly compared. The comparison is necessarily based on fitted dose response models. The essential idea of the deviance test is to evaluate whether a significantly better fit to the data is obtained by fitting the studies separately than with the same dose-response curve. The null hypothesis is that all parameters of a dose-response model are equal for the two studies. The idea of a parametric model-based evaluation of the compatibility of dose-response datasets has been previously recognized (Stiteler et al. (1993)).

Based on a graphical evaluation, the dose-response relationship is practically flat up to a C_{max} of 250 mg/l for the Saillenfait et al. (2002) oral study, and is practically flat across the full range of doses evaluated in the Saillenfait et al. (2003) inhalation study. If the combined data are modeled then (under an assumption that dose-response parameters are equal in the two studies) the background level

parameter would be informed by data from both studies, primarily by data for $C_{max} \leq 250$ mg/l. Parameters defining the shape of the dose-response curves would, EPA expects, be informed primarily by higher doses, which were evaluated only in the Saillenfait et al. (2002) oral study.

For the model-based comparison of this section, EPA approximated the dose-response curves for C_{max} up to 250 mg/l using linear regressions. The approach would be substantially incorrect if there is appreciable deviation from linearity in the dose range evaluated; however, substantial nonlinearity appears only in the Saillenfait et al. (2002) oral study, at C_{max} values > 250 mg/l. In practice any smooth, nonlinear curve can be approximated to an arbitrary degree of precision by a straight line, in some range of doses. The more nonlinear curve, the more narrow such a range of doses. A separate trend analysis (Table_Apx B-4) provides a test for nonlinearity based on a decomposition of chi-square and suggests no statistical evidence of nonlinearity in the dose range of interest. While the comparison in this section could in principle have been based on a nonlinear model that would apply to the entire dose range of both studies, EPA did not think the essential results would be affected, because the estimated nonlinear effects would be based on a higher dose range, evaluated in the Saillenfait et al. (2002) oral study.

As a general principle, it is suggested that such a statistical test is not necessarily to be treated as a definitive rule by itself for deciding whether to combine the studies in dose-response modeling. If the scientific arguments as a whole point to combining the datasets, non-significant results from the test may be seen as having a “confirmatory” role, possibly suggesting that the scientific model is consistent with the data as analyzed using a specific statistical criterion. Then, any apparent differences might be considered consistent with sampling variability. However, data may be consistent with a variety of interpretations, especially if few or highly variable. This viewpoint is similar to the concept of goodness of fit testing and statistical model diagnostics.

The original design of this analysis was restricted to C_{max} values ≤ 250 mg/l (based on interpretation of the graphical analysis of all the data suggesting a linear response in that range). However, EPA repeated the statistical tests with the dose of 531 mg/L (based on C_{max}) from the Saillenfait et al. (2002) oral study included. This extension did not change the conclusion that the dose-response relationships are similar in the two studies.

B.2 Data

Data used in the statistical analyses are presented in Table_Apx B-1. Saillenfait et al. (2002) is an oral exposure study, while Saillenfait et al. (2003) is an inhalation exposure study. The dichotomous-response data used for the statistical tests are shown in the columns labelled "RS-implants" and "RS-dead." To account for potential litter effects in the developmental toxicity data, the data were adjusted for clustering using the Rao-Scott (RS) approach (Shoukri and Chaudhary (2018); Fox et al. (2016)). Estimated response proportions are shown in the column labelled "proportion dead fetuses." Note that RS adjustment does not change the estimated response proportion at a given dose level. The aim of the adjustment is to set the effective number on test to reflect the amount of information in the data, without changing the estimated proportion that responded. Corresponding non-adjusted counts are shown in the column labelled "Total Dead Fetuses" and "Total Implants." Note that these are also not necessarily integer-valued. This is because the total number of dead fetuses is estimated as the product of a mean number of fetuses, reported with limited precision, and a number of litters. The effect on calculations is not expected to be severe.

After RS adjustment the pseudo-counts for number (number dead) and denominator (number of implants) are not generally integer-valued. The software, which may be designed for dichotomous responses, must process non-integer input correctly, using the same formula as used for integer-valued inputs. The data used for this analysis are reported in the tables to 4-5 digits. Some intermediate computations involve fewer digits. This precision is judged adequate for the type of result reported.

Table_Apx B-1 Post-Implantation Losses/Implants from Oral (Saillenfait et al. (2002)) and Inhalation (Saillenfait et al. (2003)) Studies and Estimates of Internal C_{max}

Reference and Endpoint	C_{max} (mg/L)	Litters w/ Implants	Mean Implants	Total Implants	Live Litters	Mean Live Fetuses	Total Live Fetuses	Total Dead Fetuses	Proportion Dead Fetuses	RS-Implants	RS-Dead
Saillenfait et al. (2002) Post-implant-ation loss	0	21	13.3	279.3	21	12.7	266.7	12.6	0.0451	134.20	6.0541
	120	22	13.6	299.2	21	13.1	275.1	24.1	0.0805	117.34	9.4516
	250	24	13.3	319.2	24	12.7	304.8	14.4	0.0451	153.37	6.9190
	531	25	14	350	25	12.4	310	40	0.1143	121.42	13.877
	831	25	13.8	345	8	2.4	19.2	325.8	0.9443	57.044	53.870
Saillenfait et al. (2003) Post-implant-ation loss	0	24	14.3	343.2	24	13.9	333.6	9.6	0.0280	194.94	5.4529
	15	20	13.4	268	20	12.6	252	16	0.0597	116.73	6.9692
	30	20	14.1	282	19	14	266	16	0.0567	125.04	7.0946
	62	25	12.9	322.5	25	12	300	22.5	0.0698	133.01	9.2798

B.3 Statistical Approaches

The statistical test applied for the comparison of slopes of dose-response curves and intercepts is a deviance test or likelihood ratio test. The test was applied to determine if response increase with dose is sometimes termed a chi-squared test for trend. Both approaches are exemplified by a variety of tests reported routinely by BMDS, and the general concepts are discussed in the Benchmark Dose Technical Guidance manual, particularly in connection with the analysis of deviance table.

Given that the internal serum doses do not match in the Saillenfait et al. (2002) and (2003) studies, the deviance test has to be based on a statistical modeling approach. Herein, the deviance test is based on modeling with a form of linear regression, but with the response variable assumed to have a binomial distribution (an ordinary, least-squares linear regression actually gives point estimates of slope and intercept comparable to the estimates in Appendix B). The deviance test here was designed to be sensitive to a difference in intercept or a difference in slope, when comparing the two Saillenfait et al. studies (*i.e.*, the null hypothesis is equivalence of intercepts and equivalence of slopes).

EPA used a generalized linear model (GLM) for the deviance test but with non-default software settings as explained in Appendix B.4 (this is not exactly SAS Proc GLM, which implements the "general linear model"). The literature on GLMs is very extensive and includes texts that are very application-oriented. Hothorn (2016) provides considerable treatment specific to toxicological data analysis.

R code for the deviance test is provided in Appendix B.6[9]. The test has been implemented here with base R software that is well-established for the current analyses. Likewise, the chi-squared test for trend we have applied using the EPITOOLS software is a common trend test, and the EPITOOLS software has been available for many years, having been cited often for use in similar analyses.

[9] R is available for download from the CRAN website at https://cran.r-project.org/ and EPITOOLS (Sergeant ESG (2018)) is compilation of statistical tools developed "for the use of researchers and epidemiologists." The Cochran-Armitage trend test available in BMDS 2.7 is not applied here because it requires integer data for incidences. The EPITOOLS software used here appears to be completely distinct from an R package of the same name. The approach in EPITOOLS is based on a breakdown of chi-square, apparently as described in Agresti (1990). The references given by the software are to be found at https://epitools.ausvet.com.au/references.

B.4 Details of Deviance Test for a Difference in Dose-Response Relationship

Because internal serum doses do not match in the two Saillenfait et al. studies, the test for a difference is based on a statistical multiple regression model presented below.

Expected proportion = intercept + slope*C_{max} + $I_{Study = 2}$*(D.intercept$_2$ + D.slope$_2$*C_{max})

where D.intercept$_2$ is an intercept increment associated with the Saillenfait et al. (2003) inhalation study;

D.slope$_2$ is a slope increment associated with the Saillenfait et al. (2003) inhalation study; and

$I_{Study = 2}$ = 0 for Saillenfait et al. (2002), and $I_{Study = 2}$= 1 for Saillenfait et al. (2003) results.

This is a parametrization of a model that specifies two separate regressions, one for each study. In terms of this parametrization, the null hypothesis may be stated as H_0: D.intercept$_2$ = 0 and D.slope2 = 0. Rejection could result from a difference in intercept, a difference in slope, or a difference in both intercept and slope.

The general approach of a deviance test is discussed in a toxicological-pharmacological journal, in an article on evaluating "compatibility of two datasets to a common dose-response model" (Stiteler et al. (1993)). However, the approach is well-known and more general literature sources are likely to provide clearer descriptions of the degrees of freedom for an asymptotic chi-square test. As indicated in that article, extension to nonlinear models (*e.g.*, BMDS) is straightforward. Specialization to a linear regression model here is convenient in avoiding a need for model selection. Also, issues related to parameter constraints are avoided.

Here, the data was modeled in two ways (*i.e.*, a single regression for both studies combined and separate regressions for each study individually), and the results are compared based on deviance (log-likelihood times negative). The R function anova() can be used to generate an analysis of deviance table if supplied model objects corresponding to the two modeling options, provided parameters are named in each to allow recognition of nesting. It is convenient to parametrize the separate-regressions model in terms of intercept, slope, intercept difference, and slope difference. The anova() function will compute the test statistic (difference of deviances) and degrees of freedom (*i.e.*, two degrees of freedom here) for the test, but does not compute a *p*-value. The conventional, asymptotic *p*-value may be computed by referring the deviance difference to a chi-square distribution with two degrees of freedom.

Technical details

EPA used the R function glm() with binomial response family and linear link. The default link with a binomial family is the logit link, resulting in a logistic regression. EPA assumed that the results are not very sensitive to modeling the role of exposure in a range where the dose-response is practically flat, and chose the link based on some concept of simplicity or familiarity.

The function glm() as such is not restricted to dichotomous responses, and EPA has found it most simple in coding glm() to specify the binomial response family. It is reasonable to ask whether the computations are correct, when an option designed for dichotomous data is used with non-integer response data. EPA has found no specific statement on this to date; however, EPA does not believe that this is an issue for the following reasons. First, the glm() function returns a warning when the responses

are non-integer, rather than a fatal error, suggesting that thought has been given to the possibility of non-integer inputs. Second, EPA has been able to generate the same results in glm(), bypassing the binomial response specification. In place of the binomial family we used the “quasi” (quasi likelihood approach), with appropriate weights and a variance function based on the binomial distribution. Statistically, there is no reason to restrict the quasi option to be restricted to a discrete response scale, and the warning generated with the binomial response family does not appear. Finally, the glm() function is one of the most used R modeling option for dichotomous responses, and EPA believes the issue of possibly non-integer inputs has probably come up before in the long history of this function.

B.5 Results

Table_Apx B-2 presents an "analysis of deviance" including the p-value from the test for a difference using the Rao-Scott transformed responses for the 0, 120 mg/L and 250 mg/L doses (based on C_{max}) of the Saillenfait et al. (2002) oral study and for all doses of Saillenfait et al. (2003) inhalation study shown in Table_Apx B-1. Confidence intervals for parameters of the separate-regressions model of the data from the Saillenfait et al. studies are shown in Table_Apx B-3. Table_Apx B-4 provides the results of the chi-squared test for trend applied separately to each study for the same dose-response data, along with an additional analysis of the Saillenfait et al. (2002) oral study with the 531 mg/l dose included.

The p-value resulting from applying the deviance test to the 0, 120 mg/L and 250 mg/l doses (based on C_{max}) of the Saillenfait et al. (2002) oral study and for all doses of Saillenfait et al. (2003) inhalation study is 0.27, while the p-value of the additional analysis of the Saillenfait et al. (2002) oral study with the 531 mg/l dose included is 0.4. The Table_Apx B-4 trend test results for the post-implantation loss data from the Saillenfait et al. (2002) oral study without the 531 mg/L dose, Saillenfait et al. (2002) with the 531 mg/L dose and the Saillenfait et al. (2003) inhalation study were 0.94, 0.053 and 0.11, respectively. Thus, the results are not significant at cutoffs commonly used (*i.e.*, at p-values of 0.05 and 0.01). These data are consistent with equal intercepts and equal slopes between the two studies, and no significant increase in response with increasing dose for either study, *in the dose ranges evaluated*.

Table_Apx B-2 Analysis of Deviance Results for Test for a Difference of Regressions

Model	Num. dose-response model parameters	Deviance	AIC (smaller is better)
Single binomial regression for both studies.	2	5.3896	35.687
Separate regressions	4	2.7855	37.019
Absolute Difference (test statistic and d.f. for test)	2	2.6041	
P-value for test.		**0.27**	

Table_Apx B-3 Confidence Intervals for Parameters of the Separate-Regressions Models used in the Deviance Test

	Estimate	Standard Error	Lower bound (95%)	Upper bound (95%)	P-value
Saillenfait et al. (2002) oral study intercept	0.057	0.018	0.021	0.092	
Saillenfait et al. (2003) inhalation study intercept	-1E-05	0.0001	-0.0002	0.0002	0.92
Intercept Difference (inhalation minus oral) D.intercept$_2$ in model.	-0.023	0.021	-0.065	0.019	0.29
Slope Difference (inhalation minus oral) D.slope$_2$ in model.	0.0007	0.0004	-0.0001	0.0015	0.099

Table_Apx B-4 Trend Analysis Results

	Data	Chi-square statistic	Degrees of freedom	P-value	Slope	Interpretation
Pearson's Chi-square	Saillenfait et al. (2002) (oral) [a]	2.0003	2	0.3678		Not-significant (at the 5% level), association between score and outcome not supported.
	Saillenfait et al. (2002) (oral) [b]	6.6774	3	**0.0829**		
	Saillenfait et al. (2003) (inhalation)	3.3979	3	0.3343		
Chi-square for slope (linear trend)	Saillenfait et al. (2002) (oral) [a]	0.0066	1	0.9353	0	Slope does not differ from 0 (at the strict 5% significance level). Some indication of a trend if 531 mg/l is included.
	Saillenfait et al. (2002) (oral) [b]	3.7515	1	0.**0528** ≈ **0.05**	1e-04	
	Saillenfait et al. (2003) (inhalation)	2.5611	1	0.1095	6e-04	
Chi-square for non-linearity	Saillenfait et al. (2002) (oral) [a]	2.9259	1	0.158		Trend does not differ significantly at the 1% level from linearity
	Saillenfait et al. (2002) (oral) [b]	1.9937	2	0.2316		
	Saillenfait et al. (2003) (inhalation)	0.8368	2	0.6581		

[a] Using Rao-Scott transformed responses for 0, 120 and 250 mg/l doses.
[b] Using Rao-Scott transformed responses for 0, 120, 250 and 531 mg/l doses.

B.6 Code (R)

```
##
## NMP data from Saillenfait 2002 (first) and 2003 (second).
## Obtained April 21 from Allen Davis, extracted from report table.
## Data were copied electronically.
##   N = number of implantations
##   r = number of fetal deaths
##   Cmax = Cmax internal dose (mg/L) from PBPK
## ----------------------------------------------------------------##
## Assume a linear regression of r/N on Cmax and test for a difference
## in regression lines (difference in slope or intercept)
## The approach has restricted applicability, as a rule to doses
## no larger than the lowest NOAEL. The regression is based on glm().
## The default use of the function with binomial response family would
## result in logistic regression. A linear link was chosen for
## perceived ease of explanation (the approach is linear regression
## for response proportions with binomial response).
## ----------------------------------------------------------------##
##
## data has been included initially for all groups.
## data for doses LE 250 mg/L subsequently selected for analysis.
Cmax.cutoff <- 250
## Saillenfait(2002)
Cmax2002 <- c(0,      120,    250,    531,    831  )
r2002    <- c(6.0541, 9.4516,  6.919,  13.877,          53.87)
N2002    <- c(134.2, 117.34, 153.37, 121.42, 57.044)
stdy2002  <- rep("Sll2002", length(Cmax2002))

## Saillenfait(2003)
Cmax2003 <- c(0, 15,30,62)
r2003    <- c(5.4529, 6.9692,  7.0946, 9.2798)
N2003    <- c(194.94, 116.73, 125.04, 133.01)
stdy2003  <- rep("Sll2003", length(Cmax2003))
## ----------------------------------------------------------------##

## combined data frame
##
d2002 <- data.frame( stdy=stdy2002, Cmax=Cmax2002, r=r2002, N=N2002 )
```

```
d2003 <- data.frame( stdy=stdy2003, Cmax=Cmax2003, r=r2003, N=N2003 )
d0    <- rbind(d2002,d2003)

## ------------------------------------------------------------------##
## transformations and selection

## dummy for 2003 study (regressor for intercept diff.)
d0$is2003 <- with(d0, as.numeric(stdy) == 2)

## analysis dataset is a selection based on dose
danly <- subset(d0, Cmax <= Cmax.cutoff)

View(danly)

## ------------------------------------------------------------------##
## graph of response proportions (confidence intervals desirable)
##

dpl <- danly
dpl$pr <- with(danly, r / N)
with(dpl, plot(Cmax,pr, type = "n", ylab = "response proportion"))
with(subset(dpl, is2003), points(Cmax, pr, pch=19))
with(subset(dpl,!is2003), points(Cmax, pr, pch=17))

## ------------------------------------------------------------------##
## function to report params to specified number of digits, and a label
## for model.

printCoeffs <- function(model, mod.label, dig = 3 ) {
  cat("\n", mod.label, signif(coef(model), dig), "\n")
  invisible()
  }
## ------------------------------------------------------------------##
##
## Models with a single slope and intecept for both datasets.
## A preliminary ordinary linear regression of response proportion
## on dose is given for illustration, giving slope and intercept
```

```
## estimates comparable to those of the preferred, binomial response
## approach.
##
printCoeffs(
  lm(r / N ~ Cmax, data=danly),
  "ordinary linear regression (interc., slope)"
  )
## model with same slope and intercept for both datasets.
model.1reg <- glm(
  cbind(r, N - r) ~ Cmax,
  data   = danly,
  family = binomial(link = "identity")
  )
printCoeffs( model.1reg,
  "binomial linear regression (interc., slope)" )
## same result without explicitly binomial family, using quasi family
## final model uses variance function (variance as function of mean)
# final1reg <- glm(
#   pr ~ Cmax, data=danly, weights = N,
#   family = quasi(link = "identity", variance = "mu(1-mu)"))
## ------------------------------------------------------------------##
## model with slope and intercept estimated separately.
## The parametrization is in terms of a slope difference an d
## intecept difference for the 2nd dataset. This is convenient
## for computing an analysis of deviance table using anova(),
## requiring an recognizable nesting of the 2 models.
## anova([model1], model[2])
##
## regressor for estimating slope difference
danly$dslope03 <- with(danly, is2003*Cmax)

View(danly)

model.2reg <- glm(
  cbind(r, N - r) ~ Cmax + is2003 + dslope03,
  data   = danly,
  family = binomial(link = "identity")
```

```
        )
        printCoeffs( model.2reg, "separate binomial-response regressions" )
## ------------------------------------------------------------------------##
        ## deviance test for difference in intercept or difference in slope

        ## analysis of deviance table (does not compute p-value)
        print(anova(model.1reg, model.2reg))

        ## p-value
        chi   <- deviance( model.1reg ) - deviance( model.2reg )
        degfr <- length(coef(model.2reg)) - length(coef(model.1reg))
        cat("\n\nchi-square = ", signif(chi,4),
           "\nd.f. =", degfr,
           "\np = ", signif(pchisq(chi, degfr, lower.tail=FALSE ), 2)
           )
## ------------------------------------------------------------------------##
        ## alternative - use binomial response as for logistic reg.
        ## see glm function in R manual
        ## default logit link
        # m.glm1 <- glm(Ymat ~ Cmax, family = binomial, data=danly)
        # coef(m.glm1)
```